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An abstract of
a dissertation submitted to the faculty of the
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Abstract

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Abstract

Genetic and environmental influences during *in utero* development may contribute to an individual's risk of adverse health outcomes in both early life and adulthood. As the master regulator of early development, the placenta is responsible for initiating, and maintaining, changes in maternal physiology to sustain pregnancy as well as for promoting fetal growth and development. The placenta acts as a unique window into early development allowing the study of the molecular mechanisms underlying these genetic and environmental impacts toward adverse lifelong health outcomes and risk of chronic disease. One such mechanism involves the regulation of gene expression through microRNAs. MicroRNAs (miRNAs) are post-transcriptional regulators of gene expression that participate in critical processes, including embryogenesis, implantation and placentation. Aberrant expression of placental microRNAs is associated with variation in newborn birth weight, an early life predictor of life-long health. In this study, placentae from the New Hampshire Birth Cohort Study (NHBCS) and from the Rhode Island Child Health Study (RICHS) were selected for genotyping, trace element profiling and small RNA transcriptomic analysis. The design of these placenta-focused cohort studies resulted in the collection of anthropomorphic and medical data from mother-infant pairs, placental trace metal concentrations and placental miRNA transcript abundances. Within RICHS alone, fetal genotypes and total mRNA sequencing data were also obtained. Here, we characterize associations between various genetic and environmental risk factors throughout gestation with the expression of placental miRNAs. The mRNA targets of these miRNAs were predicted to influence endothelial maintenance and function, metabolic programming, and potentially, nervous system development. The characterization of placental miRNA transcriptomic profiles as they associate with genetic and environmental sources of variation during gestation offers critical insight into the molecular mechanisms underlying the developmental origins of health and disease. The identification of such relationships may allow for the utilization of placental miRNAs as biomarkers, offering the opportunity to develop interventional methods, or implementation of preventative measures to alter an individual's lifelong risk of chronic illness.

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My parents were not afforded the same opportunities that they worked tirelessly to create for my brother and I. My father bravely immigrated to America from Iran in hopes to obtain a strong education to foster a happy life for himself and his future family. Circumstances beyond his control prevented him from finishing his college education. My mother was born into a family with minimal resources, greatly limiting her opportunity to continue education beyond high school. The completion of this work is dedicated to my mother, Tammy Thomas Tehrani, and my father, Hamid Morad Tehrani, in honor of their resilience and perseverance through the injustices of poverty, xenophobia and racism. The immense sacrifices of my parents are the reason I have been able to pursue a higher education and I will be forever grateful for their unconditional love and patience. Mom and Dad, we did it.

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Chapter 1 - Introduction

The developmental origins of health and disease

Epidemiological and experimental relationships have been defined between both maternal and fetal stressors throughout gestation, and the development of lifelong adverse health outcomes in offspring. Fetal stressors, including maternal health and behaviors, and environmental exposures serve as significant risk indicators for the development of long-term chronic disease (1-4). These relationships were originally highlighted in observational studies of economically disadvantaged areas of England and Wales, and found that these regions experienced higher rates of mortality due to cardiovascular disease as opposed to wealthier geographies (5). This relationship initially appeared counterintuitive, as cardiovascular complications were expected to be higher in wealthier communities where indulgent, fattier foods were much more abundant and accessible. However, a strong correlation was identified between that of geographical infant mortality between 1921-1925 and ischemic heart disease related mortality in 1968-1978 (5). This work resulted in the postulation of the Developmental Origins of Health and Disease hypothesis (DOHaD). The DOHaD hypothesis speculates that variability in gestational conditions (ex: prenatal caloric insufficiency) may play a role in developmentally programming, and priming, offspring for specific postnatal conditions, ultimately creating hyper susceptibilities to the development of chronic diseases resulting from differing environmental conditions than those experienced *in utero* (ex: postnatal caloric sufficiency) (5).

Birth weight outcomes are an early life predictor of chronic disease risk

Birth weight serves as an early life metric that has been identified as a strong risk indicator for not only infant mortality, but also exhibits a strong relationship with risk of developing cardiometabolic diseases in adulthood (6, 7). Throughout gestation, humans experience an immense amount of developmental plasticity which allows for environmental stimuli to promote advantageous adaptations in offspring (8). This plasticity quickly diminishes following birth; however, physiological and metabolic modifications that occurred *in utero* may initiate lifelong changes within the offspring (8). Birth weight is the product of a fetal growth trajectory that is established very early in development and is highly influenced by *in utero* conditions which may alter the capacity of gestational tissues to support and sustain this trajectory (9). While birth weight itself is not thought to contribute directly to the etiology of these chronic diseases, it is hypothesized that the conditions of the *in utero* environment may act in a way to developmentally program lifelong health outcomes, which may manifest postnatally as birth weight (10-12). Both low and high birth weight are associated with development of adult onset cardiometabolic diseases. Individuals born within low birth weight categories are at higher risk of developing cardiovascular disease in adulthood, whereas high birth weight individuals are at increased risk of both type II diabetes and obesity in adulthood (13, 14). The metabolic consequences of adverse gestational conditions which manifest as differential birth weight outcomes may lead to metabolic overcompensation in offspring once these conditions are removed postpartum (9). The lingering impacts of these gestational conditions and their manifestation as adult onset cardiometabolic illness suggests a significant role of developmental programming as a mechanism for propagation of chronic diseases (Figure 1-1).

While the initial studies supporting the DOHaD hypothesis largely investigated relationships between maternal nutrition, birth weight and cardiometabolic outcomes, these relationships have since proven to be much more complex. These studies have become multifaceted and are now interested in the role of various gestational environmental conditions as they relate to newborn metabolic and neurological traits and how these conditions may manifest as long-term health outcomes.

Developmental programming via changes in placental physiology and function

As a central, vascular organ critical to overseeing fetal growth and development, proper functionality of the placenta is essential to successful gestational outcomes. The placenta is the largest gestational tissue of fetal origin and begins formation following implantation and invasion of the blastocyst into the maternal decidua (15). Trophoblast cells invade into the decidua to gain access to the maternal blood supply, allowing the placenta to facilitate a myriad of molecular processes such as nutrient transport, gas and waste exchange, immunomodulation, endocrine signaling and overall environmental surveillance (Figure 1-2) (15). The execution of the placenta's diverse capabilities is made possible through the construction of a highly complex villi-based vasculature system (3, 16-19).

Maternal cardiometabolic conditions and environmental exposures during pregnancy have been implicated in abnormal development of placental micro and macro-vascularization networks, which are a key pathological characteristic of placental insufficiencies, such as preeclampsia (20). During normal placental implantation, cytotrophoblasts migrate and invade deep into the myometrium to establish the necessary vascular network (21). In cases of preeclampsia, abnormal remodeling of maternal arteries following implantation and invasion may lead to narrower maternal vessels in addition to various other endothelial perturbations, resulting in inadequate vascularization and manifesting as maternal hypertension (21). These deficiencies in placental function are associated with adverse gestational outcomes, such as fetal growth restriction, which serves as a significant risk indicator for the development of chronic disease later in life (6, 7, 22). However, these clinical placental pathologies are somewhat uncommon in the general population, and thus cannot completely account for the prevalence of the adverse gestational outcomes that they are potentially responsible for programming. The subtle alterations in placental function that occur in response to gestational conditions may partly be responsible for the developmental programming of longitudinal health outcomes in offspring. Additionally, while the relationship between the overall quality of gestational conditions, placental function and lifelong health outcomes in offspring is well defined, the molecular mechanisms that oversee this developmental programming are poorly understood (20, 23, 24).

MicroRNAs are dynamic, post-transcriptional regulators of gene expression

MicroRNAs (miRNAs) are small RNA molecules (~22 nucleotides) capable of post-transcriptional regulation of gene expression that utilize base-pairing to bind target mRNAs resulting in either translational repression or mRNA degradation (25). MicroRNAs have been identified as playing a significant role in almost all cellular processes, particularly ones that modulate regulatory and signaling pathways involved in development, differentiation and overall health and disease states (25). Biogenesis of miRNAs begins in the nucleus, where they are initially transcribed, and spontaneously shaped into complex, multiple hairpin RNA structures, known as pri-miRNA, that are estimated to be around 2 kilobases in length (25). They are first cleaved by Drosha, an RNAse III enzyme, into pre-miRNA that are single hairpin structures around 60-100 nucleotides in length, prior to being exported into the nucleus through the Exportin 5 active nuclear transporter (25). Within the cytoplasm, these pre-miRNA hairpins are then processed by Dicer, an additional RNAse III enzyme, into a double stranded RNA molecule(25). It is in this double stranded state that the miRNA is then loaded into the RNA-induced Silencing Complex (RISC) through association with Argonaut proteins (25). During this loading stage, one of the two strands from the final double stranded miRNA duplex is released and degraded. This leaves only a single strand to be used as a targeting mechanism via sequence complementarity for the RISC RNA:protein complex to bind to relevant mRNAs, and to exert its regulatory function (25). Interestingly, miRNAs do not require directly complementarity with their mRNA targets which greatly increases the capabilities of a single miRNA to regulate multiple mRNAs, and to have significant physiological impacts when dysregulated. It is currently estimated that miRNAs in humans are capable of regulating at least 60% of all known expressed genes (25).

Placental microRNA expression is essential to successful gestational outcomes

While initially discovered, and functionally characterized, within the nematode *Caenorhabditis elegans* in 1993, miRNAs quickly were discovered in humans, with initial work linking specific miRNAs to fetal cardiac development, cardiac remodeling and adult onset cardiovascular diseases (26-30). The importance of microRNAs as potential biomarkers of disease, particularly in cardiovascular disease and various cancers, was initially highlighted in 2008 when miRNAs were identified as stable in human circulation, capable of being isolated from both serum and plasma to characterize patient disease states (31).

MiRNAs in the context of pregnancy are particularly unique considering they can be transcribed by either the mother or the fetus, many of which are capable of crossing the placental interface to regulate gene expression, adding to the complex, yet sensitive, regulatory potential of miRNAs during pregnancy (32, 33). Considering the placenta's significant circulatory function, and the commonality of humoral growth signals with the cardiovascular system, this critical role of miRNAs in cardiac development and function remained true for the placenta as well (34-36).

Select miRNAs may be specifically relevant to pregnancy, such as the two primate specific miRNA clusters, chromosome 19 and 14 clusters (C19MC and C14MC) (37-39). They are the largest miRNA clusters currently known, spanning 40-100 kilobases in length and each containing more than 40 individual miRNAs (37-39). Both clusters are expressed almost exclusively in the placenta wherein they demonstrate differential expression trajectories throughout gestation, likely influencing processes such as invasion, implantation and placentation (37-39). While invasion of embryonic cells into the uterus is not a process specific to the development of humans, the most pronounced levels of invasion amongst all eutherian mammals is seen in humans, distinguishing the role of miRNAs as they contribute to the specific needs of a successful birth (38-40).

Placental microRNAs are potential biomarkers of maternal and fetal health outcomes

Many miRNAs have been identified as stable in maternal serum and have since been utilized as biomarkers of pregnancy-related conditions, including ectopic pregnancies, preeclampsia, gestational diabetes, and preterm birth (41, 42). While the functional role of miRNAs in each of these specific conditions is not well understood, the dysregulation of placental miRNA expression has been implicated in preeclampsia and fetal growth restriction, highlighting their potential role as modifiers of newborn and maternal health outcomes (43). Interestingly, placental miRNAs that enter maternal circulation have previously been shown to exhibit signature expression profiles in maternal serum within individuals that develop both mild and severe preeclampsia as compared to non-preeclamptic mothers (44). These miRNAs that enter circulation offer the unique advantage of being monitored throughout gestation, and may serve as strong biomarkers of both maternal and fetal health outcomes as they relate to placental physiology and function throughout gestation. Additionally, the expression profiles of placental miRNAs are also associated with birthweight percentile (45). Specifically, these birth weight associated miRNAs were predicted to regulate the expression of genes within the adipokine signaling pathway (45). Disruption to adipokine signaling during gestation is known to correlate with the both onset and severity of preeclampsia (46). Additionally, birth weight-associated miRNAs were also predicted to target genes broadly involved in angiogenesis, energy metabolism and endocrine signaling, suggesting their dysregulation could lead to significant consequences to normal placental function (45). Given their association with newborn health outcomes, and their potential role in regulating critical pathways relevant to placental function and physiology, miRNA expression may serve as a mechanism in the developmental programming of lifelong risk of chronic disease (Figure 1-3) (45).

Toxic metal exposures are implicated in placental insufficiencies

Humans are constantly exposed to numerous toxic metals through contaminated food and drinking water, airborne sources and through occupational means. With the increase in industrialization and urbanization, the ubiquitous nature of metals in the environment has increased the general population’s rate of chronic exposure to trace metals such as cadmium and arsenic. Gestation is an extremely vulnerable point of development by which these environmental contaminants may exert their toxic effects to impact the lifelong health of an offspring exposed *in utero* (47-49). While the placenta acts as a selective barrier to prevent the passage of certain chemicals across the maternal-fetal interface, some toxic metals are able to freely pass through the interface, while others are shown to accumulate within the tissue itself (50). Toxic metal exposures may influence both maternal and fetal health through placental insufficiencies, where gestational exposure of toxic metals is associated with increased risk of preeclampsia, including: cadmium, arsenic, and mercury (17, 51-53).

The regulation of miRNAs is known to be responsive to acute exposure and accumulation of both cadmium and arsenic, indicating that expression profiles of specific miRNAs may be capable of serving as biomarkers of exposure (53-55). MiRNAs have been shown to be extremely sensitive in their expression levels when challenged with cadmium and arsenic in various tissues and may contribute to carcinogenesis and neurodegeneration that occurs in response to exposure (56).

Gestational Cd exposure is associated with adverse pregnancy and birth outcomes including: decreased overall placental efficiency, and increased risk of preeclampsia and low birth weight (17-19, 57). A growing body of evidence suggests that the atypical neurobehavioral outcomes and intellectual deficits seen in children exposed to Cd *in utero* are linked to Cd levels in cord blood and maternal circulation during pregnancy(57-61). Given the placenta's ability to produce neurotransmitters and its involvement in supporting fetal brain development, these data suggest that gestational Cd may affect exposure as a potential mediator of neurodevelopment by acting through the placenta (62-64).

Arsenic exposure occurs through primarily through inhalation or the consumption of contaminated food and drinking water (65). Research out of Bangladesh, a country with abnormally high levels of inorganic arsenic in the soil and water, have showcased arsenic-associated changes in miRNA expression as a casual mediator of adverse birthweight outcomes (65). The arsenic-associated miRNAs identified within this study were predicted to regulate the expression of biochemical pathways contributing to Insulin-like Growth Factor (IGF) signaling cascades; a pathway which contributes greatly to fetal growth and metabolism (65).

However, the direct role of miRNA expression in the placenta in response to toxic metal exposure, and the onset of placental insufficiencies in response to metal exposure *in vivo*, is not well understood. The molecular response to trace metal exposure may manifest as changes in placental physiology and, in turn, contribute to the development of placental insufficiencies. Profound insufficiencies, such as preeclampsia, are relatively rare within the general population

(5-8% of all pregnancies), and thus do not completely account for the entirety of long term offspring health outcomes that may arise from adverse environmental exposures during pregnancy (66). Subtle alterations in placental physiology may occur throughout gestation in response to chronic trace metal exposure *in utero*, playing a larger role in the developmental origins of chronic disease by acting through dysregulation of placental miRNA expression.

Human genetic variation may influence microRNA regulatory potential

Genetic variation introduces multiple facets of complexity with respect to miRNA-mediated regulation of gene expression. The location at which this variation occurs may have differential consequences in terms of the functional significance of that variant and how it may influence the miRNA regulatory pathway (67, 68). Variants introduced within the sequence of the miRNAs themselves, or that of their mRNA targets may alters the miRNA:mRNA interaction capabilities within a tissue-specific transcriptome (67, 68). Additionally, other genomic variants, may influence the transcriptional patterns of specific miRNAs through alteration of chromatin accessibility or transcription factor activity (67, 68). Given the sensitive nature of miRNA-mediated regulation of gene expression to genetic variation, there may exist a quantitative relationship between specific variants and the expression of miRNAs. Variants holding this specific relationship, coined as miRNA quantitative trait loci (miR-QTLs), have been characterized in various tissues, including whole blood and neuronal tissue (69, 70).

The quantitative relationship that exists between specific genetic variants, phenotypic outcomes and transcriptomic patterns is carefully outlined with respect to cardiovascular disease on the mRNA level (expression QTLs – eQTLs). These relationships explain upwards of 13% of inter-individual variation in cardiometabolic traits, including hyperlipidemia and hyperglycemia (71). The presence of eQTLs have been characterized within placental tissue in a study which outlined relationships surrounding the expression of various mRNAs in the placenta and their quantitative relationship with genetic variants that are implicated in fetal growth, birth weight outcomes and metabolic syndromes (72, 73). Considering the critical role of placental miRNA expression to successful gestational outcomes, miRNA expression is believed to be sensitive to genetic variation, as well, within the placenta.

Heritability estimates of common metabolic syndromes within the US are speculated to have anywhere between 16% to 60% genetic contributions, meaning chronic conditions relevant to the DOHaD hypothesis may have strong genetic components (74). With the highly variable contribution of genetic predisposition to the development of cardiometabolic conditions, these genetic variants may also act through the placenta to alter miRNA expression, effectively acting through miRNA expression to developmentally program an increased risk of disease later in life (75).

Dissertation Overview

In conclusion, placental miRNA expression is a critical molecular component of early development, and may play an even more significant role in the developmental programming of chronic disease. Dysregulation of human placental miRNA expression, as a result of both environmental and genetic variation, are hypothesized to initiate downstream impacts on newborn health outcomes. This dissertation investigates how both genetic and environmental exposures disrupt placental miRNA expression in the placenta utilizing epidemiological, anthropomorphic and molecular data gathered from two large mother-infant cohorts from the northeastern United States. The primary aims of this work are:

Aim 1: Investigate the genetic influence of cardiometabolic disease toward placental miRNA expression in the Rhode Island Child Health Study (RICHS). Hypothesis: Placental miRNA expression is associated with the incidence of familial cardiovascular disease within RICHS.

Aim 2: Characterize the influence of gestational environmental conditions, in the form of trace metal exposure, toward placental miRNA expression within both RICHS and the New Hampshire Birth Cohort Study (NHBCS). Hypothesis: Placental miRNA expression is associated with placental cadmium accumulation within both RICHS and NHBCS.

These aims are addressed in the following dissertation chapters, two of which have been submitted for publication as stand-alone manuscripts. Chapter 2 addresses Aim 1 by investigating the influence of maternal family history of cardiovascular disease as it relates to miRNA expression in the placenta. The goal of this study was to analyze combined genetic and environmental risk factors associated with familial cardiovascular disease and their influence toward placental miRNA expression. Chapter 3 also addresses Aim 1 by further investigating the implication of cardiovascular disease genetics as it relates to placental miRNA expression. The goal of this study was to calculate a cardiovascular disease polygenic risk score for each individual, and characterize its influence toward placental miRNA expression. Chapter 4 addresses Aim 2 by investigating the role of gestational toxic metal exposure, namely cadmium, and its role in placental miRNA expression patterns. The goal of this study was to characterize cadmium-sensitive miRNAs, and to analyze the ability of these expression profiles to predict longitudinal health outcomes in exposed offspring. Lastly, Chapter 5 summarizes the research conclusions and discusses future directions.

FIGURES

Figure 1-1: Developmental programming of chronic disease. Developmental plasticity and the risk of developing chronic disease are inversely proportional throughout the lifespan of an individual with the highest level of plasticity occurring during early development. Genetic influences of developmental programming remain relatively constant while environmental influences are much more dynamic, in both temporality and magnitude, with respect to how they contribute to the developmental programming of chronic disease. Created with www.BioRender.com.

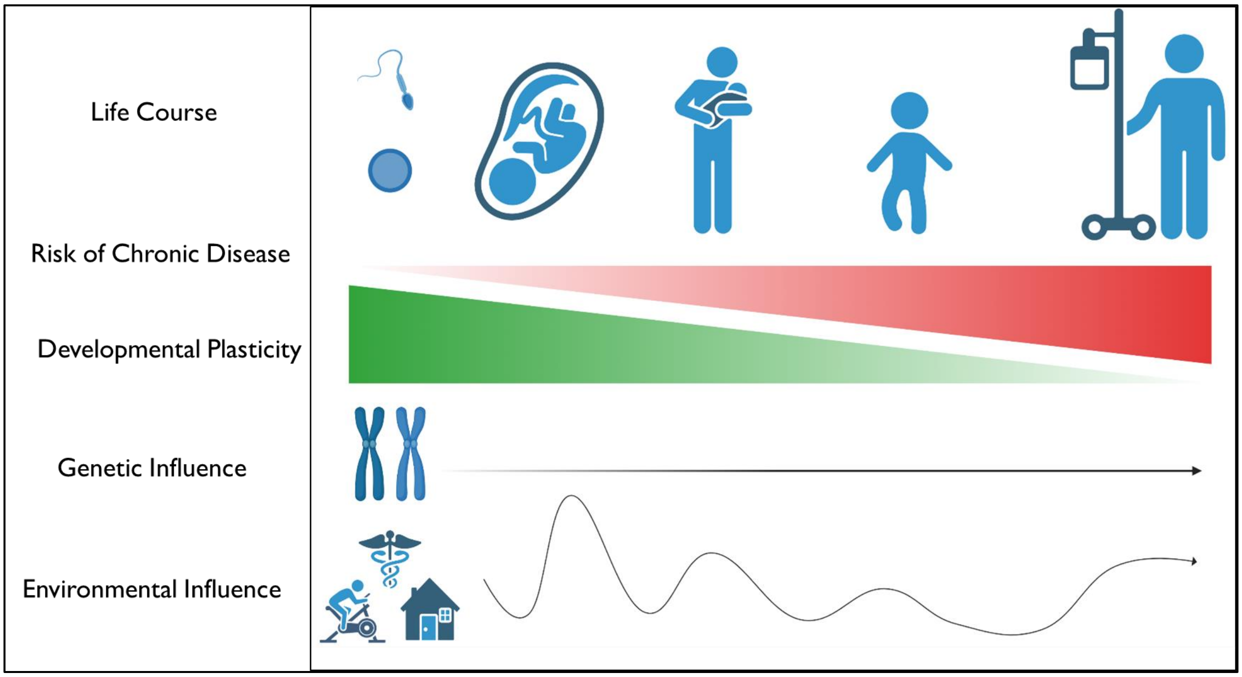


Figure 1-2: Overview of the critical functions of the placenta. The placenta is responsible for various processes to support and sustain gestational growth and development, including nutrient transport, environmental surveillance, gas and waste exchange, in addition to immunomodulation. These functions of the placenta work in unison to support growth and development and regulate maternal immune responses, all while responding to gestational stressors to allow for fetal adaptations to best support life postnatally. Created with www.BioRender.com.

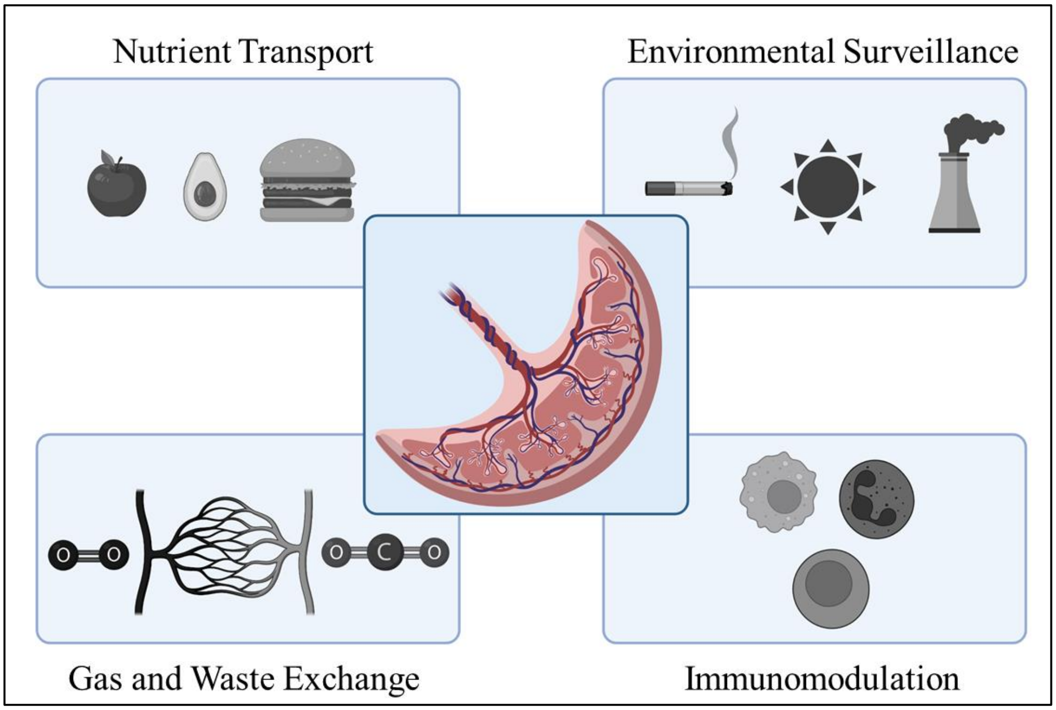
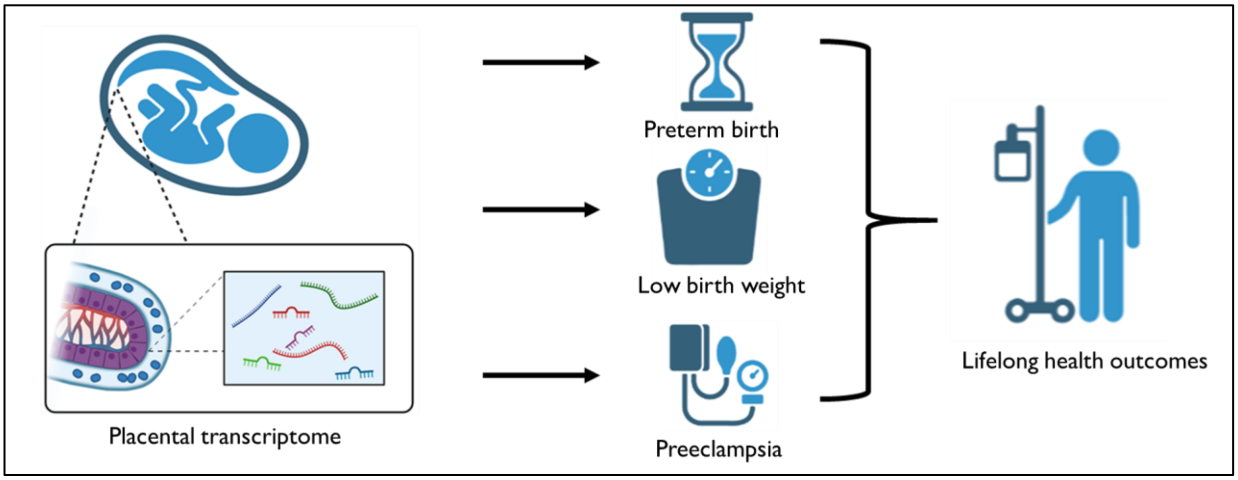


Figure 1-3: Placental miRNA expression is associated with gestational outcomes and may be predictive of chronic disease risk. Dysregulation of placental miRNA expression in the placenta has been implicated in gestational outcomes such as preterm birth, low birth weight and preeclampsia. These gestational outcomes are thought to arise largely from abnormalities in placental physiology, and are associated with increased risk of adverse cardiometabolic health in adulthood, suggesting placental miRNA expression may serve as a mechanism of developmental programming of lifelong health outcomes *in utero*. Created with www.BioRender.com.



REFERENCES

1. Alsnes IV, Vatten LJ, Fraser A, Bjørngaard JH, Rich-Edwards J, Romundstad PR, Åsvold BO. Hypertension in Pregnancy and Offspring Cardiovascular Risk in Young Adulthood: Prospective and Sibling Studies in the HUNT Study (Nord-Trøndelag Health Study) in Norway. Hypertension. 2017;69(4):591-8. Epub 2017/02/23. doi: 10.1161/hypertensionaha.116.08414. PubMed PMID: 28223467.
2. Christensen JJ, Retterstøl K, Godang K, Roland MC, Qvigstad E, Bollerslev J, Ueland T, Henriksen T, Holven KB. LDL cholesterol in early pregnancy and offspring cardiovascular disease risk factors. J Clin Lipidol. 2016;10(6):1369-78.e7. Epub 2016/12/07. doi: 10.1016/j.jacl.2016.08.016. PubMed PMID: 27919354.
3. Hudson KM, Belcher SM, Cowley M. Maternal cadmium exposure in the mouse leads to increased heart weight at birth and programs susceptibility to hypertension in adulthood. Scientific Reports. 2019;9(1):13553. doi: 10.1038/s41598-019-49807-5.
4. Knopik VS, Maccani MA, Francazio S, McGeary JE. The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. Dev Psychopathol. 2012;24(4):1377-90. doi: 10.1017/S0954579412000776. PubMed PMID: 23062304.
5. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet. 1986;1(8489):1077-81. Epub 1986/05/10. doi: 10.1016/s0140-6736(86)91340-1. PubMed PMID: 2871345.
6. Barker DJ, Osmond C. Low birth weight and hypertension. BMJ. 1988;297(6641):134-5. doi: 10.1136/bmj.297.6641.134-b. PubMed PMID: 3408942.
7. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989;2(8663):577-80. Epub 1989/09/09. doi: 10.1016/s0140-6736(89)90710-1. PubMed PMID: 2570282.
8. Barker DJP. Developmental origins of chronic disease. Public Health. 2012;126(3):185-9. doi: https://doi.org/10.1016/j.puhe.2011.11.014.
9. Barker ED, McAuliffe FM, Alderdice F, Unterscheider J, Daly S, Geary MP, Kennelly MM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD. The Role of Growth Trajectories in Classifying Fetal Growth Restriction. Obstetrics & Gynecology. 2013;122(2 PART 1):248-54. doi: 10.1097/AOG.0b013e31829ca9a7. PubMed PMID: 00006250-201308000-00010.
10. Li X, Huang S, Jiao A, Yang X, Yun J, Wang Y, Xue X, Chu Y, Liu F, Liu Y, Ren M, Chen X, Li N, Lu Y, Mao Z, Tian L, Xiang H. Association between ambient fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis. Environ Pollut. 2017;227:596-605. Epub 2017/05/02. doi: 10.1016/j.envpol.2017.03.055. PubMed PMID: 28457735.
11. Rich-Edwards JW, Stampfer MJ, Manson JE, Rosner B, Hankinson SE, Colditz GA, Willett WC, Hennekens CH. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. BMJ. 1997;315(7105):396-400. Epub 1997/08/16. doi: 10.1136/bmj.315.7105.396. PubMed PMID: 9277603; PMCID: PMC2127275.
12. Wang S, Yang L, Shang L, Yang W, Qi C, Huang L, Xie G, Wang R, Chung MC. Changing trends of birth weight with maternal age: a cross-sectional study in Xi’an city of Northwestern China. BMC Pregnancy and Childbirth. 2020;20(1):744. doi: 10.1186/s12884-020-03445-2.
13. Smith CJ, Ryckman KK, Barnabei VM, Howard BV, Isasi CR, Sarto GE, Tom SE, Van Horn LV, Wallace RB, Robinson JG. The impact of birth weight on cardiovascular disease risk

in the Women's Health Initiative. Nutrition, Metabolism and Cardiovascular Diseases. 2016;26(3):239-45. doi: https://doi.org/10.1016/j.numecd.2015.10.015.
14. Johnsson IW, Haglund B, Ahlsson F, Gustafsson J. A high birth weight is associated with increased risk of type 2 diabetes and obesity. Pediatric Obesity. 2015;10(2):77-83. doi: https://doi.org/10.1111/ijpo.230.
15. Turco MY, Moffett A. Development of the human placenta. Development. 2019;146(22). doi: 10.1242/dev.163428.
16. Cross JC, Baczyk D, Dobric N, Hemberger M, Hughes M, Simmons DG, Yamamoto H, Kingdom JC. Genes, development and evolution of the placenta. Placenta. 2003;24(2-3):123-30. Epub 2003/02/25. doi: 10.1053/plac.2002.0887. PubMed PMID: 12596737.
17. Laine JE, Ray P, Bodnar W, Cable PH, Boggess K, Offenbacher S, Fry RC. Placental Cadmium Levels Are Associated with Increased Preeclampsia Risk. PLoS One. 2015;10(9):e0139341. Epub 2015/10/01. doi: 10.1371/journal.pone.0139341. PubMed PMID: 26422011; PMCID: PMC4589375.
18. Hussey MR, Burt A, Deyssenroth MA, Jackson BP, Hao K, Peng S, Chen J, Marsit CJ, Everson TM. Placental lncRNA expression associated with placental cadmium concentrations and birth weight. Environ Epigenet. 2020;6(1):dvaa003. Epub 2020/05/16. doi: 10.1093/eep/dvaa003. PubMed PMID: 32411397; PMCID: PMC7211362.
19. Punshon T, Li Z, Jackson BP, Parks WT, Romano M, Conway D, Baker ER, Karagas MR. Placental metal concentrations in relation to placental growth, efficiency and birth weight. Environ Int. 2019;126:533-42. Epub 2019/03/10. doi: 10.1016/j.envint.2019.01.063. PubMed PMID: 30851484; PMCID: PMC6475117.
20. Sobrevia L, Abarzúa F, Nien JK, Salomón C, Westermeier F, Puebla C, Cifuentes F, Guzmán-Gutiérrez E, Leiva A, Casanello P. Review: Differential placental macrovascular and microvascular endothelial dysfunction in gestational diabetes. Placenta. 2011;32 Suppl 2:S159-64. Epub 2011/01/11. doi: 10.1016/j.placenta.2010.12.011. PubMed PMID: 21215450.
21. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: Pathophysiology, Challenges, and Perspectives. Circ Res. 2019;124(7):1094-112. Epub 2019/03/29. doi: 10.1161/CIRCRESAHA.118.313276. PubMed PMID: 30920918.
22. Audette MC, Kingdom JC. Screening for fetal growth restriction and placental insufficiency. Semin Fetal Neonatal Med. 2018;23(2):119-25. Epub 2017/12/10. doi: 10.1016/j.siny.2017.11.004. PubMed PMID: 29221766.
23. Odegård RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R. Preeclampsia and fetal growth. Obstet Gynecol. 2000;96(6):950-5. Epub 2000/11/21. PubMed PMID: 11084184.
24. Leiva A, de Medina CD, Salsoso R, Sáez T, San Martín S, Abarzúa F, Farías M, Guzmán-Gutiérrez E, Pardo F, Sobrevia L. Maternal hypercholesterolemia in pregnancy associates with umbilical vein endothelial dysfunction: role of endothelial nitric oxide synthase and arginase II. Arterioscler Thromb Vasc Biol. 2013;33(10):2444-53. Epub 2013/08/21. doi: 10.1161/atvbaha.113.301987. PubMed PMID: 23950140.
25. Mouillet JF, Ouyang Y, Coyne CB, Sadovsky Y. MicroRNAs in placental health and disease. Am J Obstet Gynecol. 2015;213(4 Suppl):S163-72. Epub 2015/10/03. doi: 10.1016/j.ajog.2015.05.057. PubMed PMID: 26428496; PMCID: PMC4592520.
26. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75(5):843-54. doi: https://doi.org/10.1016/0092-8674(93)90529-Y.

27. Thum T, Galuppo P, Wolf C, Fiedler J, Kneitz S, van Laake LW, Doevendans PA, Mummery CL, Borlak J, Haverich A, Gross C, Engelhardt S, Ertl G, Bauersachs J. MicroRNAs in the human heart: a clue to fetal gene reprogramming in heart failure. Circulation. 2007;116(3):258-67. Epub 2007/07/04. doi: 10.1161/CIRCULATIONAHA.107.687947. PubMed PMID: 17606841.
28. Thum T, Catalucci D, Bauersachs J. MicroRNAs: novel regulators in cardiac development and disease. Cardiovascular Research. 2008;79(4):562-70. doi: 10.1093/cvr/cvn137.
29. Marques FZ, Booth SA, Charchar FJ. The emerging role of non-coding RNA in essential hypertension and blood pressure regulation. Journal of Human Hypertension. 2015;29(8):459-67. doi: 10.1038/jhh.2014.99.
30. Bang C, Batkai S, Dangwal S, Gupta SK, Foinquinos A, Holzmann A, Just A, Remke J, Zimmer K, Zeug A, Ponimaskin E, Schmiedl A, Yin X, Mayr M, Halder R, Fischer A, Engelhardt S, Wei Y, Schober A, Fiedler J, Thum T. Cardiac fibroblast–derived microRNA passenger strand-enriched exosomes mediate cardiomyocyte hypertrophy. The Journal of Clinical Investigation. 2014;124(5):2136-46. doi: 10.1172/JCI70577.
31. Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, Peterson A, Noteboom J, O'Briant KC, Allen A, Lin DW, Urban N, Drescher CW, Knudsen BS, Stirewalt DL, Gentleman R, Vessella RL, Nelson PS, Martin DB, Tewari M. Circulating microRNAs as stable blood-based markers for cancer detection. Proceedings of the National Academy of Sciences. 2008;105(30):10513-8. doi: 10.1073/pnas.0804549105.
32. Gross N, Kropp J, Khatib H. MicroRNA Signaling in Embryo Development. Biology (Basel). 2017;6(3). Epub 2017/09/15. doi: 10.3390/biology6030034. PubMed PMID: 28906477; PMCID: PMC5617922.
33. Geng Y, He J, Ding Y, Chen X, Zhou Y, Liu S, Liu X, Wang Y. The Differential Expression of MicroRNAs Between Implantation Sites and Interimplantation Sites in Early Pregnancy in Mice and Their Potential Functions. Reproductive Sciences. 2014;21(10):1296-306. doi: 10.1177/1933719114525273. PubMed PMID: 24604233.
34. Cohen JA, Rychik J, Savla JJ. The placenta as the window to congenital heart disease. Curr Opin Cardiol. 2021;36(1):56-60. Epub 2020/10/20. doi: 10.1097/hco.0000000000000816. PubMed PMID: 33074934.
35. Camm EJ, Botting KJ, Sferruzzi-Perri AN. Near to One's Heart: The Intimate Relationship Between the Placenta and Fetal Heart. Front Physiol. 2018;9:629. Epub 2018/07/13. doi: 10.3389/fphys.2018.00629. PubMed PMID: 29997513; PMCID: PMC6029139.
36. Azhar M, Runyan RB, Gard C, Sanford LP, Miller ML, Andringa A, Pawlowski S, Rajan S, Doetschman T. Ligand-specific function of transforming growth factor beta in epithelial-mesenchymal transition in heart development. Dev Dyn. 2009;238(2):431-42. Epub 2009/01/24. doi: 10.1002/dvdy.21854. PubMed PMID: 19161227; PMCID: PMC2805850.
37. Mouillet JF, Chu T, Sadovsky Y. Expression patterns of placental microRNAs. Birth Defects Res A Clin Mol Teratol. 2011;91(8):737-43. Epub 2011/03/23. doi: 10.1002/bdra.20782. PubMed PMID: 21425434; PMCID: PMC5030720.
38. Bortolin-Cavaillé ML, Dance M, Weber M, Cavaillé J. C19MC microRNAs are processed from introns of large Pol-II, non-protein-coding transcripts. Nucleic Acids Res. 2009;37(10):3464-73. Epub 2009/04/03. doi: 10.1093/nar/gkp205. PubMed PMID: 19339516; PMCID: PMC2691840.

39. Paquette AG, Chu T, Wu X, Wang K, Price ND, Sadovsky Y. Distinct communication patterns of trophoblastic miRNA among the maternal-placental-fetal compartments. Placenta. 2018;72-73:28-35. Epub 2018/12/07. doi: 10.1016/j.placenta.2018.10.004. PubMed PMID: 30501878; PMCID: PMC6329371.
40. Grigsby PL. Animal Models to Study Placental Development and Function throughout Normal and Dysfunctional Human Pregnancy. Semin Reprod Med. 2016;34(1):11-6. Epub 2016/01/12. doi: 10.1055/s-0035-1570031. PubMed PMID: 26752715; PMCID: PMC4799492.
41. Zhao Z, Moley KH, Gronowski AM. Diagnostic potential for miRNAs as biomarkers for pregnancy-specific diseases. Clin Biochem. 2013;46(10-11):953-60. Epub 2013/02/12. doi: 10.1016/j.clinbiochem.2013.01.026. PubMed PMID: 23396163.
42. Barchitta M, Maugeri A, Quattrocchi A, Agrifoglio O, Agodi A. The Role of miRNAs as Biomarkers for Pregnancy Outcomes: A Comprehensive Review. Int J Genomics. 2017;2017:8067972-. Epub 2017/08/13. doi: 10.1155/2017/8067972. PubMed PMID: 28884117.
43. Ospina-Prieto S, Chaiwangyen W, Herrmann J, Groten T, Schleussner E, Markert UR, Morales-Prieto DM. MicroRNA-141 is upregulated in preeclamptic placentae and regulates trophoblast invasion and intercellular communication. Transl Res. 2016;172:61-72. Epub 2016/03/26. doi: 10.1016/j.trsl.2016.02.012. PubMed PMID: 27012474.
44. Martinez-Fierro ML, Garza-Veloz I. Analysis of Circulating microRNA Signatures and Preeclampsia Development. Cells. 2021;10(5):1003. doi: 10.3390/cells10051003. PubMed PMID: 33923172.
45. Kennedy EM, Hermetz K, Burt A, Everson TM, Deyssenroth M, Hao K, Chen J, Karagas MR, Pei D, Koestler DC, Marsit CJ. Placental microRNA expression associates with birthweight through control of adipokines: results from two independent cohorts. Epigenetics. 2021;16(7):770-82. Epub 2020/10/06. doi: 10.1080/15592294.2020.1827704. PubMed PMID: 33016211; PMCID: PMC8216179.
46. Wang L, Yang T, Ding Y, Zhong Y, Yu L, Peng M. Chemerin plays a protective role by regulating human umbilical vein endothelial cell-induced nitric oxide signaling in preeclampsia. Endocrine. 2015;48(1):299-308. doi: 10.1007/s12020-014-0286-y.
47. Davis MA, Li Z, Gilbert-Diamond D, Mackenzie TA, Cottingham KL, Jackson BP, Lee JS, Baker ER, Marsit CJ, Karagas MR. Infant toenails as a biomarker of in utero arsenic exposure. Journal of Exposure Science & Environmental Epidemiology. 2014;24(5):467-73. doi: 10.1038/jes.2014.38.
48. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of In Utero and Early-Life Conditions on Adult Health and Disease. New England Journal of Medicine. 2008;359(1):61-73. doi: 10.1056/NEJMra0708473. PubMed PMID: 18596274.
49. Punshon T, Li Z, Jackson BP, Parks WT, Romano M, Conway D, Baker ER, Karagas MR. Placental metal concentrations in relation to placental growth, efficiency and birth weight. Environment International. 2019;126:533-42. doi: https://doi.org/10.1016/j.envint.2019.01.063.
50. Needham LL, Grandjean P, Heinzow B, Jørgensen PJ, Nielsen F, Patterson DG, Sjödin A, Turner WE, Weihe P. Partition of Environmental Chemicals between Maternal and Fetal Blood and Tissues. Environmental Science & Technology. 2011;45(3):1121-6. doi: 10.1021/es1019614.
51. da Cunha Martins A, Carneiro MFH, Grotto D, Adeyemi JA, Barbosa F. Arsenic, cadmium, and mercury-induced hypertension: mechanisms and epidemiological findings. Journal of Toxicology and Environmental Health, Part B. 2018;21(2):61-82. doi: 10.1080/10937404.2018.1432025.

52. Sandoval-Carrillo A, Méndez-Hernández EM, Antuna-Salcido EI, Salas-Pacheco SM, Vázquez-Alaniz F, Téllez-Valencia A, Aguilar-Durán M, Barraza-Salas M, Castellanos-Juárez FX, La Llave-León O, Salas-Pacheco JM. Arsenic exposure and risk of preeclampsia in a Mexican mestizo population. BMC Pregnancy and Childbirth. 2016;16(1):153. doi: 10.1186/s12884-016-0946-4.

53. Brooks SA, Martin E, Smeester L, Grace MR, Boggess K, Fry RC. miRNAs as common regulators of the transforming growth factor (TGF)-β pathway in the preeclamptic placenta and cadmium-treated trophoblasts: Links between the environment, the epigenome and preeclampsia. Food and Chemical Toxicology. 2016;98:50-7. doi: https://doi.org/10.1016/j.fct.2016.06.023.

54. Vrijens K, Bollati V, Nawrot TS. MicroRNAs as potential signatures of environmental exposure or effect: a systematic review. Environ Health Perspect. 2015;123(5):399-411. Epub 2015/01/24. doi: 10.1289/ehp.1408459. PubMed PMID: 25616258; PMCID: PMC4421768.

55. Addo KA, Palakodety N, Hartwell HJ, Tingare A, Fry RC. Placental microRNAs: Responders to environmental chemicals and mediators of pathophysiology of the human placenta. Toxicol Rep. 2020;7:1046-56. Epub 2020/09/12. doi: 10.1016/j.toxrep.2020.08.002. PubMed PMID: 32913718; PMCID: PMC7472806.

56. Wallace DR, Taalab YM, Heinze S, Tariba Lovaković B, Pizent A, Renieri E, Tsatsakis A, Farooqi AA, Javorac D, Andjelkovic M, Bulat Z, Antonijević B, Buha Djordjevic A. Toxic-Metal-Induced Alteration in miRNA Expression Profile as a Proposed Mechanism for Disease Development. Cells. 2020;9(4):901. PubMed PMID: doi:10.3390/cells9040901.

57. Hudson KM, Shiver E, Yu J, Mehta S, Jima DD, Kane MA, Patisaul HB, Cowley M. Transcriptomic, proteomic, and metabolomic analyses identify candidate pathways linking maternal cadmium exposure to altered neurodevelopment and behavior. Scientific Reports. 2021;11(1). doi: 10.1038/s41598-021-95630-2.

58. Liu J, Martin LJ, Dinu I, Field CJ, Dewey D, Martin JW. Interaction of prenatal bisphenols, maternal nutrients, and toxic metal exposures on neurodevelopment of 2-year-olds in the APrON cohort. Environ Int. 2021;155:106601. Epub 2021/05/08. doi: 10.1016/j.envint.2021.106601. PubMed PMID: 33962233.

59. Tian LL, Zhao YC, Wang XC, Gu JL, Sun ZJ, Zhang YL, Wang JX. Effects of gestational cadmium exposure on pregnancy outcome and development in the offspring at age 4.5 years. Biol Trace Elem Res. 2009;132(1-3):51-9. Epub 2009/05/01. doi: 10.1007/s12011-009-8391-0. PubMed PMID: 19404590.

60. Wang Y, Chen L, Gao Y, Zhang Y, Wang C, Zhou Y, Hu Y, Shi R, Tian Y. Effects of prenatal exposure to cadmium on neurodevelopment of infants in Shandong, China. Environ Pollut. 2016;211:67-73. Epub 2016/01/07. doi: 10.1016/j.envpol.2015.12.038. PubMed PMID: 26736057.

61. Tung PW, Burt A, Karagas M, Jackson BP, Punshon T, Lester B, Marsit CJ. Association between placental toxic metal exposure and NICU Network Neurobehavioral Scales (NNNS) profiles in the Rhode Island Child Health Study (RICHS). Environ Res. 2021;204(Pt A):111939. Epub 2021/08/31. doi: 10.1016/j.envres.2021.111939. PubMed PMID: 34461121.

62. Lester BM, Marsit CJ. Epigenetic mechanisms in the placenta related to infant neurodevelopment. Epigenomics. 2018;10(3):321-33. Epub 2018/01/31. doi: 10.2217/epi-2016-0171. PubMed PMID: 29381081; PMCID: PMC6219448.

63. Rosenfeld CS. The placenta-brain-axis. J Neurosci Res. 2021;99(1):271-83. Epub 2020/02/29. doi: 10.1002/jnr.24603. PubMed PMID: 32108381; PMCID: PMC7483131.

64. Shallie PD, Naicker T. The placenta as a window to the brain: A review on the role of placental markers in prenatal programming of neurodevelopment. Int J Dev Neurosci. 2019;73:41-9. Epub 2019/01/12. doi: 10.1016/j.ijdevneu.2019.01.003. PubMed PMID: 30634053.
65. Rahman ML, Liang L, Valeri L, Su L, Zhu Z, Gao S, Mostofa G, Qamruzzaman Q, Hauser R, Baccarelli A, Christiani DC. Regulation of birthweight by placenta-derived miRNAs: evidence from an arsenic-exposed birth cohort in Bangladesh. Epigenetics. 2018;13(6):573-90. Epub 2018/08/14. doi: 10.1080/15592294.2018.1481704. PubMed PMID: 30099960; PMCID: PMC6140906.
66. Jim B, Karumanchi SA. Preeclampsia: Pathogenesis, Prevention, and Long-Term Complications. Seminars in Nephrology. 2017;37(4):386-97. doi: https://doi.org/10.1016/j.semnephrol.2017.05.011.
67. Borel C, Antonarakis SE. Functional genetic variation of human miRNAs and phenotypic consequences. Mammalian Genome. 2008;19(7):503-9. doi: 10.1007/s00335-008-9137-6.
68. Hogg DR, Harries Lorna W. Human genetic variation and its effect on miRNA biogenesis, activity and function. Biochemical Society Transactions. 2014;42(4):1184-9. doi: 10.1042/bst20140055.
69. Huan T, Rong J, Liu C, Zhang X, Tanriverdi K, Joehanes R, Chen BH, Murabito JM, Yao C, Courchesne P, Munson PJ, O'Donnell CJ, Cox N, Johnson AD, Larson MG, Levy D, Freedman JE. Genome-wide identification of microRNA expression quantitative trait loci. Nature Communications. 2015;6(1):6601. doi: 10.1038/ncomms7601.
70. Williamson VS, Mamdani M, McMichael GO, Kim AH, Lee D, Bacanu S, Vladimirov VI. Expression quantitative trait loci (eQTLs) in microRNA genes are enriched for schizophrenia and bipolar disorder association signals. Psychological Medicine. 2015;45(12):2557-69. Epub 2015/03/30. doi: 10.1017/S0033291715000483.
71. Yao C, Chen BH, Joehanes R, Otlu B, Zhang X, Liu C, Huan T, Tastan O, Cupples LA, Meigs JB, Fox CS, Freedman JE, Courchesne P, O'Donnell CJ, Munson PJ, Keles S, Levy D. Integromic analysis of genetic variation and gene expression identifies networks for cardiovascular disease phenotypes. Circulation. 2015;131(6):536-49. Epub 2014/12/24. doi: 10.1161/CIRCULATIONAHA.114.010696. PubMed PMID: 25533967; PMCID: PMC4369387.
72. Peng S, Deyssenroth MA, Di Narzo AF, Cheng H, Zhang Z, Lambertini L, Ruusalepp A, Kovacic JC, Bjorkegren JLM, Marsit CJ, Chen J, Hao K. Genetic regulation of the placental transcriptome underlies birth weight and risk of childhood obesity. PLOS Genetics. 2019;14(12):e1007799. doi: 10.1371/journal.pgen.1007799.
73. Bhattacharya A, Freedman AN, Avula V, Harris R, Liu W, Pan C, Lusis AJ, Joseph RM, Smeester L, Hartwell HJ, Kuban KCK, Marsit CJ, Li Y, O'Shea TM, Fry RC, Santos HP, Jr. Placental genomics mediates genetic associations with complex health traits and disease. Nat Commun. 2022;13(1):706. Epub 2022/02/06. doi: 10.1038/s41467-022-28365-x. PubMed PMID: 35121757.
74. Ghosh A, Dutta R, Sarkar A. Heritability estimation of conventional cardiovascular disease risk factors in Asian Indian families: The Calcutta family study. Indian J Hum Genet. 2010;16(1):28-32. Epub 2010/09/15. doi: 10.4103/0971-6866.64944. PubMed PMID: 20838489; PMCID: PMC2927791.
75. Tada H, Fujino N, Hayashi K, Kawashiri M-a, Takamura M. Human genetics and its impact on cardiovascular disease. Journal of Cardiology. 2022;79(2):233-9. doi: https://doi.org/10.1016/j.jjcc.2021.09.005.

Chapter 2 - Variation in placental microRNA expression associates with maternal family history of cardiovascular disease

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ABSTRACT

In the United States, cardiovascular disease is the leading cause of death and the rate of maternal mortality remains among the highest of any industrialized nation. Maternal cardiometabolic health throughout gestation and postpartum is representative of placental health and physiology. Both proper placental functionality and placental microRNA expression are essential to successful pregnancy outcomes, and both are highly sensitive to genetic and environmental sources of variation. Placental pathologies, such as preeclampsia, are associated with maternal cardiovascular health but may also contribute to the developmental programming of chronic disease in offspring. However, the role of more subtle alterations to placental function and microRNA expression in this developmental programming remains poorly understood. We performed small RNA sequencing to investigate microRNA in placentae from the Rhode Island Child Health Study (n=230). MicroRNA counts were modeled on maternal family history of cardiovascular disease using negative binomial generalized linear models. MicroRNAs were considered to be differentially expressed at a false discovery rate (FDR) less than 0.10. Parallel mRNA sequencing data and bioinformatic target prediction software were then used to identify potential mRNA targets of differentially expressed microRNAs. Nine differentially expressed microRNAs were identified (FDR< 0.1). Bioinformatic target prediction revealed 66 potential mRNA targets of these microRNAs, many of which are implicated in TGFβ signaling pathway but also in pathways involving cellular metabolism and immunomodulation. A robust association exists between familial cardiovascular disease and placental microRNA expression which may be implicated in both placental insufficiencies and the developmental programming of chronic disease.

INTRODUCTION

As the leading cause of death in the United States, cardiovascular disease (CVD) is expected to affect 44.1% of the population by 2035 (1). CVD has an extremely complex, multifactorial etiology, where neither genetic nor environmental influences act alone to contribute to disease onset (2, 3). There is growing body of literature linking maternal cardiometabolic health during pregnancy to adverse cardiovascular health outcomes in offspring later in life (4, 5). These developmental origins of long-term cardiovascular health outcomes are thought to be the consequence of changes to placental physiology.

The state of a mother's cardiometabolic health during gestation and postpartum is related to the health and functionality of the placenta. As a central vascular organ overseeing fetal growth, development and the intrauterine environment, proper functionality of the placental remains central to successful gestational outcomes. Resting at the interface of the maternal and fetal environment, the placenta participates in a variety of molecular processes, such as nutrient transport, immunomodulation, and endocrine signaling, all of which are made possible through the development of a villi-based vasculature system which allows for communication between mother and offspring (6). Maternal cardiovascular and metabolic conditions during pregnancy, including type II diabetes, hypertension and hypercholesterolemia have been implicated in dysfunction of placental micro and macro-vasculature. In addition, pathophysiologic characteristics of placental insufficiency, similar to those occurring in preeclampsia, manifests in cardiovascular effects including hypertension and kidney malfunction (7, 8). Additionally, such placental insufficiencies are associated with adverse gestational outcomes, such as fetal growth restriction, which itself serves as a significant risk indicator for the development of cardiovascular disease (CVD) later in life (9-11). Considering placental development occurs concurrently with fetal heart development, and each organ utilizes common humoral growth signals, such as transforming growth factor-beta (TGFβ) and vascular endothelial growth factor (VEGF), deficiencies in the organogenesis of either organ may alter the formation of the other, initiating physiological changes with potential lifelong cardiovascular consequences (12-14). While the associations between maternal cardiometabolic risk factors, placental insufficiency and offspring lifelong health outcomes are well defined (7, 8, 15), the molecular mechanisms by which this developmental programming is established have yet to be robustly delineated. Additionally, these overt placental pathologies are relatively rare, and cannot account for the prevalence of cardiovascular disease and deficiencies in maternal health, postpartum.

MicroRNAs (miRNA) are small noncoding RNA molecules (~22 nucleotides) capable of post-transcriptional regulation of gene expression. These molecules utilize base-pairing to bind to the 3'-untranslated region of target mRNAs resulting in either translational repression or mRNA degradation, by which the exact mechanism largely depends on the degree of sequence complementarity between the miRNA and target mRNA. Dysregulation of placental miRNA have previously been implicated in both preeclampsia and fetal growth restriction, suggesting their potential role as modifiers of newborn and maternal health outcomes in response to various genetic and/or environmental conditions (16-21). However, many of these studies were conducted on small sample sizes (n<100), and largely focused on newborn outcomes as they associate with placental miRNA expression as opposed to the relationship between gestational characteristics and expression of placental miRNA (16-19, 21).

To explore the influence of maternal familial cardiovascular disease on the placental miRNA landscape, we utilized placental miRNA sequencing data from the Rhode Island Child Health Study (RICHS; n=230) and examined the relationship between maternal family history of CVD and placental miRNA expression. Through this clinical history variable, we capture maternally inherited genetic risk of CVD, as well as shared familial behaviors and environmental risk factors that may associate with CVD, such as diet and exercise, that contribute to the overall health of the gestational environment (3, 22). Bioinformatic target prediction was then used to identify potential mRNA targets of miRNAs significantly associated with maternal CVD risk, followed by overrepresentation analyses to characterize the biological pathways in which these mRNAs participate.

METHODS

Cohort

The Rhode Island Child Health Study (RICHS) is a cohort of mother-infant pairs from the Women & Infants Hospital in Providence, Rhode Island, enrolled between September 2010 and February 2013. All mothers were at least 18 years of age, had no life-threatening conditions, and delivered singletons free of congenital/chromosomal abnormalities at or after 37 weeks of gestation. All participants provided written informed consent and all protocols were approved by the IRBs at the Women & Infants Hospital of Rhode Island and Emory University, respectively. Data provided by this study include placental microRNA transcript abundance (n=230). Interviewer-administered questionnaires were utilized to collect sociodemographic and lifestyle data. Structured medical record review was used to collect anthropometric and medical history data. Maternal family history of CVD was reported and coded as a binary variable (yes/no). Follow-up questions regarding which primary relative had been afflicted, coded as “mother”,” father”,” brother”, and “sister”. Instances where the mother reported a family history of CVD but did not identify a specific primary relative were not included in the study in order to prevent improper classification of familial CVD incidence.

Tissue Collection

Fetal placental samples from all subjects were collected as previously described (23). Briefly, placental samples were collected within two hours of birth; fragments were obtained two centimeters (cm) from the umbilical cord and free of maternal decidua. Collected tissue was immediately placed in RNA later solution (Life Technologies, Grand Island, NY, USA) and stored at 4 °C for at least 72 hours. Subsequently, tissue segments were blotted dry, snap frozen in liquid nitrogen, homogenized by pulverization using a stainless-steel cup and piston unit (Cellcrusher, Cork, Ireland) and stored at −80 °C.

miRNA isolation and sequencing

Total RNA was extracted from placenta using the Qiagen miRNeasy Mini Kit and a TissueLyser LT (Qiagen, Germantown, MD, USA) following manufacturer's protocol. Briefly, 25-35 mg of frozen, powdered placental tissue was placed in a 2 ml round bottom tube with 700 ul of Qiazol Lysing Reagent and one 5 mm stainless steel bead. The tissue was homogenized in a pre-chilled tube holder on the TissueLyser LT for two, 5-minute cycles at 30 Hz. The resulting homogenate was processed with the Qiagen miRNeasy Mini Kit with on-column DNAse digestion and eluted in 50 µl RNase-free water. The RNA was quantitated on a NanoDrop (Thermo Fisher, Waltham, MA, USA) and quality checked on Agilent Bioanalyzer using the Agilent RNA 6000 Nano kit (Agilent, Santa Clara, CA, USA). Single end, 1 x 50 bp next generation sequencing of placental miRNA was performed by Omega Bioservices (Norcross, Georgia) as previously described (24).

miRNA Seq Processing and QC

Raw FASTQ reads obtained from a total of 230 RICHS samples were subject to adaptor trimming with cutadapt v1.1634. The 3' adaptor sequence were trimmed (TGGAATTCTCGGGTGCCAAGG) and then four bases were trimmed from each end of the read following vendor's recommendation (BIOO scientific, Austin TX). We then used trimmed reads and miRDeep2 to quantify microRNA (25). miRDeep2 was used to first perform alignment using bowtie1 with human genome hg38 (26). The 'Quantifier' module in miRDeep2 was used to obtain raw counts of microRNAs with 27iRbase version 22 (27).

Transcript Filtering and Normalization

Raw miRNA counts were imported into *DESeq2* for normalization and differential expression analysis. Only miRNA transcripts with more than one count per million in at least 10 percent of samples were included, leaving 802 miRNA transcripts to be analyzed of the initial 2656 sequenced transcripts. Dispersion estimates were then calculated, followed by generation of median ratio size factor estimates to normalize counts for analysis with in *DESeq2* (28). Normalized counts were then exported from *DESeq2* for Surrogate Variable Analysis (SVA). The Variance Stabilization Transformation (VST) was applied to count matrices to yield approximately normalized and $\log_2$-transformed abundances, which were utilized in correlation analyses (24).

Statistical Analyses

SVA

In an effort to adjust for unknown confounders, such as cell-type heterogeneity and unmeasured sources of technical variation, surrogate variables were estimated for normalized miRNA transcript reads using the *sva* package (29, 30). The full model used in the *svaseq* includes variation attributable to family history of CVD while the null model included only an intercept term. One surrogate variable was utilized as a covariate in our differential expression analysis.

DESeq2 Differential Expression Analysis

miRNA transcript counts were modeled using a negative binomial generalized linear model to identify differentially expressed transcripts in *DESeq2* (30). For each of the 802 individual miRNA transcripts which passed strict filtering and quality criteria, the variance stabilized transformed transcript abundance was regressed on the history of familial CVD (No = 0, Yes = 1), while adjusting for the first surrogate variable to control for unknown confounders (29, 30). We considered miRNAs with a false discovery rate (FDR) less than 10% to be considered a differentially expressed miRNA (DemiR) with respect to family history of CVD. Extensive sensitivity analyses were performed by including various parameters as covariates to the original model to assess the robustness DemiR effect sizes (Fig S2-1).

Target Prediction and Filtering

Potential DemiR targets were identified using miRDIP, an online database of miRNA target predictions (31). Only targets within the top 1% of confidence scores were returned. We then calculated Pearson correlation coefficients for each miRNA:mRNA pair utilizing normalized miRNA and mRNA sequencing counts from RICHS (24). Only miRNA:mRNA target pairs with negative correlation coefficients (q-value < 0.05) were returned to be used in network and pathway analyses. Correlation coefficients ranged between -0.41 and -0.21.

Pathway Analysis

Predicted DemiR targets were tested for pathway overrepresentation within ConsensusPathDB (CPDB) (32, 33), against all genes that passed general QC filtering in RICHS whole transcriptome RNA-seq analysis (24, 32, 33). CPDB utilizes 12 separate biological pathway databases, and calculates an enrichment p-value from the hypergeometric distribution of genes in the list of miRNA targets and the pathway gene set. Only mRNAs that were expressed >1cpm in at least 10% of the RICHS samples were included as the background for the pathway analysis (24). False discovery rates were calculated from the enrichment p-values, and a q-value less than 0.05 was considered a significant enrichment of miRNA targets in the tested pathway.

RESULTS

This study analyzed miRNA sequencing data from 230 placentae from the Rhode Island Child Health Study (RICHS). The demographics of the participants are displayed in Table 2-1. In general, placentae collected in this study were from full term pregnancies (≥37 weeks), all from relatively healthy mothers who did not experience serious pregnancy complications. Forty-nine percent (n=113 of 230) of maternal participants reported a family history of cardiovascular disease, and forty-nine percent (n=112 of 230) were either overweight or obese, n=57 of those also reporting a family history of CVD.

To analyze the association between maternal family history of CVD and placental miRNA expression, we performed differential expression analysis using negative binomial generalized linear models constructed in *DESeq2* on placental small RNA sequencing data. We identified 9 **D**ifferentially **E**xpressed **miR**NAs (DEmiRs) associated with familial CVD history (FDR < 0.1), 4 of which (miR-1246, miR-324-5p, miR-1307-3p, and miR-520a-3p) met a strict Bonferroni threshold (p-value < 6.23e-05) (Fig 2-1). Sensitivity analyses were performed to adjust for various biological and technical covariates (RNA integrity, flow cell lane, pregnancy smoking, maternal race, infant sex and infant birth weight percentile) in order to characterize the robustness of DEmiR effect sizes, and the DEmiR $\log_2$ fold changes were strikingly consistent even with these additional adjustments to the original model (Fig S2-1 & Fig S2-2).

Bioinformatic targets of all 9 DEmiRs were predicted using the miRNA Data Integration Portal (miRDIP) (31). miRDIP predicted 4,516 targets across all 9 DEmiRs. However, given that miRNA do not require perfect complementarity with a target mRNA and can only target mRNAs expressed in the examined tissue, bioinformatic target prediction is prone to generating false positives. To enhance our dataset with true miRNA:mRNA relationships we utilized parallel total RNA sequencing data in RICHS (24). Only miRNA:mRNA pairs where the transcript abundance of a DEmiR and its miRDIP predicted target were negatively correlated (Pearson's correlation, p-value < 0.05) were considered in downstream pathway analyses. This correlation-based filtering revealed 7 DEmiRs and 66 predicted mRNA targets (Table S2-1) (24).

The 66 predicted DEmiR targets were tested for pathway overrepresentation within ConsensusPathDB (CPDB) (24, 32, 33). Pathways related to TGFβ signaling, cellular metabolism, and immunomodulation were overrepresented among DEmiR targets (q-value < 0.05). These enrichment results are largely driven by targets of miR-574-5p, miR-324-5p, miR-326 and miR-520a-3p (Table S2-1).

DISCUSSION

Maternal mortality rates in the United States are higher than any other industrialized country and continue to rise. More than 15% of these deaths are caused by CVD-related health complications, and over half of these deaths have been deemed preventable as they occur post-partum, increasing the opportunity for intervention (34). Physiological and functional abnormalities of the placenta serve as an indicator of maternal cardiometabolic health, as well as newborn health outcomes that potentially manifest as risk of chronic disease (16-21). While our study does not investigate placentae from mothers diagnosed with CVD, the chronic nature of the disease provides a unique opportunity to study how the accumulation of genetic and environmental insults, such as those suggested by familial CVD, influences placental functionality and the molecular mechanisms governing adverse gestational outcomes and the developmental programming of chronic disease.

Our small RNA-seq analysis identified fetoplacental miRNAs whose expression associate with maternal family history of CVD (Fig 2-1). The expression of microRNAs is known to be sensitive to various gestational environments, including maternal obesity and hypoxia (35, 36). Oxidative stress resulting from the potential comorbidities of familial CVD throughout gestation may contribute to the dysregulation of placental miRNAs. There is also a known relationship between genetic variation specific to CVD, and various facets of miRNA biogenesis, activity and function (37, 38), where genetic risk of disease may ultimately be influencing the expression of placental miRNAs and further disrupting the biological pathways they regulate. Fetal inheritance of maternal CVD genetic risk alleles may be relevant to the transcript abundance of specific miRNAs if a quantitative relationship exists between specific genetic loci and microRNA expression levels within the placenta, similar to those previously identified within RICHS placentae on the mRNA level (39)

The functional relevance of miRNAs is largely dictated by the mRNAs available for them to interact with. These interactions are heavily influenced by the tissue of origin of both miRNAs and their target mRNAs. While many of the DEmiRs we identified (miR 324-5p, miR-520a-3p, miR-574-5p, miR-326) are implicated in cardiometabolic conditions during pregnancy, including preeclampsia and diabetes (40-43), their functional role remains largely understudied in the context of placental physiology.

Pathway overrepresentation analyses of DEmiR predicted targets overwhelmingly suggested TGFβ signaling to be influenced by dysregulation of placental miRNAs whose expression associates with maternal family history of CVD (Table 2-2). TGFβ signaling encompasses a large family of genes that participate in a myriad of cellular processes, but these genes are particularly important to vascular tissues for neovascularization as well as remodeling and repair of existing tissue (44).

Among our predicted DEmiR targets, specifically those of miR-574-5p, are *SMAD2* and *SMAD4*; two activators and nuclear translocators of the SMAD-dependent TGFβ pathway, whose dysregulation are implicated in preeclampsia pathogenesis in human umbilical vein cells (HUVEC) *in vitro* (45-47). *SMAD2/4* also appear frequently throughout the various biological pathways reported as overrepresented, many of which contribute toward TGFβ signaling (including activin and nodal signaling pathways), highlighting their importance to a diverse set of endothelial cellular processes and placental physiology as a whole (Table 2-2) (48).

TGFβ signaling in the placenta is known to play critical roles in preimplantation and initial decidualization, and is also active throughout gestation in endometrial remodeling (45, 46). While neovascularization is required for successful fetal development, aberrant regulation of the signaling pathways overseeing this process may lead to improper vessel network development in the form of hypervascularization or vasculature malformation (49, 50). MiR-574-5p was found to increase in expression with respect to maternal family history of CVD, and was also negatively correlated with two TGFβ pathway activators *SMAD2* and *SMAD4*. The upregulation of miR-574-5p may lead to deficient SMAD2/4 levels, therefore preventing downstream activation of the TGFβ pathway (Fig. 2-2). This inhibition may result in broad changes to endothelial function in the placenta, leading to less optimal placental vasculature networks, or to the construction of immature vessels, ultimately manifesting as placental insufficiencies, and consequently, adverse gestational outcomes.

While miR-1246 was also shown to increase in expression with respect to maternal family history of CVD, its predicted targets did not pass our strict filtering criteria to be included in the pathway analysis. However, increased expression of miR-1246 has been shown to also promote angiogenesis through activation of TGFβ signaling via VEGF-mediated angiogenic pathways in HUVEC *in vitro*, but the exact mechanism by which this activation is achieved is not well understood (51). The diverse regulatory potential of miR-574-5p and miR-1246 in overseeing multiple facets of the TGFβ pathway, and their dysregulation with respect to maternal family history of CVD, suggests an intricate balance of both positive and negative regulatory phases of endothelial processes that may be sensitive to both genetic and environmental risk factors associated with CVD.

These endothelial abnormalities are associated with placental insufficiencies, which, in turn, could result in adverse newborn health outcomes, acute maternal cardiometabolic complications and lifelong risk of chronic disease in offspring. This relationship between placental physiology and gestational outcomes in both mother and offspring may allow placental miRNAs to serve as biomarkers for risk of postpartum maternal cardiometabolic health complications as well as for early life chronic disease risk indicators in offspring, providing an opportunity for clinical implementation of early intervention and preventative measures to potentially alleviate the societal burden of CVD (12, 13, 52).

While the data presented here are incapable of concluding the direct impact of placental miRNA dysregulation, there is a growing body of literature, as well as the associations outlined here, that suggest dysregulation of placental miRNAs may be contributing to the developmental programming and propagation of chronic diseases, such as CVD. However, these findings should be interpreted within the context of this study’s limitations.

This study only includes term placentae from live births, where premature births and other birth defects were excluded. The cross-sectional design of this study limits the interpretation of miRNA associations temporally, and may not be representative of miRNA associations throughout gestational development. This study relies on self-reported family history of CVD, and which may ultimately lead to variation in results attributable to recall bias. While we tested for various confounders to the best of our ability, there is still a possibility of unmeasured confounding which remains in our analysis. Lastly, the RICHS cohort consists predominantly of healthy, white mothers and their offspring from the New England region of the United States, potentially limiting the ability of these results to be generalized to those with acute cardiometabolic complications, and to more racially diverse populations.

CONCLUSION

MiRNAs serve as an important form of post-transcriptional gene regulation during early development, and are sensitive to both genetic and environmental conditions. Here we have shown that the expression of 9 placental miRNAs are associated with maternal family history of CVD, and that the mRNA targets of these miRNAs largely play a role in TGFβ signaling, indicating their involvement in endothelial cell functionality and placental physiology as a whole. Dysregulation of miRNA expression in the placenta may contribute to adverse newborn and maternal health outcomes, ultimately playing a role in the developmental programming of chronic diseases, including CVD.

ACKNWOLEDGEMENTS

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DECLARATION OF COMPETING INTEREST

The authors declare they have no competing interests or personal relationships that would potentially influence the work presented in this paper.

ETHICAL STANDARDS

All participants provided written, informed consent and all protocols were approved by the IRBs at the Women & Infants Hospital of Rhode Island and Emory University, respectively.

TABLES

Table 2-1. Demographic characteristics of RICHS participants included in the miRNA sequencing analysis (n=230)

MATERNAL CHARACTERISTICS	
Age (yrs) – *mean (range)*	30.9 (18 - 40)
Family History of CVD (Yes) – *% (n)*	49% (112)
Race (White) – *% (n)*	77% (178)
Pregnancy Smoking – *% (n)*	9% (20)
Pre-Pregnancy Body Mass Index (BMI) (kg/m^2) – *mean (range)*	26.5 (16 - 46.7)
Pre-Pregnancy BMI Group	
Normal and Underweight – *% (n)*	51.3% (118)
Overweight – *% (n)*	27.0% (62)
Obese – *% (n)*	21.7% (50)
INFANT CHARACTERISTICS	
Gestational Age (wks) – *mean (range)*	39.4 (37 - 41.4)
Sex (Female) – *% (n)*	49% (113)
Birthweight (g) – *mean (range)*	3563.7 (2030 - 5465)
Birthweight Group	
Small for Gestational Age (SGA) – *% (n)*	14.3% (33)
Average for Gestational Age (AGA) – *% (n)*	54.3% (125)
Large for Gestational Age (LGA) – *% (n)*	31.3% (72)

Table 2-2: DEmiR Target Pathway Enrichment Analysis Results

Pathway	Enriched Pathway Components	p-Value	q-Value	Source
Signaling by Activin	SMAD4; ACVR2B; SMAD2	2.5E-05	0.00196	Reactome
Signaling by NODAL	SMAD4; ACVR2B; SMAD2	2.5E-05	0.00196	Reactome
Activation of BAD and translocation to mitochondria	AKT3; YWHAQ; BCL2	6.8E-05	0.00278	Reactome
Intrinsic Pathway for Apoptosis	AKT3; BCL2L1; YWHAQ; BCL2	7.7E-05	0.00278	Reactome
The NLRP1 inflammasome	BCL2L1; BCL2	8.8E-05	0.00278	Reactome
Role of Calcineurin-dependent NFAT signaling in lymphocytes	RAN; BCL2L1; YWHAQ; BCL2	1.7E-04	0.00435	PID
Downregulation of SMAD2/3:SMAD4 transcriptional activity	SMAD4; NEDD4L; SMAD2	1.9E-04	0.00435	Reactome
Platelet degranulation	APP; APLP2; PHACTR2; TAGLN2; CALU	3.4E-04	0.00665	Reactome
Response to elevated platelet cytosolic Ca2+	APP; APLP2; PHACTR2; TAGLN2; CALU	4.0E-04	0.00697	Reactome
Activation of BH3-only proteins	AKT3; YWHAQ; BCL2	5.1E-04	0.00812	Reactome
TGF-beta receptor signaling activates SMADs	SMAD4; NEDD4L; SMAD2	6.9E-04	0.00990	Reactome
BH3-only proteins associate with and inactivate anti-apoptotic BCL-2 members	BCL2L1; BCL2	8.1E-04	0.01064	Reactome
Class I PI3K signaling events mediated by Akt	AKT3; BCL2L1; YWHAQ	9.0E-04	0.01093	PID
TGF-Core	SMAD4; ACVR2B; SMAD2	9.8E-04	0.01103	Signalink

FIGURES

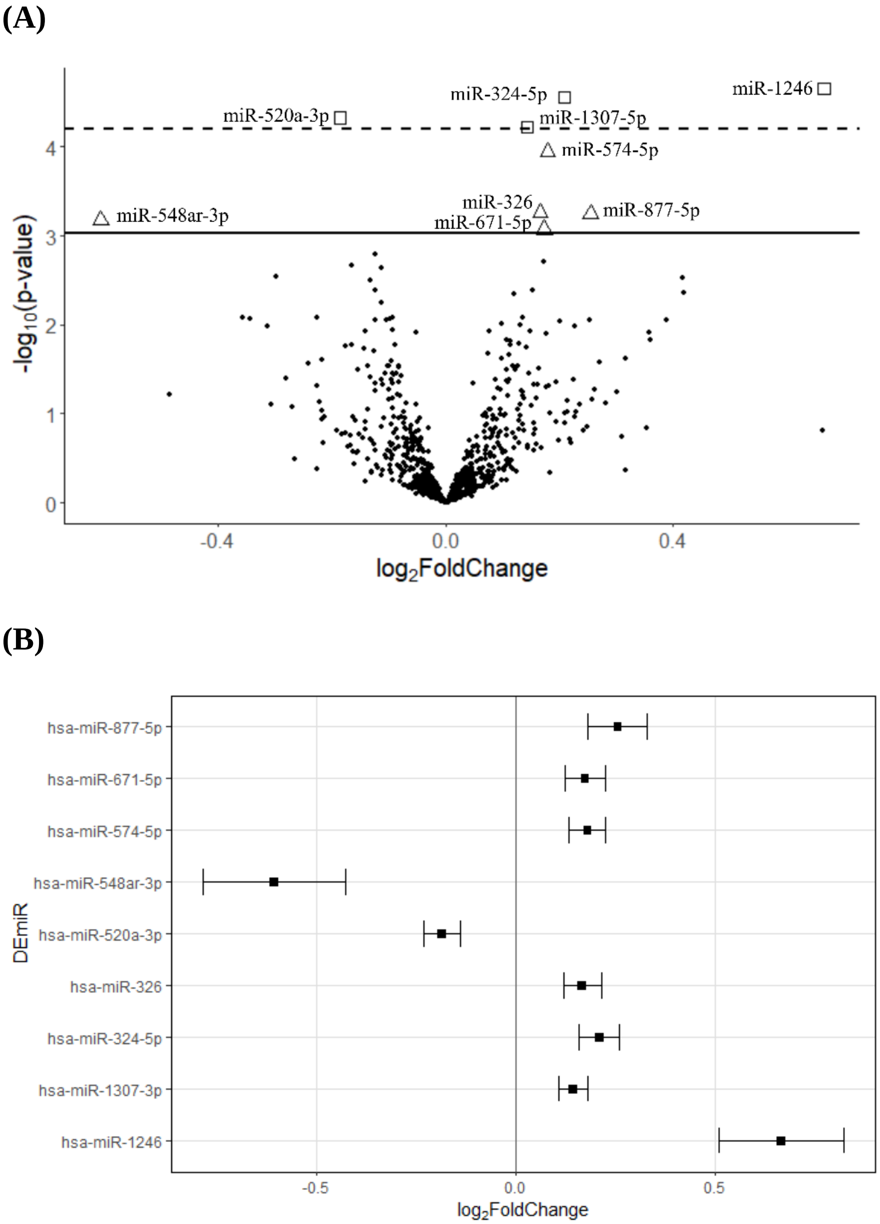

Figure 2-1: Placental miRNA associates with maternal family history of CVD.

(A) Volcano plot representing the results of the differential expression analysis. The y-axis shows the $-\log_{10}$(p-values) in the association of each miRNA with family history of CVD. The x-axis displays the effect estimates in units of $\log_2$ fold change in each miRNA's transcript abundance in individuals with familial incidence of CVD. 9 miRNAs are significantly (FDR <0.1) associated with familial CVD history and 4 of those (square shaped) reach are significant after Bonferroni correction (p-value < 6.23e-05). **(B)** Estimates of $\log_2$ fold change of miRNA transcript abundance of miRNAs significantly associated with familial CVD history. Squares represent the effect size estimate, while error bars represent standard error of the effect size estimate.

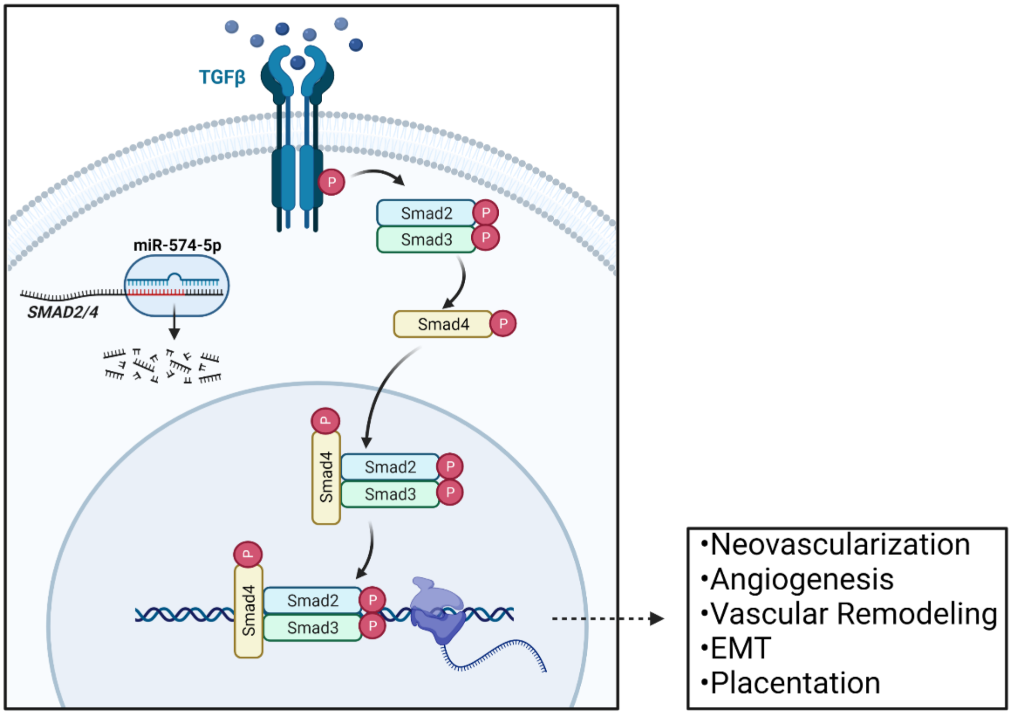

Figure 2-2: Regulation of TGFβ signaling in the placenta via miR-574-5p mediated SMAD2/4 regulation. SMAD2 serves as an activator of the TGFβ pathway, and SMAD4 serves as a nuclear translocator. The mRNA transcripts of these genes are both predicted targets of miR-574-5p, and their dysregulation within the placenta may impact various TGFβ-controlled processes in endothelial cells throughout gestation, including: neovascularization, angiogenesis, vascular remodeling, epithelial to mesenchymal transitions, and overall placentation. Adapted from “TGFb Signaling Pathway”, by BioRender.com (2019). Retrieved from https://app.biorender.com/biorender-templates.

SUPPLEMENTARY TABLES

Table S2-1. Filtered miRDIP Output: Predicted DEmiR mRNA Targets

MicroRNA	Gene Symbol	Uniprot ID	Integrated Score
hsa-miR-324-5p	VDAC1	P21796	0.81
hsa-miR-324-5p	APP	P05067	0.73
hsa-miR-324-5p	RAN	P62826	0.73
hsa-miR-324-5p	KLF3	P57682	0.72
hsa-miR-324-5p	KCTD20	Q7Z5Y7	0.63
hsa-miR-324-5p	RACGAP1	Q9H0H5	0.54
hsa-miR-324-5p	DRAM1	Q8N682	0.54
hsa-miR-324-5p	SLC16A1	P53985	0.53
hsa-miR-324-5p	YWHAQ	P27348	0.49
hsa-miR-324-5p	ST8SIA4	Q92187	0.46
hsa-miR-324-5p	H2AFV	Q71UI9	0.45
hsa-miR-324-5p	TRIP13	Q15645	0.42
hsa-miR-324-5p	CCT5	P48643	0.39
hsa-miR-324-5p	APLP2	Q06481	0.39
hsa-miR-326	BSDC1	Q9NW68	0.68
hsa-miR-326	PPP4R1	Q8TF05	0.63
hsa-miR-326	BCL2L1	Q07817	0.52
hsa-miR-326	MAD2L1BP	Q15013	0.51
hsa-miR-326	TES	Q9UGI8	0.50
hsa-miR-326	NSUN2	Q08J23	0.47
hsa-miR-326	JOSD1	Q15040	0.45
hsa-miR-326	APMAP	Q9HDC9	0.43
hsa-miR-326	RHOC	P08134	0.41
hsa-miR-326	EIF4A1	P60842	0.40
hsa-miR-326	TAGLN2	P37802	0.39
hsa-miR-520a-3p	FEM1C	Q96JP0	0.77
hsa-miR-520a-3p	PKD2	Q13563	0.75
hsa-miR-520a-3p	TRPV6	Q9H1D0	0.73
hsa-miR-520a-3p	SLC25A27	O95847	0.70
hsa-miR-520a-3p	ZNF697	Q5TEC3	0.63
hsa-miR-520a-3p	GLUL	P15104	0.56
hsa-miR-520a-3p	NEDD4L	Q96PU5	0.52
hsa-miR-520a-3p	SH3TC2	Q8TF17	0.44
hsa-miR-520a-3p	RNASEL	Q05823	0.42
hsa-miR-548ar-3p	CLASP2	O75122	0.40
hsa-miR-574-5p	MKRN1	Q9UHC7	0.61
hsa-miR-574-5p	G3BP2	Q9UN86	0.59
hsa-miR-574-5p	BDNF	P23560	0.59
hsa-miR-574-5p	PAPPA	Q13219	0.55
hsa-miR-574-5p	SEL1L	Q9UBV2	0.52
hsa-miR-574-5p	AKT3	Q9Y243	0.50
hsa-miR-574-5p	KLHL18	O94889	0.50
hsa-miR-574-5p	PAK3	O75914	0.49
hsa-miR-574-5p	RAB3B	P20337	0.46
hsa-miR-574-5p	CEP350	Q5VT06	0.46

hsa-miR-574-5p	SMAD4	Q13485	0.45
hsa-miR-574-5p	SMAD2	Q15796	0.45
hsa-miR-574-5p	GPR107	Q5VW38	0.44
hsa-miR-574-5p	OSBPL2	Q9H1P3	0.43
hsa-miR-574-5p	CALU	O43852	0.42
hsa-miR-574-5p	ZCCHC2	Q9C0B9	0.41
hsa-miR-574-5p	MAN1C1	Q9NR34	0.41
hsa-miR-574-5p	ACVR2B	Q13705	0.41
hsa-miR-574-5p	PCM1	Q15154	0.41
hsa-miR-574-5p	PHACTR2	O75167	0.40
hsa-miR-574-5p	BCL2	P10415	0.40
hsa-miR-574-5p	KCMF1	Q9P0J7	0.39
hsa-miR-574-5p	HS3ST3B1	Q9Y662	0.39
hsa-miR-574-5p	IL1RAP	Q9NPH3	0.39
hsa-miR-574-5p	CANX	P27824	0.39
hsa-miR-574-5p	ARFGEF2	Q9Y6D5	0.39
hsa-miR-574-5p	NAB2	Q15742	0.39
hsa-miR-574-5p	ASNA1	O43681	0.38
hsa-miR-671-5p	VPS26A	O75436	0.43
hsa-miR-877-5p	REV3L	O60673	0.56

Table S2-2: Differential Expression Analysis Results: DESeq2 Output

miRNA	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
hsa-miR-1246	11.18281	0.669411	0.15776	4.243231	2.20E-05	0.011501
hsa-miR-324-5p	442.2114	0.207299	0.049897	4.15453	3.26E-05	0.011501
hsa-miR-1307-3p	231.2808	0.145454	0.035795	4.063543	4.83E-05	0.011501
hsa-miR-520a-3p	4467.423	-0.18419	0.04578	-4.02341	5.74E-05	0.011501
hsa-miR-574-5p	141.4321	0.177356	0.046682	3.799211	0.000145	0.023283
hsa-miR-877-5p	19.95303	0.257032	0.074393	3.455069	0.00055	0.065886
hsa-miR-548ar-3p	5.748148	-0.61569	0.178819	-3.44311	0.000575	0.065886
hsa-miR-671-5p	26.25664	0.174944	0.052067	3.359969	0.00078	0.077472
hsa-miR-326	109.7311	0.158264	0.047531	3.329704	0.000869	0.077472
hsa-miR-504-5p	119.4893	0.172725	0.05612	3.077767	0.002086	0.167264
hsa-miR-3664-3p	30.96286	-0.16231	0.053802	-3.01681	0.002555	0.186247
hsa-miR-1291	8.222744	-0.29872	0.100535	-2.97126	0.002966	0.198218
hsa-miR-516a-5p	119490.8	-0.12584	0.042818	-2.93905	0.003292	0.203106
hsa-miR-30b-3p	81.81935	-0.12672	0.043993	-2.88041	0.003972	0.21399
hsa-miR-576-5p	117.5721	-0.12504	0.043446	-2.87798	0.004002	0.21399
hsa-miR-132-3p	136.682	0.156339	0.054734	2.856362	0.004285	0.214799
hsa-miR-30e-5p	19778.59	-0.11626	0.041276	-2.81656	0.004854	0.220843
hsa-miR-4785	2.567669	0.412346	0.146751	2.809842	0.004957	0.220843
hsa-miR-197-3p	734.8855	0.118019	0.042607	2.769933	0.005607	0.236665
hsa-miR-153-3p	4.754388	0.379993	0.138491	2.743813	0.006073	0.243528
hsa-miR-520a-5p	6614.068	-0.11041	0.041151	-2.68292	0.007298	0.25459
hsa-miR-548i	21.0024	-0.329	0.123225	-2.66996	0.007586	0.25459
hsa-miR-487b-5p	6.278803	0.256875	0.096719	2.655879	0.00791	0.25459
hsa-miR-12135	19.17241	-0.34416	0.130867	-2.62984	0.008542	0.25459
hsa-miR-345-5p	89.55427	0.134167	0.051259	2.617426	0.00886	0.25459
hsa-miR-744-5p	212.2488	0.100134	0.0383	2.614475	0.008936	0.25459
hsa-miR-212-3p	5.122445	0.386526	0.14865	2.600236	0.009316	0.25459
hsa-miR-99b-3p	262.9153	0.079865	0.030774	2.595219	0.009453	0.25459
hsa-miR-29b-2-5p	56.22335	0.134321	0.051842	2.590992	0.00957	0.25459
hsa-miR-548q	7.921538	-0.22108	0.086017	-2.57021	0.010164	0.25459
hsa-miR-1295a	4.041318	-0.34807	0.135646	-2.56601	0.010288	0.25459
hsa-miR-1323	62830.92	-0.09829	0.038582	-2.54765	0.010845	0.25459
hsa-miR-584-3p	21.44651	0.195818	0.077138	2.538546	0.011131	0.25459
hsa-miR-940	7.855971	0.223841	0.088269	2.53589	0.011216	0.25459
hsa-miR-517a-3p	188074.8	-0.08711	0.03444	-2.52934	0.011428	0.25459
hsa-miR-517b-3p	188074.4	-0.08711	0.03444	-2.52933	0.011428	0.25459
hsa-miR-100-5p	64698.68	-0.14198	0.056527	-2.51165	0.012017	0.260473
hsa-miR-30d-5p	160252	-0.08989	0.036178	-2.48477	0.012964	0.268128
hsa-miR-708-5p	6.015316	0.353711	0.142733	2.478131	0.013207	0.268128

hsa-miR-2276-3p	2.617005	0.361816	0.148334	2.439192	0.01472	0.268128
hsa-miR-93-3p	65.79296	0.114685	0.047066	2.436716	0.014821	0.268128
hsa-miR-4659a-3p	2.548178	0.36275	0.148888	2.436389	0.014835	0.268128
hsa-miR-151b	521.1014	-0.11722	0.048134	-2.43535	0.014877	0.268128
hsa-miR-4286	116.1808	0.131962	0.054301	2.43021	0.01509	0.268128
hsa-miR-342-5p	19.33372	0.14948	0.061653	2.424522	0.015329	0.268128
hsa-miR-342-3p	578.3995	0.108184	0.044988	2.404758	0.016183	0.268128
hsa-miR-212-5p	2.936817	0.338374	0.140991	2.399969	0.016396	0.268128
hsa-miR-26a-5p	175655.8	-0.05015	0.020905	-2.39908	0.016436	0.268128
hsa-miR-874-5p	24.61257	0.169748	0.070916	2.39365	0.016682	0.268128
hsa-miR-151a-5p	8265.31	-0.09017	0.037681	-2.39289	0.016716	0.268128
hsa-miR-551b-3p	184.6023	0.140646	0.059121	2.378932	0.017363	0.27304
hsa-miR-100-3p	65.01547	-0.1493	0.063127	-2.36512	0.018024	0.277986
hsa-miR-625-3p	471.6468	-0.12673	0.054291	-2.33426	0.019582	0.289892
hsa-miR-299-5p	273.4642	0.10964	0.046993	2.333085	0.019644	0.289892
hsa-miR-28-5p	1776.309	-0.08561	0.036815	-2.32548	0.020046	0.289892
hsa-miR-31-5p	630.4791	-0.15496	0.066741	-2.32183	0.020242	0.289892
hsa-miR-331-3p	296.1336	0.099895	0.043296	2.30725	0.021041	0.291721
hsa-miR-484	1211.486	0.076919	0.03342	2.301602	0.021358	0.291721
hsa-miR-27a-5p	237.8061	-0.16798	0.073068	-2.29893	0.021509	0.291721
hsa-miR-196b-5p	925.8636	0.110412	0.048143	2.293409	0.021824	0.291721
hsa-miR-3679-5p	5.866886	0.273426	0.122479	2.232432	0.025586	0.336399
hsa-miR-548j-5p	6.729765	-0.21339	0.09682	-2.20403	0.027522	0.355822
hsa-miR-146b-3p	10.62672	0.244019	0.111436	2.189763	0.028541	0.355822
hsa-miR-365a-5p	11.82298	-0.2376	0.109033	-2.17911	0.029323	0.355822
hsa-miR-3065-3p	41.35725	0.163721	0.075554	2.16693	0.03024	0.355822
hsa-miR-675-5p	122.3978	0.118575	0.054725	2.166752	0.030254	0.355822
hsa-miR-450a-1-3p	105.5286	-0.13672	0.063185	-2.16388	0.030473	0.355822
hsa-miR-126-3p	65744.93	-0.08285	0.038309	-2.16277	0.030559	0.355822
hsa-miR-518f-5p	1897.502	-0.09257	0.042815	-2.16207	0.030613	0.355822
hsa-miR-766-3p	45.66933	0.120845	0.057084	2.116967	0.034263	0.389834
hsa-miR-92b-3p	314.2983	0.106161	0.050519	2.101404	0.035605	0.389834
hsa-miR-520c-5p	1696.043	-0.09646	0.046089	-2.09289	0.036359	0.389834
hsa-miR-526a-5p	1693.761	-0.09634	0.046043	-2.09239	0.036404	0.389834
hsa-miR-10a-5p	2151.504	-0.08748	0.041825	-2.09165	0.03647	0.389834
hsa-miR-518d-5p	1693.475	-0.09618	0.046059	-2.08813	0.036786	0.389834
hsa-miR-548ad-5p	34.77367	-0.11523	0.055449	-2.07818	0.037693	0.389834
hsa-miR-433-5p	39.88965	-0.14967	0.07215	-2.07439	0.038043	0.389834
hsa-miR-590-3p	525.5373	-0.10118	0.048804	-2.07312	0.038161	0.389834
hsa-miR-665	24.51933	0.120536	0.058214	2.070558	0.0384	0.389834
hsa-miR-23b-3p	23471.31	0.049937	0.02427	2.05754	0.039634	0.397334

hsa-miR-516b-5p	58084.14	-0.08992	0.043905	-2.04799	0.040561	0.401604
hsa-miR-125b-2-3p	58.12959	0.112008	0.055031	2.035346	0.041816	0.406646
hsa-miR-487a-5p	30.84936	0.143763	0.070726	2.032686	0.042084	0.406646
hsa-miR-517c-3p	22090.85	-0.07796	0.038944	-2.00188	0.045298	0.421175
hsa-miR-539-3p	393.8376	-0.13479	0.067599	-1.99394	0.046158	0.421175
hsa-miR-937-3p	2.890136	0.270057	0.135575	1.991936	0.046378	0.421175
hsa-miR-770-5p	6.010246	0.192534	0.096671	1.991632	0.046411	0.421175
hsa-miR-5100	14.25386	0.179762	0.090451	1.987397	0.046878	0.421175
hsa-miR-605-3p	2.623259	-0.27299	0.137599	-1.98397	0.04726	0.421175
hsa-miR-629-5p	747.3811	-0.08178	0.041261	-1.98211	0.047467	0.421175
hsa-miR-125b-5p	23719.41	-0.12252	0.062124	-1.97212	0.048595	0.421175
hsa-miR-154-5p	147.1742	0.101636	0.051736	1.964518	0.04947	0.421175
hsa-miR-517-5p	1721.687	-0.07689	0.03919	-1.96194	0.04977	0.421175
hsa-miR-574-3p	879.3298	0.086887	0.044287	1.961931	0.049771	0.421175
hsa-miR-519c-3p	4409.078	-0.09257	0.047209	-1.96091	0.04989	0.421175
hsa-miR-141-3p	6277.285	-0.10905	0.055862	-1.95215	0.050921	0.4235
hsa-miR-376a-2-5p	62.07091	-0.13521	0.069488	-1.94587	0.051671	0.4235
hsa-miR-125a-5p	40675.95	-0.09278	0.047698	-1.94521	0.051749	0.4235
hsa-miR-95-3p	87.95185	0.261975	0.135782	1.929383	0.053683	0.434889
hsa-miR-6511b-3p	6.506528	0.177488	0.092746	1.913692	0.05566	0.44257
hsa-miR-25-5p	3.94456	0.227138	0.118728	1.913101	0.055735	0.44257
hsa-miR-145-5p	14421.97	0.090067	0.04721	1.907782	0.056419	0.443611
hsa-miR-3065-5p	108.2134	0.131357	0.069519	1.889505	0.058824	0.450757
hsa-miR-146b-5p	2170.802	0.138053	0.073181	1.886458	0.059233	0.450757
hsa-miR-183-3p	4.959596	-0.2159	0.11475	-1.88151	0.059903	0.450757
hsa-miR-26a-2-3p	44.49686	-0.10418	0.055443	-1.87906	0.060236	0.450757
hsa-miR-381-5p	11.47675	0.145865	0.077669	1.878037	0.060376	0.450757
hsa-miR-3194-3p	2.087859	0.296228	0.158136	1.873247	0.061034	0.450757
hsa-miR-548k	46.41036	-0.08595	0.045924	-1.8716	0.061263	0.450757
hsa-miR-148b-5p	139.7155	-0.10044	0.05431	-1.84933	0.06441	0.459305
hsa-let-7b-5p	1419.712	0.134286	0.072658	1.848204	0.064573	0.459305
hsa-miR-1299	26.25591	-0.47735	0.258674	-1.84535	0.064986	0.459305
hsa-miR-944	55.75	-0.1032	0.055997	-1.84302	0.065326	0.459305
hsa-miR-1197	20.57825	0.147709	0.080434	1.836412	0.066297	0.459305
hsa-miR-181a-3p	309.1777	0.090139	0.04909	1.836201	0.066328	0.459305
hsa-miR-1277-5p	10.98409	-0.15144	0.082534	-1.83488	0.066523	0.459305
hsa-miR-30a-5p	122806.2	-0.05466	0.02984	-1.83163	0.067006	0.459305
hsa-miR-1910-5p	3.259852	0.258916	0.141804	1.825865	0.067871	0.46129
hsa-miR-376c-3p	6679.876	-0.07185	0.039512	-1.81855	0.068979	0.464886
hsa-miR-378f	7.233125	0.156835	0.086921	1.804345	0.071177	0.47132
hsa-miR-520e-3p	114.2718	0.104716	0.058139	1.801146	0.07168	0.47132

hsa-miR-374b-3p	42.36721	-0.09312	0.051783	-1.79827	0.072134	0.47132
hsa-miR-23b-5p	22.20359	0.110133	0.061384	1.794171	0.072786	0.47132
hsa-miR-548n	3.246763	-0.22288	0.124353	-1.79229	0.073086	0.47132
hsa-miR-127-3p	2654.222	0.083193	0.046478	1.789962	0.07346	0.47132
hsa-miR-143-5p	440.4343	0.101584	0.05774	1.759334	0.078521	0.496391
hsa-miR-5695	10.38601	0.241433	0.137269	1.758835	0.078606	0.496391
hsa-miR-4802-5p	2.757462	-0.22643	0.129169	-1.75298	0.079605	0.498774
hsa-miR-887-3p	33.35348	0.129971	0.07453	1.743873	0.081181	0.504636
hsa-miR-589-3p	2.08075	-0.27141	0.155951	-1.74034	0.081799	0.504636
hsa-miR-412-5p	123.3578	-0.30266	0.174742	-1.73203	0.083268	0.508824
hsa-miR-103a-1-5p	2.034224	0.274377	0.158659	1.72935	0.083747	0.508824
hsa-miR-526b-5p	18684.29	-0.07257	0.042381	-1.71242	0.08682	0.52353
hsa-miR-496	71.44714	0.095188	0.056818	1.675308	0.093874	0.55734
hsa-miR-5001-3p	3.498017	0.212169	0.126939	1.671425	0.094638	0.55734
hsa-miR-576-3p	71.7039	-0.07477	0.044821	-1.66815	0.095286	0.55734
hsa-miR-1301-3p	110.9892	0.088911	0.053463	1.663025	0.096307	0.55734
hsa-miR-1268b	7.745973	0.183707	0.110531	1.662046	0.096504	0.55734
hsa-let-7e-5p	2497.44	0.07277	0.043808	1.661123	0.096689	0.55734
hsa-miR-141-5p	62.06828	-0.07916	0.047917	-1.65195	0.098544	0.55734
hsa-miR-561-5p	30.82158	-0.1165	0.070546	-1.65145	0.098646	0.55734
hsa-miR-34a-5p	999.7528	0.075545	0.045749	1.651281	0.098681	0.55734
hsa-miR-155-5p	207.0753	0.21225	0.129374	1.640595	0.100882	0.564863
hsa-miR-511-3p	11.99811	0.121643	0.074263	1.638	0.101422	0.564863
hsa-miR-140-3p	6781.386	0.074214	0.045413	1.634198	0.102217	0.565367
hsa-miR-34a-3p	20.40905	0.121272	0.07467	1.624099	0.104355	0.572565
hsa-miR-519e-3p	244.4315	-0.08121	0.050089	-1.62133	0.104946	0.572565
hsa-miR-32-5p	389.3305	-0.06702	0.041467	-1.61625	0.10604	0.574621
hsa-miR-548e-3p	22.51805	-0.09152	0.056859	-1.60956	0.107495	0.576742
hsa-miR-10527-5p	6.145522	0.144498	0.090204	1.601896	0.109179	0.576742
hsa-miR-1304-3p	6.026916	-0.16446	0.102669	-1.60188	0.109182	0.576742
hsa-miR-767-3p	3.061714	0.227791	0.142336	1.600377	0.109515	0.576742
hsa-miR-652-5p	12.86715	0.130439	0.081733	1.595915	0.110508	0.576742
hsa-miR-6516-5p	2.854915	0.201588	0.12674	1.590558	0.111709	0.576742
hsa-miR-431-5p	2580.78	0.082167	0.051725	1.588528	0.112167	0.576742
hsa-miR-874-3p	132.1112	0.102599	0.06459	1.588452	0.112184	0.576742
hsa-miR-590-5p	11.30379	-0.12514	0.07975	-1.56919	0.116604	0.589446
hsa-let-7c-5p	690.0529	0.091869	0.058579	1.568291	0.116813	0.589446
hsa-let-7d-5p	485.1571	0.14121	0.090052	1.568089	0.11686	0.589446
hsa-miR-195-5p	829.4301	0.098257	0.062788	1.564893	0.117608	0.58951
hsa-miR-16-2-3p	327.738	-0.09068	0.058286	-1.55582	0.119751	0.596523
hsa-miR-24-3p	149236.2	-0.075	0.04861	-1.54295	0.122844	0.604953

hsa-miR-513a-5p	3.712624	-0.20399	0.132249	-1.54248	0.122958	0.604953
hsa-miR-181d-5p	86.79148	0.062613	0.040674	1.539402	0.123706	0.604953
hsa-miR-550a-3p	13.19146	0.126412	0.08249	1.532449	0.125412	0.609577
hsa-miR-6511a-3p	5.556796	0.155184	0.101611	1.527241	0.126701	0.612134
hsa-miR-376a-3p	1441.902	-0.06174	0.040591	-1.52094	0.128275	0.614738
hsa-miR-181b-2-3p	9.034826	-0.15444	0.101673	-1.51896	0.128773	0.614738
hsa-miR-346	4.46071	0.208831	0.137966	1.513643	0.130116	0.617475
hsa-miR-29c-5p	98.957	0.066446	0.044016	1.509582	0.13115	0.617563
hsa-let-7d-3p	67.95453	0.124029	0.08255	1.502467	0.132977	0.617563
hsa-miR-548az-5p	2.835366	0.251351	0.167836	1.497597	0.134238	0.617563
hsa-miR-1294	11.52251	-0.13755	0.091889	-1.49691	0.134417	0.617563
hsa-miR-1180-3p	31.66718	0.091172	0.060929	1.496362	0.134559	0.617563
hsa-miR-450a-5p	3605.993	-0.07422	0.049632	-1.49548	0.134789	0.617563
hsa-miR-33b-3p	4.299625	-0.20695	0.138644	-1.49266	0.135525	0.617563
hsa-miR-224-5p	6706.332	0.073757	0.049635	1.485988	0.137282	0.622036
hsa-miR-501-5p	60.49733	0.071462	0.04833	1.478626	0.13924	0.624142
hsa-miR-582-5p	64.20136	0.078793	0.053297	1.478389	0.139304	0.624142
hsa-miR-135a-2-3p	1.58627	0.358024	0.24319	1.472197	0.140968	0.62809
hsa-miR-144-3p	1119.605	-0.18278	0.124738	-1.46532	0.142834	0.632889
hsa-miR-4454	29.88724	0.130158	0.089583	1.452936	0.146241	0.644427
hsa-miR-450a-2-3p	91.61546	-0.07596	0.052575	-1.44485	0.148499	0.649917
hsa-miR-455-3p	1997.052	0.078714	0.05459	1.441911	0.149328	0.649917
hsa-miR-4728-3p	7.465812	0.139078	0.096594	1.43982	0.149918	0.649917
hsa-miR-29a-3p	24624.01	-0.06962	0.0488	-1.42673	0.153658	0.653377
hsa-miR-12136	19.75338	0.15371	0.107806	1.425797	0.153927	0.653377
hsa-miR-548aw	4.979965	-0.13934	0.0978	-1.42477	0.154222	0.653377
hsa-miR-214-3p	850.4148	0.072362	0.05084	1.423324	0.154642	0.653377
hsa-miR-135a-5p	184.4521	0.243693	0.171275	1.422814	0.15479	0.653377
hsa-miR-509-3p	12.36067	0.119972	0.084823	1.414386	0.157249	0.657761
hsa-miR-526a-3p	250.4865	-0.08991	0.063599	-1.41364	0.157469	0.657761
hsa-miR-22-3p	36221.46	-0.07244	0.051572	-1.40457	0.16015	0.66539
hsa-miR-125b-1-3p	41.43016	-0.08895	0.063454	-1.40187	0.160955	0.66539
hsa-miR-27b-3p	63161.66	-0.02977	0.021366	-1.3935	0.16347	0.671425
hsa-miR-497-5p	218.97	0.082029	0.059002	1.390272	0.164446	0.671425
hsa-miR-191-5p	11780.71	-0.0464	0.033411	-1.38869	0.164926	0.671425
hsa-miR-144-5p	3469.092	-0.15328	0.110783	-1.38358	0.166487	0.674055
hsa-miR-23a-5p	15.1704	0.108137	0.078299	1.381084	0.167253	0.674055
hsa-miR-1268a	6.521436	0.157076	0.11413	1.376285	0.168733	0.676621
hsa-miR-3074-5p	2.143928	0.210113	0.153446	1.369301	0.170905	0.68192
hsa-miR-2116-5p	2.913196	-0.18304	0.134187	-1.36405	0.172551	0.685078
hsa-miR-101-3p	15995.86	-0.05773	0.04253	-1.35731	0.174681	0.69012

hsa-miR-5010-3p	22.70424	0.092676	0.068455	1.353832	0.17579	0.691096
hsa-miR-548ay-5p	31.20122	-0.07514	0.055619	-1.35098	0.176702	0.691293
hsa-miR-584-5p	1607.762	0.071465	0.053152	1.344527	0.178778	0.692348
hsa-miR-203a-3p	1795.69	0.093698	0.069754	1.343267	0.179185	0.692348
hsa-miR-424-5p	32160.03	-0.06525	0.048615	-1.34211	0.179561	0.692348
hsa-miR-548x-3p	5.197426	0.619142	0.463256	1.336501	0.181385	0.696034
hsa-miR-424-3p	2169.718	-0.0404	0.030365	-1.33038	0.183393	0.699035
hsa-miR-29c-3p	1861.651	-0.04638	0.034977	-1.32608	0.184814	0.699035
hsa-miR-106a-3p	6.914653	-0.13338	0.10065	-1.32523	0.185095	0.699035
hsa-miR-27a-3p	87834.29	-0.04486	0.034014	-1.31874	0.187255	0.699035
hsa-miR-641	44.42342	-0.08689	0.066162	-1.31324	0.189101	0.699035
hsa-miR-515-3p	2474.861	-0.06963	0.053056	-1.31232	0.189412	0.699035
hsa-miR-132-5p	40.24161	0.08052	0.061364	1.312166	0.189464	0.699035
hsa-miR-339-3p	223.2327	-0.05612	0.042808	-1.31096	0.189872	0.699035
hsa-miR-548ba	3.513794	0.304956	0.232707	1.310473	0.190036	0.699035
hsa-miR-499a-5p	52.7919	-0.06815	0.052105	-1.30797	0.190884	0.699035
hsa-miR-548aa	11.22324	-0.0989	0.076182	-1.29827	0.194195	0.705431
hsa-miR-148b-3p	6137.35	0.053407	0.041156	1.297672	0.1944	0.705431
hsa-miR-338-3p	35.31868	-0.07779	0.060062	-1.29515	0.195269	0.705431
hsa-miR-548aq-3p	9.036935	-0.13267	0.103007	-1.28793	0.19777	0.709652
hsa-miR-378a-5p	55.96156	0.076644	0.0596	1.285984	0.198449	0.709652
hsa-miR-218-5p	2525.023	-0.07048	0.054887	-1.28414	0.199092	0.709652
hsa-miR-3179	3.194064	-0.16904	0.132121	-1.27944	0.200743	0.711131
hsa-miR-483-5p	269.9523	0.068329	0.053534	1.276378	0.201822	0.711131
hsa-miR-675-3p	114.4366	0.075402	0.059441	1.268519	0.204613	0.711131
hsa-miR-188-5p	27.7009	0.073502	0.057979	1.267731	0.204894	0.711131
hsa-miR-520h	6037.008	-0.04861	0.038391	-1.2662	0.20544	0.711131
hsa-miR-556-5p	2.555593	-0.17355	0.1377	-1.26035	0.207545	0.711131
hsa-miR-505-5p	3.877824	0.150231	0.119278	1.259508	0.207847	0.711131
hsa-miR-3613-3p	9.28168	0.117239	0.093351	1.255885	0.209158	0.711131
hsa-miR-548w	49.95598	-0.05953	0.047431	-1.25513	0.209431	0.711131
hsa-miR-6514-5p	5.839103	0.129143	0.103186	1.251556	0.210732	0.711131
hsa-miR-423-3p	5606.847	-0.03997	0.031964	-1.25037	0.211163	0.711131
hsa-miR-656-3p	292.9495	-0.06979	0.056234	-1.241	0.214606	0.711131
hsa-miR-671-3p	15.95991	0.092157	0.074426	1.238227	0.215632	0.711131
hsa-miR-548s	5.616616	-0.13648	0.110245	-1.23796	0.215731	0.711131
hsa-miR-21-3p	268.3763	0.084114	0.06808	1.235519	0.216638	0.711131
hsa-miR-33a-3p	12.55593	0.092574	0.074987	1.234529	0.217006	0.711131
hsa-miR-194-3p	3.001316	-0.15505	0.125665	-1.23386	0.217254	0.711131
hsa-miR-4521	6.772415	-0.12636	0.102428	-1.23367	0.217324	0.711131
hsa-miR-425-3p	216.1828	0.040803	0.033094	1.23295	0.217594	0.711131

hsa-miR-519a-5p	10195.13	-0.05497	0.044698	-1.22973	0.2188	0.711131
hsa-miR-524-5p	6674.25	-0.04853	0.039468	-1.22955	0.218864	0.711131
hsa-miR-518d-3p	78.53112	0.100625	0.082032	1.226657	0.219951	0.711131
hsa-miR-498-5p	8621.035	-0.05747	0.047091	-1.22031	0.222349	0.711131
hsa-miR-548ak	19.7913	-0.09626	0.079076	-1.21726	0.223505	0.711131
hsa-miR-382-5p	928.2283	0.051446	0.042294	1.216401	0.223832	0.711131
hsa-miR-1226-3p	4.399239	0.1264	0.10418	1.213282	0.225022	0.711131
hsa-miR-3144-3p	3.606181	-0.17416	0.143792	-1.2112	0.225819	0.711131
hsa-miR-381-3p	2230.771	-0.05961	0.049219	-1.21117	0.225832	0.711131
hsa-miR-485-5p	52.04291	0.058114	0.048376	1.201315	0.229629	0.711131
hsa-miR-370-3p	389.8698	-0.07562	0.063191	-1.1967	0.231424	0.711131
hsa-miR-548ae-5p	28.63501	-0.07071	0.059101	-1.19636	0.231555	0.711131
hsa-miR-6881-3p	3.797742	0.156521	0.130905	1.195682	0.231821	0.711131
hsa-miR-9985	128.6586	-0.09426	0.078873	-1.19504	0.23207	0.711131
hsa-miR-3154	1.900782	0.210961	0.17718	1.190656	0.233789	0.711131
hsa-let-7g-3p	2.409193	0.198583	0.167669	1.184378	0.236263	0.711131
hsa-miR-3925-5p	2.035139	-0.20562	0.173873	-1.18262	0.236961	0.711131
hsa-miR-561-3p	8.936126	-0.10896	0.092375	-1.17952	0.23819	0.711131
hsa-miR-378a-3p	1720.607	0.04979	0.042303	1.176978	0.239204	0.711131
hsa-miR-222-3p	5157.736	0.042723	0.036309	1.176653	0.239334	0.711131
hsa-miR-519a-3p	8803.427	-0.04728	0.040237	-1.17514	0.239937	0.711131
hsa-miR-525-5p	9535.921	-0.04825	0.041157	-1.17241	0.241032	0.711131
hsa-miR-519b-5p	9148.885	-0.05074	0.043301	-1.1718	0.241279	0.711131
hsa-miR-519c-5p	9148.885	-0.05074	0.043301	-1.1718	0.241279	0.711131
hsa-miR-522-5p	9148.885	-0.05074	0.043301	-1.1718	0.241279	0.711131
hsa-miR-523-5p	9148.885	-0.05074	0.043301	-1.1718	0.241279	0.711131
hsa-miR-518e-5p	9147.242	-0.05073	0.043302	-1.17156	0.241373	0.711131
hsa-miR-889-3p	1099.658	-0.07044	0.060249	-1.16912	0.242356	0.711131
hsa-miR-873-5p	8.570059	-0.12792	0.109652	-1.16662	0.243364	0.711131
hsa-miR-548ay-3p	3.464828	0.14431	0.123774	1.165921	0.243646	0.711131
hsa-miR-320e	5.659453	0.107069	0.092188	1.161425	0.245469	0.711131
hsa-miR-520g-3p	10699.43	-0.04103	0.0354	-1.15901	0.246451	0.711131
hsa-miR-548ag	2.529821	-0.16265	0.1405	-1.15767	0.246999	0.711131
hsa-miR-769-3p	2.155412	0.165707	0.143275	1.156564	0.24745	0.711131
hsa-miR-181a-2-3p	515.514	-0.07995	0.06924	-1.15468	0.248222	0.711131
hsa-miR-24-1-5p	223.7596	-0.0452	0.039149	-1.15455	0.248275	0.711131
hsa-miR-147b-5p	11.0665	0.107992	0.094282	1.145419	0.252036	0.718702
hsa-miR-204-5p	113.5955	-0.16305	0.142557	-1.14379	0.252711	0.718702
hsa-miR-1247-5p	629.1851	-0.06775	0.059564	-1.13743	0.255359	0.718721
hsa-miR-320d	25.6019	0.075191	0.066345	1.133333	0.257075	0.718721
hsa-miR-503-5p	2953.61	0.043407	0.038451	1.128891	0.258944	0.718721

hsa-miR-941	73.40598	0.06848	0.060686	1.128417	0.259144	0.718721
hsa-miR-7-5p	1211.332	-0.0601	0.053281	-1.12801	0.259314	0.718721
hsa-miR-203b-3p	4.659101	0.156907	0.139203	1.127177	0.259668	0.718721
hsa-miR-337-3p	884.4253	0.045861	0.040772	1.124815	0.260667	0.718721
hsa-miR-519d-5p	648.5131	-0.04638	0.041307	-1.12281	0.26152	0.718721
hsa-miR-518c-5p	968.8271	-0.0394	0.03515	-1.12078	0.262383	0.718721
hsa-miR-589-5p	18.92115	0.083282	0.074508	1.117762	0.263669	0.718721
hsa-miR-26b-5p	81923.04	-0.03084	0.027628	-1.11628	0.264302	0.718721
hsa-miR-335-5p	23432.35	-0.05776	0.051816	-1.1148	0.264937	0.718721
hsa-miR-1-3p	2964.805	-0.09818	0.088296	-1.11199	0.266141	0.718721
hsa-miR-548d-5p	31.55195	-0.0627	0.056541	-1.10894	0.267457	0.718721
hsa-miR-4662a-5p	27.92396	-0.08822	0.0796	-1.10832	0.267724	0.718721
hsa-miR-20b-5p	96.43842	0.094623	0.085692	1.104223	0.269496	0.718721
hsa-miR-1306-5p	23.16465	0.07937	0.0719	1.1039	0.269636	0.718721
hsa-miR-3912-3p	14.51611	-0.06938	0.062871	-1.1035	0.269812	0.718721
hsa-miR-616-5p	10.39886	-0.08599	0.078027	-1.10204	0.270443	0.718721
hsa-miR-27b-5p	156.7136	0.041357	0.037543	1.101588	0.270641	0.718721
hsa-miR-152-3p	2260.296	0.051928	0.047293	1.09799	0.272209	0.71901
hsa-miR-505-3p	189.6647	0.043813	0.039931	1.097227	0.272542	0.71901
hsa-miR-542-3p	5221.043	-0.06263	0.057257	-1.09388	0.274008	0.720506
hsa-miR-320a-3p	6262.907	0.046378	0.042599	1.0887	0.276286	0.724123
hsa-miR-103a-2-5p	14.3177	0.078992	0.073565	1.073785	0.282919	0.733924
hsa-miR-518f-3p	5584.004	-0.04929	0.045968	-1.07237	0.283555	0.733924
hsa-miR-4677-3p	4.907392	-0.10396	0.09697	-1.07211	0.283671	0.733924
hsa-miR-328-3p	103.546	0.055476	0.051794	1.071099	0.284125	0.733924
hsa-miR-181b-3p	10.26832	-0.0955	0.089251	-1.07004	0.284601	0.733924
hsa-miR-548y	6.930007	-0.10797	0.101257	-1.06629	0.286291	0.735916
hsa-miR-1271-5p	24.19023	0.070613	0.066459	1.062514	0.288002	0.737949
hsa-miR-149-5p	1940.763	0.045838	0.043251	1.059823	0.289225	0.738721
hsa-miR-3613-5p	630.0446	-0.07055	0.067194	-1.04988	0.293772	0.747953
hsa-miR-1287-5p	16.73717	0.06396	0.061651	1.037461	0.299521	0.757808
hsa-miR-369-3p	7020.642	-0.04573	0.044123	-1.03649	0.299972	0.757808
hsa-miR-519b-3p	3055.6	-0.05046	0.048879	-1.03236	0.301902	0.757808
hsa-miR-223-3p	3163.603	-0.07375	0.071472	-1.03182	0.302157	0.757808
hsa-miR-1261	4.400924	-0.15132	0.146718	-1.03137	0.302367	0.757808
hsa-miR-519d-3p	13713.64	-0.04284	0.041982	-1.02057	0.30746	0.768172
hsa-miR-503-3p	15.08544	0.070684	0.069886	1.01142	0.311816	0.776225
hsa-let-7b-3p	26.519	0.08546	0.084636	1.009741	0.312619	0.776225
hsa-miR-377-5p	96.76133	0.044562	0.044477	1.001918	0.316383	0.783146
hsa-miR-181c-5p	668.2507	-0.04441	0.044461	-0.99882	0.317881	0.784434
hsa-miR-147b-3p	6.83	-0.1113	0.112007	-0.99365	0.320395	0.78676

hsa-miR-3909	53.30611	0.051251	0.051642	0.992418	0.320994	0.78676
hsa-miR-181a-5p	46015.06	-0.0422	0.042591	-0.99083	0.321767	0.78676
hsa-miR-17-3p	50.1809	-0.05561	0.056242	-0.98875	0.322785	0.786849
hsa-miR-126-5p	4568.605	-0.03908	0.039667	-0.98518	0.324537	0.788723
hsa-miR-548t-3p	10.52147	-0.07717	0.078673	-0.98086	0.326662	0.791489
hsa-miR-30e-3p	1676.489	-0.0438	0.044797	-0.9777	0.328221	0.79287
hsa-miR-5585-3p	8.043954	-0.09985	0.103269	-0.96686	0.333614	0.803478
hsa-miR-1305	4.271224	0.106475	0.11138	0.955966	0.339089	0.814221
hsa-miR-412-3p	1.873688	-0.25412	0.26674	-0.9527	0.340741	0.815744
hsa-miR-98-3p	3.69085	0.116264	0.124431	0.934368	0.350114	0.832061
hsa-miR-23c	49.80695	-0.06006	0.064341	-0.93344	0.350592	0.832061
hsa-miR-4433b-5p	2.809551	-0.1703	0.182475	-0.93329	0.350669	0.832061
hsa-miR-10399-3p	7.154323	0.093133	0.100052	0.93085	0.351931	0.832593
hsa-miR-30d-3p	87.42215	0.0361	0.039039	0.924735	0.355104	0.835525
hsa-let-7f-2-3p	4.410862	0.111257	0.12035	0.924445	0.355255	0.835525
hsa-miR-548o-3p	34.6671	-0.04648	0.050622	-0.91828	0.358475	0.838594
hsa-miR-369-5p	452.4378	-0.0445	0.04848	-0.91794	0.35865	0.838594
hsa-miR-4661-5p	10.49341	0.086414	0.095218	0.907544	0.364119	0.848905
hsa-miR-513b-5p	3.605507	-0.12364	0.137396	-0.89989	0.36818	0.855885
hsa-miR-495-3p	5036.683	-0.03601	0.040171	-0.89634	0.370072	0.857797
hsa-miR-769-5p	318.228	0.02866	0.032062	0.893898	0.371377	0.85834
hsa-miR-651-5p	49.47252	-0.04677	0.052664	-0.88807	0.374502	0.863076
hsa-miR-96-5p	166.4856	-0.06346	0.071718	-0.88486	0.37623	0.863336
hsa-miR-29b-3p	1697.544	-0.04029	0.045694	-0.88179	0.377893	0.863336
hsa-miR-10a-3p	22.36735	-0.05015	0.056984	-0.88013	0.378791	0.863336
hsa-miR-374a-3p	422.4033	-0.05334	0.060696	-0.87873	0.379547	0.863336
hsa-miR-6803-3p	3.150189	0.106452	0.121476	0.876322	0.380855	0.863336
hsa-miR-320b	121.5008	0.039609	0.04522	0.87592	0.381074	0.863336
hsa-miR-432-5p	460.2769	0.042577	0.048786	0.872717	0.382817	0.864843
hsa-miR-186-5p	4271.478	-0.02931	0.03374	-0.86859	0.385074	0.86679
hsa-miR-518e-3p	10645.74	0.038946	0.044956	0.866307	0.386322	0.86679
hsa-miR-193b-5p	49.9313	-0.08239	0.095399	-0.86369	0.38776	0.86679
hsa-miR-543	1229.676	-0.05009	0.058377	-0.85806	0.390857	0.86679
hsa-miR-124-3p	4.651666	0.352177	0.411086	0.856698	0.391612	0.86679
hsa-miR-136-3p	4512.951	-0.03837	0.044891	-0.85479	0.392669	0.86679
hsa-miR-185-3p	6.951429	0.085581	0.100136	0.854642	0.392749	0.86679
hsa-miR-545-5p	5.460488	0.093726	0.109799	0.853609	0.393322	0.86679
hsa-miR-548bc	7.638009	-0.08308	0.097349	-0.85346	0.393406	0.86679
hsa-let-7e-3p	42.80134	0.048788	0.057906	0.842543	0.399484	0.875432
hsa-miR-324-3p	56.18687	0.036073	0.042843	0.841976	0.399802	0.875432
hsa-miR-5701	2.689237	-0.14602	0.173872	-0.83981	0.401016	0.875432

hsa-miR-539-5p	67.94015	-0.04354	0.051919	-0.8386	0.401695	0.875432
hsa-miR-23a-3p	91973.53	0.03139	0.03759	0.835071	0.403678	0.876408
hsa-miR-582-3p	24.69962	0.065344	0.078486	0.83256	0.405093	0.876408
hsa-miR-2116-3p	11.14537	-0.07935	0.095375	-0.83198	0.40542	0.876408
hsa-miR-380-5p	4.174425	0.100061	0.121459	0.823826	0.410038	0.876801
hsa-miR-4636	3.154912	-0.11296	0.137505	-0.8215	0.411362	0.876801
hsa-miR-3614-5p	23.86942	0.06081	0.074029	0.821442	0.411394	0.876801
hsa-miR-3145-3p	11.27016	0.065484	0.079744	0.821181	0.411543	0.876801
hsa-miR-105-5p	37.60623	0.066129	0.08076	0.81883	0.412884	0.876801
hsa-miR-4326	8.67425	0.107227	0.131446	0.815751	0.414643	0.876801
hsa-miR-106b-3p	505.821	-0.03658	0.045034	-0.81229	0.416623	0.876801
hsa-miR-18a-5p	317.5932	-0.05876	0.072352	-0.81221	0.41667	0.876801
hsa-miR-518c-3p	17480.12	-0.03381	0.041655	-0.81175	0.416937	0.876801
hsa-miR-130b-3p	272.1553	-0.06452	0.079731	-0.80928	0.418355	0.876801
hsa-miR-3927-3p	31.09862	-0.22394	0.276941	-0.8086	0.418743	0.876801
hsa-miR-3615	39.42479	0.04547	0.056358	0.806799	0.419782	0.876801
hsa-miR-493-3p	1105.886	0.030977	0.038398	0.806743	0.419815	0.876801
hsa-miR-652-3p	1405.869	0.030612	0.038377	0.797663	0.425066	0.883426
hsa-miR-643	2.225216	0.117226	0.147272	0.795982	0.426043	0.883426
hsa-miR-511-5p	52.78124	0.046161	0.058024	0.795554	0.426292	0.883426
hsa-miR-3913-5p	8.98797	0.068784	0.087497	0.786121	0.431796	0.886077
hsa-miR-142-3p	502.9578	-0.05856	0.074835	-0.78249	0.433925	0.886077
hsa-miR-99b-5p	17787.9	-0.02289	0.02935	-0.77986	0.435475	0.886077
hsa-miR-522-3p	16658.49	-0.02815	0.036138	-0.77898	0.435994	0.886077
hsa-miR-375-3p	95.23434	0.128834	0.165437	0.77875	0.436127	0.886077
hsa-miR-450b-5p	2284.633	-0.03311	0.042543	-0.77837	0.436352	0.886077
hsa-miR-377-3p	449.9788	-0.03879	0.049838	-0.77827	0.436407	0.886077
hsa-miR-548ar-5p	1.992904	-0.1254	0.161128	-0.77827	0.436409	0.886077
hsa-miR-194-5p	1250.485	0.030948	0.039966	0.774349	0.438724	0.886523
hsa-miR-1269a	77.16744	-0.13073	0.168866	-0.77415	0.43884	0.886523
hsa-miR-107	900.2024	0.041038	0.053345	0.769302	0.441714	0.887335
hsa-miR-373-5p	12.12754	0.113003	0.147466	0.766302	0.443497	0.887335
hsa-miR-7706	15.01262	0.052225	0.068361	0.763962	0.44489	0.887335
hsa-miR-1284	2.561572	-0.10797	0.141804	-0.76139	0.446425	0.887335
hsa-miR-92a-3p	10802.19	-0.03719	0.048926	-0.76018	0.447144	0.887335
hsa-miR-532-3p	104.3968	0.043971	0.057964	0.758593	0.448096	0.887335
hsa-miR-628-5p	16.16349	0.051955	0.068739	0.755839	0.449746	0.887335
hsa-miR-520d-5p	1480.471	-0.03462	0.045838	-0.75521	0.450125	0.887335
hsa-miR-548p	3.627089	-0.0941	0.124624	-0.75507	0.450205	0.887335
hsa-miR-373-3p	189.657	0.103457	0.137046	0.754905	0.450306	0.887335
hsa-miR-18a-3p	12.88655	0.066616	0.088727	0.750801	0.452773	0.890009

hsa-miR-191-3p	8.445833	-0.06009	0.080585	-0.74569	0.455854	0.893876
hsa-miR-340-3p	130.8317	-0.03357	0.045583	-0.73646	0.461454	0.900833
hsa-miR-365b-3p	2539.576	-0.05362	0.073025	-0.73432	0.462754	0.900833
hsa-miR-365a-3p	2539.479	-0.05362	0.073022	-0.73429	0.462772	0.900833
hsa-miR-512-3p	14601.54	-0.02652	0.036333	-0.72992	0.465439	0.902406
hsa-miR-139-3p	11.7335	0.055561	0.076186	0.72928	0.46583	0.902406
hsa-miR-758-3p	70.68768	0.037349	0.051416	0.726404	0.467591	0.903634
hsa-miR-760	2.919758	0.09113	0.126467	0.720582	0.471167	0.90808
hsa-let-7a-3p	212.4329	0.026418	0.036792	0.71803	0.472738	0.90808
hsa-miR-21-5p	304822.9	0.031787	0.044325	0.717139	0.473289	0.90808
hsa-miR-7977	24.35761	0.046021	0.064355	0.715101	0.474547	0.908321
hsa-miR-130b-5p	151.8796	-0.06898	0.097249	-0.70932	0.478124	0.909781
hsa-miR-500a-3p	428.6766	-0.02232	0.031509	-0.70826	0.478787	0.909781
hsa-miR-654-5p	66.6071	0.035993	0.050884	0.707358	0.479344	0.909781
hsa-miR-4443	8.403032	0.076928	0.109164	0.704699	0.480997	0.909781
hsa-miR-1262	6.409422	0.067876	0.097068	0.699265	0.484387	0.909781
hsa-miR-520b-3p	351.0479	-0.03716	0.05324	-0.69802	0.485163	0.909781
hsa-miR-579-3p	8.642051	-0.05747	0.082495	-0.69669	0.485994	0.909781
hsa-miR-4775	10.49307	0.066868	0.096448	0.693308	0.488116	0.909781
hsa-miR-1296-5p	161.6141	0.03893	0.056179	0.692969	0.488329	0.909781
hsa-miR-299-3p	117.6919	-0.03018	0.043711	-0.69033	0.489986	0.909781
hsa-miR-6852-5p	2.147129	-0.09859	0.142821	-0.69029	0.490015	0.909781
hsa-miR-3940-3p	10.14313	-0.0732	0.106646	-0.68637	0.492478	0.909781
hsa-miR-99a-5p	2001.111	0.036258	0.052874	0.685743	0.492875	0.909781
hsa-miR-2277-3p	3.909043	0.081116	0.118322	0.685548	0.492998	0.909781
hsa-miR-411-5p	4506.494	-0.03503	0.051502	-0.68012	0.496432	0.909781
hsa-miR-9-5p	755.0444	-0.0547	0.080537	-0.6792	0.49701	0.909781
hsa-miR-5683	2.402533	0.171045	0.252269	0.678026	0.497755	0.909781
hsa-miR-1185-1-3p	105.0692	0.04255	0.062887	0.676607	0.498655	0.909781
hsa-miR-379-5p	4872.909	-0.03999	0.059107	-0.67657	0.49868	0.909781
hsa-miR-19b-1-5p	3.373349	0.083436	0.123713	0.674431	0.500038	0.909781
hsa-miR-1260a	1061.283	0.046124	0.068398	0.674343	0.500093	0.909781
hsa-miR-1260b	1087.855	0.046437	0.068903	0.673944	0.500347	0.909781
hsa-miR-487a-3p	502.4875	0.03099	0.046111	0.672082	0.501531	0.909781
hsa-miR-29b-1-5p	13.01962	-0.06428	0.095869	-0.67051	0.502535	0.909781
hsa-miR-1247-3p	9.535393	0.066515	0.099916	0.665711	0.505596	0.912727
hsa-miR-340-5p	1170.985	0.026386	0.039715	0.664394	0.506438	0.912727
hsa-miR-518a-5p	833.1183	-0.02796	0.042386	-0.65961	0.509505	0.914171
hsa-miR-526b-3p	630.1067	-0.03477	0.052842	-0.65801	0.510533	0.914171
hsa-miR-423-5p	762.936	-0.03465	0.052671	-0.65781	0.510659	0.914171
hsa-miR-570-3p	5.447506	0.076046	0.115991	0.655619	0.512069	0.914654

hsa-miR-133b	7.176833	0.072664	0.11156	0.65134	0.514827	0.915563
hsa-miR-146a-5p	1194.052	-0.05471	0.084006	-0.65129	0.514862	0.915563
hsa-miR-190b-5p	17.43429	0.049865	0.077411	0.644158	0.519473	0.918285
hsa-miR-6501-3p	4.827733	0.07621	0.118327	0.644066	0.519533	0.918285
hsa-miR-524-3p	812.6589	-0.02853	0.044326	-0.64361	0.519827	0.918285
hsa-miR-4791	3.169551	-0.07765	0.121044	-0.64149	0.521206	0.918698
hsa-miR-494-3p	669.5241	-0.02843	0.044541	-0.63833	0.523256	0.920289
hsa-miR-624-5p	24.83856	0.035469	0.056006	0.633315	0.526528	0.922287
hsa-miR-338-5p	15.29842	-0.04608	0.073099	-0.63033	0.528479	0.922287
hsa-miR-143-3p	673274.9	-0.03616	0.057525	-0.62852	0.529663	0.922287
hsa-miR-339-5p	523.7193	0.022726	0.036252	0.626899	0.530725	0.922287
hsa-miR-320c	49.07258	0.034416	0.05493	0.626547	0.530956	0.922287
hsa-miR-3925-3p	3.25361	-0.0787	0.125711	-0.62603	0.531293	0.922287
hsa-let-7g-5p	8489.287	-0.03768	0.060675	-0.62104	0.534576	0.925983
hsa-miR-549a-3p	2.075047	0.112221	0.183157	0.612707	0.54007	0.93096
hsa-miR-378c	110.8351	0.029253	0.047947	0.610104	0.541793	0.93096
hsa-miR-498-3p	274.606	0.023636	0.038765	0.609737	0.542036	0.93096
hsa-miR-17-5p	1516.911	0.025592	0.04207	0.608318	0.542976	0.93096
hsa-miR-1228-3p	3.836187	0.080777	0.132879	0.6079	0.543254	0.93096
hsa-miR-454-3p	499.0709	0.019134	0.031636	0.604807	0.545307	0.932487
hsa-miR-200b-3p	243.5119	-0.0315	0.052552	-0.59941	0.548898	0.934699
hsa-miR-653-5p	88.98335	0.047226	0.07898	0.597957	0.549869	0.934699
hsa-miR-30a-3p	4410.179	-0.02445	0.040973	-0.59674	0.550683	0.934699
hsa-miR-7-1-3p	26.374	0.033579	0.056841	0.590757	0.554683	0.934699
hsa-miR-30b-5p	46668.01	0.02385	0.040387	0.590541	0.554828	0.934699
hsa-miR-134-3p	3.945814	0.070132	0.119183	0.588435	0.556241	0.934699
hsa-miR-337-5p	217.1913	0.038417	0.065435	0.587094	0.557141	0.934699
hsa-miR-378d	16.32492	-0.04072	0.069516	-0.58578	0.558024	0.934699
hsa-miR-30c-5p	18473.72	0.018036	0.03085	0.584629	0.558797	0.934699
hsa-miR-34b-3p	36.07814	-0.0526	0.090248	-0.58278	0.560039	0.934699
hsa-miR-137-3p	64.88111	-0.09392	0.161185	-0.5827	0.560095	0.934699
hsa-miR-664b-3p	36.5223	0.037792	0.064938	0.581971	0.560586	0.934699
hsa-miR-758-5p	4.197026	0.062016	0.10689	0.58018	0.561793	0.934768
hsa-miR-10b-3p	14.2658	0.074519	0.130117	0.572713	0.566839	0.938584
hsa-miR-30c-1-3p	15.71138	-0.03565	0.062395	-0.57143	0.567711	0.938584
hsa-miR-101-5p	10.93981	-0.04367	0.076479	-0.57104	0.567975	0.938584
hsa-miR-433-3p	326.8594	0.028512	0.050293	0.566914	0.570773	0.938584
hsa-miR-217-5p	21.68994	-0.14002	0.250335	-0.55933	0.57594	0.938584
hsa-miR-92a-1-5p	7.550347	-0.05214	0.093262	-0.5591	0.576091	0.938584
hsa-miR-1307-5p	37.48751	0.031738	0.056905	0.557733	0.577027	0.938584
hsa-miR-376b-5p	184.1085	-0.02923	0.052505	-0.55667	0.577754	0.938584

hsa-miR-22-5p	769.2147	-0.02088	0.037664	-0.55432	0.579358	0.938584
hsa-miR-193b-3p	4325.737	-0.05294	0.095856	-0.55231	0.580734	0.938584
hsa-miR-7705	11.61044	-0.03867	0.070301	-0.55011	0.582247	0.938584
hsa-miR-520g-5p	408.9752	-0.03737	0.068127	-0.54847	0.583369	0.938584
hsa-miR-181c-3p	26.51562	-0.02966	0.054259	-0.54663	0.584631	0.938584
hsa-miR-495-5p	13.34781	0.03488	0.063898	0.545867	0.585157	0.938584
hsa-miR-5699-5p	2.475198	0.078642	0.14415	0.545556	0.585371	0.938584
hsa-miR-221-3p	14139.64	0.016469	0.030306	0.543441	0.586826	0.938584
hsa-miR-449a	5.483316	0.053276	0.098434	0.541237	0.588344	0.938584
hsa-miR-485-3p	220.8984	0.023593	0.043621	0.540859	0.588605	0.938584
hsa-miR-655-3p	785.0246	-0.02253	0.041721	-0.53993	0.589244	0.938584
hsa-miR-548b-5p	7.442943	-0.05204	0.096493	-0.53934	0.589654	0.938584
hsa-miR-6513-5p	7.900697	-0.0473	0.088123	-0.53675	0.591443	0.938584
hsa-miR-24-2-5p	1865.048	-0.02049	0.038458	-0.53271	0.594237	0.938584
hsa-miR-1843	24.05033	-0.03356	0.063171	-0.53119	0.595287	0.938584
hsa-miR-628-3p	9.870472	-0.04278	0.080754	-0.52979	0.596259	0.938584
hsa-miR-542-5p	71.26075	-0.02314	0.043814	-0.52818	0.597377	0.938584
hsa-miR-1249-3p	14.60658	0.044854	0.084954	0.52798	0.597513	0.938584
hsa-miR-660-3p	19.20918	0.03233	0.06183	0.522886	0.601054	0.938584
hsa-miR-490-3p	8.428889	-0.06822	0.130521	-0.52264	0.601228	0.938584
hsa-miR-221-5p	497.3824	-0.01888	0.036156	-0.52211	0.601592	0.938584
hsa-miR-32-3p	40.66883	0.025095	0.048111	0.521611	0.601941	0.938584
hsa-miR-224-3p	563.2488	0.026985	0.051737	0.521587	0.601958	0.938584
hsa-miR-34b-5p	28.78903	-0.05159	0.098916	-0.52151	0.602013	0.938584
hsa-miR-122-5p	2.120205	0.098846	0.190153	0.519824	0.603186	0.938584
hsa-miR-19a-3p	116.0444	-0.03478	0.067201	-0.51762	0.604724	0.938584
hsa-miR-181b-5p	2727.571	0.014645	0.028319	0.517156	0.605047	0.938584
hsa-miR-376c-5p	188.3802	-0.02675	0.052275	-0.51165	0.608893	0.938952
hsa-miR-372-5p	9.335684	0.085206	0.166565	0.511552	0.608965	0.938952
hsa-miR-527	619.2556	-0.02191	0.043	-0.50959	0.610341	0.938952
hsa-miR-335-3p	4477.964	0.027934	0.054901	0.508805	0.610889	0.938952
hsa-miR-34c-3p	33.65988	-0.04617	0.090801	-0.50845	0.611139	0.938952
hsa-let-7f-1-3p	3.148545	0.07393	0.147032	0.502812	0.615096	0.938973
hsa-miR-519e-5p	545.875	0.024735	0.049306	0.50166	0.615907	0.938973
hsa-let-7i-3p	66.75749	0.050562	0.101035	0.500435	0.616769	0.938973
hsa-miR-33a-5p	3.203024	-0.06657	0.133064	-0.50031	0.616858	0.938973
hsa-miR-136-5p	480.5529	-0.02566	0.051317	-0.49997	0.617093	0.938973
hsa-miR-500a-5p	169.1296	0.020943	0.042028	0.498304	0.61827	0.938973
hsa-miR-130a-5p	10.94018	0.03762	0.075728	0.496775	0.619348	0.938973
hsa-miR-1343-3p	2.940839	0.07064	0.14428	0.4896	0.624417	0.944567
hsa-miR-7976	12.15551	-0.0428	0.087696	-0.48804	0.625522	0.944567

hsa-miR-20b-3p	2.279285	-0.07205	0.148075	-0.48656	0.626571	0.944567
hsa-miR-2115-3p	7.102369	-0.0517	0.106733	-0.48436	0.62813	0.94514
hsa-miR-372-3p	1166.133	-0.0755	0.156624	-0.48207	0.62976	0.945819
hsa-miR-6724-5p	7.84536	0.042082	0.088066	0.477841	0.632763	0.945971
hsa-miR-222-5p	6.597139	0.04578	0.09616	0.476084	0.634015	0.945971
hsa-miR-4742-5p	2.306332	-0.06933	0.14643	-0.47344	0.635898	0.945971
hsa-miR-1248	2.561589	0.065783	0.139041	0.473119	0.636129	0.945971
hsa-miR-34c-5p	363.8841	-0.03693	0.078642	-0.46962	0.638623	0.945971
hsa-miR-134-5p	136.8442	0.02094	0.044605	0.469458	0.638742	0.945971
hsa-miR-374b-5p	1058.276	-0.02318	0.049678	-0.46655	0.640821	0.945971
hsa-miR-323b-3p	39.24783	0.03803	0.081789	0.464983	0.641944	0.945971
hsa-miR-192-3p	2.923859	0.06062	0.130383	0.464938	0.641976	0.945971
hsa-miR-3690	8.090693	0.060851	0.1311	0.464155	0.642537	0.945971
hsa-miR-519a-2-5p	1942.127	0.016379	0.035907	0.456167	0.64827	0.945971
hsa-miR-520b-5p	1941.918	0.016372	0.035905	0.455975	0.648408	0.945971
hsa-miR-548ab	3.695777	0.062486	0.137376	0.45485	0.649217	0.945971
hsa-miR-2115-5p	12.76894	-0.04297	0.094531	-0.45453	0.649446	0.945971
hsa-miR-154-3p	592.9171	-0.02089	0.046162	-0.45246	0.650941	0.945971
hsa-miR-466	6.382772	0.044886	0.099933	0.449164	0.653313	0.945971
hsa-miR-382-3p	712.2138	-0.02162	0.0484	-0.44661	0.655155	0.945971
hsa-miR-876-3p	3.767295	-0.06908	0.154895	-0.44597	0.655617	0.945971
hsa-miR-362-3p	120.2631	0.018434	0.041359	0.445691	0.655821	0.945971
hsa-miR-151a-3p	2770.355	-0.0168	0.037707	-0.44554	0.655932	0.945971
hsa-miR-301a-5p	17.31409	0.027096	0.060822	0.445492	0.655964	0.945971
hsa-miR-1283	6234.77	-0.02408	0.054364	-0.44296	0.657796	0.945971
hsa-miR-28-3p	933.6904	0.017831	0.040431	0.441029	0.659192	0.945971
hsa-miR-106a-5p	167.4338	0.027929	0.063536	0.439578	0.660243	0.945971
hsa-miR-409-3p	1189.053	0.01745	0.039808	0.438357	0.661128	0.945971
hsa-miR-210-5p	4.203658	-0.0584	0.13347	-0.43757	0.661697	0.945971
hsa-miR-199a-5p	10397.65	0.016632	0.038011	0.437556	0.661708	0.945971
hsa-miR-185-5p	1099.608	-0.02606	0.060044	-0.43403	0.664267	0.947595
hsa-miR-215-5p	21.56611	0.026883	0.062593	0.429487	0.667569	0.947595
hsa-miR-6507-5p	4.259324	0.056671	0.132247	0.428526	0.668269	0.947595
hsa-miR-16-5p	17969.26	-0.02618	0.061459	-0.42593	0.670157	0.947595
hsa-miR-361-5p	1604.772	-0.01467	0.03444	-0.42582	0.670236	0.947595
hsa-miR-210-3p	126.009	-0.03361	0.079101	-0.42487	0.67093	0.947595
hsa-miR-664a-3p	373.1305	-0.0213	0.050303	-0.42344	0.671976	0.947595
hsa-miR-380-3p	87.6724	-0.0252	0.059572	-0.423	0.672296	0.947595
hsa-miR-139-5p	919.6493	0.022777	0.05415	0.420631	0.674025	0.947783
hsa-miR-148a-5p	36.22448	0.02813	0.067159	0.418861	0.675318	0.947783
hsa-miR-130a-3p	1309.713	0.012411	0.029695	0.417962	0.675975	0.947783

hsa-miR-20a-5p	1847.959	-0.0182	0.043726	-0.41616	0.677296	0.947978
hsa-miR-374c-5p	17.99283	0.031165	0.075785	0.411225	0.680908	0.949506
hsa-miR-192-5p	919.1742	0.014399	0.035364	0.407158	0.683892	0.949506
hsa-miR-6513-3p	7.939459	-0.03412	0.084219	-0.40512	0.685393	0.949506
hsa-miR-598-3p	11.61514	-0.04005	0.09948	-0.40258	0.687259	0.949506
hsa-miR-4999-5p	6.510432	0.037378	0.092852	0.40255	0.687279	0.949506
hsa-miR-523-3p	4549.15	-0.02284	0.056968	-0.40086	0.688524	0.949506
hsa-miR-6715b-3p	6.919099	0.058811	0.146985	0.400115	0.689072	0.949506
hsa-miR-515-5p	14793.76	-0.01906	0.04768	-0.39984	0.689271	0.949506
hsa-miR-506-3p	4.030214	-0.04611	0.115611	-0.39882	0.690029	0.949506
hsa-miR-548z	14.22924	-0.02963	0.07486	-0.39577	0.692278	0.949506
hsa-miR-502-3p	462.3845	-0.01342	0.033934	-0.39535	0.692586	0.949506
hsa-miR-520f-3p	1734.064	0.030159	0.076333	0.395093	0.692774	0.949506
hsa-miR-125a-3p	88.23969	0.014859	0.037868	0.392384	0.694774	0.949506
hsa-miR-4662b	2.49423	0.055195	0.140972	0.39153	0.695406	0.949506
hsa-miR-618	15.99228	-0.04271	0.109368	-0.39053	0.696146	0.949506
hsa-miR-4708-3p	4.602669	0.042143	0.109003	0.386623	0.699035	0.949525
hsa-miR-190a-5p	46.59521	0.031937	0.083874	0.380779	0.703367	0.949525
hsa-miR-6501-5p	18.5931	-0.03198	0.084604	-0.37801	0.705425	0.949525
hsa-miR-548h-3p	14.14257	-0.0282	0.075064	-0.37567	0.707159	0.949525
hsa-miR-133a-3p	303.7453	-0.02753	0.073375	-0.37515	0.707548	0.949525
hsa-miR-629-3p	10.66532	-0.03368	0.089936	-0.37443	0.708083	0.949525
hsa-miR-9903	11.75749	0.031614	0.084566	0.37384	0.708524	0.949525
hsa-miR-3143	2.982466	-0.05545	0.14834	-0.3738	0.708552	0.949525
hsa-miR-150-5p	143.2536	-0.03478	0.093254	-0.373	0.709151	0.949525
hsa-miR-378g	2.029242	-0.05447	0.147455	-0.3694	0.711828	0.949525
hsa-miR-550a-5p	8.379241	0.034828	0.094804	0.367364	0.713347	0.949525
hsa-miR-3688-3p	13.15908	-0.02554	0.070153	-0.36409	0.71579	0.949525
hsa-miR-548e-5p	3.060684	0.048705	0.1339	0.36374	0.716053	0.949525
hsa-miR-451a	53082.9	-0.04336	0.11937	-0.36323	0.716431	0.949525
hsa-miR-374a-5p	4475.846	-0.02397	0.066263	-0.3618	0.717499	0.949525
hsa-miR-619-5p	11.42556	-0.02788	0.077146	-0.36143	0.71778	0.949525
hsa-miR-410-5p	2.109937	0.071172	0.19711	0.361077	0.718042	0.949525
hsa-miR-98-5p	557.043	0.024535	0.068223	0.35963	0.719124	0.949525
hsa-miR-514a-3p	50.97566	-0.0271	0.075768	-0.35772	0.720555	0.949525
hsa-miR-4742-3p	3.685261	0.039582	0.112066	0.353202	0.723937	0.949525
hsa-miR-4662a-3p	4.174001	0.038447	0.109136	0.352281	0.724627	0.949525
hsa-miR-25-3p	2730.289	0.023741	0.067548	0.351476	0.725231	0.949525
hsa-miR-509-3-5p	7.336196	0.040321	0.115579	0.348858	0.727196	0.949525
hsa-miR-4645-3p	2.439226	0.047859	0.137407	0.348303	0.727612	0.949525
hsa-miR-1285-3p	10.48195	-0.02618	0.07553	-0.34668	0.728834	0.949525

hsa-miR-323a-5p	1.993946	0.05427	0.156962	0.345753	0.729528	0.949525
hsa-miR-29a-5p	42.09154	0.020331	0.058972	0.344752	0.730281	0.949525
hsa-miR-625-5p	96.91345	-0.0176	0.051426	-0.34227	0.73215	0.949525
hsa-miR-362-5p	782.3239	-0.01199	0.035036	-0.34212	0.732264	0.949525
hsa-miR-556-3p	2.537778	-0.04604	0.134775	-0.34161	0.732642	0.949525
hsa-miR-193a-5p	122.8965	-0.03579	0.107811	-0.33195	0.739927	0.949525
hsa-miR-183-5p	530.4139	-0.02072	0.06345	-0.32658	0.743987	0.949525
hsa-miR-487b-3p	6108.724	-0.0142	0.043565	-0.32601	0.744419	0.949525
hsa-miR-135b-5p	5108.473	-0.02958	0.090867	-0.32554	0.744771	0.949525
hsa-miR-223-5p	25.36433	0.027336	0.084235	0.324523	0.745542	0.949525
hsa-miR-1275	5.993009	-0.0343	0.105903	-0.32386	0.746044	0.949525
hsa-miR-152-5p	3.360409	0.037597	0.117067	0.321159	0.74809	0.949525
hsa-miR-140-5p	1156.786	-0.01435	0.045008	-0.31892	0.749787	0.949525
hsa-miR-31-3p	4.354323	0.039088	0.122662	0.318667	0.749979	0.949525
hsa-miR-16-1-3p	3.478399	0.037611	0.118257	0.318043	0.750452	0.949525
hsa-miR-668-3p	39.28129	0.018142	0.057057	0.317959	0.750516	0.949525
hsa-miR-548ai	5.584643	-0.03491	0.110447	-0.3161	0.751928	0.949525
hsa-miR-570-5p	5.584643	-0.03491	0.110447	-0.3161	0.751928	0.949525
hsa-miR-627-5p	8.00061	-0.03058	0.096781	-0.316	0.752002	0.949525
hsa-miR-2277-5p	4.179399	-0.03558	0.113902	-0.31239	0.754742	0.949525
hsa-miR-548av-3p	2.144904	-0.04616	0.148075	-0.31171	0.755261	0.949525
hsa-miR-520d-3p	2764.516	0.010335	0.033432	0.309126	0.757225	0.949525
hsa-miR-514a-5p	6.386873	-0.03242	0.105004	-0.30872	0.757536	0.949525
hsa-miR-330-5p	79.87611	0.017408	0.056466	0.308295	0.757858	0.949525
hsa-miR-376b-3p	139.0142	-0.0158	0.051511	-0.30676	0.759029	0.949525
hsa-miR-19b-3p	1183.639	0.016142	0.052968	0.304755	0.760553	0.949525
hsa-miR-205-3p	3.323409	0.035774	0.11827	0.302474	0.76229	0.949525
hsa-miR-4652-5p	2.116966	0.046794	0.154819	0.30225	0.762462	0.949525
hsa-miR-6516-3p	3.456058	0.036928	0.122593	0.30122	0.763247	0.949525
hsa-miR-767-5p	84.21007	-0.02193	0.072918	-0.30078	0.763582	0.949525
hsa-miR-138-1-3p	8.448953	-0.04118	0.137107	-0.30036	0.763904	0.949525
hsa-miR-520c-3p	1127.869	0.013306	0.044333	0.30014	0.76407	0.949525
hsa-miR-6503-3p	4.504725	0.037056	0.123874	0.299145	0.76483	0.949525
hsa-miR-520e-5p	123.0014	-0.01323	0.045544	-0.29048	0.77145	0.955194
hsa-miR-15b-5p	2756.851	-0.02079	0.071679	-0.29005	0.771778	0.955194
hsa-miR-486-3p	9.62567	0.038507	0.136698	0.281694	0.778178	0.959576
hsa-miR-1185-2-3p	25.40741	0.019614	0.070234	0.279261	0.780045	0.959576
hsa-miR-4781-3p	4.563414	-0.03158	0.114699	-0.27536	0.78304	0.959576
hsa-miR-616-3p	2.322035	0.039027	0.142389	0.274085	0.78402	0.959576
hsa-miR-9898	6.605104	0.02506	0.092012	0.272355	0.785349	0.959576
hsa-miR-410-3p	1343.177	-0.01538	0.056552	-0.27202	0.785608	0.959576

hsa-miR-548am-3p	2.202856	-0.03999	0.148211	-0.26981	0.787309	0.959576
hsa-miR-10399-5p	11.5543	-0.02313	0.085877	-0.26934	0.787671	0.959576
hsa-miR-106b-5p	2747.401	-0.0123	0.046714	-0.26327	0.792344	0.959576
hsa-miR-1303	15.37552	-0.01744	0.066326	-0.26296	0.792578	0.959576
hsa-miR-3158-3p	10.64607	0.024161	0.092206	0.262029	0.793299	0.959576
hsa-miR-1306-3p	4.866026	0.025958	0.100122	0.259265	0.795431	0.959576
hsa-miR-889-5p	2.690043	-0.03821	0.147614	-0.25882	0.795773	0.959576
hsa-miR-3188	2.300542	-0.04879	0.189955	-0.25686	0.797284	0.959576
hsa-miR-133a-5p	6.925501	0.029705	0.115682	0.25678	0.797348	0.959576
hsa-miR-455-5p	430.564	-0.01527	0.060483	-0.25255	0.800618	0.959576
hsa-miR-548aj-5p	2.623956	-0.03719	0.148825	-0.2499	0.802667	0.959576
hsa-miR-26b-3p	39.87426	0.012403	0.049676	0.249676	0.802838	0.959576
hsa-miR-548h-5p	10.146	-0.02141	0.085952	-0.24911	0.803276	0.959576
hsa-miR-934	886.5642	0.014154	0.056876	0.248857	0.803472	0.959576
hsa-miR-199b-3p	22108.09	0.01134	0.045719	0.248044	0.8041	0.959576
hsa-miR-199a-3p	22255	0.011292	0.045672	0.247229	0.804731	0.959576
hsa-miR-509-5p	3.551476	-0.03334	0.134951	-0.24706	0.804864	0.959576
hsa-miR-3664-5p	2.956474	-0.03329	0.135198	-0.24622	0.805514	0.959576
hsa-miR-550a-3-5p	8.141542	0.02294	0.095156	0.241075	0.809497	0.959576
hsa-miR-6866-5p	2.033258	-0.03517	0.14619	-0.24061	0.809859	0.959576
hsa-miR-329-3p	467.2978	-0.01089	0.045588	-0.23883	0.811234	0.959576
hsa-miR-18b-5p	6.996903	-0.02703	0.113262	-0.23868	0.811356	0.959576
hsa-miR-214-5p	130.8432	-0.01053	0.044468	-0.23669	0.812898	0.959576
hsa-miR-371a-3p	57.38343	0.036174	0.153427	0.235774	0.813608	0.959576
hsa-miR-548au-5p	29.55792	0.012527	0.053394	0.234621	0.814503	0.959576
hsa-miR-5699-3p	2.615482	0.036492	0.155771	0.234266	0.814778	0.959576
hsa-miR-490-5p	3.3536	0.039263	0.167714	0.234107	0.814902	0.959576
hsa-miR-7704	1.937242	0.035412	0.152982	0.231477	0.816944	0.959576
hsa-miR-1278	7.405562	0.019962	0.086358	0.231154	0.817195	0.959576
hsa-miR-491-5p	12.04447	-0.01672	0.073562	-0.22727	0.820215	0.960696
hsa-miR-491-3p	2.268383	-0.03394	0.149598	-0.22684	0.820545	0.960696
hsa-miR-196a-5p	100.342	-0.02198	0.101976	-0.21555	0.829338	0.968261
hsa-miR-202-5p	31.43912	0.017291	0.080258	0.215445	0.82942	0.968261
hsa-miR-378i	32.08414	-0.01408	0.067398	-0.20894	0.834493	0.972484
hsa-miR-452-5p	2081.649	0.007659	0.036875	0.2077	0.835463	0.972484
hsa-miR-199b-5p	2808.335	-0.00974	0.048023	-0.20288	0.839225	0.975447
hsa-miR-664a-5p	26.75441	-0.01011	0.050501	-0.20022	0.841311	0.976456
hsa-miR-182-5p	904.7325	-0.0143	0.073286	-0.1951	0.845311	0.977692
hsa-miR-211-5p	12.12418	-0.01791	0.092467	-0.19368	0.846427	0.977692
hsa-miR-3064-5p	2.549701	0.027644	0.14283	0.193544	0.846533	0.977692
hsa-miR-656-5p	2.383976	0.026256	0.139812	0.187791	0.85104	0.977692

hsa-miR-521	3199.561	0.009513	0.050724	0.187543	0.851235	0.977692
hsa-miR-518a-3p	9544.536	0.006627	0.035695	0.185645	0.852723	0.977692
hsa-miR-548at-5p	3.416824	-0.02338	0.126133	-0.18535	0.852952	0.977692
hsa-miR-493-5p	3716.12	-0.00834	0.045257	-0.18438	0.853713	0.977692
hsa-miR-486-5p	3383.282	-0.02123	0.115749	-0.18344	0.854455	0.977692
hsa-miR-659-5p	4.458505	0.018748	0.102579	0.182772	0.854977	0.977692
hsa-miR-548l	16.77471	0.011559	0.063635	0.181645	0.855861	0.977692
hsa-miR-421	109.1079	0.00741	0.041857	0.177033	0.859482	0.977692
hsa-miR-518b	26422.14	0.009231	0.052487	0.175868	0.860398	0.977692
hsa-miR-548am-5p	27.04399	0.009077	0.053635	0.169229	0.865616	0.977692
hsa-miR-512-5p	5593.813	-0.00861	0.051104	-0.16845	0.86623	0.977692
hsa-miR-193a-3p	21.54136	0.018512	0.110023	0.168255	0.866383	0.977692
hsa-miR-3145-5p	5.291769	0.017395	0.105247	0.165282	0.868722	0.977692
hsa-miR-500b-5p	127.2513	0.007107	0.043745	0.162476	0.870931	0.977692
hsa-miR-3157-5p	2.550626	0.022833	0.141171	0.161742	0.871509	0.977692
hsa-miR-15b-3p	58.4272	-0.01512	0.093493	-0.16169	0.871548	0.977692
hsa-miR-379-3p	186.884	0.007721	0.047915	0.161129	0.871992	0.977692
hsa-miR-2110	25.90483	-0.00964	0.059991	-0.16075	0.872291	0.977692
hsa-let-7f-5p	12857.78	-0.01078	0.067657	-0.15933	0.873412	0.977692
hsa-miR-508-3p	23.72097	-0.01248	0.078445	-0.15914	0.873555	0.977692
hsa-miR-99a-3p	5.620498	-0.01726	0.108959	-0.15845	0.874106	0.977692
hsa-miR-501-3p	112.9206	-0.00648	0.041174	-0.1573	0.875011	0.977692
hsa-miR-516a-3p	6.936361	-0.01712	0.109781	-0.15598	0.876052	0.977692
hsa-miR-548g-5p	3.635126	-0.01952	0.125733	-0.15526	0.876618	0.977692
hsa-miR-370-5p	20.38799	-0.00916	0.059544	-0.15385	0.877728	0.977692
hsa-miR-2355-3p	8.771468	0.013363	0.089824	0.148766	0.881738	0.980757
hsa-miR-3617-5p	5.175281	0.023017	0.156363	0.147202	0.882972	0.980757
hsa-miR-520f-5p	75.54259	-0.00953	0.066736	-0.14274	0.886497	0.980757
hsa-miR-4684-3p	2.474515	-0.02415	0.171559	-0.14075	0.888069	0.980757
hsa-miR-3614-3p	126.9674	-0.00783	0.056028	-0.13979	0.888825	0.980757
hsa-miR-411-3p	370.0629	0.006164	0.045443	0.135637	0.892108	0.980757
hsa-miR-548ah-3p	3.576345	-0.01753	0.129701	-0.13513	0.892508	0.980757
hsa-miR-4639-5p	2.870255	-0.01726	0.127896	-0.13493	0.892668	0.980757
hsa-miR-15a-5p	1434.018	-0.00861	0.064741	-0.13302	0.894175	0.980757
hsa-miR-548b-3p	4.967972	0.01537	0.116572	0.131848	0.895104	0.980757
hsa-miR-205-5p	5230.317	0.005771	0.044402	0.129968	0.896592	0.980757
hsa-miR-653-3p	67.57911	0.009283	0.071717	0.129435	0.897014	0.980757
hsa-miR-1292-5p	2.338021	0.017816	0.13807	0.129034	0.897331	0.980757
hsa-miR-30c-2-3p	170.7443	0.004157	0.032569	0.127642	0.898432	0.980757
hsa-miR-409-5p	189.2183	0.006198	0.048748	0.127148	0.898824	0.980757
hsa-miR-489-3p	42.92588	-0.00954	0.078124	-0.1221	0.902819	0.98186

hsa-miR-148a-3p	6797.571	0.007944	0.06699	0.118584	0.905605	0.98186
hsa-miR-502-5p	38.91699	0.006031	0.051428	0.117278	0.906639	0.98186
hsa-miR-942-5p	16.21716	-0.0091	0.0781	-0.11648	0.907268	0.98186
hsa-miR-429	10.06831	-0.02067	0.178334	-0.11592	0.90772	0.98186
hsa-miR-195-3p	41.35361	-0.00556	0.048151	-0.11544	0.908098	0.98186
hsa-miR-361-3p	730.1179	0.004374	0.038638	0.113194	0.909877	0.98186
hsa-miR-103a-3p	22378.16	0.003276	0.029339	0.111646	0.911104	0.98186
hsa-miR-548x-5p	2.656564	0.017115	0.157949	0.10836	0.91371	0.98186
hsa-miR-216a-5p	8.348759	0.028406	0.263331	0.107873	0.914097	0.98186
hsa-miR-516b-3p	6.967034	-0.01179	0.109478	-0.10767	0.914254	0.98186
hsa-miR-431-3p	18.22142	0.006848	0.065917	0.103893	0.917254	0.98186
hsa-miR-200c-5p	17.24614	0.00671	0.06617	0.101413	0.919223	0.98186
hsa-let-7a-5p	36901.54	-0.00422	0.042414	-0.09947	0.920766	0.98186
hsa-miR-371a-5p	316.9375	0.01534	0.158982	0.096488	0.923133	0.98186
hsa-miR-654-3p	1179.75	-0.00343	0.036267	-0.0945	0.92471	0.98186
hsa-miR-145-3p	1651.243	-0.00433	0.045898	-0.09425	0.924908	0.98186
hsa-miR-3173-5p	2.283093	-0.01284	0.140746	-0.09124	0.9273	0.98186
hsa-miR-513c-5p	1.991972	0.015455	0.174112	0.088764	0.929269	0.98186
hsa-miR-585-3p	11.84036	-0.01127	0.128946	-0.08744	0.930322	0.98186
hsa-miR-301b-3p	11.14423	0.00895	0.102813	0.087049	0.930633	0.98186
hsa-miR-376a-5p	187.5959	0.004339	0.051876	0.083637	0.933345	0.98186
hsa-miR-551b-5p	4.381347	-0.00938	0.113074	-0.08295	0.933891	0.98186
hsa-miR-627-3p	4.06089	0.008901	0.109248	0.081475	0.935064	0.98186
hsa-miR-331-5p	66.91812	-0.00311	0.038934	-0.07978	0.936416	0.98186
hsa-miR-26a-1-3p	5.863052	-0.00718	0.090668	-0.07923	0.936847	0.98186
hsa-miR-483-3p	2729.994	0.004534	0.058895	0.07698	0.93864	0.98186
hsa-miR-200c-3p	28779.39	-0.00288	0.037542	-0.07675	0.938824	0.98186
hsa-miR-200a-3p	66.31566	-0.00734	0.096595	-0.07599	0.939428	0.98186
hsa-miR-128-3p	341.3977	-0.00211	0.028019	-0.07546	0.93985	0.98186
hsa-miR-744-3p	7.72498	-0.0067	0.090503	-0.07398	0.941026	0.98186
hsa-miR-301a-3p	88.45716	0.004554	0.061894	0.073584	0.941341	0.98186
hsa-miR-525-3p	1611.713	-0.00316	0.044427	-0.07118	0.943254	0.98186
hsa-miR-488-3p	5.594255	0.009317	0.13251	0.070309	0.943947	0.98186
hsa-miR-363-3p	695.1267	0.004548	0.065357	0.069586	0.944523	0.98186
hsa-miR-138-5p	139.9617	-0.00943	0.135773	-0.06943	0.94465	0.98186
hsa-miR-1185-5p	34.65538	-0.00451	0.065779	-0.06856	0.945339	0.98186
hsa-let-7i-5p	4220.332	-0.00562	0.08359	-0.06728	0.946356	0.98186
hsa-miR-660-5p	1535.488	-0.00218	0.034552	-0.06313	0.949661	0.982865
hsa-miR-425-5p	2607.208	0.002198	0.03489	0.062988	0.949776	0.982865
hsa-miR-624-3p	9.587269	-0.00505	0.084527	-0.0597	0.952396	0.984306
hsa-miR-296-5p	18.489	0.004309	0.07578	0.056857	0.954659	0.985375

hsa-miR-454-5p	7.95253	-0.00418	0.078764	-0.05305	0.95769	0.987233
hsa-miR-142-5p	941.0712	-0.00407	0.08456	-0.04816	0.961585	0.988742
hsa-miR-615-3p	90.98589	0.002445	0.052271	0.046776	0.962692	0.988742
hsa-miR-3139	2.664253	-0.00613	0.13636	-0.04498	0.964124	0.988742
hsa-miR-9-3p	156.501	0.003641	0.081864	0.044475	0.964526	0.988742
hsa-miR-452-3p	5.873478	0.004091	0.102328	0.039983	0.968107	0.988742
hsa-miR-3605-3p	7.327	-0.00349	0.088344	-0.03948	0.968509	0.988742
hsa-miR-3611	2.068043	-0.00692	0.177026	-0.03909	0.968818	0.988742
hsa-miR-188-3p	3.960913	0.004425	0.113929	0.038841	0.969017	0.988742
hsa-miR-184	154.2013	-0.0022	0.064576	-0.03407	0.972824	0.991366
hsa-miR-1269b	63.35845	0.013363	0.424048	0.031513	0.97486	0.99218
hsa-miR-330-3p	172.1745	0.001344	0.045555	0.029504	0.976463	0.992551
hsa-miR-2682-5p	3.171234	-0.00533	0.207291	-0.0257	0.979497	0.993791
hsa-miR-3605-5p	1.828018	0.004087	0.164362	0.024868	0.98016	0.993791
hsa-miR-135b-3p	5.701605	-0.00279	0.124554	-0.02238	0.982143	0.994543
hsa-miR-93-5p	5934.225	0.000719	0.043022	0.016715	0.986664	0.996644
hsa-miR-548o-5p	37.42233	0.000765	0.04588	0.016666	0.986703	0.996644
hsa-miR-127-5p	961.2378	0.000457	0.043642	0.01048	0.991639	0.997298
hsa-miR-20a-3p	33.10542	0.000462	0.044688	0.010332	0.991756	0.997298
hsa-miR-323a-3p	268.1224	-0.00046	0.047805	-0.00958	0.992358	0.997298
hsa-miR-3199	2.660653	-0.00131	0.14148	-0.00928	0.992595	0.997298
hsa-miR-10b-5p	2032.4	0.000884	0.12235	0.007228	0.994233	0.997298
hsa-miR-2114-5p	3.317089	-0.00105	0.162135	-0.0065	0.994811	0.997298
hsa-miR-532-5p	1629.745	0.000102	0.039865	0.00256	0.997957	0.998297
hsa-miR-548c-5p	37.41438	9.79E-05	0.045865	0.002135	0.998297	0.998297

SUPPLEMENTARY FIGURES

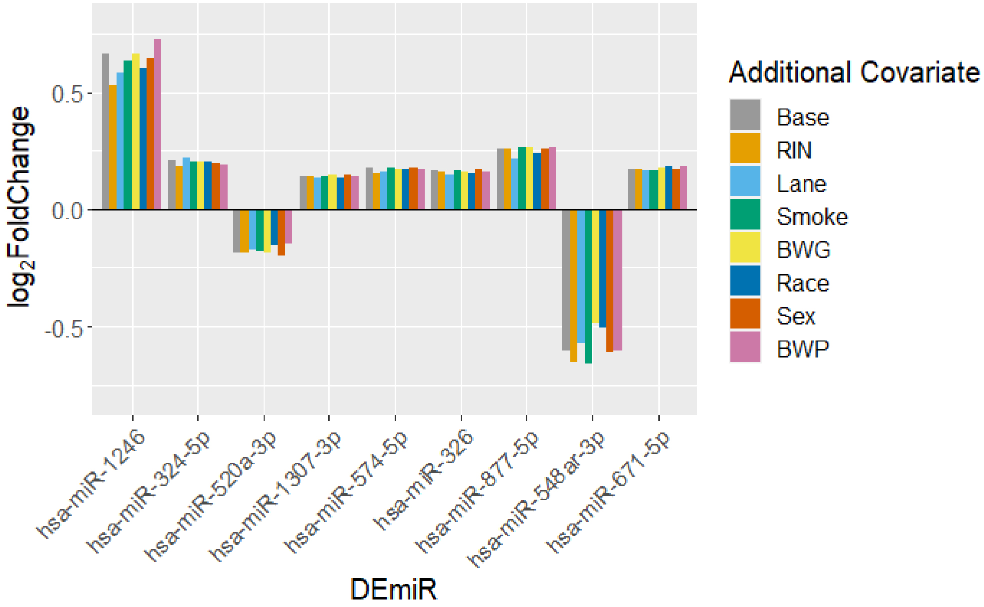

Fig S2-1: Effect size estimates of DEmiRs are highly robust to various suspected technical and biological covariates. Bar plot showing effect size estimates for all DEmiRs after correction for suspected technical and biological covariates not included in the original (base) model. RIN = RNA integrity, Lane = Flow cell lane, Smoke = maternal smoking status, BWG = birth weight group, Race = maternal race, Sex = offspring sex, YOB = year of birth, BWP = birth weight percentile

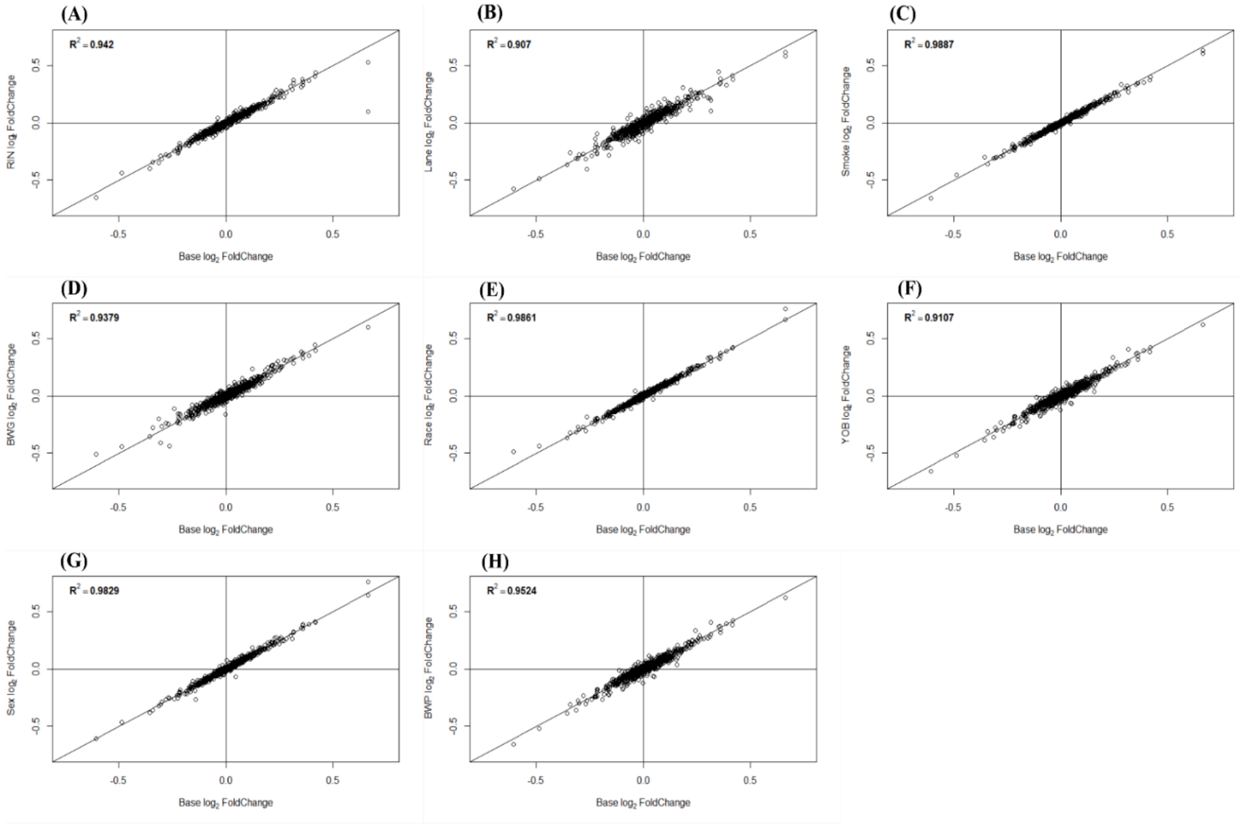

Fig S2-2: Effect size estimates of placental miRNAs are highly robust on a transcriptome-wide scale to various suspected technical and biological covariates. Scatter plots displaying the coefficient of determination (R^2) to emphasize the relationship between the estimates produced by the original (base) model and estimates of various models which correct for additional, suspected technical and biological covariates across all miRNAs analyzed. (A) RIN = RNA integrity, (B) Lane = Flow cell lane, (C) Smoke = maternal smoking status, (D) Race = maternal race, (E) BWG = birth weight group, (F) Sex = offspring sex, (G) YOB = year of birth, (H) BWP = birth weight percentile.

REFERENCES

1. Khavjou O, Phelps D, Leib A. RTI International. Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035: Technical Report. Epub November 2016.

2. Knopik VS, Maccani MA, Francazio S, McGeary JE. The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. Dev Psychopathol. 2012;24(4):1377-90. Epub 2012/10/16. doi: 10.1017/S0954579412000776. PubMed PMID: 23062304; PMCID: PMC3581096.

3. Sing CF, Stengard JH, Kardia SL. Genes, environment, and cardiovascular disease. Arterioscler Thromb Vasc Biol. 2003;23(7):1190-6. Epub 2003/05/06. doi: 10.1161/01.ATV.0000075081.51227.86. PubMed PMID: 12730090.

4. Christensen JJ, Retterstol K, Godang K, Roland MC, Qvigstad E, Bollerslev J, Ueland T, Henriksen T, Holven KB. LDL cholesterol in early pregnancy and offspring cardiovascular disease risk factors. J Clin Lipidol. 2016;10(6):1369-78 e7. Epub 2016/12/07. doi: 10.1016/j.jacl.2016.08.016. PubMed PMID: 27919354.

5. Alsnes IV, Vatten LJ, Fraser A, Bjorngaard JH, Rich-Edwards J, Romundstad PR, Asvold BO. Hypertension in Pregnancy and Offspring Cardiovascular Risk in Young Adulthood: Prospective and Sibling Studies in the HUNT Study (Nord-Trondelag Health Study) in Norway. Hypertension. 2017;69(4):591-8. Epub 2017/02/23. doi: 10.1161/HYPERTENSIONAHA.116.08414. PubMed PMID: 28223467.

6. Cross JC, Baczyk D, Dobric N, Hemberger M, Hughes M, Simmons DG, Yamamoto H, Kingdom JC. Genes, development and evolution of the placenta. Placenta. 2003;24(2-3):123-30. Epub 2003/02/25. doi: 10.1053/plac.2002.0887. PubMed PMID: 12596737.

7. Leiva A, de Medina CD, Salsoso R, Saez T, San Martin S, Abarzua F, Farias M, Guzman-Gutierrez E, Pardo F, Sobrevia L. Maternal hypercholesterolemia in pregnancy associates with umbilical vein endothelial dysfunction: role of endothelial nitric oxide synthase and arginase II. Arterioscler Thromb Vasc Biol. 2013;33(10):2444-53. Epub 2013/08/21. doi: 10.1161/ATVBAHA.113.301987. PubMed PMID: 23950140.

8. Sobrevia L, Abarzua F, Nien JK, Salomon C, Westermeier F, Puebla C, Cifuentes F, Guzman-Gutierrez E, Leiva A, Casanello P. Review: Differential placental macrovascular and microvascular endothelial dysfunction in gestational diabetes. Placenta. 2011;32 Suppl 2:S159-64. Epub 2011/01/11. doi: 10.1016/j.placenta.2010.12.011. PubMed PMID: 21215450.

9. Audette MC, Kingdom JC. Screening for fetal growth restriction and placental insufficiency. Semin Fetal Neonatal Med. 2018;23(2):119-25. Epub 2017/12/10. doi: 10.1016/j.siny.2017.11.004. PubMed PMID: 29221766.

10. D.J Barker CO. Low birth weight and hypertension. BMJ. 1988.

11. D.J Barker PDW, B. Margetts, C. Osmond, S.J Simmonds. Weight in Infancy and Death from Ischemic Heart Disease. The Lancet. 1989.

12. Cohen JA, Rychik J, Savla JJ. The placenta as the window to congenital heart disease. Curr Opin Cardiol. 2020. Epub 2020/10/20. doi: 10.1097/HCO.0000000000000816. PubMed PMID: 33074934.

13. Camm EJ, Botting KJ, Sferruzzi-Perri AN. Near to One's Heart: The Intimate Relationship Between the Placenta and Fetal Heart. Front Physiol. 2018;9:629. Epub 2018/07/13. doi: 10.3389/fphys.2018.00629. PubMed PMID: 29997513; PMCID: PMC6029139.

14. Azhar M, Runyan RB, Gard C, Sanford LP, Miller ML, Andringa A, Pawlowski S, Rajan S, Doetschman T. Ligand-specific function of transforming growth factor beta in epithelial-mesenchymal transition in heart development. Dev Dyn. 2009;238(2):431-42. Epub 2009/01/24. doi: 10.1002/dvdy.21854. PubMed PMID: 19161227; PMCID: PMC2805850.

15. Odegard RA VL, Nilsen ST, Salvesen KA, Austgulen R. . Preeclampsia and fetal growth. Obstetrics and gynecology.96(6):950-5. Epub 2000/11/21. doi: 10.1016/S0029-7844(00)01040-1.

16. Ostling H, Kruse R, Helenius G, Lodefalk M. Placental expression of microRNAs in infants born small for gestational age. Placenta. 2019;81:46-53. Epub 2019/05/30. doi: 10.1016/j.placenta.2019.05.001. PubMed PMID: 31138431.

17. Thamotharan S, Chu A, Kempf K, Janzen C, Grogan T, Elashoff DA, Devaskar SU. Differential microRNA expression in human placentas of term intra-uterine growth restriction that regulates target genes mediating angiogenesis and amino acid transport. PLoS One. 2017;12(5):e0176493. Epub 2017/05/04. doi: 10.1371/journal.pone.0176493. PubMed PMID: 28463968; PMCID: PMC5413012.

18. Meng M, Cheng YKY, Wu L, Chaemsaithong P, Leung MBW, Chim SSC, Sahota DS, Li W, Poon LCY, Wang CC, Leung TY. Whole genome miRNA profiling revealed miR-199a as potential placental pathogenesis of selective fetal growth restriction in monochorionic twin pregnancies. Placenta. 2020;92:44-53. Epub 2020/02/18. doi: 10.1016/j.placenta.2020.02.002. PubMed PMID: 32063549.

19. Wang D, Na Q, Song WW, Song GY. Altered Expression of miR-518b and miR-519a in the placenta is associated with low fetal birth weight. Am J Perinatol. 2014;31(9):729-34. Epub 2014/04/01. doi: 10.1055/s-0033-1361832. PubMed PMID: 24683074.

20. Awamleh Z, Gloor GB, Han VKM. Placental microRNAs in pregnancies with early onset intrauterine growth restriction and preeclampsia: potential impact on gene expression and pathophysiology. BMC Med Genomics. 2019;12(1):91. Epub 2019/06/30. doi: 10.1186/s12920-019-0548-x. PubMed PMID: 31248403; PMCID: PMC6598374.

21. Higashijima A, Miura K, Mishima H, Kinoshita A, Jo O, Abe S, Hasegawa Y, Miura S, Yamasaki K, Yoshida A, Yoshiura K, Masuzaki H. Characterization of placenta-specific microRNAs in fetal growth restriction pregnancy. Prenat Diagn. 2013;33(3):214-22. Epub 2013/01/29. doi: 10.1002/pd.4045. PubMed PMID: 23354729.

22. Christakis NA FJ. The Spread of Obesity in a Large Social Network over 32 Years. The New Englad Journal of Medicine. 2007(357):370-9. doi: 10.1056/NEJMsa066082.

23. Lesseur C, Armstrong DA, Paquette AG, Koestler DC, Padbury JF, Marsit CJ. Tissue-specific Leptin promoter DNA methylation is associated with maternal and infant perinatal factors. Mol Cell Endocrinol. 2013;381(1-2):160-7. Epub 2013/08/06. doi: 10.1016/j.mce.2013.07.024. PubMed PMID: 23911897; PMCID: PMC3795868.

24. Kennedy EM, Hermetz K, Burt A, Everson TM, Deyssenroth M, Hao K, Chen J, Karagas MR, Pei D, Koestler DC, Marsit CJ. Placental microRNA expression associates with birthweight through control of adipokines: results from two independent cohorts. Epigenetics. 2020:1-13. Epub 2020/10/06. doi: 10.1080/15592294.2020.1827704. PubMed PMID: 33016211.

25. Friedlander MR, Mackowiak SD, Li N, Chen W, Rajewsky N. miRDeep2 accurately identifies known and hundreds of novel microRNA genes in seven animal clades. Nucleic Acids Res. 2012;40(1):37-52. Epub 2011/09/14. doi: 10.1093/nar/gkr688. PubMed PMID: 21911355; PMCID: PMC3245920.

26. Langmead B, Trapnell C, Pop M, Salzberg SL. Ultrafast and memory-efficient alignment of short DNA sequences to the human genome. Genome Biol. 2009;10(3):R25. Epub 2009/03/06. doi: 10.1186/gb-2009-10-3-r25. PubMed PMID: 19261174; PMCID: PMC2690996.

27. Griffiths-Jones S, Saini HK, van Dongen S, Enright AJ. miRBase: tools for microRNA genomics. Nucleic Acids Res. 2008;36(Database issue):D154-8. Epub 2007/11/10. doi: 10.1093/nar/gkm952. PubMed PMID: 17991681; PMCID: PMC2238936.

28. Anders S, Huber W. Differential expression analysis for sequence count data. Genome Biology. 2010;11(10):R106. doi: 10.1186/gb-2010-11-10-r106.

29. Leek JT. svaseq: removing batch effects and other unwanted noise from sequencing data. Nucleic Acids Res. 2014;42(21). Epub 2014/10/09. doi: 10.1093/nar/gku864. PubMed PMID: 25294822; PMCID: PMC4245966.

30. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biology. 2014;15(12):550. doi: 10.1186/s13059-014-0550-8.

31. Tokar T, Pastrello C, Rossos AEM, Abovsky M, Hauschild AC, Tsay M, Lu R, Jurisica I. mirDIP 4.1-integrative database of human microRNA target predictions. Nucleic Acids Res.

2018;46(D1):D360-D70. Epub 2017/12/02. doi: 10.1093/nar/gkx1144. PubMed PMID: 29194489; PMCID: PMC5753284.

32. Kamburov A, Pentchev K, Galicka H, Wierling C, Lehrach H, Herwig R. ConsensusPathDB: toward a more complete picture of cell biology. Nucleic Acids Res. 2011;39(Database issue):D712-7. Epub 2010/11/13. doi: 10.1093/nar/gkq1156. PubMed PMID: 21071422; PMCID: PMC3013724.

33. Kamburov A, Wierling C, Lehrach H, Herwig R. ConsensusPathDB--a database for integrating human functional interaction networks. Nucleic Acids Res. 2009;37(Database issue):D623-8. Epub 2008/10/23. doi: 10.1093/nar/gkn698. PubMed PMID: 18940869; PMCID: PMC2686562.

34. Wong PC, Kitsantas P. A review of maternal mortality and quality of care in the USA. J Matern Fetal Neonatal Med. 2020;33(19):3355-67. Epub 2019/01/17. doi: 10.1080/14767058.2019.1571032. PubMed PMID: 30646778.

35. Olejniczak M, Kotowska-Zimmer A, Krzyzosiak W. Stress-induced changes in miRNA biogenesis and functioning. Cell Mol Life Sci. 2018;75(2):177-91. Epub 2017/07/17. doi: 10.1007/s00018-017-2591-0. PubMed PMID: 28717872.

36. Carreras-Badosa G, Bonmatí A, Ortega FJ, Mercader JM, Guindo-Martínez M, Torrents D, Prats-Puig A, Martinez-Calcerrada JM, de Zegher F, Ibáñez L, Fernandez-Real JM, Lopez-Bermejo A, Bassols J. Dysregulation of Placental miRNA in Maternal Obesity Is Associated With Pre- and Postnatal Growth. J Clin Endocrinol Metab. 2017;102(7):2584-94. Epub 2017/04/04. doi: 10.1210/jc.2017-00089. PubMed PMID: 28368446.

37. Hogg DR, Harries LW. Human genetic variation and its effect on miRNA biogenesis, activity and function. Biochem Soc Trans. 2014;42(4):1184-9. Epub 2014/08/12. doi: 10.1042/bst20140055. PubMed PMID: 25110023.

38. Huan T, Rong J, Tanriverdi K, Meng Q, Bhattacharya A, McManus DD, Joehanes R, Assimes TL, McPherson R, Samani NJ, Erdmann J, Schunkert H, Courchesne P, Munson PJ, Johnson AD, O'Donnell CJ, Zhang B, Larson MG, Freedman JE, Levy D, Yang X. Dissecting the roles of microRNAs in coronary heart disease via integrative genomic analyses. Arteriosclerosis, thrombosis, and vascular biology. 2015;35(4):1011-21. Epub 2015/02/05. doi: 10.1161/ATVBAHA.114.305176. PubMed PMID: 25657313.

39. Peng S, Deyssenroth MA, Di Narzo AF, Cheng H, Zhang Z, Lambertini L, Ruusalepp A, Kovacic JC, Bjorkegren JLM, Marsit CJ, Chen J, Hao K. Genetic regulation of the placental transcriptome underlies birth weight and risk of childhood obesity. PLoS Genet. 2018;14(12):e1007799-e. doi: 10.1371/journal.pgen.1007799. PubMed PMID: 30596636.

40. Tuba Gunel MKH, Ece Gumusoglu, Ismail Dolekcap, and Kilic Aydinli. Future Perspective of Preeclampsia by miRNA. Global Journal of Human Genetics & Gene Therapy. 2014;2:14.

41. Zhao G, Zhou, X., Chen, S. et al. Differential expression of microRNAs in decidua-derived mesenchymal stem cells from patients with pre-eclampsia. J Biomed Sci 2014;21(81). doi: https://doi.org/10.1186/s12929-014-0081-3.

42. Wu L, Zhou H, Lin H, Qi J, Zhu C, Gao Z, Wang H. Circulating microRNAs are elevated in plasma from severe preeclamptic pregnancies. Reproduction. 2012;143(3):389-97. Epub 2011/12/22. doi: 10.1530/REP-11-0304. PubMed PMID: 22187671.

43. Jayabalan N, Nair S, Nuzhat Z, Rice GE, Zuniga FA, Sobrevia L, Leiva A, Sanhueza C, Gutierrez JA, Lappas M, Freeman DJ, Salomon C. Cross Talk between Adipose Tissue and Placenta in Obese and Gestational Diabetes Mellitus Pregnancies via Exosomes. Front Endocrinol (Lausanne). 2017;8:239. Epub 2017/10/13. doi: 10.3389/fendo.2017.00239. PubMed PMID: 29021781; PMCID: PMC5623931.

44. Goumans MJ, Liu Z, ten Dijke P. TGF-beta signaling in vascular biology and dysfunction. Cell Res. 2009;19(1):116-27. Epub 2008/12/31. doi: 10.1038/cr.2008.326. PubMed PMID: 19114994.

45. Jones RL, Stoikos C, Findlay JK, Salamonsen LA. TGF-beta superfamily expression and actions in the endometrium and placenta. Reproduction. 2006;132(2):217-32. Epub 2006/08/04. doi: 10.1530/rep.1.01076. PubMed PMID: 16885531.

46. Ni N, Li Q. TGFbeta superfamily signaling and uterine decidualization. Reprod Biol Endocrinol. 2017;15(1):84. Epub 2017/10/17. doi: 10.1186/s12958-017-0303-0. PubMed PMID: 29029620; PMCID: PMC5640934.

47. Yaling Feng NW, Jianjuan Xu, Jinfang Zou, Xi Liang, Huan Liu and Ying Chen. Alpha-1-antitrypsin functions as a protective factor in preeclampsia through activating Smad2 and inhibitor of DNA binding 4. Oncotarget. 2017;8(68):113002-12.

48. Watabe T, Miyazono K. Roles of TGF-beta family signaling in stem cell renewal and differentiation. Cell Res. 2009;19(1):103-15. Epub 2008/12/31. doi: 10.1038/cr.2008.323. PubMed PMID: 19114993.

49. Arroyo JA, Winn VD. Vasculogenesis and angiogenesis in the IUGR placenta. Semin Perinatol. 2008;32(3):172-7. Epub 2008/05/17. doi: 10.1053/j.semperi.2008.02.006. PubMed PMID: 18482617.

50. Kiba A, Sagara H, Hara T, Shibuya M. VEGFR-2-specific ligand VEGF-E induces non-edematous hyper-vascularization in mice. Biochemical and Biophysical Research Communications. 2003;301(2):371-7. doi: 10.1016/s0006-291x(02)03033-4.

51. Bai Y, Wang W, Zhang Y, Zhang F, Zhang H. lncRNA MIAT suppression alleviates corneal angiogenesis through regulating miR-1246/ACE. Cell Cycle. 2019;18(6-7):661-9. Epub 2019/02/21. doi: 10.1080/15384101.2019.1578143. PubMed PMID: 30782069; PMCID: PMC6464576.

52. Ghulmiyyah L, Sibai B. Maternal mortality from preeclampsia/eclampsia. Semin Perinatol. 2012;36(1):56-9. Epub 2012/01/28. doi: 10.1053/j.semperi.2011.09.011. PubMed PMID: 22280867.

Chapter 3 - Cardiovascular disease polygenic risk scores predict expression patterns of placental miRNAs relevant to metabolic programming

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ABSTRACT

In the United States, cardiovascular disease has remained the leading cause of death for the past decade and remains among the highest of any industrialized nation. Both proper placental functionality and placental microRNA expression are critical to successful pregnancy outcomes, and both are highly sensitive to genetic sources of variation. Heritability estimates of common metabolic syndromes within the US are speculated to have anywhere between 16% to 60% genetic contributions, suggesting a potential majority role of genetic predisposition to CVD etiology. Dysregulation of miRNAs in the placenta is implicated in adverse gestational outcomes, such as preeclampsia and fetal growth restriction. These gestational outcomes have known genetic predispositions as well signature miRNA expression patterns, suggesting a potential role of cardiometabolic-related genetic variation as a modifier of newborn and maternal health outcomes by acting through miRNA expression. The role of these subtle genetic predispositions in placental function and microRNA expression as they relate to the developmental programming of chronic disease remains poorly understood. We performed fetal genotyping and small RNA sequencing to investigate microRNA in placentae from the Rhode Island Child Health Study (n=102). MicroRNA counts were modeled on a normalized polygenic risk score of cardiovascular disease using negative binomial generalized linear models. MicroRNAs were considered to be differentially expressed at a false discovery rate (FDR) less than 0.15. Parallel mRNA sequencing data and bioinformatic target prediction software were then used to identify potential mRNA targets of differentially expressed microRNAs. Three differentially expressed microRNAs were identified (FDR< 0.15). Bioinformatic target prediction revealed 164 potential mRNA targets of these microRNAs, many of which are implicated in energy metabolism and metabolic programming but also in pathways involving

small RNA biogenesis, and cell cycle regulation. A robust association exists between cardiovascular disease genetic predisposition and placental microRNA expression, and may be implicated in both placental insufficiencies and the developmental programming of chronic disease.

INTRODUCTION

Globally, and within the United States, Cardiovascular Disease (CVD) is the leading cause of death, and is expected to affect over 44% of the US population by 2035 (1, 2). Given the complex, multifactorial and chronic nature of CVD delineating the genetic and environmental influences that influence disease etiology remains challenging (3). There exists a growing body of evidence linking overall cardiometabolic health, of both mother and fetus during pregnancy, to adverse cardiovascular health outcomes in offspring later in life (4, 5). Pregnancy related outcomes, such as placental insufficiencies and birth weight, have been postulated to play a major role in the developmental programming of chronic disease, such as CVD, under the Developmental Origins of Health and Disease (DOHaD) hypothesis.

The DOHaD hypothesis outlines the potential role of gestational conditions, including both environmental and genetic influences, in shaping the lifelong risk of chronic disease of an individual (6). As a central vascular organ overseeing fetal growth, development and the intrauterine environment, proper functionality of the placental remains central to successful gestational outcomes. Resting at the interface of the maternal and fetal environment, the placenta participates in a variety of molecular processes, such as nutrient transport, immunomodulation, and endocrine signaling, all of which are made possible through the development of a villi-based vasculature system which allows for communication between mother and offspring (7). Additionally, placental insufficiencies are associated with adverse gestational outcomes, such as fetal growth restriction, which itself serves as a significant risk indicator for the development of cardiovascular disease (CVD) later in life (8-10). Placental development occurs concurrently with fetal heart development, utilizing similar growth signals, including endothelial signaling pathways such as transforming growth factor-beta (TGFβ) and vascular endothelial growth factor (VEGF). Deficiencies in the organogenesis of either vascular organ may alter the formation of the other, initiating physiological changes with potential lifelong cardiovascular consequences (11-13).

While initial DOHaD studies focused largely on the role of environmental contributions toward chronic disease development, heritability estimates of common metabolic syndromes within the US are speculated to have anywhere between 16% to 60% genetic contributions, suggesting a potential majority role of genetic predisposition to CVD etiology (14). While genetic predisposition is established at conception, genetic variants implicated in birth weight, fetal growth outcomes and metabolic syndromes have been shown to hold quantitative relationships with the expression of various mRNAs within placental tissue, and may work to developmentally program lifelong risk of chronic cardiometabolic health outcomes (15, 16). However, the relationship between CVD-related genetic risk factors and placental miRNA expression remain undefined.

MicroRNAs (miRNA) are small noncoding RNA molecules (~22 nucleotides) capable of post-transcriptional regulation of gene expression. These molecules utilize base-pairing to bind to the 3’-untranslated region of target mRNAs resulting in either translational repression or mRNA degradation, by which the exact mechanism largely depends on the degree of sequence complementarity between the miRNA and target mRNA. The biogenesis, structure and function of miRNAs are each known to be sensitive to genetic variation in general (17, 18). Genetic variation relevant to cholesterol homeostasis have been shown to inhibit the functionality of critical miRNAs overseeing high density lipoprotein levels in circulation, highlighting the role of miRNA in regulating overall cardiometabolic health (19, 20). Within the context of the placenta, dysregulation of miRNAs is implicated in both preeclampsia and fetal growth restriction. These gestational outcomes have known genetic predispositions as well signature miRNA expression patterns, suggesting a potential role of cardiometabolic-related genetic variation as a modifier of newborn and maternal health outcomes by acting through miRNA expression (21-28).

To explore the cumulative genetic risk of cardiovascular disease on the placental miRNA landscape, we utilized placental miRNA sequencing data and fetal genotype data from the Rhode Island Child Health Study (RICHS; n=102). We analyzed the relationship between a cardiovascular disease polygenic risk score (PRS), and placental miRNA expression (29). Through this cumulative genetic risk variable in the form of a PRS, we isolate the genetic risk component of cardiometabolic disease that may contribute to CVD etiology to better understand how genetic predispositions may act through changes in placental miRNA expression to developmentally program risk of chronic disease. Bioinformatic target prediction was then used to identify potential mRNA targets of miRNAs significantly associated with maternal CVD risk, followed by overrepresentation analyses to characterize the biological pathways in which these mRNAs participate.

RESULTS

This study analyzed miRNA sequencing and genotype data from 102 placentae from the Rhode Island Child Health Study (RICHS). The demographics of the participants are outlined in Table 3-1. In brief, placentae collected in this study were from full term pregnancies (≥37 weeks gestation), all from relatively health mothers who did not experience serious complications during their pregnancy. Amongst the mothers, 56% were reported to be either overweight or obese, and 11% were self-reported smokers.

To analyze the association between genetic predisposition to CVD and placental miRNA expression, we performed differential expression analysis using negative binomial generalized linear models constructed in *DESeq2* on placental small RNA sequencing data. Genetic predisposition was proxied through the calculation of a polygenic risk score, which was derived from the summation of risk alleles outlined by a large-scale cardiovascular disease GWAS conducted by Nikpay et al, (*Nature Genetics*, 2015). We identified 3 Differentially Expressed miRNAs (DEmiRs) (miR-1197, miR-668-3p and miR-224-3p) associated with the CVD PRS (FDR <0.15). Sensitivity analyses were performed to ensure maternal smoking status and scaling of the PRS did not impact significant findings, as well as to assess the robustness of DEmiR effect sizes.

Bioinformatic targets of DEmiRs were predicted using the miRNA Data Integration Portal (miRDIP) (30). miRDIP predicted 500 targets between miR-1197, miR-668-3p and miR-224-3p, 477 of which were found to be expressed in placental total RNA seq data derived from RICHS samples. These predicted targets were tested (individually for each DEmiR's set of targets) for pathway overrepresentation within ConsensusPathDB (CPDB) (31-33). Pathways related to miRNA biogenesis, overall metabolism, and cell cycle regulation were found to be overrepresented amongst miR-1197 gene targets. Both miR-668-3p and miR-224-3p targets were enriched in pathways relevant to cell cycle regulation and endothelial function.

DISCUSSION

Cardiovascular disease has remained the leading cause of death across the world, is expected to affect over 44% of the US population in the next decade, and is predicted to result in over $1.1 trillion in direct and indirect medical costs by the year 2035 (1, 2). Heritability estimates of CVD predict anywhere between 16% to 60% genetic contributions, but the collective role of this genetic risk in the etiology of CVD remain understudied (14). Physiological and functional outcomes of the placenta serve as an indicator of lifelong cardiometabolic health. Placental insufficiencies may lead to adverse gestational outcomes, including fetal growth restriction, and are associated with dysregulated placental miRNA expression patterns (21-26). Considering the sensitive window of development that gestation offers in terms of developmental plasticity, CVD-related genetic variants may act through the placenta as to program lifelong risk of chronic disease via changes in placental miRNA expression. While our study does not investigate placentae from mothers diagnosed with CVD, the potentially large genetic contributions of CVD heritability provides a unique opportunity to study how these genetic predispositions influence placental functionality and the molecular mechanisms governing adverse gestational outcomes and the developmental origins of chronic disease.

From our small RNA sequencing analysis, we identified 3 placental miRNAs whose expression associate with an estimated CVD PRS calculated from previous CVD GWAS studies **(Figure 3-1)** (34, 35). The expression of miRNA is known to be sensitive to genetic variation relevant to CVD risk (19, 20). The inherited genetic risk of CVD experienced by the fetus may in part influence the biogenesis, activity and function of placental miRNAs (36, 37). Additionally, this genetic predisposition may also manifest as variation in the expression of levels of placental miRNAs, further disrupting biological pathways relevant to the etiology of chronic cardiometabolic conditions. The relationship between fetal inheritance of CVD-related genetic variants and placental miRNA transcript abundances may prove to be increasingly relevant if they display quantitative relationships with one another, similar to those that have been identified within RICHS on the mRNA level (38).

The functional relevance of miRNAs is largely dictated by the mRNAs available for them to interact with. These interactions are heavily influenced by the tissue of origin of both miRNAs and their target mRNAs. While many miR-1197 is implicated in cardiometabolic conditions during pregnancy, the functional roles of miR-224-3p and miR-668-3p largely understudied in the context of placental physiology (39). Previous work has shown downregulation of miR-1197 in human umbilical vein endothelial cells (HUVECs), a placental derived cell line, in response to high levels of oxidized low-density lipoproteins *in vitro* (39). While this environmentally-driven change is not representative of the genetic risks analyzed in our study, it does highlight the specific role of miR-1197 in responding to cardiometabolic risk factors, such as high cholesterol.

Bioinformatic target prediction and pathway enrichment analysis further revealed potential functional impacts of miR-1197. Of the 164 unique transcripts predicted to be targeted by miR-1197, these potential gene targets were enriched in biological pathways relevant to miRNA biogenesis, energy metabolism, and cell cycle regulation pathways **(Table 3-2)**. Among the predicted targets within energy metabolism are peroxisome proliferator-activated receptors (PPARs) co-activators *PPARGC1A* and *PPARGC1B.* The PPAR gamma co-activator (PGC1) family has been highlighted as an important component of various metabolic processes including: mitochondrial biogenesis, cellular respiration, gluconeogenesis, glucose transport, glycogenolysis, fatty acid oxidation, peroxisomal remodeling and adaptive thermogenesis (40, 41). Our findings suggest downregulation of miR-1197 in association with CVD genetic predisposition, *PPARGC1A* and *PPARGC1B* transcripts may face less miRNA-mediated degradation, thus resulting in higher abundances of PCG1 family gene transcripts in those at increased genetic risk for CVD. The role of the PCG1 family in these various metabolic pathways has earned a high level of interest in utilizing these genes in potential therapeutics to combat type 2 diabetes mellitus. Previous work has shown that PCG1 family protein levels within placental are positively associated with maternal blood glucose levels amongst mothers diagnosed with gestational diabetes, suggesting their role in the developmental programming of chronic cardiometabolic disease in offspring (42).

Interestingly, two predicted targets of miR-1197 are *AGO1* and *AGO2*, members of the Argonaut protein family and central catalytic components of the miRNA silencing complex (43). As a critical member of the RNA Induced Silencing Complex (RISC), *AGO2* is a central component involved in the endonuclease activity executed during miRNA mediated regulation of gene expression. The essential role played by *AGO2* may allow for miR-1197 dysregulation to potentially disrupt overall miRNA function within the placenta (44). However, given the major consequences to development that occur following disruption of Argonaut family proteins, and the utilization of an overall healthy cohort in our analysis, this specific interaction *in vivo* within our specific cohort is unlikely (45).

While the functional role of miR-224-3p and miR-668-3p have not been directly validated within placental tissue, they each target genes enriched for various cellular processes involved in endothelial functionality and maintenance **(Tables 3-3 & 3-4)**. MiR-224-3p was identified to target genes specifically enriched in Epidermal Growth Factor (EGF) signaling pathways, which is highly active within the placenta **(Table 3-3)**. The EGF transmembrane receptor (EGFR) exhibits the highest expression within placenta tissue, and aberrant regulation of this pathway is associated with adverse gestational outcomes, including fetal growth restriction and preeclampsia (46-48). While miR-224-3p was not predicted to target the specific mRNA responsible for the production of EGFR, the dysregulation of EGF signaling targets downstream of activation, such as GAB2 and KRAS, may lead to EGF pathway disruption, and consequently, placental insufficiency (49, 50).

Pathway enrichment analysis of miR-668-3p targets revealed potential disruption to N-methyl-D-aspartate (NMDA) signaling pathways **(Table 3-4)**. While NMDA receptors and the signaling cascades, they initiate are traditionally studied in the context of neurological disease, their aberrant regulation are also associated with hypoxic conditions within the placenta (51). Placental insufficiencies are implicated in adverse neurodevelopmental outcomes, and may be predictive of long-term neurobehavior (52). Given the placenta’s ability to produce neurotransmitters and its involvement in supporting fetal brain development, these data suggest that placental miRNA expression may serve as a mediator of neurodevelopmental outcomes by acting through changes in placental physiology (53-55).

This study only includes term placentae from live births, where premature births and other birth defects were excluded. The cross-sectional design of this study limits the interpretation of miRNA associations temporally, and may not be representative of miRNA associations throughout gestational development. This study relies on a small sample size of n=102, which may ultimately lead to difficulty in application to the general population. While we tested for various confounders to the best of our ability, there is still a possibility of unmeasured confounding which remains in our analysis. Lastly, the RICHS cohort consists predominantly of healthy, white mothers and their offspring from the New England region of the United States, potentially limiting the ability of these results to be generalized to those with acute cardiometabolic complications, and to more racially diverse populations.

CONCLUSIONS

MiRNAs serve as a critical form of post-transcriptional gene regulation during early development, and are sensitive to genetic variation. Here we have shown that the expression of 3 placental miRNAs is associated with a polygenic risk score of cardiovascular disease, and that the mRNA targets of these miRNAs largely play a role in energy metabolism, indicating their involvement in the disruption of normal placental function and physiology *in utero*. The dysregulation of placental miRNA expression in response to genetic predispositions may contribute to adverse newborn health outcomes, ultimately revealing miRNA expression as a mediator in the developmental programming of lifelong risk of chronic diseases.

METHODS

The Rhode Island Child Health Study (RICHS) is a cohort of mother-infant pairs from the Women & Infants Hospital in Providence, Rhode Island, enrolled between September 2010 and February 2013. All mothers were at least 18 years of age, had no life-threatening conditions, and delivered singletons free of congenital/chromosomal abnormalities at or after 37 weeks of gestation. All participants provided written informed consent and all protocols were approved by the IRBs at the Women & Infants Hospital of Rhode Island and Emory University, respectively. Data provided by this study include placental microRNA transcript abundance (n=102). Interviewer-administered questionnaires were utilized to collect sociodemographic and lifestyle data. Structured medical record review was used to collect anthropometric and medical history data.

Tissue collection

Fetal placental samples from all subjects were collected as previously described (56). Briefly, placental samples were collected within two hours of birth; fragments were obtained two centimeters (cm) from the umbilical cord and free of maternal decidua. Collected tissue was immediately placed in RNA later solution (Life Technologies, Grand Island, NY, USA) and stored at 4 °C for at least 72 hours. Subsequently, tissue segments were blotted dry, snap frozen in liquid nitrogen, homogenized by pulverization using a stainless-steel cup and piston unit (Cellcrusher, Cork, Ireland) and stored at −80 °C.

Fetal genotyping

Genomic DNA was extracted from the placenta using the QIamp DNA mini kit (Qiagen, #51306), according to manufacturer's instruction. Genomic DNA was then quantified using a Nanodrop ND-1000 (Thermo Fisher, CA, USA). Genome wide SNP genotyping was performed on a subset of RICHS samples (n=102) utilizing the Illumina MegaEX chip; 1,730,225 SNP remained following initial QC and 19,499,087 SNPs were utilized in the final analysis following imputation utilizing the Haplotype Reference Consortium (HRC) reference panel (57). SNPs with an imputation $r^2 < 0.3$ were removed prior to analysis.

miRNA isolation and sequencing

Total RNA was extracted from the placenta using the Qiagen miRNeasy Mini Kit and a TissueLyser LT (Qiagen, Germantown, MD, USA) following manufacturer's protocol. Briefly, 25-35 mg of frozen, powdered placental tissue was placed in a 2 ml round bottom tube with 700 ul of Qiazol Lysing Reagent and one 5 mm stainless steel bead. The tissue was homogenized in a pre-chilled tube holder on the TissueLyser LT for two, 5-minute cycles at 30 Hz. The resulting homogenate was processed with the Qiagen miRNeasy Mini Kit with on-column DNAse digestion and eluted in 50 µl RNase-free water. The RNA was quantitated on a NanoDrop (Thermo Fisher, Waltham, MA, USA) and quality checked on Agilent Bioanalyzer using the Agilent RNA 6000 Nano kit (Agilent, Santa Clara, CA, USA). Single end, 1 x 50 bp next generation sequencing of placental miRNA was performed by Omega Bioservices (Norcross, Georgia) as previously described (33).

miRNA seq processing and QC

Raw FASTQ reads obtained from a total of 230 RICHS samples were subject to adaptor trimming with cutadapt v1.1634. The 3' adaptor sequence were trimmed (TGGAATTCTCGGGTGCCAAGG) and then four bases were trimmed from each end of the read following vendor's recommendation (BIOO scientific, Austin TX). We then used trimmed reads and miRDeep2 to quantify microRNA (58). miRDeep2 was used to first perform alignment using bowtie1 with human genome hg38 (59). The 'Quantifier' module in miRDeep2 was used to obtain raw counts of microRNAs with 84iRbase version 22 (60).

Transcript filtering and normalization

Raw miRNA counts were imported into *DESeq2* for normalization and differential expression analysis. Only miRNA transcripts with more than one count per million in at least 10 percent of samples were included, leaving 795 miRNA transcripts to be analyzed of the initial 2656 sequenced transcripts. Dispersion estimates were then calculated, followed by generation of median ratio size factor estimates to normalize counts for analysis with in *DESeq2* (61). Normalized counts were then exported from *DESeq2* for Surrogate Variable Analysis (SVA).

Statistical Analyses

Cardiovascular disease polygenic risk score calculation

Detailed information about the original genotyping and imputation scheme for the initial cardiovascular disease GWAS study on which this analysis is based on has been provided elsewhere (34, 35). Polygenic risk scores were derived through the weighted sum of all risk alleles from the GWAS conducted by Nikpay et al, (*Nature Genetics*, 2015). Among those analyzed, 297,862 alleles were included in the final calculation of the CVD PRS score. Prior to being implemented as the predictor variable in the differential expression analyses, PRS scores were then normalized to follow a normal distribution with a final mean of 0 and standard deviation of 1. Normalized scores ranged from -2.43 to 2.86.

SVA

In an effort to adjust for unknown confounders, such as cell-type heterogeneity and unmeasured sources of technical variation, surrogate variables were estimated for normalized miRNA transcript reads using the *sva* package (62, 63). The full model used in the *svaseq* includes the CVD PRS while the null model included only an intercept term. One surrogate variable was utilized as a covariate in our differential expression analysis.

DESeq2 differential expression analysis

miRNA transcript counts were modeled using a negative binomial generalized linear model to identify differentially expressed transcripts in *DESeq2* (63). For each of the 795 individual miRNA transcripts which passed strict filtering and quality criteria, the variance stabilized transformed transcript abundance was regressed on the normalized CVD PRS while adjusting for the first surrogate variable to control for unknown confounders (62, 63). We considered miRNAs with a false discovery rate (FDR) less than 15% to be considered a differentially expressed miRNA (DemiR) with respect to the CVD PRS. Extensive sensitivity analyses were performed by including various parameters as covariates to the original model to assess the robustness DemiR effect sizes.

Target prediction and filtering

Potential DemiR targets were identified using miRDIP, an online database of miRNA target predictions (30). Only targets within the top 1% of confidence scores were returned. Potential targets of DEmiRs were identified using miRDIP (64). Only targets within the top 1% of confidence scores were returned. To further enhance the biological relevance of target mRNAs we then utilized existing whole transcriptome RNA-seq data from RICHS to only allow mRNAs that were expressed >1cpm in at least 10% of RICHS whole transcriptome RNA-seq samples to be considered a potential biological target (33).

Pathway analysis

A total of 476 predicted DemiR targets were tested for pathway overrepresentation within ConsensusPathDB (CPDB) (31, 32), against all genes that passed general QC filtering in RICHS whole transcriptome RNA-seq analysis (31-33). CPDB utilizes 12 separate biological pathway databases, and calculates an enrichment p-value from the hypergeometric distribution of genes in the list of miRNA targets and the pathway gene set. Only mRNAs that were expressed >1cpm in at least 10% of the RICHS samples were included as the background for the pathway analysis (33). False discovery rates were calculated from the enrichment p-values, and a q-value less than 0.05 was considered a significant enrichment of miRNA targets in the tested pathway.

TABLES

Table 3-1: RICHS Cohort Demographics

MATERNAL CHARACTERISTICS	
Age (yrs) – *mean (range)*	31 (21 - 40)
Race (White) – *% (n)*	100% (102)
Pregnancy Smoking – *% (n)*	11.7% (12)
Pre-Pregnancy Body Mass Index (BMI) (kg/m^2) – *mean (range)*	26.1(16 - 46.7)
Pre-Pregnancy BMI Group	
Normal and Underweight – *% (n)*	51.9% (53)
Overweight – *% (n)*	28.4% (29)
Obese – *% (n)*	28.4% (20)
INFANT CHARACTERISTICS	
Gestational Age (wks) – *mean (range)*	39.4 (37 - 41.4)
Sex (Female) – *% (n)*	49% (50)
CVD Polygenic Risk Score – *mean (range)*	0 (-2.4 – 2.86)
Birthweight (g) – *mean (range)*	3588 (2160 - 4640)
Birthweight Group	
Small for Gestational Age (SGA) – *% (n)*	11.7% (12)
Average for Gestational Age (AGA) – *% (n)*	59.8% (61)
Large for Gestational Age (LGA) – *% (n)*	28.4% (29)

Table 3-2: MiR-1197 Target Pathway Enrichment Analysis

Pathway	Enriched Targets	p-value	q-value
Post-transcriptional silencing by small RNAs	AGO1; TNRC6A; AGO2	5.54E-05	0.015277
Competing endogenous RNAs (ceRNAs) regulate PTEN translation	AGO1; TNRC6A; AGO2	8.78E-05	0.015277
Regulation of PTEN mRNA translation	AGO1; TNRC6A; AGO2	8.78E-05	0.015277
Energy Metabolism	PRKAG2; CREB1; PPARGC1A; PPARGC1B; MEF2D	0.000163423	0.021327
p38 mapk signaling pathway	MAP3K1; MAP3K9; CREB1; MEF2D	0.000231689	0.024188
Adipogenesis	EGR2; CREB1; PPARGC1A; CELF1; SMAD3; SPOCK1; MEF2D	0.00034342	0.028881
FOXO-mediated transcription	BCL6; BCL2L11; PPARGC1A; FBXO32; SMAD3	0.000432984	0.028881
Regulation of MECP2 expression and activity	AGO1; CREB1; TNRC6A; AGO2	0.000465797	0.028881
FoxO signaling pathway - Homo sapiens (human)	BCL2L11; PRKAG2; SMAD3; MAPK10; FBXO32; NLK; BCL6	0.000497946	0.028881
p38 MAPK Signaling Pathway	MAP3K9; MAP3K1; CREB1; MEF2D	0.000667947	0.034867
Brain-derived neurotrophic factor (BDNF) signaling pathway	BCL2L11; EGR2; GRIA3; MAP3K1; CREB1; FRS2; MAPK10	0.000887719	0.036761
regulation of pgc-1a	HDAC5; PPARGC1A; MEF2D	0.000985922	0.036761
Galanin receptor pathway	BCL2L11; PPARGC1A; CREB1	0.000985922	0.036761
Regulation of RUNX1 Expression and Activity	AGO1; TNRC6A; AGO2	0.000985922	0.036761

Table 3-3: MiR-224-3p Target Pathway Enrichment Analysis

Pathway	Enriched Targets	p-value	q-value
ErbB2/ErbB3 signaling events	USP8; RAC1; PTPN11; JUN; DOCK7; KRAS	4.57E-06	0.002667
Pathways affected in adenoid cystic carcinoma	FOXP2; KMT2C; ARID5B; NFIB; ATRX; MYB	4.75E-05	0.007655
Neurotrophic factor-mediated Trk receptor signaling	PRKCI; RAC1; PTPN11; GAB2; RASA1; KRAS	5.24E-05	0.007655
EGF-EGFR signaling pathway	PRKCI; USP8; RAC1; GAB2; PTPN11; JUN; MEF2C; RASA1; KRAS	6.86E-05	0.008012
IL2-mediated signaling events	GAB2; PTPN11; JUN; RASA1; KRAS	0.000296	0.02555
PIP3 activates AKT signaling	RAC1; JUN; PTPN11; OTUD3; GAB2; TNRC6B; TNRC6A; NRG3; RNF2	0.000306	0.02555
PTK6 Regulates RHO GTPases, RAS GTPase and MAP kinases	RAC1; RASA1; KRAS	0.000378	0.027581
IL1-mediated signaling events	PRKCI; IL1RAP; JUN; UBE2N	0.000447	0.02785
Signaling by FLT3 ITD and TKD mutants	PTPN11; GAB2; KRAS	0.000477	0.02785
IL2 signaling events mediated by PI3K	PTPN11; MYB; GAB2; RAC1	0.000634	0.033683
Signaling events regulated by Ret tyrosine kinase	PTPN11; JUN; RASA1; RAC1	0.000786	0.034652
Regulation of RUNX1 Expression and Activity	PTPN11; TNRC6B; TNRC6A	0.000869	0.034652

Table 3-4: MiR-668-3p Target Pathway Enrichment Analysis

Pathway	Enriched Targets	p-value	q-value
Post NMDA receptor activation events	CAMK2G; NRAS; PRKAA2; MAPK1; PRKAR1A; MAPT	1.54E-05	0.00845
Activation of NMDA receptors and postsynaptic events	CAMK2G; NRAS; PRKAA2; MAPK1; PRKAR1A; MAPT	5.38E-05	0.014707
Calnexin/calreticulin cycle	SEL1L; PRKCSH; CANX; UGGT1	9.97E-05	0.018176
Thyroid-stimulating hormone	LEP; GNAO1; HSPA5; CANX	0.00014	0.019151
Signaling pathways regulating pluripotency of stem cells - Homo sapiens (human)	ID4; NRAS; CTNNB1; PAX6; LIFR; SMARCAD1; MAPK1	0.000221	0.024184
Melanogenesis - Homo sapiens (human)	GNAO1; CAMK2G; NRAS; CTNNB1; MAPK1; KITLG	0.000293	0.026725
N-glycan trimming in the ER and Calnexin/Calreticulin cycle	SEL1L; PRKCSH; CANX; UGGT1	0.000375	0.029342
Maturation of spike protein	PRKCSH; CANX	0.000693	0.037881
Class IB PI3K non-lipid kinase events	MAPK1; PDE3B	0.000693	0.037881

FIGURES

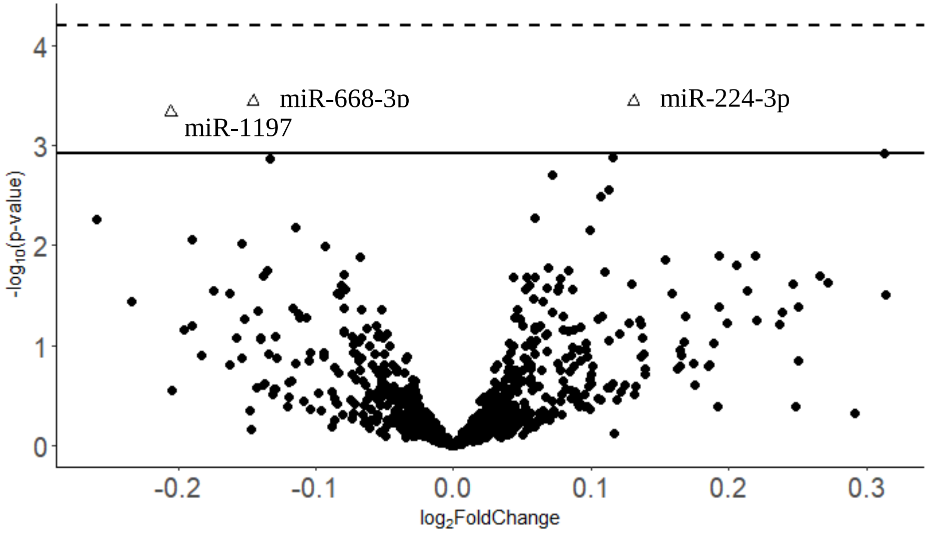

Figure 3-1: Cardiovascular Disease Polygenic Risk Scores of RICHS participants are associated with the expression of three placental miRNAs. Volcano plot representing the results of the miRNA sequencing differential expression analysis. The y-axis shows the -log$_{10}$(p-values) in the association of each miRNA with respect to the calculated CVD PRS of each participant. The x-axis displays the effect estimates in units of log$_2$ fold change in each miRNA’s transcript abundance per standard deviation change in the individual’s CVD PRS. 3 miRNAs are associated with the calculated CVD PRS (FDR < 0.15, triangle shaped); however, none are significant following Bonferroni correction (p-value < 6.29e-05).

SUPPLEMENTARY TABLES

Table S3-1: Significant differential expression analysis results

miRNA	Log2(Fold-Change)	Standard Error	p-value	FDR (%)
hsa-miR-668-3p	-0.1451	0.0407	3.62e-4	12.2
hsa-miR-224-3p	0.1312	0.0368	3.66e-4	12.2
hsa-miR-1197	-0.2053	0.0586	4.62e-4	12.2

Table S3-2: Smoking Sensitivity Analyses

miRNA	Log2(Fold-Change)	Standard Error	p-value	FDR (%)
hsa-miR-668-3p	-0.1523	0.3915	1.00e-4	7.99
hsa-miR-224-3p	0.1336	0.0371	3.17e-4	8.42
hsa-miR-1197	-0.2150	0.0586	2.43e-4	8.42

Table S3-3: Table of DEmiR Targets

mRNA Target	DEmiR
EMC7	hsa-miR-1197
ZNF501	hsa-miR-1197
TENM1	hsa-miR-1197
ADD3	hsa-miR-1197
BCL2L11	hsa-miR-1197
HS2ST1	hsa-miR-1197
MAP3K1	hsa-miR-1197
UPF3B	hsa-miR-1197
MAP3K9	hsa-miR-1197
SPOCK1	hsa-miR-1197
AK2	hsa-miR-1197
PAXBP1	hsa-miR-1197
EIF5	hsa-miR-1197
TNRC6A	hsa-miR-1197
ARGLU1	hsa-miR-1197
CBL	hsa-miR-1197
ATP6V0C	hsa-miR-1197
AGO1	hsa-miR-1197
PRPF38B	hsa-miR-1197
ARID2	hsa-miR-1197
BZW1	hsa-miR-1197
CA10	hsa-miR-1197
HAO1	hsa-miR-1197
PPARGC1B	hsa-miR-1197
ZSWIM5	hsa-miR-1197
MADD	hsa-miR-1197
PDE7A	hsa-miR-1197
CLSTN1	hsa-miR-1197
COPS2	hsa-miR-1197
OPCML	hsa-miR-1197
CCDC88A	hsa-miR-1197
MGMT	hsa-miR-1197
ELL	hsa-miR-1197
BACE2	hsa-miR-1197
KDM7A	hsa-miR-1197
FCHSD2	hsa-miR-1197
AFTPH	hsa-miR-1197
CREM	hsa-miR-1197
NMNAT2	hsa-miR-1197
TSPAN3	hsa-miR-1197
TMEM47	hsa-miR-1197
USP34	hsa-miR-1197
XPO4	hsa-miR-1197
SCN2A	hsa-miR-1197
DCX	hsa-miR-1197
GLCCI1	hsa-miR-1197
SRL	hsa-miR-1197
HNRNPAB	hsa-miR-1197
PPARGC1A	hsa-miR-1197
DDX3X	hsa-miR-1197
CMTM4	hsa-miR-1197
SESTD1	hsa-miR-1197
SYT2	hsa-miR-1197
EGR2	hsa-miR-1197
ATP1B3	hsa-miR-1197
FBXO32	hsa-miR-1197
CHST11	hsa-miR-1197
UBE4A	hsa-miR-1197
UBFD1	hsa-miR-1197
TNIK	hsa-miR-1197
PAX6	hsa-miR-1197
MARS2	hsa-miR-1197
GTDC1	hsa-miR-1197
RBFOX2	hsa-miR-1197
FARSB	hsa-miR-1197
MAT2A	hsa-miR-1197
TEAD1	hsa-miR-1197
SOCS5	hsa-miR-1197
NLK	hsa-miR-1197
HS3ST2	hsa-miR-1197
CELF1	hsa-miR-1197
POLR3K	hsa-miR-1197
NFIB	hsa-miR-1197
ANKRD17	hsa-miR-1197
HRK	hsa-miR-1197
NEO1	hsa-miR-1197
ZMYM2	hsa-miR-1197
FAM216A	hsa-miR-1197
CBX3	hsa-miR-1197
LGALSL	hsa-miR-1197
PPP1R26	hsa-miR-1197
MBNL3	hsa-miR-1197
NPEPPS	hsa-miR-1197
METAP1	hsa-miR-1197
TIMP3	hsa-miR-1197
UBAP1	hsa-miR-1197
THRB	hsa-miR-1197
KDM5A	hsa-miR-1197
REPS2	hsa-miR-1197
KLHL29	hsa-miR-1197
PICALM	hsa-miR-1197
CHCHD4	hsa-miR-1197
CTDSPL2	hsa-miR-1197
KIAA1549L	hsa-miR-1197
FRS2	hsa-miR-1197
SCG2	hsa-miR-1197
PTPN5	hsa-miR-1197
RAPGEF2	hsa-miR-1197
DRGX	hsa-miR-1197
IPO7	hsa-miR-1197
IRX6	hsa-miR-1197
PDE6C	hsa-miR-1197
ZRANB1	hsa-miR-1197
ISLR2	hsa-miR-1197
FEZ2	hsa-miR-1197
ZADH2	hsa-miR-1197
SGSM1	hsa-miR-1197
DNAJC18	hsa-miR-1197
RARB	hsa-miR-1197
TRAF7	hsa-miR-1197
LZIC	hsa-miR-1197

mRNA Target	DEmiR
CKAP5	hsa-miR-1197
SMOC2	hsa-miR-1197
ZC2HC1C	hsa-miR-1197
STAG1	hsa-miR-1197
MAPK10	hsa-miR-1197
ZC3H11A	hsa-miR-1197
SMAD3	hsa-miR-1197
ZNRF1	hsa-miR-1197
TENM3	hsa-miR-1197
CREB1	hsa-miR-1197
DAAM2	hsa-miR-1197
CD84	hsa-miR-1197
ASAH2B	hsa-miR-1197
UBE2V2	hsa-miR-1197
ZNF592	hsa-miR-1197
USP35	hsa-miR-1197
AP1G1	hsa-miR-1197
VKORC1L1	hsa-miR-1197
PURA	hsa-miR-1197
GRIK3	hsa-miR-1197
SSH1	hsa-miR-1197
MMP16	hsa-miR-1197
EHF	hsa-miR-1197
ITGB1BP1	hsa-miR-1197
TMPO	hsa-miR-1197
BTBD7	hsa-miR-1197
RAB11FIP4	hsa-miR-1197
MEIS2	hsa-miR-1197
CAV3	hsa-miR-1197
ARPP19	hsa-miR-1197
TNPO1	hsa-miR-1197
ATP2B4	hsa-miR-1197
HDAC5	hsa-miR-1197
GRIA3	hsa-miR-1197
SLC25A36	hsa-miR-1197
CLASP2	hsa-miR-1197
MOCS2	hsa-miR-1197
SH3PXD2A	hsa-miR-1197

mRNA Target	DEmiR
PLCB1	hsa-miR-1197
HOXC11	hsa-miR-1197
MEF2D	hsa-miR-1197
DYRK2	hsa-miR-1197
PTPRK	hsa-miR-1197
NKAIN2	hsa-miR-1197
TREML2	hsa-miR-1197
PRKAG2	hsa-miR-1197
AGO2	hsa-miR-1197
FTSJ1	hsa-miR-1197
MMAB	hsa-miR-1197
BCL6	hsa-miR-1197
NPAS3	hsa-miR-1197
CIAPIN1	hsa-miR-1197
CHST1	hsa-miR-1197
ID4	hsa-miR-668-3p
TOX3	hsa-miR-668-3p
GLCCI1	hsa-miR-668-3p
S100PBP	hsa-miR-668-3p
CNOT4	hsa-miR-668-3p
ABHD13	hsa-miR-668-3p
HOXB4	hsa-miR-668-3p
ATP6AP2	hsa-miR-668-3p
PCED1A	hsa-miR-668-3p
EMX2	hsa-miR-668-3p
ZBTB34	hsa-miR-668-3p
SKAP2	hsa-miR-668-3p
NEGR1	hsa-miR-668-3p
CAMK2G	hsa-miR-668-3p
PPP1R12C	hsa-miR-668-3p
EPHA4	hsa-miR-668-3p
SYNGR3	hsa-miR-668-3p
MED1	hsa-miR-668-3p
USP37	hsa-miR-668-3p
MTMR3	hsa-miR-668-3p
ZBTB5	hsa-miR-668-3p
PRKAR1A	hsa-miR-668-3p
YPEL2	hsa-miR-668-3p

mRNA Target	DEmiR
WAPL	hsa-miR-668-3p
PROX2	hsa-miR-668-3p
TUT4	hsa-miR-668-3p
LMOD3	hsa-miR-668-3p
ZMYM4	hsa-miR-668-3p
AK4	hsa-miR-668-3p
TPD52	hsa-miR-668-3p
ZBTB10	hsa-miR-668-3p
PAOX	hsa-miR-668-3p
CNPY4	hsa-miR-668-3p
CWC25	hsa-miR-668-3p
TXK	hsa-miR-668-3p
MOSPD1	hsa-miR-668-3p
LIFR	hsa-miR-668-3p
KLF3	hsa-miR-668-3p
ZZEF1	hsa-miR-668-3p
KPNA4	hsa-miR-668-3p
TRIQK	hsa-miR-668-3p
HEMK1	hsa-miR-668-3p
GNAO1	hsa-miR-668-3p
FREM2	hsa-miR-668-3p
BMS1	hsa-miR-668-3p
CTNNB1	hsa-miR-668-3p
FGD4	hsa-miR-668-3p
TLCD2	hsa-miR-668-3p
TMOD2	hsa-miR-668-3p
SP2	hsa-miR-668-3p
KITLG	hsa-miR-668-3p
CAND1	hsa-miR-668-3p
PCDH9	hsa-miR-668-3p
CANX	hsa-miR-668-3p
PHF20L1	hsa-miR-668-3p
PRRX1	hsa-miR-668-3p
BSND	hsa-miR-668-3p
EPG5	hsa-miR-668-3p
DIP2B	hsa-miR-668-3p
CDH2	hsa-miR-668-3p
GTF2I	hsa-miR-668-3p

mRNA Target	DEmiR
PRKCSH	hsa-miR-668-3p
HNRNPA1	hsa-miR-668-3p
SMUG1	hsa-miR-668-3p
LEP	hsa-miR-668-3p
TAT	hsa-miR-668-3p
PDCD7	hsa-miR-668-3p
GPR156	hsa-miR-668-3p
DNAJB5	hsa-miR-668-3p
LCMT2	hsa-miR-668-3p
RHOBTB3	hsa-miR-668-3p
POLR1D	hsa-miR-668-3p
GPR153	hsa-miR-668-3p
MAPT	hsa-miR-668-3p
SH3TC2	hsa-miR-668-3p
FBXO30	hsa-miR-668-3p
CCDC15	hsa-miR-668-3p
FP15737	hsa-miR-668-3p
CEP85	hsa-miR-668-3p
PSMF1	hsa-miR-668-3p
FTCD	hsa-miR-668-3p
TFRC	hsa-miR-668-3p
KLF12	hsa-miR-668-3p
NFATC2IP	hsa-miR-668-3p
FKTN	hsa-miR-668-3p
PAX6	hsa-miR-668-3p
RALGPS1	hsa-miR-668-3p
SYT11	hsa-miR-668-3p
FBXO3	hsa-miR-668-3p
UBE2Z	hsa-miR-668-3p
SP4	hsa-miR-668-3p
TFDP2	hsa-miR-668-3p
SMARCAD1	hsa-miR-668-3p
SPPL3	hsa-miR-668-3p
FUT8	hsa-miR-668-3p
SYNPO	hsa-miR-668-3p
PRKAA2	hsa-miR-668-3p
TM4SF1	hsa-miR-668-3p
DZIP3	hsa-miR-668-3p
BMP8B	hsa-miR-668-3p
HSPA5	hsa-miR-668-3p
STK40	hsa-miR-668-3p
MRS2	hsa-miR-668-3p
PITPNA	hsa-miR-668-3p
STOX2	hsa-miR-668-3p
ITPKB	hsa-miR-668-3p
TEAD1	hsa-miR-668-3p
CTDNEP1	hsa-miR-668-3p
ZHX3	hsa-miR-668-3p
PFKM	hsa-miR-668-3p
SLC6A14	hsa-miR-668-3p
MPZL1	hsa-miR-668-3p
ZDHHC21	hsa-miR-668-3p
LRRC57	hsa-miR-668-3p
MINDY2	hsa-miR-668-3p
HHAT	hsa-miR-668-3p
MAPK1	hsa-miR-668-3p
KBTBD11	hsa-miR-668-3p
NRAS	hsa-miR-668-3p
ACSBG1	hsa-miR-668-3p
IPO9	hsa-miR-668-3p
PDE3B	hsa-miR-668-3p
C1orf189	hsa-miR-668-3p
FAXC	hsa-miR-668-3p
POU2F2	hsa-miR-668-3p
UGGT1	hsa-miR-668-3p
ASXL1	hsa-miR-668-3p
NOL4	hsa-miR-668-3p
TRIB1	hsa-miR-668-3p
DCAF12	hsa-miR-668-3p
SANBR	hsa-miR-668-3p
FGFBP2	hsa-miR-668-3p
SYNE2	hsa-miR-668-3p
FBXO33	hsa-miR-668-3p
C11orf16	hsa-miR-668-3p
SCN2B	hsa-miR-668-3p
RCHY1	hsa-miR-668-3p
GNRHR	hsa-miR-668-3p
HM13	hsa-miR-668-3p
XIAP	hsa-miR-668-3p
NAV3	hsa-miR-668-3p
SEL1L	hsa-miR-668-3p
ANKRD33B	hsa-miR-668-3p
PCBD2	hsa-miR-668-3p
GCC1	hsa-miR-668-3p
NFIB	hsa-miR-668-3p
FAT2	hsa-miR-668-3p
GINS2	hsa-miR-668-3p
ZNF281	hsa-miR-668-3p
MMD2	hsa-miR-668-3p
STAG1	hsa-miR-668-3p
CCDC25	hsa-miR-668-3p
PTPRG	hsa-miR-668-3p
H3-5	hsa-miR-668-3p
BMT2	hsa-miR-668-3p
TCTE1	hsa-miR-668-3p
PDK3	hsa-miR-668-3p
CD28	hsa-miR-668-3p
CRACR2B	hsa-miR-668-3p
AGO3	hsa-miR-668-3p
SLC6A19	hsa-miR-668-3p
PHKA2	hsa-miR-668-3p
DOCK7	hsa-miR-224-3p
ARHGAP5	hsa-miR-224-3p
BEND4	hsa-miR-224-3p
GEM	hsa-miR-224-3p
ELAVL1	hsa-miR-224-3p
FEM1C	hsa-miR-224-3p
ETV1	hsa-miR-224-3p
NRG3	hsa-miR-224-3p
RBM47	hsa-miR-224-3p
ABI2	hsa-miR-224-3p
MYEF2	hsa-miR-224-3p
TNRC6A	hsa-miR-224-3p
RFX7	hsa-miR-224-3p

mRNA Target	DEmiR
FMR1	hsa-miR-224-3p
RNF2	hsa-miR-224-3p
AMMECR1L	hsa-miR-224-3p
DYRK1A	hsa-miR-224-3p
PHAX	hsa-miR-224-3p
ACAP2	hsa-miR-224-3p
HNRNPM	hsa-miR-224-3p
NSD2	hsa-miR-224-3p
MTDH	hsa-miR-224-3p
PPM1E	hsa-miR-224-3p
NPAT	hsa-miR-224-3p
CDK13	hsa-miR-224-3p
UBE2Q2	hsa-miR-224-3p
AKAP6	hsa-miR-224-3p
SLC39A9	hsa-miR-224-3p
SUCO	hsa-miR-224-3p
RASA1	hsa-miR-224-3p
ZNF275	hsa-miR-224-3p
TNRC6B	hsa-miR-224-3p
FLRT3	hsa-miR-224-3p
VAPA	hsa-miR-224-3p
AMMECR1	hsa-miR-224-3p
HORMAD1	hsa-miR-224-3p
ATP1B1	hsa-miR-224-3p
PHIP	hsa-miR-224-3p
RAPGEF6	hsa-miR-224-3p
CELF2	hsa-miR-224-3p
PLAG1	hsa-miR-224-3p
SCAI	hsa-miR-224-3p
EIF2A	hsa-miR-224-3p
GARRE1	hsa-miR-224-3p
CSDE1	hsa-miR-224-3p
RSBN1	hsa-miR-224-3p
CNOT6L	hsa-miR-224-3p
ZNF532	hsa-miR-224-3p
DIMT1	hsa-miR-224-3p
KCTD12	hsa-miR-224-3p
PERP	hsa-miR-224-3p
FOXP1	hsa-miR-224-3p
LRP1B	hsa-miR-224-3p
MED13	hsa-miR-224-3p
UBR3	hsa-miR-224-3p
CUL1	hsa-miR-224-3p
UBTD2	hsa-miR-224-3p
GIGYF2	hsa-miR-224-3p
SALL1	hsa-miR-224-3p
NFIB	hsa-miR-224-3p
RCAN3	hsa-miR-224-3p
ATXN7	hsa-miR-224-3p
TRPM7	hsa-miR-224-3p
ADCYAP1	hsa-miR-224-3p
WDFY3	hsa-miR-224-3p
FOXP2	hsa-miR-224-3p
SLC2A13	hsa-miR-224-3p
STAG1	hsa-miR-224-3p
ATRX	hsa-miR-224-3p
LTBP1	hsa-miR-224-3p
MBTD1	hsa-miR-224-3p
CBLL1	hsa-miR-224-3p
MYH10	hsa-miR-224-3p
PPFIA2	hsa-miR-224-3p
ZC3H7A	hsa-miR-224-3p
PPP4R3B	hsa-miR-224-3p
RBL2	hsa-miR-224-3p
TTN	hsa-miR-224-3p
SRSF12	hsa-miR-224-3p
RC3H1	hsa-miR-224-3p
MEF2C	hsa-miR-224-3p
RTN3	hsa-miR-224-3p
PTPN11	hsa-miR-224-3p
CSPG5	hsa-miR-224-3p
DYRK2	hsa-miR-224-3p
RBMX	hsa-miR-224-3p
WDTC1	hsa-miR-224-3p
RABEP1	hsa-miR-224-3p
ARHGAP29	hsa-miR-224-3p
WDR26	hsa-miR-224-3p
KMT2C	hsa-miR-224-3p
MZT1	hsa-miR-224-3p
KLHL31	hsa-miR-224-3p
JADE1	hsa-miR-224-3p
SNAP25	hsa-miR-224-3p
ATAD2B	hsa-miR-224-3p
LGI2	hsa-miR-224-3p
PRPF39	hsa-miR-224-3p
GAB2	hsa-miR-224-3p
DHFR	hsa-miR-224-3p
SVEP1	hsa-miR-224-3p
TOP1	hsa-miR-224-3p
OTUD3	hsa-miR-224-3p
PRPF4B	hsa-miR-224-3p
PHYHIPL	hsa-miR-224-3p
DNAJB6	hsa-miR-224-3p
TMED7	hsa-miR-224-3p
FUT8	hsa-miR-224-3p
UBFD1	hsa-miR-224-3p
MTMR3	hsa-miR-224-3p
HOOK3	hsa-miR-224-3p
PRKCI	hsa-miR-224-3p
MPP2	hsa-miR-224-3p
KRAS	hsa-miR-224-3p
EXOC5	hsa-miR-224-3p
MYB	hsa-miR-224-3p
SC5D	hsa-miR-224-3p
RTKN2	hsa-miR-224-3p
RAC1	hsa-miR-224-3p
YWHAQ	hsa-miR-224-3p
LCORL	hsa-miR-224-3p
C8orf34	hsa-miR-224-3p
KCNA1	hsa-miR-224-3p
CLDND1	hsa-miR-224-3p
PRKAA1	hsa-miR-224-3p
ST8SIA4	hsa-miR-224-3p
CCDC141	hsa-miR-224-3p

mRNA Target	DEmiR
USP8	hsa-miR-224-3p
VBP1	hsa-miR-224-3p
UBE2N	hsa-miR-224-3p
IL1RAP	hsa-miR-224-3p
RTF1	hsa-miR-224-3p
HMGA2	hsa-miR-224-3p
RB1CC1	hsa-miR-224-3p
RAP2A	hsa-miR-224-3p

mRNA Target	DEmiR
TXNDC9	hsa-miR-224-3p
ZNF704	hsa-miR-224-3p
SPAG9	hsa-miR-224-3p
SYNCRIP	hsa-miR-224-3p
ATXN1L	hsa-miR-224-3p
ENTPD4	hsa-miR-224-3p
RPGRIP1L	hsa-miR-224-3p
WWTR1	hsa-miR-224-3p

mRNA Target	DEmiR
JCAD	hsa-miR-224-3p
JUN	hsa-miR-224-3p
ARID5B	hsa-miR-224-3p
ZNF384	hsa-miR-224-3p
NFKBIZ	hsa-miR-224-3p
ZRANB2	hsa-miR-224-3p
C11orf58	hsa-miR-224-3p
OTUD4	hsa-miR-224-3p

REFERENCES

1. Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, Aboyans V, Adetokunboh O, Afshin A, Agrawal A, Ahmadi A, Ahmed MB, Aichour AN, Aichour MTE, Aichour I, Aiyar S, Alahdab F, Al-Aly Z, Alam K, Alam N, Alam T, Alene KA, Al-Eyadhy A, Ali SD, Alizadeh-Navaei R, Alkaabi JM, Alkerwi Aa, Alla F, Allebeck P, Allen C, Al-Raddadi R, Alsharif U, Altirkawi KA, Alvis-Guzman N, Amare AT, Amini E, Ammar W, Amoako YA, Anber N, Andersen HH, Andrei CL, Androudi S, Ansari H, Antonio CAT, Anwari P, Ärnlöv J, Arora M, Artaman A, Aryal KK, Asayesh H, Asgedom SW, Atey TM, Avila-Burgos L, Avokpaho EFG, Awasthi A, Babalola TK, Bacha U, Balakrishnan K, Barac A, Barboza MA, Barker-Collo SL, Barquera S, Barregard L, Barrero LH, Baune BT, Bedi N, Beghi E, Béjot Y, Bekele BB, Bell ML, Bennett JR, Bensenor IM, Berhane A, Bernabé E, Betsu BD, Beuran M, Bhatt S, Biadgilign S, Bienhoff K, Bikbov B, Bisanzio D, Bourne RRA, Breitborde NJK, Bulto LNB, Bumgarner BR, Butt ZA, Cahuana-Hurtado L, Cameron E, Campuzano JC, Car J, Cárdenas R, Carrero JJ, Carter A, Casey DC, Castañeda-Orjuela CA, Catalá-López F, Charlson FJ, Chibueze CE, Chimed-Ochir O, Chisumpa VH, Chitheer AA, Christopher DJ, Ciobanu LG, Cirillo M, Cohen AJ, Colombara D, Cooper C, Cowie BC, Criqui MH, Dandona L, Dandona R, Dargan PI, das Neves J, Davitoiu DV, Davletov K, de Courten B, Defo BK, Degenhardt L, Deiparine S, Deribe K, Deribew A, Dey S, Dicker D, Ding EL, Djalalinia S, Do HP, Doku DT, Douwes-Schultz D, Driscoll TR, Dubey M, Duncan BB, Echko M, El-Khatib ZZ, Ellingsen CL, Enayati A, Ermakov SP, Erskine HE, Eskandarieh S, Esteghamati A, Estep K, Farinha CSeS, Faro A, Farzadfar F, Feigin VL, Fereshtehnejad S-M, Fernandes JC, Ferrari AJ, Feyissa TR, Filip I, Finegold S, Fischer F, Fitzmaurice C, Flaxman AD, Foigt N, Frank T, Fraser M, Fullman N, Fürst T, Furtado JM, Gakidou E, Garcia-Basteiro AL, Gebre T, Gebregergs GB, Gebrehiwot TT, Gebremichael DY, Geleijnse JM, Genova-Maleras R, Gesesew HA, Gething PW, Gillum RF, Giref AZ, Giroud M, Giussani G, Godwin WW, Gold AL, Goldberg EM, Gona PN, Gopalani SV, Gouda HN, Goulart AC, Griswold M, Gupta R, Gupta T, Gupta V, Gupta PC, Haagsma JA, Hafezi-Nejad N, Hailu AD, Hailu GB, Hamadeh RR, Hambisa MT, Hamidi S, Hammami M, Hancock J, Handal AJ, Hankey GJ, Hao Y, Harb HL, Hareri HA, Hassanvand MS, Havmoeller R, Hay SI, He F, Hedayati MT, Henry NJ, Heredia-Pi IB, Herteliu C, Hoek HW, Horino M, Horita N, Hosgood HD, Hostiuc S, Hotez PJ, Hoy DG, Huynh C, Iburg KM, Ikeda C, Ileanu BV, Irenso AA, Irvine CMS, Islam SMS, Jacobsen KH, Jahanmehr N, Jakovljevic MB, Javanbakht M, Jayaraman SP, Jeemon P, Jha V, John D, Johnson CO, Johnson SC, Jonas JB, Jürisson M, Kabir Z, Kadel R, Kahsay A, Kamal R, Karch A, Karimi SM, Karimkhani C, Kasaeian A, Kassaw NA, Kassebaum NJ, Katikireddi SV, Kawakami N, Keiyoro PN, Kemmer L, Kesavachandran CN, Khader YS, Khan EA, Khang Y-H, Khoja ATA, Khosravi MH, Khosravi A, Khubchandani J, Kiadaliri AA, Kieling C, Kievlan D, Kim YJ, Kim D, Kimokoti RW, Kinfu Y, Kissoon N, Kivimaki M, Knudsen AK, Kopec JA, Kosen S, Koul PA, Koyanagi A, Kulikoff XR, Kumar GA, Kumar P, Kutz M, Kyu HH, Lal DK, Lalloo R, Lambert TLN, Lan Q, Lansingh VC, Larsson A, Lee PH, Leigh J, Leung J, Levi M, Li Y, Li Kappe D, Liang X, Liben ML, Lim SS, Liu PY, Liu A, Liu Y, Lodha R, Logroscino G, Lorkowski S, Lotufo PA, Lozano R, Lucas TCD, Ma S, Macarayan ERK, Maddison ER, Magdy Abd El Razek M, Majdan M, Majdzadeh R, Majeed A, Malekzadeh R, Malhotra R, Malta DC, Manguerra H, Manyazewal T, Mapoma CC, Marczak LB, Markos D, Martinez-Raga J, Martins-Melo FR, Martopullo I, McAlinden C, McGaughey M, McGrath JJ, Mehata S, Meier T, Meles KG,

Memiah P, Memish ZA, Mengesha MM, Mengistu DT, Menota BG, Mensah GA, Meretoja TJ, Meretoja A, Millear A, Miller TR, Minnig S, Mirarefin M, Mirrakhimov EM, Misganaw A, Mishra SR, Mohamed IA, Mohammad KA, Mohammadi A, Mohammed S, Mokdad AH, Mola GLD, Mollenkopf SK, Molokhia M, Monasta L, Montañez JC, Montico M, Mooney MD, Moradi-Lakeh M, Moraga P, Morawska L, Morozoff C, Morrison SD, Mountjoy-Venning C, Mruts KB, Muller K, Murthy GVS, Musa KI, Nachega JB, Naheed A, Naldi L, Nangia V, Nascimento BR, Nasher JT, Natarajan G, Negoi I, Ngunjiri JW, Nguyen CT, Nguyen QL, Nguyen TH, Nguyen G, Nguyen M, Nichols E, Ningrum DNA, Nong VM, Noubiap JJN, Ogbo FA, Oh I-H, Okoro A, Olagunju AT, Olsen HE, Olusanya BO, Olusanya JO, Ong K, Opio JN, Oren E, Ortiz A, Osman M, Ota E, Pa M, Pacella RE, Pakhale S, Pana A, Panda BK, Panda-Jonas S, Papachristou C, Park E-K, Patten SB, Patton GC, Paudel D, Paulson K, Pereira DM, Perez-Ruiz F, Perico N, Pervaiz A, Petzold M, Phillips MR, Pigott DM, Pinho C, Plass D, Pletcher MA, Polinder S, Postma MJ, Pourmalek F, Purcell C, Qorbani M, Quintanilla BPA, Radfar A, Rafay A, Rahimi-Movaghar V, Rahman MHU, Rahman M, Rai RK, Ranabhat CL, Rankin Z, Rao PC, Rath GK, Rawaf S, Ray SE, Rehm J, Reiner RC, Reitsma MB, Remuzzi G, Rezaei S, Rezai MS, Rokni MB, Ronfani L, Roshandel G, Roth GA, Rothenbacher D, Ruhago GM, Sa R, Saadat S, Sachdev PS, Sadat N, Safdarian M, Safi S, Safiri S, Sagar R, Sahathevan R, Salama J, Salamati P, Salomon JA, Samy AM, Sanabria JR, Sanchez-Niño MD, Santomauro D, Santos IS, Santric Milicevic MM, Sartorius B, Satpathy M, Schmidt MI, Schneider IJC, Schulhofer-Wohl S, Schutte AE, Schwebel DC, Schwendicke F, Sepanlou SG, Servan-Mori EE, Shackelford KA, Shahraz S, Shaikh MA, Shamsipour M, Shamsizadeh M, Sharma J, Sharma R, She J, Sheikhbahaei S, Shey M, Shi P, Shields C, Shigematsu M, Shiri R, Shirude S, Shiue I, Shoman H, Shrime MG, Sigfusdottir ID, Silpakit N, Silva JP, Singh JA, Singh A, Skiadaresi E, Sligar A, Smith DL, Smith A, Smith M, Sobaih BHA, Soneji S, Sorensen RJD, Soriano JB, Sreeramareddy CT, Srinivasan V, Stanaway JD, Stathopoulou V, Steel N, Stein DJ, Steiner C, Steinke S, Stokes MA, Strong M, Strub B, Subart M, Sufiyan MB, Sunguya BF, Sur PJ, Swaminathan S, Sykes BL, Tabarés-Seisdedos R, Tadakamadla SK, Takahashi K, Takala JS, Talongwa RT, Tarawneh MR, Tavakkoli M, Taveira N, Tegegne TK, Tehrani-Banihashemi A, Temsah M-H, Terkawi AS, Thakur JS, Thamsuwan O, Thankappan KR, Thomas KE, Thompson AH, Thomson AJ, Thrift AG, Tobe-Gai R, Topor-Madry R, Torre A, Tortajada M, Towbin JA, Tran BX, Troeger C, Truelsen T, Tsoi D, Tuzcu EM, Tyrovolas S, Ukwaja KN, Undurraga EA, Updike R, Uthman OA, Uzochukwu BSC, van Boven JFM, Vasankari T, Venketasubramanian N, Violante FS, Vlassov VV, Vollset SE, Vos T, Wakayo T, Wallin MT, Wang Y-P, Weiderpass E, Weintraub RG, Weiss DJ, Werdecker A, Westerman R, Whetter B, Whiteford HA, Wijeratne T, Wiysonge CS, Woldeyes BG, Wolfe CDA, Woodbrook R, Workicho A, Xavier D, Xiao Q, Xu G, Yaghoubi M, Yakob B, Yano Y, Yaseri M, Yimam HH, Yonemoto N, Yoon S-J, Yotebieng M, Younis MZ, Zaidi Z, Zaki MES, Zegeye EA, Zenebe ZM, Zerfu TA, Zhang AL, Zhang X, Zipkin B, Zodpey S, Lopez AD, Murray CJL. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017;390(10100):1151-210. doi: 10.1016/s0140-6736(17)32152-9.

2. Khavjou O PD, Leib A. . Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035: Technical Report. . RTI International. 2016. Epub November 2016.

3. Sing CF, Stengård JH, Kardia SL. Genes, environment, and cardiovascular disease. Arterioscler Thromb Vasc Biol. 2003;23(7):1190-6. Epub 2003/05/06. doi: 10.1161/01.Atv.0000075081.51227.86. PubMed PMID: 12730090.
4. Christensen JJ, Retterstol K, Godang K, Roland MC, Qvigstad E, Bollerslev J, Ueland T, Henriksen T, Holven KB. LDL cholesterol in early pregnancy and offspring cardiovascular disease risk factors. J Clin Lipidol. 2016;10(6):1369-78 e7. Epub 2016/12/07. doi: 10.1016/j.jacl.2016.08.016. PubMed PMID: 27919354.
5. Alsnes IV, Vatten LJ, Fraser A, Bjorngaard JH, Rich-Edwards J, Romundstad PR, Asvold BO. Hypertension in Pregnancy and Offspring Cardiovascular Risk in Young Adulthood: Prospective and Sibling Studies in the HUNT Study (Nord-Trondelag Health Study) in Norway. Hypertension. 2017;69(4):591-8. Epub 2017/02/23. doi: 10.1161/HYPERTENSIONAHA.116.08414. PubMed PMID: 28223467.
6. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet. 1986;1(8489):1077-81. Epub 1986/05/10. doi: 10.1016/s0140-6736(86)91340-1. PubMed PMID: 2871345.
7. Cross JC, Baczyk D, Dobric N, Hemberger M, Hughes M, Simmons DG, Yamamoto H, Kingdom JC. Genes, development and evolution of the placenta. Placenta. 2003;24(2-3):123-30. Epub 2003/02/25. doi: 10.1053/plac.2002.0887. PubMed PMID: 12596737.
8. Audette MC, Kingdom JC. Screening for fetal growth restriction and placental insufficiency. Semin Fetal Neonatal Med. 2018;23(2):119-25. Epub 2017/12/10. doi: 10.1016/j.siny.2017.11.004. PubMed PMID: 29221766.
9. D.J Barker CO. Low birth weight and hypertension. BMJ. 1988.
10. D.J Barker PDW, B. Margetts, C. Osmond, S.J Simmonds. Weight in Infancy and Death from Ischemic Heart Disease. The Lancet. 1989.
11. Cohen JA, Rychik J, Savla JJ. The placenta as the window to congenital heart disease. Curr Opin Cardiol. 2020. Epub 2020/10/20. doi: 10.1097/HCO.0000000000000816. PubMed PMID: 33074934.
12. Camm EJ, Botting KJ, Sferruzzi-Perri AN. Near to One's Heart: The Intimate Relationship Between the Placenta and Fetal Heart. Front Physiol. 2018;9:629. Epub 2018/07/13. doi: 10.3389/fphys.2018.00629. PubMed PMID: 29997513; PMCID: PMC6029139.
13. Azhar M, Runyan RB, Gard C, Sanford LP, Miller ML, Andringa A, Pawlowski S, Rajan S, Doetschman T. Ligand-specific function of transforming growth factor beta in epithelial-mesenchymal transition in heart development. Dev Dyn. 2009;238(2):431-42. Epub 2009/01/24. doi: 10.1002/dvdy.21854. PubMed PMID: 19161227; PMCID: PMC2805850.
14. Ghosh A, Dutta R, Sarkar A. Heritability estimation of conventional cardiovascular disease risk factors in Asian Indian families: The Calcutta family study. Indian J Hum Genet. 2010;16(1):28-32. Epub 2010/09/15. doi: 10.4103/0971-6866.64944. PubMed PMID: 20838489; PMCID: PMC2927791.
15. Peng S, Deyssenroth MA, Di Narzo AF, Cheng H, Zhang Z, Lambertini L, Ruusalepp A, Kovacic JC, Bjorkegren JLM, Marsit CJ, Chen J, Hao K. Genetic regulation of the placental transcriptome underlies birth weight and risk of childhood obesity. PLOS Genetics. 2019;14(12):e1007799. doi: 10.1371/journal.pgen.1007799.
16. Bhattacharya A, Freedman AN, Avula V, Harris R, Liu W, Pan C, Lusis AJ, Joseph RM, Smeester L, Hartwell HJ, Kuban KCK, Marsit CJ, Li Y, O'Shea TM, Fry RC, Santos HP, Jr.

Placental genomics mediates genetic associations with complex health traits and disease. Nat Commun. 2022;13(1):706. Epub 2022/02/06. doi: 10.1038/s41467-022-28365-x. PubMed PMID: 35121757.

17. Cammaerts S, Strazisar M, De Rijk P, Del Favero J. Genetic variants in microRNA genes: impact on microRNA expression, function, and disease. Frontiers in Genetics. 2015;6. doi: 10.3389/fgene.2015.00186.

18. Han M, Zheng Y. Comprehensive Analysis of Single Nucleotide Polymorphisms in Human MicroRNAs. PLOS ONE. 2013;8(11):e78028. doi: 10.1371/journal.pone.0078028.

19. Rayner KJ, Esau CC, Hussain FN, McDaniel AL, Marshall SM, van Gils JM, Ray TD, Sheedy FJ, Goedeke L, Liu X, Khatsenko OG, Kaimal V, Lees CJ, Fernandez-Hernando C, Fisher EA, Temel RE, Moore KJ. Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. Nature. 2011;478(7369):404-7. doi: 10.1038/nature10486.

20. Rayner KJ, Sheedy FJ, Esau CC, Hussain FN, Temel RE, Parathath S, van Gils JM, Rayner AJ, Chang AN, Suarez Y, Fernandez-Hernando C, Fisher EA, Moore KJ. Antagonism of miR-33 in mice promotes reverse cholesterol transport and regression of atherosclerosis. The Journal of Clinical Investigation. 2011;121(7):2921-31. doi: 10.1172/JCI57275.

21. Ostling H, Kruse R, Helenius G, Lodefalk M. Placental expression of microRNAs in infants born small for gestational age. Placenta. 2019;81:46-53. Epub 2019/05/30. doi: 10.1016/j.placenta.2019.05.001. PubMed PMID: 31138431.

22. Thamotharan S, Chu A, Kempf K, Janzen C, Grogan T, Elashoff DA, Devaskar SU. Differential microRNA expression in human placentas of term intra-uterine growth restriction that regulates target genes mediating angiogenesis and amino acid transport. PLoS One. 2017;12(5):e0176493. Epub 2017/05/04. doi: 10.1371/journal.pone.0176493. PubMed PMID: 28463968; PMCID: PMC5413012.

23. Meng M, Cheng YKY, Wu L, Chaemsaithong P, Leung MBW, Chim SSC, Sahota DS, Li W, Poon LCY, Wang CC, Leung TY. Whole genome miRNA profiling revealed miR-199a as potential placental pathogenesis of selective fetal growth restriction in monochorionic twin pregnancies. Placenta. 2020;92:44-53. Epub 2020/02/18. doi: 10.1016/j.placenta.2020.02.002. PubMed PMID: 32063549.

24. Wang D, Na Q, Song WW, Song GY. Altered Expression of miR-518b and miR-519a in the placenta is associated with low fetal birth weight. Am J Perinatol. 2014;31(9):729-34. Epub 2014/04/01. doi: 10.1055/s-0033-1361832. PubMed PMID: 24683074.

25. Awamleh Z, Gloor GB, Han VKM. Placental microRNAs in pregnancies with early onset intrauterine growth restriction and preeclampsia: potential impact on gene expression and pathophysiology. BMC Med Genomics. 2019;12(1):91. Epub 2019/06/30. doi: 10.1186/s12920-019-0548-x. PubMed PMID: 31248403; PMCID: PMC6598374.

26. Higashijima A, Miura K, Mishima H, Kinoshita A, Jo O, Abe S, Hasegawa Y, Miura S, Yamasaki K, Yoshida A, Yoshiura K, Masuzaki H. Characterization of placenta-specific microRNAs in fetal growth restriction pregnancy. Prenat Diagn. 2013;33(3):214-22. Epub 2013/01/29. doi: 10.1002/pd.4045. PubMed PMID: 23354729.

27. Sharma D, Sharma P, Shastri S. Genetic, metabolic and endocrine aspect of intrauterine growth restriction: an update. J Matern Fetal Neonatal Med. 2017;30(19):2263-75. Epub 2016/10/11. doi: 10.1080/14767058.2016.1245285. PubMed PMID: 27718783.

28. Williams PJ, Broughton Pipkin F. The genetics of pre-eclampsia and other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol. 2011;25(4):405-17. Epub 2011/03/25. doi: 10.1016/j.bpobgyn.2011.02.007. PubMed PMID: 21429808; PMCID: PMC3145161.
29. Elliott J, Bodinier B, Bond TA, Chadeau-Hyam M, Evangelou E, Moons KGM, Dehghan A, Muller DC, Elliott P, Tzoulaki I. Predictive Accuracy of a Polygenic Risk Score–Enhanced Prediction Model vs a Clinical Risk Score for Coronary Artery Disease. JAMA. 2020;323(7):636-45. doi: 10.1001/jama.2019.22241.
30. Tokar T, Pastrello C, Rossos AEM, Abovsky M, Hauschild AC, Tsay M, Lu R, Jurisica I. mirDIP 4.1-integrative database of human microRNA target predictions. Nucleic Acids Res. 2018;46(D1):D360-D70. Epub 2017/12/02. doi: 10.1093/nar/gkx1144. PubMed PMID: 29194489; PMCID: PMC5753284.
31. Kamburov A, Pentchev K, Galicka H, Wierling C, Lehrach H, Herwig R. ConsensusPathDB: toward a more complete picture of cell biology. Nucleic Acids Res. 2011;39(Database issue):D712-7. Epub 2010/11/13. doi: 10.1093/nar/gkq1156. PubMed PMID: 21071422; PMCID: PMC3013724.
32. Kamburov A, Wierling C, Lehrach H, Herwig R. ConsensusPathDB--a database for integrating human functional interaction networks. Nucleic Acids Res. 2009;37(Database issue):D623-8. Epub 2008/10/23. doi: 10.1093/nar/gkn698. PubMed PMID: 18940869; PMCID: PMC2686562.
33. Kennedy EM, Hermetz K, Burt A, Everson TM, Deyssenroth M, Hao K, Chen J, Karagas MR, Pei D, Koestler DC, Marsit CJ. Placental microRNA expression associates with birthweight through control of adipokines: results from two independent cohorts. Epigenetics. 2020:1-13. Epub 2020/10/06. doi: 10.1080/15592294.2020.1827704. PubMed PMID: 33016211.
34. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, Webb TR, Zeng L, Dehghan A, Alver M, Armasu SM, Auro K, Bjonnes A, Chasman DI, Chen S, Ford I, Franceschini N, Gieger C, Grace C, Gustafsson S, Huang J, Hwang SJ, Kim YK, Kleber ME, Lau KW, Lu X, Lu Y, Lyytikainen LP, Mihailov E, Morrison AC, Pervjakova N, Qu L, Rose LM, Salfati E, Saxena R, Scholz M, Smith AV, Tikkanen E, Uitterlinden A, Yang X, Zhang W, Zhao W, de Andrade M, de Vries PS, van Zuydam NR, Anand SS, Bertram L, Beutner F, Dedoussis G, Frossard P, Gauguier D, Goodall AH, Gottesman O, Haber M, Han BG, Huang J, Jalilzadeh S, Kessler T, Konig IR, Lannfelt L, Lieb W, Lind L, Lindgren CM, Lokki ML, Magnusson PK, Mallick NH, Mehra N, Meitinger T, Memon FU, Morris AP, Nieminen MS, Pedersen NL, Peters A, Rallidis LS, Rasheed A, Samuel M, Shah SH, Sinisalo J, Stirrups KE, Trompet S, Wang L, Zaman KS, Ardissino D, Boerwinkle E, Borecki IB, Bottinger EP, Buring JE, Chambers JC, Collins R, Cupples LA, Danesh J, Demuth I, Elosua R, Epstein SE, Esko T, Feitosa MF, Franco OH, Franzosi MG, Granger CB, Gu D, Gudnason V, Hall AS, Hamsten A, Harris TB, Hazen SL, Hengstenberg C, Hofman A, Ingelsson E, Iribarren C, Jukema JW, Karhunen PJ, Kim BJ, Kooner JS, Kullo IJ, Lehtimaki T, Loos RJF, Melander O, Metspalu A, Marz W, Palmer CN, Perola M, Quertermous T, Rader DJ, Ridker PM, Ripatti S, Roberts R, Salomaa V, Sanghera DK, Schwartz SM, Seedorf U, Stewart AF, Stott DJ, Thiery J, Zalloua PA, O'Donnell CJ, Reilly MP, Assimes TL, Thompson JR, Erdmann J, Clarke R, Watkins H, Kathiresan S, McPherson R, Deloukas P, Schunkert H, Samani NJ, Farrall M. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis

of coronary artery disease. Nat Genet. 2015;47(10):1121-30. Epub 2015/09/08. doi: 10.1038/ng.3396. PubMed PMID: 26343387; PMCID: PMC4589895.

35. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, Cortes A, Welsh S, Young A, Effingham M, McVean G, Leslie S, Allen N, Donnelly P, Marchini J. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562(7726):203-9. Epub 2018/10/12. doi: 10.1038/s41586-018-0579-z. PubMed PMID: 30305743; PMCID: PMC6786975 Peptide Groove LLP. G.M. and P.D. are founders and directors of Genomics Plc. The remaining authors declare no competing financial interests.

36. Hogg DR, Harries LW. Human genetic variation and its effect on miRNA biogenesis, activity and function. Biochem Soc Trans. 2014;42(4):1184-9. Epub 2014/08/12. doi: 10.1042/bst20140055. PubMed PMID: 25110023.

37. Huan T, Rong J, Tanriverdi K, Meng Q, Bhattacharya A, McManus DD, Joehanes R, Assimes TL, McPherson R, Samani NJ, Erdmann J, Schunkert H, Courchesne P, Munson PJ, Johnson AD, O'Donnell CJ, Zhang B, Larson MG, Freedman JE, Levy D, Yang X. Dissecting the roles of microRNAs in coronary heart disease via integrative genomic analyses. Arteriosclerosis, thrombosis, and vascular biology. 2015;35(4):1011-21. Epub 2015/02/05. doi: 10.1161/ATVBAHA.114.305176. PubMed PMID: 25657313.

38. Peng S, Deyssenroth MA, Di Narzo AF, Cheng H, Zhang Z, Lambertini L, Ruusalepp A, Kovacic JC, Bjorkegren JLM, Marsit CJ, Chen J, Hao K. Genetic regulation of the placental transcriptome underlies birth weight and risk of childhood obesity. PLoS Genet. 2018;14(12):e1007799-e. doi: 10.1371/journal.pgen.1007799. PubMed PMID: 30596636.

39. Qin B, Lu Z. GW29-e0233 Analysis of microRNA expression profile in apoptotic endothelial cells induced by ox-LDL. Journal of the American College of Cardiology. 2018;72(16_Supplement):C78-C. doi: 10.1016/j.jacc.2018.08.435.

40. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell. 1998;92(6):829-39. Epub 1998/04/07. doi: 10.1016/s0092-8674(00)81410-5. PubMed PMID: 9529258.

41. Corona J, Duchen M. PPARgamma and PGC-1alpha as therapeutic targets in Parkinson’s. Neurochemical Research. 2015;40:308-16.

42. Xie X, Gao H, Zeng W, Chen S, Feng L, Deng D, Qiao FY, Liao L, McCormick K, Ning Q, Luo X. Placental DNA methylation of peroxisome-proliferator-activated receptor-γ co-activator-1α promoter is associated with maternal gestational glucose level. Clin Sci (Lond). 2015;129(4):385-94. Epub 2015/04/16. doi: 10.1042/cs20140688. PubMed PMID: 25875376.

43. Höck J, Weinmann L, Ender C, Rüdel S, Kremmer E, Raabe M, Urlaub H, Meister G. Proteomic and functional analysis of Argonaute-containing mRNA-protein complexes in human cells. EMBO Rep. 2007;8(11):1052-60. Epub 2007/10/13. doi: 10.1038/sj.embor.7401088. PubMed PMID: 17932509; PMCID: PMC2247381.

44. Dueck A, Ziegler C, Eichner A, Berezikov E, Meister G. microRNAs associated with the different human Argonaute proteins. Nucleic Acids Res. 2012;40(19):9850-62. Epub 2012/07/31. doi: 10.1093/nar/gks705. PubMed PMID: 22844086; PMCID: PMC3479175.

45. Kim YR, Ryu CS, Kim JO, An HJ, Cho SH, Ahn EH, Kim JH, Lee WS, Kim NK. Association study of AGO1 and AGO2 genes polymorphisms with recurrent pregnancy loss. Scientific Reports. 2019;9(1):15591. doi: 10.1038/s41598-019-52073-0.

46. Hastie R, Brownfoot FC, Pritchard N, Hannan NJ, Cannon P, Nguyen V, Palmer K, Beard S, Tong S, Kaitu'u-Lino TJ. EGFR (Epidermal Growth Factor Receptor) Signaling and the Mitochondria Regulate sFlt-1 (Soluble FMS-Like Tyrosine Kinase-1) Secretion. Hypertension. 2019;73(3):659-70. Epub 2019/01/15. doi: 10.1161/HYPERTENSIONAHA.118.12300. PubMed PMID: 30636550.

47. Faxén M, Nasiell J, Blanck A, Nisell H, Lunell NO. Altered mRNA expression pattern of placental epidermal growth factor receptor (EGFR) in pregnancies complicated by preeclampsia and/or intrauterine growth retardation. Am J Perinatol. 1998;15(1):9-13. Epub 1998/02/25. doi: 10.1055/s-2007-993890. PubMed PMID: 9475680.

48. Fondacci C, Alsat E, Gabriel R, Blot P, Nessmann C, Evain-Brion D. Alterations of human placental epidermal growth factor receptor in intrauterine growth retardation. The Journal of Clinical Investigation. 1994;93(3):1149-55. doi: 10.1172/JCI117067.

49. Wöhrle FU, Daly RJ, Brummer T. Function, regulation and pathological roles of the Gab/DOS docking proteins. Cell Communication and Signaling. 2009;7(1):22. doi: 10.1186/1478-811X-7-22.

50. Wee P, Wang Z. Epidermal Growth Factor Receptor Cell Proliferation Signaling Pathways. Cancers (Basel). 2017;9(5). Epub 2017/05/18. doi: 10.3390/cancers9050052. PubMed PMID: 28513565; PMCID: PMC5447962.

51. Scott H, Phillips Tom J, Stuart Greer C, Rogers Mark F, Steinkraus Bruno R, Grant S, Case CP. Preeclamptic placentae release factors that damage neurons: implications for foetal programming of disease. Neuronal Signaling. 2018;2(4). doi: 10.1042/ns20180139.

52. Figueras F, Oros D, Cruz-Martinez R, Padilla N, Hernandez-Andrade E, Botet F, Costas-Moragas C, Gratacos E. Neurobehavior in term, small-for-gestational age infants with normal placental function. Pediatrics. 2009;124(5):e934-41. Epub 2009/10/28. doi: 10.1542/peds.2008-3346. PubMed PMID: 19858151.

53. Lester BM, Marsit CJ. Epigenetic mechanisms in the placenta related to infant neurodevelopment. Epigenomics. 2018;10(3):321-33. Epub 2018/01/31. doi: 10.2217/epi-2016-0171. PubMed PMID: 29381081; PMCID: PMC6219448.

54. Rosenfeld CS. The placenta-brain-axis. J Neurosci Res. 2021;99(1):271-83. Epub 2020/02/29. doi: 10.1002/jnr.24603. PubMed PMID: 32108381; PMCID: PMC7483131.

55. Shallie PD, Naicker T. The placenta as a window to the brain: A review on the role of placental markers in prenatal programming of neurodevelopment. Int J Dev Neurosci. 2019;73:41-9. Epub 2019/01/12. doi: 10.1016/j.ijdevneu.2019.01.003. PubMed PMID: 30634053.

56. Lesseur C, Armstrong DA, Paquette AG, Koestler DC, Padbury JF, Marsit CJ. Tissue-specific Leptin promoter DNA methylation is associated with maternal and infant perinatal factors. Mol Cell Endocrinol. 2013;381(1-2):160-7. Epub 2013/08/06. doi: 10.1016/j.mce.2013.07.024. PubMed PMID: 23911897; PMCID: PMC3795868.

57. Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, Vrieze SI, Chew EY, Levy S, McGue M, Schlessinger D, Stambolian D, Loh PR, Iacono WG, Swaroop A, Scott LJ, Cucca F, Kronenberg F, Boehnke M, Abecasis GR, Fuchsberger C. Next-generation genotype imputation service and methods. Nat Genet. 2016;48(10):1284-7. Epub 2016/08/30. doi: 10.1038/ng.3656. PubMed PMID: 27571263; PMCID: PMC5157836.

58. Friedlander MR, Mackowiak SD, Li N, Chen W, Rajewsky N. miRDeep2 accurately identifies known and hundreds of novel microRNA genes in seven animal clades. Nucleic Acids Res. 2012;40(1):37-52. Epub 2011/09/14. doi: 10.1093/nar/gkr688. PubMed PMID: 21911355; PMCID: PMC3245920.
59. Langmead B, Trapnell C, Pop M, Salzberg SL. Ultrafast and memory-efficient alignment of short DNA sequences to the human genome. Genome Biol. 2009;10(3):R25. Epub 2009/03/06. doi: 10.1186/gb-2009-10-3-r25. PubMed PMID: 19261174; PMCID: PMC2690996.
60. Griffiths-Jones S, Saini HK, van Dongen S, Enright AJ. miRBase: tools for microRNA genomics. Nucleic Acids Res. 2008;36(Database issue):D154-8. Epub 2007/11/10. doi: 10.1093/nar/gkm952. PubMed PMID: 17991681; PMCID: PMC2238936.
61. Anders S, Huber W. Differential expression analysis for sequence count data. Genome Biology. 2010;11(10):R106. doi: 10.1186/gb-2010-11-10-r106.
62. Leek JT. svaseq: removing batch effects and other unwanted noise from sequencing data. Nucleic Acids Res. 2014;42(21). Epub 2014/10/09. doi: 10.1093/nar/gku864. PubMed PMID: 25294822; PMCID: PMC4245966.
63. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biology. 2014;15(12):550. doi: 10.1186/s13059-014-0550-8.
64. Tokar T, Pastrello C, Rossos AEM, Abovsky M, Hauschild A-C, Tsay M, Lu R, Jurisica I. mirDIP 4.1-integrative database of human microRNA target predictions. Nucleic acids research. 2018;46(D1):D360-D70. doi: 10.1093/nar/gkx1144. PubMed PMID: 29194489.

Chapter 4 - Human placental microRNAs dysregulated by cadmium exposure predict neurobehavioral outcomes at birth

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ABSTRACT

Background: Prenatal cadmium (Cd) exposure has been implicated in both placental toxicity and adverse neurobehavioral outcomes. Placental microRNAs (miRNAs) may function to developmentally program adverse pregnancy and newborn health outcomes in response to gestational Cd exposure.

Methods: In a subset of the Rhode Island Child Health Study (RICHS, n=115) and the New Hampshire Birth Cohort Study (NHBCS, =281), we used small RNA sequencing and trace metal analysis to identify Cd-associated expression of placental miRNAs using negative binomial generalized linear models. We predicted mRNAs targeted by Cd-associated miRNAs and relate them to neurobehavioral outcomes at birth through the integration of transcriptomic data and summary scores from the NICU Network Neurobehavioral Scale (NNNS).

Results: Placental Cd concentrations are significantly associated with the expression level of five placental miRNAs in NHBCS, with similar effect sizes in RICHS. The targets of these miRNA are overrepresented in nervous system development, and the expression of these miRNAs are correlated with NNNS metrics suggestive of atypical neurobehavioral outcomes at birth.

Conclusions: Gestational Cd exposure is associated with the expression of placental miRNAs. Predicted targets of these miRNAs are involved in nervous system development and may also regulate placental physiology, allowing their dysregulation to modify developmental programming of newborn and early life health outcomes.

IMPACTS:

- This research aims to address the poor understanding of the molecular mechanisms governing adverse pregnancy and newborn health outcomes in response to Gestational cadmium (Cd) exposure.
- Our results outline a robust relationship between Cd-associated placental microRNA expression and NICU Network Neurobehavioral Scales (NNNS) at birth indicative of atypical neurobehavior.
- This study utilized healthy mother-infant cohorts to describe the role of Cd-associated dysregulation of placental microRNAs as a potential mechanism by which adverse neurobehavioral outcomes are developmentally programmed.

INTRODUCTION

Toxic metal exposure during pregnancy can influence fetal development, and may have lifelong consequences to offspring health. Ranked 7th on the Agency for Toxic Substances and Disease Registry list of environmental toxicants, cadmium (Cd) remains a prominent public health concern. Cd is a naturally occurring, ubiquitous environmental toxicant with no known biological role in humans (1). As a result of various industrial and agricultural processes, Cd exposure has dramatically increased over the last several decades (1). Exposure primarily occurs through the consumption of contaminated foods and drinking water, with well-water posing an increased risk of exposure, in addition to the inhalation of cigarette smoke and other occupational-related exposures(2). Chronic exposure to Cd is known to negatively impact overall cardiovascular health, renal function, and increases overall risk of mortality resulting from various cancers (3-5).

Prenatal Cd exposure poses a particularly unique health risk as Cd can accumulate within the placenta itself and does not readily enter fetal circulation, potentially influencing both fetal and maternal health through placental impacts(6). Resting at the interface of the maternal and fetal environment, the placenta participates in a variety of molecular processes, including gas and waste exchange, nutrient transport, immunomodulation, and endocrine signaling (7). As a central vascular organ of fetal growth and development, proper functionality of the placenta remains critical to successful gestational outcomes.

Gestational Cd exposure is associated with adverse pregnancy and birth outcomes including: decreased overall placental efficiency, and increased risk of preeclampsia and low birth weight (6, 8-10). A growing body of evidence suggests that the atypical neurobehavioral outcomes and intellectual deficits seen in children exposed to Cd *in utero* are linked to Cd levels in cord blood and maternal circulation during pregnancy (10-14). Given the placenta's ability to produce neurotransmitters and its involvement in supporting fetal brain development, these data suggest that gestational Cd may affect exposure as a potential mediator of neurodevelopment by acting through the placenta (15-17). In support of this hypothesis, our group has demonstrated that a doubling of placental Cd concentration was associated with an over 2-fold increased risk of a newborn being classified in a NICU Network Neurobehavioral Network Scales (NNNS) profile that is considered atypical (14). While the exact molecular mechanisms that underlie these relationships remain unclear, extensive research has suggested Cd-associated changes to epigenetic landscapes may play a pivotal role in the developmental programming of pregnancy and birth outcomes through disruption of placental physiology and function (8, 18-21).

While Cd-related changes in DNA methylation patterns have been thoroughly outlined in developmentally relevant tissues through human cohort studies, this same level of characterization has yet to be defined in the context of other epigenetic forms of regulation, namely placental microRNAs (miRNA)(20-22). MiRNAs are small RNA molecules (~22 nucleotides) capable of post-transcriptional regulation of gene expression that utilize base-pairing to bind target mRNAs resulting in either translational repression or mRNA degradation. The dysregulation of placental miRNA expression has previously been implicated in adverse pregnancy conditions, such as preeclampsia and fetal growth restriction, highlighting their potential role as modifiers of newborn and maternal health outcomes in response to environmental perturbations *in utero* (23-27). However, many of these studies largely focused on newborn outcomes as they associate with placental miRNA expression as opposed to the relationship between prenatal environmental factors and expression of placental miRNA (23, 24, 26, 28, 29).

In order to broaden our understanding of how gestational Cd exposure influences the placental miRNA landscape, we utilized placental miRNA sequencing data, as well as placental trace metal quantification, from the Rhode Island Child Health Study (RICHS, n=115), and the New Hampshire Birth Cohort Study (NHBCS, n=281). We also integrated specific NNNS summary scores to examine if Cd-associated miRNA were also associated with newborn neurobehavioral performance.

RESULTS

This study analyzed miRNA sequencing and trace metal data from 115 placentae from RICHS and 281 placentae from the NHBCS. The demographics of the participants are outlined in Table 1. Generally, placentae collected in these studies were from full term pregnancies (≥37 weeks) from relatively healthy mothers who did not experience serious pregnancy complications. The most notable differences between the RICHS and NHBCS cohorts are with regards to the racial diversity of participants and infant birth size. The RICHS cohort is slightly more racially diverse than the NHBCS cohort **(Table 4-1)**. RICHS, by design, was over-sampled for infants born large for gestational age (LGA) and small for gestational age (SGA). Additionally, NHBCS participants are from more rural regions, and utilize private water systems. Placental samples from the RICHS cohort exhibited higher mean Cd concentrations (4.386 ng/g) than the NHBCS sample mean (2.932 ng/g), with each cohort exhibiting approximately log-normally distributed concentrations **(Fig. S4-1)**.

Cd Differential Expression Analyses

In order to analyze associations between placental Cd concentrations and placental miRNA expression, we performed differential expression analyses using negative binomial generalized linear models on placental miRNA sequencing data. Transcript abundances were regressed against $\log_2$-transformed placental Cd concentrations while adjusting for gestational age, birth weight percentile, maternal pregnancy smoking status, RNA integrity estimates, and unknown confounders via surrogate variables in each cohort (30, 31). To further characterize the robustness of the differential expression analysis results, we utilized a meta-analytical approach where we combined parameter estimates and their respective standard-errors from each cohort using an inverse variance weighted fixed effects meta-analysis (32). The NHBCS cohort-level analysis revealed five DEmiRs (**D**ifferentially **E**xpressed **miR**NA) whose expression significantly associated with placental Cd concentrations at a False Discovery Rate (FDR) < 0.1, (miR-10b-3p, miR-10b-5p, miR-193b-5p, miR-506-3p and miR-509-3p) **(Table 4-2 & Table S4-2)**. One of these five miRNAs, miR-509-3p, met a strict Bonferroni test correction threshold ($p < 6.435e-05$). Considering the potential influence of tobacco-related Cd exposure, we performed the NHBCS differential expression analysis in a population where all reported smokers were excluded **(Fig. S4-2)**. The effect sizes resulting from the original model proved to be consistent with that of the exclusionary model where reported smokers were excluded ($R^2 = 0.86$; **Fig. S4-3A**). Additionally, 100% of the coefficients from the self-reported exclusionary model are within the estimated 95% CI's of the smoking-adjusted model (**Fig. S4-3B & S4-3C)**. In the RICHS cohort-level analysis, we did not observe any miRNAs associated with placental Cd concentrations at an FDR<0.1 **(Table S4-1)**. The meta-analysis emphasized the robustness of the miR-509-3p and miR-193b-5p association with Cd, and further revealed miR-1248 as consistently differentially expressed with respect to placental Cd concentrations, all at an FDR < 0.15 **(Fig. 4-1A, Table 4-2 &Table S4-3)**.

The effect size estimates of Cd-associated DEmiRs were largely consistent between the cohort-level and meta-analysis with the exception of miR-10b-3p and miR-10b-5p, which displayed opposing directions of effect between the RICHS and NHBCS analyses, and were therefore excluded from the meta-analysis (**Table 4-2, Fig. 4-1B)**.

Cd-DEmiR Target Prediction and Overrepresentation Analyses

Bioinformatic targets of each Cd-associated miRNA from the NHBCS cohort-level analysis were predicted using the miRNA Data Integration Portal (miRDIP) (33). MiRDIP predicted 833 targets across all five differentially expressed miRNAs. However, perfect complementarity is not required between a miRNA and the target transcript, leaving *in silico* miRNA target prediction prone to the production of false positive interactions that may not occur biologically. To further enhance our pool of predicted targets, a strict filtering approach was taken. We removed predicted transcripts that are not shown to be expressed within RICHS placentae. After this filtering step, 806 predicted targets remained **(Table S4-4).** Targets were then utilized in a pathway overrepresentation analysis within ConsensusPathDB (CPDB), where only a single DEmiR's list of predicted targets were analyzed at a time to highlight DEmiR-specific pathway dysregulation. These Cd-associated miRNA targets were largely revealed to participate in biological pathways relevant to cellular transcription, cellular metabolism and broader developmental signaling (34, 35). The predicted targets of miiR-509-3p and miR-193b-5p, which were robustly associated with Cd concentrations across the NHBCS and meta analyses were enriched among nervous system development pathways (q-value < 0.001) **(Fig. 4-2, Table S4-5 & S4-6)**.

NNNS and Cd-DEmiR Bivariate Association Analyses

Given the over-representation of target genes involved in nervous system development, we explored whether the Cd DEmiRs were associated with neurobehavioral phenotypes. Previous work from our group has constructed neurobehavioral profiles based on NICU Network Neurobehavioral Scale (NNNS) data from RICHS infants (14). Five of the 13 NNNS summary scales with the greatest variability between profiles (arousal level, quality of movement, stress abstinence, excitability and self-regulation capacity) (14) were examined for their association with normalized transcript abundances of miR-509-3p and miR-193b-5p in RICHS newborns (n=114). Simple linear regression analyses revealed nominally significant, negative associations between quality of movement scores and normalized transcript abundances of Cd-associated miR-509-3p ($\beta = -0.47 \pm 0.38$, $p \leq 0.01$) and miR-193b-5p ($\beta = -0.278 \pm 0.287$, $p \leq 0.1$) **(Fig. 4-3A &B, Table S4-8)**. Additionally, excitability scores appear to be positively associated with only miR-193b-5p transcript abundance ($\beta = 0.27 \pm 0.3$, $p \leq 0.1$) **(Fig. 4-3C, Table S4-8)**. Arousal, stress abstinence and self-regulation capacity showed no relationship to these Cd-associated miRNAs **(Table S4-8)**.

DISCUSSION

The developmental and reproductive toxicity of Cd is well documented and extensively studied, however, the relationship between Cd accumulation in the placenta, its impacts on the expression of placental miRNA and, in turn, effects on early neurobehavioral outcomes remains poorly understood (6-10, 21).

Here we have conducted an association study of mother-infant dyads from two independent cohorts to examine relationships between placental Cd concentrations and miRNA expression from human placentae. The methods for quantifying miRNA expression and Cd concentrations were identical in both cohorts, and the levels of Cd are low compared to the range of concentrations previously reported in other placenta-based studies conducted in humans (1.2ng/g to 53.3ng/g)(36). We successfully identified five Cd-associated miRNAs within the NHBCS cohort-level analysis with adjustment for covariates at an FDR <0.1 **(Fig. 4-1, Table S4-2)**. Within the RICHS cohort-level analysis we did not identify any associations between placental Cd concentrations and miRNA expression at FDR<0.1 **(Table S4-1)**. However, the association of two of the five Cd-associated miRNAs identified in NHBCS were consistent in a fixed-effects meta-analysis; (miR-509-3p and miR-193b-5p, FDR < 0.15). Importantly, the effect size estimates of Cd-associated miRNAs remain consistent between cohorts with the exception of miR-10b-3p and miR-10b-5p **(Fig. 4-3A & 3B)**. The inability to detect associations in the RICHS cohort alone may be related to the more modest sample size and the lower variability in the Cd concentrations present within RICHS placentae, even though the mean concentration was greater than that in NHBCS.

Relevance of miR-509-3p and miR-193b-5p to placental physiology

A small number of miRNAs are known to play critical roles in placental function and physiology, but the function of most miRNA, particularly in the placenta, is unclear.

Cd-associated placental miRNA miR-509-3p, is clinically relevant to the progression of medulloblastomas as well as in ovarian cancer (37-39). The expression of miR-509-3p is positively correlated with favorable disease outcomes while downregulation of miR-509-3p is associated with cellular invasion and migratory properties and poor disease prognosis (37-39). MAP3K8

(Mitogen Activated Kinase Kinase Kinase 8), regulates oncogenic pathways in cancers, including renal cancers, and contains a canonical 509-3p binding sit in its 3'UTR, which is thought to play a role in allowing miR-509-3p to exert its tumor suppressive properties (38). Mitogen-activated protein kinases (MAPKs) in general participate in the development of the trophectoderm in early placentation, but also contribute to the differentiation of trophoblasts, which is an ongoing process that plays a major role in placental maintenance and remodeling throughout development. Thus, miR-509-3p expression could contribute to similar functions involving MAPK-mediated invasion and migratory processes, as well as angiogenic processes seen in placentation (40, 41).

Originally identified as a hypoxia-inducible miRNA, miR-193b-5p is also implicated in various cancers where its upregulation is associated with improved disease prognosis resulting from decreased proliferation, migration and invasion of cancerous cells in both lung and breast cancers (42-45), similar to the roles played by miR-509-3p. The expression of miR-193b-5p has also been implicated in preeclampsia and in cases of intrauterine growth restriction (IUGR) which are thought to arise from a potential miR-193b-5p-mediated dysregulation of TGFβ-2 signaling, a gene shown to be directly regulated by miR-193b-5p and which oversees many facets of migration and invasion of trophoblasts (28, 40, 46-48).

In the context of our study, both miR-509-3p and miR-193b-5p are upregulated in association with respect to placental Cd. Their function as tumor suppressors in various cancers suggests their participation in overseeing analogous processes critical to proper placental function and successful birth outcomes; proliferation, migration, invasion, angiogenesis and differentiation (37, 38, 40, 42-44). Being critical to normal placental development and function, dysregulation of these cellular processes often manifest as various placental insufficiencies, such as preeclampsia, or IUGR, and thus may contribute to adverse maternal and/or fetal health outcomes.

Relationship between placental functional and neurobehavioral outcomes

While responsible for the transfer of nutrients and gases, the placenta is also involved in the production of various neurotransmitters, such as serotonin, dopamine, norepinephrine and epinephrine which may then circulate and directly influence fetal brain development (16, 49). Poorer neurobehavioral outcomes, in general, are known to arise more frequently in infants born SGA, which suggests proper placental function may underlie various neurobehavioral outcomes (50). Additionally, alterations in placental miRNA expression are associated with both attention scores and quality of movement scores at birth, suggesting placental miRNA expression may contribute to the developmental origins of early childhood neurobehavioral outcomes (51).

Bioinformatic target prediction and pathway analysis highlighted potential additional functional impacts of miR-509-3p and miR-193b-5p. Of their combined 370 unique predicted mRNA targets, these miRNAs were revealed to potentially target genes enriched for nervous system development pathways (**Fig. 4-2, Table S4-5 & S4-6)**. Our group has previously identified an association between NNNS atypical neurobehavioral profiles and placental Cd concentrations in RICHS participants, but the molecular mechanisms underlying this specific association have yet to be defined (14). We identified negative associations between the expression of Cd-associated DEmiRs (509-3p and 193b-5p) and NNNS quality of movement scores **(Fig. 4-3, Table S4-8)**, and a positive association between miR-193b-5p and NNNS excitability scores. The quality of movement metric is a measure of motor control, where higher scores suggest a greater quality of movement indicated by smoother movements with little or no jitteriness or tremors (52). The excitability metric is a measure of high levels of motor, state and physiologic reactivity, with higher scores indicating infants who become and remain irritable during the examination, whereas lower scores are signature for infants that display lower irritability and fewer state changes during the exam (53).

Lower quality of movement, and higher excitability scores are generally associated with higher risk pregnancies, including those associated with maternal drug use, and are predictive of long-term neurobehavioral deficits (54). Deficiencies in the performance of both quality of movement and excitability were also characteristic within the atypical neurobehavioral profile previously characterized in RICHS (14). These relationships suggest gestational Cd exposure may contribute to abnormal neurobehavioral outcomes at birth through dysregulation of placental miRNA expression. While RICHS does not have available long-term data to examine the persistence of these effects, other cohorts have linked NNNS atypical-neurobehavioral profiles to persistent adverse neurobehavioral performance through age 4.5, suggesting that Cd exposure, through placental miRNA, could have long-term developmental programming implications (54, 55). Considering these changes in miRNA expression are detectable at birth, this may allow for the development of early interventional methods to mitigate long-term developmental deficits.

This is an observational study specifically sampling full-term placentae from live births. The cross-sectional design of this study cannot address the issue of temporality, as we cannot conclude that our results are representative of miRNA and mRNA associations throughout all of development. Additionally, even though we report significant associations between placental Cd levels, miRNA abundance and neurobehavioral outcomes, these findings may not represent causal relationships. While we adjusted for likely confounders to the best of our ability, there is still a possibility of unmeasured confounding which remains in our analysis. Lastly, both RICHS and NHBCS consist of predominantly healthy, white mothers from the New England region of the United States, potentially limiting the ability of these results to be generalized to a more diverse population.

CONCLUSION

Placental miRNAs are critical molecules in post-transcriptional gene regulation. Their regulatory activities have been linked to overall physiology and function of the placenta throughout gestation and offspring developmental outcomes, marking them as essential to successful gestational outcomes. Here we have identified the abundance of miR-509-3p and miR-193b-5p to be associated with placental Cd, and with NNNS metrics indicative of atypical neurobehavior. Targets of these miRNAs are predicted to be involved in nervous system development and the transcript abundance of these Cd-associated miRNAs are also associated with individual NNNS summary scores, including quality of movement and excitability. These Cd-associated placental miRNAs may influence neurobehavioral outcomes at birth through their role in overseeing placental physiology throughout gestation, allowing for them to serve as early life indicators of long-term neurodevelopmental outcomes.

METHODS

Cohorts

New Hampshire Birth Cohort Study (NHBCS)

The New Hampshire Birth Cohort Study (NHBCS) is an ongoing birth cohort initiated in 2009 of mother-infant pairs. Pregnant women between the ages of 18 and 45 were recruited from participating prenatal care clinics in New Hampshire, USA. Women were enrolled in this study only if they reported if their primary source of drinking water was from an unregulated residential well since their previous menstrual period, and had no plans to move before delivery. All participants provided written informed consent in accordance with the requirements of the Committee for the Protection of Human Subjects, the Institutional Review Board (IRB) of Dartmouth College. Placental gross measures such as placental diameter (cm) and placental weight (g) were collected after delivery. Interviewer administered questionnaires and medical record abstraction were utilized to collect sociodemographic, lifestyle and anthropometric data. Data provided by this study include placental microRNA transcript abundance and placental trace metal concentrations (n=281).

The Rhode Island Child Health Study (RICHS)

The Rhode Island Child Health Study (RICHS) is a cohort of mother-infant pairs from the Women & Infants Hospital in Providence, Rhode Island, enrolled between September 2010 and February 2013. All mothers were at least 18 years of age, had no life-threatening conditions, and delivered singletons free of congenital/chromosomal abnormalities at or after 37 weeks of gestation. Infants who were born small for gestational age (≤ 10th birth weight percentile) or large for gestational age (≥ 90th birth weight percentile) were oversampled. Infants who were adequate for gestational age (between 10th and 90th birth weight percentile) that matched on gestational age and maternal age were coincidentally enrolled. All participants provided written informed consent and all protocols were approved by the IRBs at the Women & Infants Hospital of Rhode Island and Emory University, respectively. Data provided by this study include placental microRNA transcript abundance and placental trace metal concentrations (n=115). Interviewer-administered questionnaires were utilized to collect sociodemographic and lifestyle data. Structured medical record review was used to collect anthropometric and medical history data.

Data Collection

Anthropometric Measures and Potential Covariates

Birth weight (g), head circumference (cm), and birth length (cm) were taken from medical records. Z-Scores were calculated for each, standardized by gestational age and infant sex, via Fenton growth curves (56). Infants with standardized birth weight percentiles below the 10th percentile as small for gestational age (SGA), those above the 95th percentile as large for gestational age (LGA), and those between the 10th and 90th percentiles as adequate for gestational age (AGA).

Potential Covariates

Maternal smoking during pregnancy was defined as any self-reported smoking during any point of pregnancy versus those who reported no smoking during pregnancy. Fetal sex was obtained from medical records. Only samples with complete covariate, placental Cd, and placental miRNA sequencing data were utilized in this study.

Tissue Collection

Each cohort utilized the same sampling protocol. Placental parenchyma samples were collected within 2 hours of birth; sections were obtained two centimeters from the umbilical cord insertion side and were free of maternal decidua. One sample of collected tissue was immediately placed into RNA later solution (Life Technologies, Grace Island, NY, USA) for at least 48 hours, then blotted dry and stored at -80°C. Another sample, for trace metal analysis, was immediately snap frozen and stored at -80°C.

Cadmium Quantification

Trace element concentrations were quantified in both RICHS and NHBCS placental samples at the Dartmouth Trace Elements Analysis core through inductively coupled plasma mass spectrometry (ICP-MS); details of this analysis have been previously described(57). Given the right-tailed skewed nature of the Cd concentration distributions in each cohort, concentrations were $\log_2$ transformed for normalization to be used in differential expression analyses **(Fig. S4-1)**.

NNNS Assessment

The NICU Network Neurobehavioral Scale (NNNS) is a standardized assessment which comprehensively examines the neurological function, behavioral functioning and signs of stress in newborns (52). The NNNS yields summary scores on 13 individual behaviors and functions including habituation, attention, arousal, self-regulation, handling, quality of movement, excitability, lethargy, non-optimal reflexes, asymmetry reflexes, hypertonicity, hypotonicity, and stress/abstinence. Z-transformed measurements of individual NNNS metrics that are highly variable between atypical and neuro-typical constructed neurobehavioral profiles were utilized in downstream associative modeling (arousal level, quality of movement, stress abstinence, excitability, and self-regulation capacity) (14).

Within RICHS, NNNS was administered after the first 24 hours of life, and prior to discharge by certified psychometrists. Of the 840 enrolled participants in RICHS, 625 were assessed with NNNS, however, 114 (99%) of these participants overlap with our placental miRNA sequencing and trace metal datasets.

NHBCS microRNA isolation and sequencing

Total RNA was extracted from fixed placenta using the Qiagen miRNeasy Mini Kit and a TissueLyser LT (Qiagen, Frederick, MD, USA) following the manufacturer’s protocol. Briefly, 25-35mg of placental tissue was placed into a 2 ml round bottom tube with 700 µl of Qiazol Lysing Reagent and one 5 mm stainless steel bead. The tissue was homogenized on the TissueLyser LT for 2 minutes at 40 Hz. The resulting homogenate was processed with the Qiagen miRNeasy Mini Kit and eluted in 30 µl RNase-free water. The RNA was quantitated on a NanoDrop 2000 (Thermo Fisher, Waltham, MA, USA) and quality checked on Agilent Bioanalyzer using the Agilent RNA 6000 Nano Kit (Agilent, Santa Clara, CA, USA). Single end, 1 x 75 bp next-generation sequencing of placental microRNA was performed by Qiagen Genomic Services (Frederick, Maryland).

RICHS microRNA isolation and sequencing

Total RNA was extracted from placenta using the Qiagen miRNeasy Mini Kit and a TissueLyser LT (Qiagen, Germantown, MD, USA) following manufacturer’s protocol. Briefly, 25-35 mg of frozen, powdered placental tissue was placed in a 2 ml round bottom tube with 700 µl of Qiazol Lysing Reagent and one 5 mm stainless steel bead. The tissue was homogenized in a pre-chilled tube holder on the TissueLyser LT for two, 5-minute cycles at 30 Hz. The resulting homogenate was processed with the Qiagen miRNeasy Mini Kit with on-column DNAse digestion and eluted in 50 µl RNase-free water. The RNA was quantitated on a NanoDrop (Thermo Fisher, Waltham, MA, USA) and quality checked on Agilent Bioanalyzer using the Agilent RNA 6000 Nano kit (Agilent, Santa Clara, CA, USA). Single end, 1 x 50 bp next generation sequencing of placental miRNA was performed by Omega Bioservices (Norcross, Georgia) as previously described (58).

Small RNA-seq processing and quality control

Raw FASTQ reads obtained from a total of 115 RICHS and 281 NHBCS samples (n=396) were subject to adaptor trimming with cutadapt v1.1634. The 3' adaptor sequence were trimmed (TGGAATTCTCGGGTGCCAAGG) and then four bases were trimmed from each end of the read following vendor's recommendation (BIOO scientific, Austin TX). We then used trimmed reads and miRDeep2 to quantify microRNA (59). miRDeep2 was used to first perform alignment using bowtie1 with human genome hg38 (60). The 'Quantifier' module in miRDeep2 was used to obtain raw counts of microRNAs with miRBase version 22 (61).

Transcript Filtering and Normalization

Raw miRNA counts were imported into *DESeq2* for normalization and differential expression analysis. Only miRNA transcripts with more than one count per million in at least 10 percent of samples were included, leaving 778 miRNA transcripts to be analyzed of the initial 2656 sequenced transcripts. Dispersion estimates were then calculated, followed by generation of median ratio size factor estimates to normalize counts for analysis with in *DESeq2* (62). Normalized counts were then exported from *DESeq2* for Surrogate Variable Analysis (SVA). The Variance Stabilization Transformation (VST) was applied to count matrices to yield approximately normalized and $\log_2$-transformed abundances, which were utilized in bivariate association analyses discussed below (58).

RICHS total RNA Isolation, Sequencing, Processing and Quality Control

Total RNA was extracted from fixed, pulverized placenta using the RNeasy Mini Kit (Qiagen) and stored at −80°C until analysis. We quantified RNA using a Nanodrop Spectrophotometer (Thermo Scientific), assessed RNA integrity via Agilent Bioanalyzer (Agilent), removed ribosomal RNA with a Ribo-Zero Kit (63), performed cDNA conversion using random hexamers (Thermo Scientific), followed by transcriptome-wide 50bp single-end RNA sequencing via the HiSeq 2500 platform (Illumina)(64). Initial quality control was performed on raw reads using the FastQC software. Reads passing the quality control metrics were then mapped to the human reference genome (hg19) utilizing the Spliced Transcripts Alignment to a Reference (STAR) aligner (65). Parametric estimates of dispersion were calculated, and the median ratio method was used to estimate size factors for normalization for modelling of transcripts with *DESeq2*(62). Count matrices normalized by the Variance Stabilizing Transformation (analogous to normalization and $\log_2$-transformation) were exported from *DESeq2* for utilization in bioinformatic target prediction filtering and gene ontology analysis.

Statistical Analyses

Surrogate Variable Analysis

To adjust for unknown confounders, such as cell-type heterogeneity and unmeasured technical variation, surrogate variables were estimated for normalized miRNA transcript reads using the *sva* package (30, 31). In the *svaseq* function, the iteratively re-weighted least squares algorithm was used to estimate surrogate variables based on empirically derived control transcripts. The full model, for each RICHS and NHBCS estimations, (mod argument) contained the following covariates: $\log_2[Cd^{2+}]$, gestational age (wks), birth weight percentile, maternal pregnancy smoking status, and RNA integrity estimates. The null model, for each RICHS and NHBCS, contained all previously listed covariates while excluding $\log_2[Cd^{2+}]$. For each cohort, one surrogate variable was included as a covariate in the final model of each respective analysis.

Differential expression analyses

MiRNA transcript counts were modeled using a negative binomial generalized linear model to identify differentially expressed transcripts in *DESeq2* (31). For each of the 778 individual miRNA transcripts which passed strict filtering and quality criteria, the variance stabilized transformed transcript abundance was regressed on $\log_2$-transformed placental Cd concentrations. The following covariates were included in each independent model: gestational age (wks), birth weight percentile, maternal pregnancy smoking status, RNA integrity estimates and the first estimated surrogate variable (30, 31). MiRNAs with a false discovery rate (FDR) less than 10% were considered to be a differentially expressed miRNA (DEmiR) with respect to $\log_2[Cd^{2+}]$.

Meta-Analysis

A fixed effects meta-analysis was performed, utilizing the inverse variance-weighted method implemented in *METAL* using the standard error based method (32). Study-specific summary statistics from each differential expression analysis were utilized, allowing for adjustment for study-specific parameters prior to the final meta-analysis. From this meta-analysis, only miRNAs with consistent direction of effects across both the independent RICHS and NHBCS differential expression analyses, leaving 333 miRNAs to be investigated. Only those miRNAs displaying an $FDR < 0.15$ were considered to be meaningfully dysregulated with respect to $\log_2$-transformed placental Cd concentrations.

Target prediction and filtering

Potential targets of DEmiRs were identified using miRDIP (33). Only targets within the top 1% of confidence scores were returned. To further enhance the biological relevance of target mRNAs we then utilized existing whole transcriptome RNA-seq data from RICHS to only allow mRNAs that were expressed >1cpm in at least 10% of RICHS whole transcriptome RNA-seq samples to be considered a potential biological target (58).

Gene Ontology and Pathway analysis

Predicted and filtered DEmiR targets were then tested for pathway overrepresentation within ConsensusPathDB (CPDB) (34, 35), against all genes that passed general QC filtering in RICHS whole transcriptome RNA-seq analysis (34, 35, 58). CPDB utilizes 12 separate biological pathway databases, and calculates an enrichment p-value from the hypergeometric distribution of genes in the list of miRNA targets and the pathway gene set. False discovery rates were calculated from the enrichment p-values, and a q-value ≤0.001 was considered a significant enrichment of miRNA targets in the tested pathway/ontology group.

Bivariate Association Analyses

Simple linear regression was used to characterize the relationship between VST counts of Cd-associated placental miRNAs and z-transformed individual NNNS metrics from RICHS infants **(Fig. S4-4)** that are highly variable across estimated neurobehavioral profiles, previously described by Tung et al (14). The metrics analyzed included: arousal level, quality of movement, stress abstinence, excitability, and self-regulation capacity. Among the NNNS assessed infants, 114 (99%) of these participants overlap with between the placental miRNA sequencing data and trace metal measurements. Associations were reported as nominally significant with a p-value ≤ 0.1.

ACKNOWLEDGEMENTS:

We acknowledge the cooperation of the participants enrolled in the RICHS and NHBCS, and the contributions of the research staff who also worked on RICHS and NHBCS.

TABLES

Table 4-1: Demographic characteristics of RICHS and NHBCS participants included in the miRNA sequencing analysis

MATERNAL CHARACTERISTICS	**RICHS** (n=115)	**NHBCS** (n=281)
Age (yrs) – *mean (range)*	30 (18-40)	31 (18-44)
Race (White) – *% (n)*	72 (83)	100 (281)
Pregnancy Smoking – *% (n)*	10 (12)	13 (37)
Pre-Pregnancy Body Mass Index (BMI) (kg/m^2) – *mean (range)*	26.5 (16.0 - 45.4)	26.1 (16.9 - 49.9)
Pre-Pregnancy BMI Group		
Normal and Underweight – *% (n)*	47.8 (55)	47.6 (134)
Overweight – *% (n)*	29.5 (34)	30.6 (86)
Obese – *% (n)*	22.6 (26)	18.5 (52)
INFANT CHARACTERISTICS		
Placental Cd^{2+} (ng/g) *mean (standard deviation)*	4.39 (2.52)	2.93 (1.99)
Sex (Female) – *% (n)*	46.9 (54)	51.6 (145)
Gestational Age (wks) – *mean (range)*	39.0 (37 - 41)	39.5 (31.4 - 42.1)
Birthweight (g) – *mean (range)*	3610 (2160-5465)	3469 (1380-5216)
Birthweight Group		
Small for Gestational Age (SGA) – *% (n)*	15.6 (18)	4.3 (12)
Average for Gestational Age (AGA) – *% (n)*	45.2 (52)	85.1 (242)
Large for Gestational Age (LGA) – *% (n)*	39.1 (45)	9.6 (27)

Table 4-2: RICHS, NHBCS and Meta-Analysis Results Summary

miRNA	Study	Log2(Fold-Change)	Standard Error	p-value	-Log10(pvalue)	FDR
hsa-miR-10b-3p	RICHS	0.1808	0.1449	0.2121	0.6734	0.9971
hsa-miR-10b-3p	NHBCS	-0.3126	0.0843	0.0002	3.6831	0.0537*****
hsa-miR-10b-5p	RICHS	0.0993	0.1255	0.4289	0.3677	0.9971
hsa-miR-10b-5p	NHBCS	-0.2866	0.0771	0.0002	3.6926	0.0537*****
hsa-miR-1248	Meta	-0.2395	0.0665	0.0003	3.5022	0.1128
hsa-miR-1248	RICHS	-0.2221	0.1409	0.1149	0.9396	0.9971
hsa-miR-1248	NHBCS	-0.2444	0.0754	0.0012	2.9268	0.1381
hsa-miR-193b-5p	Meta	0.1496	0.0431	0.0005	3.2888	0.1229*****
hsa-miR-193b-5p	RICHS	0.0844	0.0841	0.3158	0.5007	0.9971
hsa-miR-193b-5p	NHBCS	0.1728	0.0502	0.0006	3.2444	0.0885*****
hsa-miR-506-3p	Meta	0.2275	0.0711	0.0014	2.8645	0.1632
hsa-miR-506-3p	RICHS	0.0735	0.1160	0.5264	0.2787	0.9971
hsa-miR-506-3p	NHBCS	0.3201	0.0899	0.0004	3.4305	0.0721*****
hsa-miR-509-3p	Meta	0.1924	0.0522	0.0002	3.6480	0.1128*
hsa-miR-509-3p	RICHS	0.0654	0.0838	0.4352	0.3613	0.9971
hsa-miR-509-3p	NHBCS	0.2728	0.0666	0.0000	4.3706	0.0331

***** Indicates FDR significance determined by analysis-specific threshold (RICHS & NHBCS: FDR ≤ 10%, Meta-analysis: FDR ≤ 15%

FIGURES

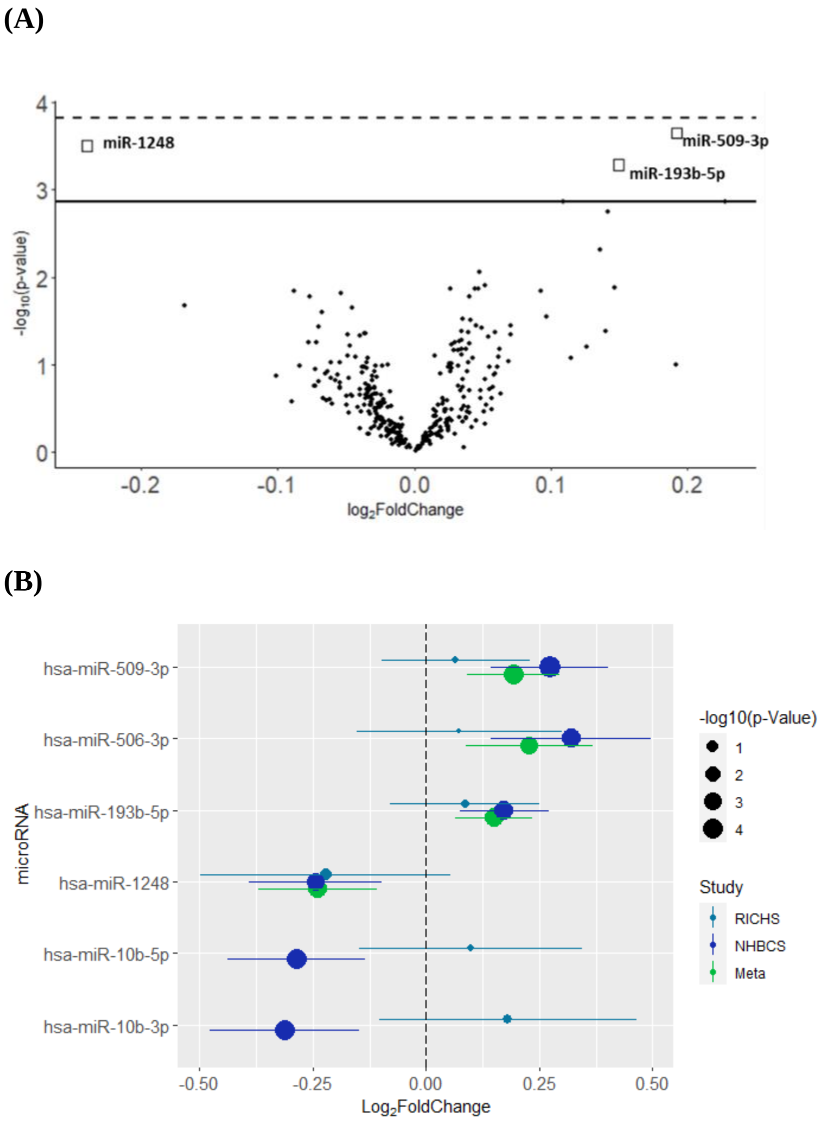


Figure 4-1: Placental Cd has associations with specific miRNA expression consistent across two independent cohorts. (A) Volcano plot representing the results of the NHBCS and RICHS meta-analysis. The y-axis shows the -$\log_{10}$(p-values) in the association of each miRNA with $\log_2$-transformed placental cadmium concentrations. The x-axis displays the effect estimates in units of $\log_2$ fold change in each miRNA's transcript abundance per doubling of placental cadmium. 3 miRNAs are associated with placental cadmium accumulation at an FDR < 0.15; however, none are significant following Bonferroni correction (p-value < 1.50e-04). **(B)** Estimates of $\log_2$ fold change of miRNA transcript abundances of Cd-associated DEmiRs identified compared across the RICHS and NHBCS cohort analyses and meta-analysis. MiR-10b-3p and miR-10b-5p do not hold meta-analysis estimates considering the opposing direction of effect estimates identified in the cohort level analyses. Error bars in each plot represent the estimated 95% confidence interval, size of the point represents the -log10(p-value) of the estimate, and the color indicates the study from which the data were generated.

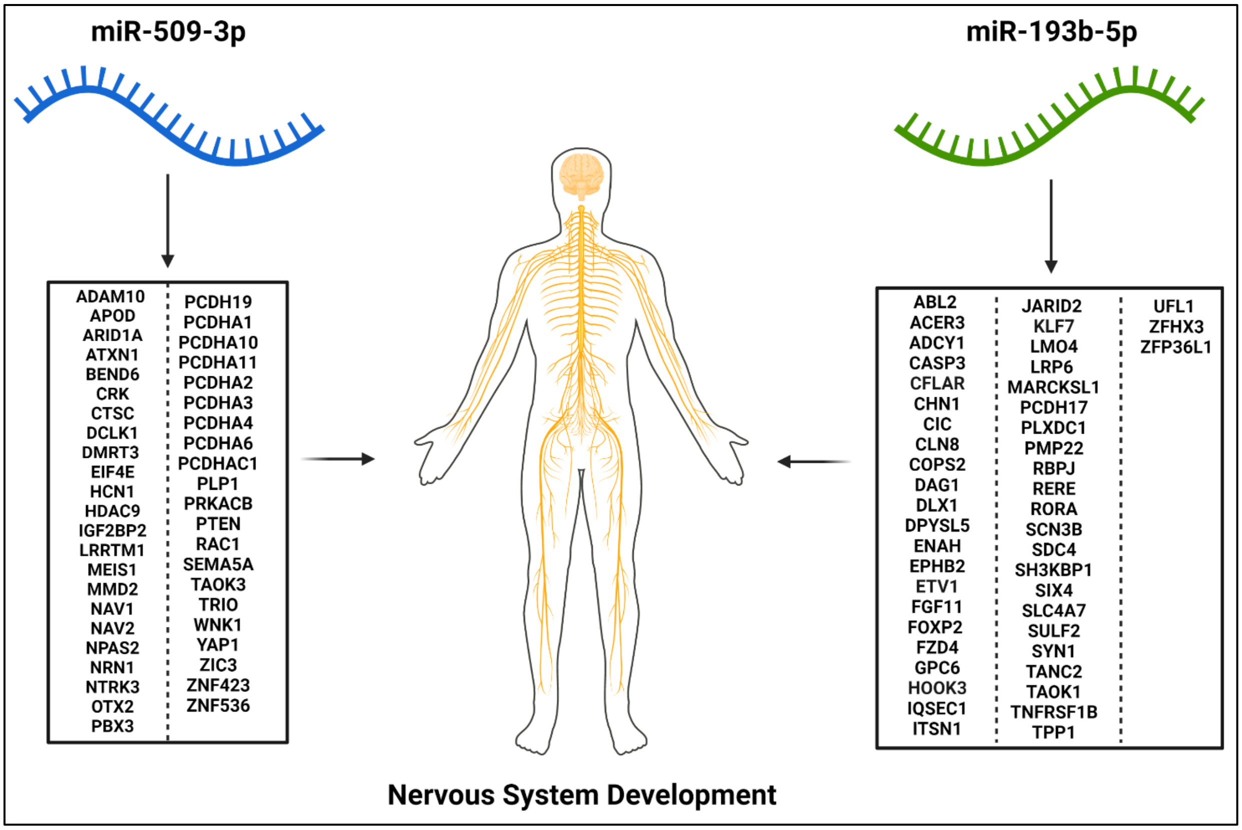
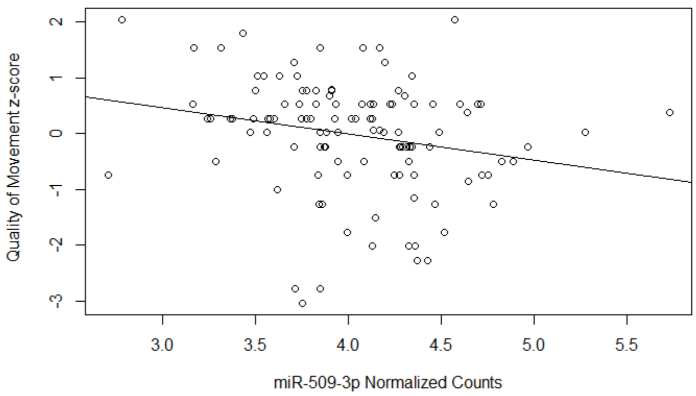
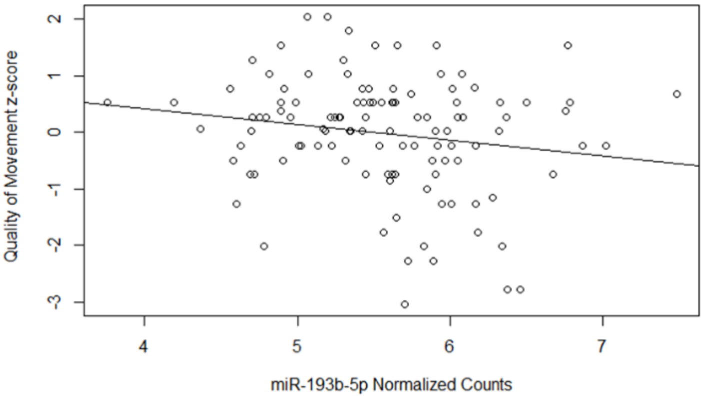


Figure 4-2. Predicted targets of Cd-associated miRNAs miR-509-3p and miR-193b-5p are overrepresented in biological pathways relevant to nervous system development. The predicted targets of miR-509-3p and miR-193b-5p commonly reported a potential influence toward nervous system development (q-value < 0.001). MiR-193b was predicted to target 47 genes involved in nervous system development while miR-509-3p was predicted to target 44 unique targets. While all genes listed contribute to the overrepresentation of nervous system development, no predicted gene is a predicted target of multiple miRNA. Of the 91 total mRNA targets involved in nervous system development, 72 were found to be expressed at >1cpm in the RICHS placental total RNA sequencing dataset **(Table S4-7)**. Created with www.BioRender.com.

(A)



(B)



(C)

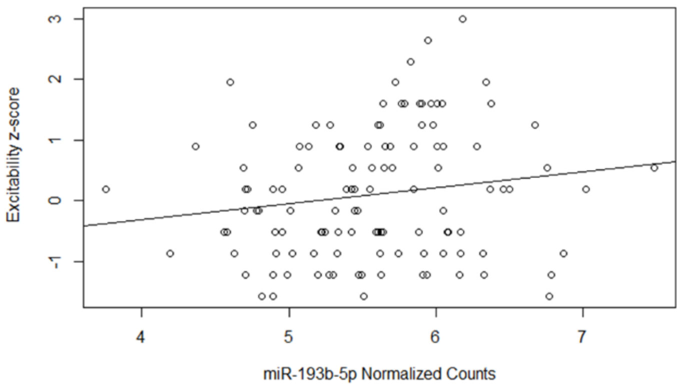


Figure 4-3. Quality of Movement and Excitability at birth are correlated with the expression of miR-509-3p and miR-193b-5p. Scatterplots depicting the relationship between normalized counts of miR-509-3p and miR-193b-5p with respect to individual, z-transformed NNNS metrics (y-axes) (n=114) as determined by simple linear regression. **(A)** There is a reported β = -0.47 ± 0.380 attenuation in quality

of movement scores per-cpm change in miR-509-3p transcript abundance ($p \leq 0.01$). **(B)** There is a reported $\beta = -0.278 \pm 0.287$ attenuation in quality of movement scores per-cpm change in miR-193b-5p transcript abundance ($p = 0.06$). **(C)** There is a reported $\beta = 0.27 \pm 0.3$ attenuation in excitability measurements per-cpm change in miR-193b-5p transcript abundance ($p = 0.09$). Error for each analysis is reported as the estimated 95% confidence interval, results are considered nominally significant at a p-value threshold of $p \leq 0.1$.

SUPPLEMENTARY TABLES

Table S4-1: RICHS: Cd miRNA Differential Expression Analysis Results

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-192-3p	0.425	0.135	0.002	0.589
hsa-miR-429	0.495	0.162	0.002	0.589
hsa-miR-95-3p	0.329	0.11	0.003	0.589
hsa-miR-625-5p	-0.142	0.048	0.003	0.589
hsa-miR-520e-3p	-0.146	0.054	0.007	0.812
hsa-miR-29a-5p	0.156	0.058	0.008	0.812
hsa-miR-502-3p	-0.079	0.031	0.01	0.812
hsa-miR-200a-3p	0.221	0.086	0.01	0.812
hsa-miR-132-5p	0.137	0.054	0.011	0.812
hsa-miR-545-5p	0.294	0.116	0.011	0.812
hsa-miR-29a-3p	0.112	0.044	0.011	0.812
hsa-miR-181a-2-3p	0.132	0.053	0.012	0.812
hsa-miR-500a-3p	-0.073	0.03	0.015	0.849
hsa-miR-497-5p	0.137	0.057	0.016	0.849
hsa-miR-2682-5p	0.417	0.173	0.016	0.849
hsa-let-7b-3p	0.187	0.079	0.018	0.9
hsa-miR-549a-3p	0.456	0.199	0.022	0.957
hsa-miR-202-5p	-0.18	0.079	0.023	0.957
hsa-miR-212-5p	0.317	0.139	0.023	0.957
hsa-miR-203a-3p	-0.171	0.077	0.027	0.973
hsa-miR-195-5p	0.125	0.057	0.027	0.973
hsa-miR-381-3p	-0.079	0.036	0.027	0.973
hsa-miR-548at-5p	0.276	0.126	0.028	0.973
hsa-miR-375-3p	0.323	0.148	0.029	0.973
hsa-miR-200b-3p	0.096	0.045	0.035	0.997
hsa-miR-1247-3p	0.184	0.088	0.036	0.997
hsa-miR-4659a-3p	-0.315	0.152	0.038	0.997
hsa-miR-329-3p	-0.078	0.039	0.043	0.997
hsa-miR-4433b-5p	-0.328	0.163	0.044	0.997
hsa-miR-1268a	0.219	0.109	0.045	0.997
hsa-miR-512-3p	-0.062	0.031	0.048	0.997
hsa-miR-22-5p	0.067	0.034	0.051	0.997
hsa-miR-548n	-0.256	0.132	0.052	0.997
hsa-miR-339-5p	0.069	0.035	0.052	0.997
hsa-miR-483-5p	-0.09	0.047	0.056	0.997
hsa-miR-212-3p	0.289	0.151	0.056	0.997
hsa-miR-18a-3p	-0.137	0.072	0.057	0.997
hsa-miR-491-3p	0.29	0.153	0.059	0.997
hsa-miR-34b-5p	0.161	0.086	0.062	0.997
hsa-miR-7-5p	-0.088	0.047	0.062	0.997
hsa-miR-185-3p	-0.176	0.095	0.064	0.997
hsa-miR-4636	0.265	0.144	0.066	0.997
hsa-miR-539-5p	-0.088	0.048	0.066	0.997
hsa-miR-181c-3p	0.093	0.051	0.069	0.997
hsa-miR-485-5p	-0.081	0.045	0.069	0.997
hsa-miR-627-3p	-0.193	0.107	0.072	0.997
hsa-miR-365a-5p	0.167	0.093	0.073	0.997
hsa-miR-652-3p	-0.066	0.037	0.076	0.997
hsa-miR-369-5p	-0.068	0.038	0.076	0.997
hsa-miR-1277-5p	0.148	0.084	0.077	0.997
hsa-miR-6507-5p	-0.204	0.117	0.081	0.997
hsa-miR-3664-5p	-0.229	0.132	0.082	0.997
hsa-miR-548ay-3p	-0.205	0.118	0.083	0.997
hsa-miR-376a-2-5p	-0.1	0.058	0.084	0.997
hsa-miR-34b-3p	0.131	0.076	0.085	0.997
hsa-miR-519e-5p	0.065	0.038	0.085	0.997
hsa-miR-511-5p	-0.088	0.051	0.087	0.997
hsa-miR-379-3p	-0.068	0.04	0.088	0.997
hsa-let-7b-5p	0.108	0.064	0.089	0.997
hsa-miR-1185-5p	-0.099	0.059	0.09	0.997
hsa-miR-450a-2-3p	-0.088	0.052	0.09	0.997
hsa-miR-135a-5p	-0.267	0.158	0.092	0.997
hsa-miR-18b-5p	-0.176	0.105	0.092	0.997
hsa-miR-376a-3p	-0.064	0.038	0.093	0.997
hsa-miR-532-5p	-0.058	0.035	0.096	0.997
hsa-miR-2114-5p	0.24	0.144	0.096	0.997
hsa-miR-6511a-3p	-0.162	0.098	0.098	0.997
hsa-miR-1228-3p	-0.199	0.121	0.099	0.997
hsa-miR-19b-3p	0.076	0.046	0.101	0.997
hsa-miR-15b-3p	0.129	0.079	0.101	0.997
hsa-miR-27a-5p	0.102	0.063	0.105	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-155-5p	-0.219	0.136	0.106	0.997
hsa-miR-376c-3p	-0.056	0.035	0.107	0.997
hsa-miR-628-3p	-0.129	0.08	0.108	0.997
hsa-miR-520c-3p	-0.064	0.04	0.11	0.997
hsa-miR-424-5p	0.063	0.04	0.112	0.997
hsa-miR-570-3p	-0.184	0.117	0.115	0.997
hsa-miR-579-3p	0.137	0.087	0.115	0.997
hsa-miR-3679-5p	0.164	0.104	0.115	0.997
hsa-miR-1248	-0.222	0.141	0.115	0.997
hsa-miR-767-5p	-0.111	0.07	0.116	0.997
hsa-miR-3064-5p	-0.235	0.15	0.119	0.997
hsa-miR-598-3p	0.145	0.094	0.121	0.997
hsa-miR-548aw	-0.146	0.094	0.122	0.997
hsa-miR-376c-5p	-0.068	0.044	0.123	0.997
hsa-miR-34c-5p	0.095	0.062	0.124	0.997
hsa-miR-337-3p	-0.056	0.037	0.128	0.997
hsa-miR-615-3p	-0.072	0.047	0.13	0.997
hsa-miR-7706	0.09	0.059	0.131	0.997
hsa-miR-338-3p	-0.088	0.058	0.131	0.997
hsa-miR-130a-3p	-0.041	0.027	0.131	0.997
hsa-miR-624-5p	-0.078	0.052	0.132	0.997
hsa-miR-4781-3p	-0.165	0.111	0.137	0.997
hsa-miR-3690	-0.182	0.123	0.138	0.997
hsa-miR-330-5p	-0.082	0.055	0.141	0.997
hsa-miR-548ar-3p	-0.223	0.153	0.144	0.997
hsa-miR-379-5p	-0.064	0.044	0.146	0.997
hsa-miR-105-5p	-0.112	0.077	0.147	0.997
hsa-miR-487a-3p	-0.061	0.043	0.15	0.997
hsa-miR-643	-0.22	0.153	0.151	0.997
hsa-miR-629-5p	-0.05	0.035	0.152	0.997
hsa-miR-376b-5p	-0.064	0.045	0.153	0.997
hsa-miR-5683	0.382	0.268	0.154	0.997
hsa-miR-550a-3-5p	-0.132	0.093	0.156	0.997
hsa-miR-29b-3p	0.054	0.038	0.156	0.997
hsa-miR-3940-3p	0.143	0.101	0.157	0.997
hsa-miR-520e-5p	-0.059	0.042	0.158	0.997
hsa-miR-6715b-3p	-0.191	0.136	0.16	0.997
hsa-let-7c-5p	0.072	0.051	0.163	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-4326	-0.152	0.109	0.163	0.997
hsa-miR-410-3p	-0.076	0.055	0.165	0.997
hsa-miR-941	-0.078	0.056	0.167	0.997
hsa-miR-4517	-0.215	0.156	0.168	0.997
hsa-miR-194-5p	0.053	0.038	0.169	0.997
hsa-miR-3925-3p	-0.174	0.127	0.171	0.997
hsa-miR-487b-3p	-0.048	0.035	0.173	0.997
hsa-miR-411-3p	-0.05	0.037	0.173	0.997
hsa-miR-224-5p	0.067	0.05	0.175	0.997
hsa-miR-548ar-5p	0.227	0.168	0.175	0.997
hsa-miR-584-5p	-0.067	0.05	0.176	0.997
hsa-miR-377-3p	-0.055	0.041	0.177	0.997
hsa-miR-655-3p	-0.046	0.034	0.177	0.997
hsa-miR-363-3p	-0.069	0.051	0.178	0.997
hsa-miR-365b-3p	0.086	0.064	0.18	0.997
hsa-miR-365a-3p	0.086	0.064	0.18	0.997
hsa-miR-519d-5p	0.047	0.035	0.181	0.997
hsa-miR-605-3p	-0.176	0.132	0.181	0.997
hsa-miR-6881-3p	-0.169	0.126	0.182	0.997
hsa-miR-3615	-0.07	0.052	0.183	0.997
hsa-miR-616-3p	0.198	0.15	0.185	0.997
hsa-miR-520f-3p	-0.115	0.087	0.186	0.997
hsa-miR-377-5p	-0.053	0.04	0.186	0.997
hsa-miR-132-3p	0.067	0.051	0.188	0.997
hsa-miR-31-5p	0.084	0.065	0.192	0.997
hsa-miR-505-3p	-0.05	0.038	0.192	0.997
hsa-miR-376a-5p	-0.061	0.047	0.195	0.997
hsa-miR-196b-5p	0.055	0.043	0.195	0.997
hsa-miR-125b-2-3p	0.07	0.055	0.199	0.997
hsa-miR-181d-5p	0.05	0.039	0.202	0.997
hsa-miR-491-5p	-0.089	0.07	0.203	0.997
hsa-miR-7109-3p	-0.222	0.175	0.203	0.997
hsa-miR-518e-3p	-0.05	0.039	0.205	0.997
hsa-miR-548aj-5p	0.19	0.151	0.208	0.997
hsa-miR-382-5p	-0.045	0.036	0.208	0.997
hsa-miR-192-5p	0.042	0.033	0.209	0.997
hsa-miR-3173-5p	0.19	0.151	0.21	0.997
hsa-miR-654-5p	-0.056	0.045	0.211	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-362-5p	-0.045	0.036	0.211	0.997
hsa-miR-214-5p	-0.05	0.04	0.211	0.997
hsa-miR-10b-3p	0.181	0.145	0.212	0.997
hsa-miR-337-5p	-0.068	0.054	0.212	0.997
hsa-miR-548o-3p	-0.067	0.054	0.215	0.997
hsa-miR-3144-3p	-0.173	0.14	0.216	0.997
hsa-miR-211-5p	0.1	0.081	0.217	0.997
hsa-miR-501-3p	-0.044	0.036	0.22	0.997
hsa-miR-659-5p	-0.127	0.104	0.222	0.997
hsa-miR-524-3p	-0.043	0.035	0.223	0.997
hsa-miR-556-3p	0.165	0.136	0.224	0.997
hsa-miR-24-2-5p	0.045	0.037	0.224	0.997
hsa-miR-10399-5p	0.107	0.089	0.228	0.997
hsa-miR-499a-5p	-0.058	0.048	0.228	0.997
hsa-miR-101-3p	0.037	0.031	0.232	0.997
hsa-miR-137-3p	0.157	0.132	0.234	0.997
hsa-miR-193a-5p	0.095	0.08	0.235	0.997
hsa-miR-548p	-0.154	0.13	0.235	0.997
hsa-miR-3157-5p	-0.164	0.139	0.236	0.997
hsa-miR-1284	-0.161	0.136	0.238	0.997
hsa-miR-2276-3p	-0.167	0.142	0.239	0.997
hsa-miR-466	0.119	0.101	0.241	0.997
hsa-miR-7-1-3p	-0.066	0.057	0.244	0.997
hsa-miR-411-5p	-0.045	0.039	0.247	0.997
hsa-miR-188-5p	-0.066	0.057	0.249	0.997
hsa-miR-3611	-0.206	0.179	0.25	0.997
hsa-miR-195-3p	0.049	0.043	0.251	0.997
hsa-let-7a-3p	0.039	0.034	0.254	0.997
hsa-miR-548am-3p	-0.186	0.164	0.257	0.997
hsa-miR-548au-5p	0.058	0.051	0.257	0.997
hsa-miR-326	-0.047	0.042	0.259	0.997
hsa-miR-4508	0.231	0.206	0.262	0.997
hsa-miR-221-5p	0.036	0.032	0.266	0.997
hsa-miR-30c-2-3p	0.034	0.03	0.267	0.997
hsa-miR-10a-5p	0.046	0.042	0.267	0.997
hsa-miR-6866-5p	-0.166	0.15	0.267	0.997
hsa-miR-628-5p	-0.074	0.067	0.268	0.997
hsa-miR-138-1-3p	0.136	0.123	0.269	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-133b	0.114	0.104	0.269	0.997
hsa-miR-323b-3p	0.079	0.072	0.27	0.997
hsa-miR-585-3p	-0.137	0.125	0.273	0.997
hsa-miR-210-5p	0.144	0.131	0.273	0.997
hsa-miR-3613-3p	-0.093	0.086	0.278	0.997
hsa-miR-126-5p	0.038	0.035	0.278	0.997
hsa-miR-664b-3p	0.058	0.054	0.279	0.997
hsa-miR-199a-5p	-0.03	0.028	0.28	0.997
hsa-miR-324-3p	-0.045	0.042	0.28	0.997
hsa-miR-4454	0.096	0.09	0.281	0.997
hsa-miR-548ah-3p	-0.142	0.132	0.282	0.997
hsa-miR-93-3p	0.043	0.04	0.283	0.997
hsa-miR-217-5p	0.274	0.258	0.288	0.997
hsa-miR-196a-5p	0.097	0.092	0.292	0.997
hsa-miR-548x-5p	0.161	0.153	0.293	0.997
hsa-miR-556-5p	-0.152	0.144	0.293	0.997
hsa-miR-3194-3p	-0.163	0.155	0.293	0.997
hsa-miR-205-3p	-0.131	0.125	0.293	0.997
hsa-miR-539-3p	-0.054	0.051	0.294	0.997
hsa-miR-30b-5p	0.037	0.036	0.296	0.997
hsa-miR-183-3p	0.12	0.115	0.297	0.997
hsa-miR-548ai	-0.123	0.118	0.298	0.997
hsa-miR-570-5p	-0.123	0.118	0.298	0.997
hsa-miR-548i	-0.126	0.122	0.301	0.997
hsa-miR-215-5p	0.065	0.063	0.302	0.997
hsa-miR-2277-5p	-0.122	0.119	0.303	0.997
hsa-miR-760	0.139	0.135	0.303	0.997
hsa-miR-758-5p	0.113	0.11	0.307	0.997
hsa-miR-296-5p	0.064	0.062	0.307	0.997
hsa-miR-146b-3p	0.114	0.112	0.308	0.997
hsa-miR-548aq-3p	-0.098	0.096	0.309	0.997
hsa-miR-92a-3p	-0.04	0.039	0.31	0.997
hsa-miR-1261	-0.142	0.14	0.31	0.997
hsa-miR-1307-3p	0.039	0.038	0.311	0.997
hsa-miR-1268b	0.105	0.103	0.311	0.997
hsa-miR-6516-5p	0.134	0.133	0.312	0.997
hsa-miR-193b-5p	0.084	0.084	0.316	0.997
hsa-miR-425-3p	-0.029	0.029	0.316	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-675-5p	-0.05	0.051	0.321	0.997
hsa-miR-452-5p	-0.037	0.037	0.322	0.997
hsa-miR-3143	0.139	0.141	0.324	0.997
hsa-miR-32-5p	-0.034	0.034	0.324	0.997
hsa-miR-520a-5p	-0.039	0.04	0.326	0.997
hsa-miR-191-3p	0.085	0.086	0.327	0.997
hsa-miR-432-5p	-0.043	0.044	0.327	0.997
hsa-miR-140-3p	0.042	0.043	0.328	0.997
hsa-miR-503-3p	0.066	0.067	0.33	0.997
hsa-miR-1185-1-3p	-0.049	0.05	0.331	0.997
hsa-miR-127-5p	-0.035	0.036	0.331	0.997
hsa-miR-1262	0.099	0.102	0.332	0.997
hsa-miR-378f	0.087	0.09	0.334	0.997
hsa-miR-574-5p	-0.046	0.047	0.336	0.997
hsa-miR-1287-5p	0.063	0.065	0.336	0.997
hsa-miR-1307-5p	0.056	0.058	0.336	0.997
hsa-miR-30c-5p	0.029	0.03	0.337	0.997
hsa-miR-1-3p	-0.066	0.069	0.338	0.997
hsa-miR-16-5p	-0.048	0.051	0.342	0.997
hsa-miR-519d-3p	-0.035	0.037	0.343	0.997
hsa-miR-627-5p	-0.089	0.094	0.343	0.997
hsa-miR-301a-3p	0.053	0.056	0.344	0.997
hsa-miR-34a-5p	0.048	0.051	0.346	0.997
hsa-miR-20a-5p	0.034	0.036	0.346	0.997
hsa-miR-4652-5p	-0.142	0.151	0.348	0.997
hsa-miR-140-5p	0.033	0.035	0.349	0.997
hsa-miR-500a-5p	-0.037	0.04	0.349	0.997
hsa-miR-6803-3p	0.115	0.123	0.35	0.997
hsa-miR-519b-3p	-0.037	0.039	0.351	0.997
hsa-let-7d-5p	-0.07	0.076	0.351	0.997
hsa-miR-301b-3p	-0.099	0.106	0.351	0.997
hsa-miR-517-5p	0.03	0.033	0.355	0.997
hsa-miR-34c-3p	0.073	0.079	0.356	0.997
hsa-miR-9-5p	0.069	0.075	0.356	0.997
hsa-miR-23a-5p	-0.071	0.078	0.357	0.997
hsa-miR-550a-5p	-0.086	0.093	0.358	0.997
hsa-miR-381-5p	-0.065	0.071	0.359	0.997
hsa-miR-1247-5p	-0.057	0.062	0.359	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-937-3p	0.122	0.133	0.359	0.997
hsa-miR-92a-1-5p	-0.089	0.098	0.36	0.997
hsa-miR-515-5p	0.036	0.039	0.36	0.997
hsa-miR-424-3p	0.024	0.026	0.361	0.997
hsa-miR-616-5p	-0.068	0.075	0.363	0.997
hsa-miR-299-5p	-0.039	0.043	0.363	0.997
hsa-miR-625-3p	-0.043	0.047	0.364	0.997
hsa-miR-4742-5p	0.135	0.148	0.364	0.997
hsa-miR-374c-5p	-0.061	0.067	0.367	0.997
hsa-miR-409-3p	-0.031	0.034	0.369	0.997
hsa-miR-1285-3p	-0.065	0.073	0.375	0.997
hsa-miR-551b-3p	-0.048	0.054	0.377	0.997
hsa-miR-26a-5p	0.016	0.018	0.379	0.997
hsa-miR-548bc	-0.081	0.093	0.38	0.997
hsa-miR-495-3p	-0.034	0.039	0.381	0.997
hsa-miR-500b-5p	-0.038	0.044	0.381	0.997
hsa-miR-3912-3p	-0.056	0.064	0.382	0.997
hsa-miR-380-5p	-0.112	0.128	0.383	0.997
hsa-miR-338-5p	-0.059	0.068	0.386	0.997
hsa-miR-3925-5p	0.144	0.168	0.392	0.997
hsa-miR-125a-5p	0.038	0.044	0.392	0.997
hsa-miR-487a-5p	-0.06	0.07	0.396	0.997
hsa-miR-1303	-0.053	0.062	0.396	0.997
hsa-miR-3128	-0.139	0.164	0.397	0.997
hsa-miR-668-3p	-0.039	0.046	0.397	0.997
hsa-miR-561-5p	-0.06	0.071	0.397	0.997
hsa-miR-32-3p	-0.039	0.046	0.397	0.997
hsa-miR-154-3p	-0.037	0.044	0.399	0.997
hsa-let-7f-2-3p	0.095	0.113	0.4	0.997
hsa-miR-518f-5p	-0.032	0.038	0.401	0.997
hsa-miR-184	-0.051	0.061	0.405	0.997
hsa-miR-518b	-0.041	0.049	0.405	0.997
hsa-miR-516b-3p	-0.091	0.109	0.407	0.997
hsa-miR-10399-3p	0.085	0.103	0.407	0.997
hsa-miR-1323	0.027	0.032	0.408	0.997
hsa-miR-576-5p	-0.033	0.04	0.409	0.997
hsa-miR-4999-5p	0.079	0.096	0.409	0.997
hsa-miR-548ae-5p	-0.043	0.053	0.41	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-203b-3p	-0.113	0.138	0.41	0.997
hsa-miR-200c-3p	0.028	0.034	0.417	0.997
hsa-miR-548k	-0.037	0.045	0.417	0.997
hsa-miR-210-3p	0.058	0.072	0.418	0.997
hsa-let-7a-5p	0.028	0.034	0.418	0.997
hsa-miR-548w	-0.041	0.051	0.419	0.997
hsa-miR-517c-3p	-0.03	0.038	0.419	0.997
hsa-miR-651-5p	0.036	0.045	0.42	0.997
hsa-miR-378g	0.119	0.148	0.421	0.997
hsa-miR-1292-5p	-0.119	0.148	0.422	0.997
hsa-miR-33a-5p	0.111	0.138	0.422	0.997
hsa-miR-374b-3p	0.04	0.049	0.422	0.997
hsa-miR-874-5p	-0.051	0.064	0.423	0.997
hsa-miR-877-5p	-0.062	0.077	0.423	0.997
hsa-miR-526a-5p	-0.033	0.041	0.425	0.997
hsa-miR-515-3p	-0.035	0.044	0.426	0.997
hsa-miR-520c-5p	-0.033	0.041	0.426	0.997
hsa-miR-134-3p	-0.097	0.122	0.427	0.997
hsa-miR-410-5p	-0.132	0.166	0.427	0.997
hsa-miR-518d-5p	-0.033	0.041	0.428	0.997
hsa-miR-10b-5p	0.099	0.126	0.429	0.997
hsa-miR-371a-3p	-0.125	0.158	0.429	0.997
hsa-miR-146a-5p	-0.065	0.082	0.431	0.997
hsa-miR-498-3p	0.026	0.033	0.432	0.997
hsa-miR-548ab	-0.106	0.135	0.433	0.997
hsa-miR-138-5p	0.09	0.116	0.435	0.997
hsa-miR-509-3p	0.065	0.084	0.435	0.997
hsa-miR-6516-3p	0.105	0.135	0.437	0.997
hsa-miR-505-5p	-0.093	0.12	0.437	0.997
hsa-miR-103a-3p	0.023	0.029	0.438	0.997
hsa-miR-502-5p	-0.042	0.054	0.444	0.997
hsa-miR-222-5p	0.079	0.104	0.447	0.997
hsa-miR-1185-2-3p	-0.06	0.08	0.448	0.997
hsa-miR-582-5p	0.038	0.051	0.448	0.997
hsa-miR-339-3p	0.032	0.043	0.45	0.997
hsa-miR-675-3p	-0.043	0.057	0.45	0.997
hsa-miR-301a-5p	-0.045	0.06	0.456	0.997
hsa-miR-767-3p	-0.109	0.147	0.456	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-216a-5p	0.206	0.277	0.457	0.997
hsa-miR-3139	-0.1	0.136	0.461	0.997
hsa-miR-3199	0.102	0.138	0.461	0.997
hsa-miR-199b-5p	-0.033	0.045	0.461	0.997
hsa-miR-516a-3p	-0.081	0.11	0.462	0.997
hsa-miR-30a-3p	0.028	0.038	0.464	0.997
hsa-miR-548b-3p	-0.08	0.11	0.465	0.997
hsa-miR-518c-5p	0.023	0.031	0.465	0.997
hsa-miR-98-3p	0.095	0.13	0.466	0.997
hsa-miR-6724-5p	-0.061	0.085	0.469	0.997
hsa-miR-548g-5p	0.094	0.13	0.47	0.997
hsa-miR-19a-3p	0.04	0.056	0.472	0.997
hsa-miR-9-3p	0.056	0.079	0.474	0.997
hsa-miR-147b-3p	-0.076	0.106	0.474	0.997
hsa-miR-511-3p	0.054	0.075	0.475	0.997
hsa-miR-361-5p	0.022	0.031	0.476	0.997
hsa-miR-26b-3p	0.036	0.05	0.476	0.997
hsa-miR-449a	-0.071	0.1	0.476	0.997
hsa-miR-128-3p	-0.018	0.025	0.477	0.997
hsa-miR-144-3p	-0.074	0.105	0.48	0.997
hsa-miR-134-5p	-0.029	0.041	0.48	0.997
hsa-miR-769-5p	0.022	0.032	0.48	0.997
hsa-miR-22-3p	-0.03	0.042	0.481	0.997
hsa-miR-4785	-0.105	0.149	0.482	0.997
hsa-miR-519a-3p	-0.024	0.035	0.484	0.997
hsa-miR-5010-3p	0.047	0.067	0.485	0.997
hsa-miR-409-5p	-0.026	0.038	0.486	0.997
hsa-miR-451a	-0.074	0.108	0.489	0.997
hsa-miR-29c-5p	-0.027	0.039	0.491	0.997
hsa-miR-433-3p	-0.032	0.047	0.491	0.997
hsa-miR-454-5p	-0.052	0.075	0.492	0.997
hsa-miR-514a-3p	0.048	0.07	0.492	0.997
hsa-miR-516a-5p	0.023	0.034	0.494	0.997
hsa-miR-520d-3p	-0.023	0.033	0.495	0.997
hsa-miR-3145-5p	0.075	0.11	0.496	0.997
hsa-miR-181b-2-3p	0.062	0.091	0.497	0.997
hsa-miR-523-3p	-0.036	0.052	0.498	0.997
hsa-miR-484	0.02	0.029	0.499	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-518c-3p	-0.022	0.032	0.499	0.997
hsa-miR-223-5p	-0.053	0.079	0.502	0.997
hsa-miR-127-3p	-0.028	0.043	0.504	0.997
hsa-miR-23a-3p	0.024	0.036	0.506	0.997
hsa-miR-543	-0.035	0.053	0.508	0.997
hsa-miR-342-3p	-0.03	0.045	0.508	0.997
hsa-miR-1275	0.067	0.102	0.511	0.997
hsa-miR-2277-3p	0.077	0.117	0.513	0.997
hsa-miR-3613-5p	-0.035	0.054	0.513	0.997
hsa-miR-320a-3p	0.026	0.039	0.514	0.997
hsa-miR-20b-3p	-0.099	0.152	0.515	0.997
hsa-miR-889-5p	-0.096	0.147	0.516	0.997
hsa-miR-346	-0.085	0.131	0.516	0.997
hsa-miR-21-5p	0.027	0.041	0.517	0.997
hsa-miR-33b-3p	-0.087	0.135	0.518	0.997
hsa-miR-26b-5p	0.018	0.028	0.518	0.997
hsa-miR-186-5p	-0.021	0.032	0.518	0.997
hsa-miR-521	-0.022	0.034	0.52	0.997
hsa-miR-96-5p	0.039	0.06	0.521	0.997
hsa-miR-551b-5p	0.067	0.105	0.522	0.997
hsa-miR-512-5p	-0.027	0.042	0.525	0.997
hsa-miR-506-3p	0.073	0.116	0.526	0.997
hsa-miR-654-3p	-0.019	0.03	0.527	0.997
hsa-miR-514a-5p	0.064	0.102	0.528	0.997
hsa-miR-1180-3p	-0.039	0.061	0.53	0.997
hsa-miR-7977	-0.039	0.062	0.531	0.997
hsa-miR-223-3p	0.038	0.061	0.532	0.997
hsa-let-7i-3p	0.057	0.092	0.533	0.997
hsa-miR-340-5p	-0.025	0.04	0.533	0.997
hsa-miR-873-5p	0.065	0.105	0.533	0.997
hsa-miR-29b-2-5p	0.033	0.054	0.537	0.997
hsa-miR-23b-5p	0.037	0.06	0.544	0.997
hsa-miR-194-3p	0.076	0.126	0.546	0.997
hsa-miR-30b-3p	0.025	0.042	0.547	0.997
hsa-miR-370-3p	-0.03	0.051	0.549	0.997
hsa-miR-618	-0.06	0.1	0.55	0.997
hsa-miR-518f-3p	-0.025	0.042	0.551	0.997
hsa-miR-548av-3p	-0.096	0.161	0.551	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-1226-3p	0.063	0.106	0.551	0.997
hsa-miR-944	-0.033	0.055	0.551	0.997
hsa-miR-146b-5p	0.043	0.072	0.552	0.997
hsa-miR-25-5p	-0.073	0.123	0.552	0.997
hsa-miR-26a-1-3p	0.054	0.092	0.553	0.997
hsa-miR-3927-3p	-0.169	0.285	0.554	0.997
hsa-miR-6514-5p	-0.061	0.104	0.557	0.997
hsa-miR-125a-3p	0.02	0.034	0.561	0.997
hsa-miR-4742-3p	-0.064	0.11	0.562	0.997
hsa-miR-548s	-0.056	0.096	0.562	0.997
hsa-miR-490-5p	-0.092	0.16	0.563	0.997
hsa-miR-5585-3p	-0.055	0.096	0.564	0.997
hsa-miR-522-3p	-0.02	0.035	0.567	0.997
hsa-let-7f-5p	0.032	0.056	0.567	0.997
hsa-miR-181a-5p	0.021	0.037	0.568	0.997
hsa-miR-6852-5p	-0.079	0.138	0.568	0.997
hsa-miR-454-3p	-0.015	0.026	0.572	0.997
hsa-miR-191-5p	0.016	0.028	0.573	0.997
hsa-miR-490-3p	-0.073	0.13	0.573	0.997
hsa-miR-4286	-0.029	0.051	0.575	0.997
hsa-miR-548ba	0.127	0.226	0.575	0.997
hsa-miR-494-3p	-0.021	0.037	0.578	0.997
hsa-miR-590-3p	0.025	0.046	0.585	0.997
hsa-miR-182-5p	0.032	0.059	0.586	0.997
hsa-miR-17-5p	0.019	0.035	0.588	0.997
hsa-miR-18a-5p	-0.035	0.064	0.588	0.997
hsa-miR-493-5p	-0.021	0.038	0.59	0.997
hsa-miR-30e-3p	0.022	0.041	0.593	0.997
hsa-miR-4661-5p	-0.054	0.102	0.595	0.997
hsa-miR-589-5p	-0.035	0.066	0.595	0.997
hsa-miR-542-5p	0.024	0.045	0.595	0.997
hsa-miR-660-5p	-0.018	0.034	0.596	0.997
hsa-miR-517a-3p	-0.018	0.034	0.596	0.997
hsa-miR-517b-3p	-0.018	0.034	0.596	0.997
hsa-miR-151b	0.019	0.036	0.596	0.997
hsa-miR-758-3p	0.024	0.046	0.598	0.997
hsa-miR-518a-3p	-0.016	0.031	0.598	0.997
hsa-miR-181b-5p	0.014	0.027	0.6	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-1306-3p	0.056	0.107	0.601	0.997
hsa-miR-1278	0.044	0.085	0.601	0.997
hsa-miR-1291	-0.047	0.089	0.602	0.997
hsa-miR-548y	-0.05	0.097	0.603	0.997
hsa-miR-1294	-0.048	0.092	0.603	0.997
hsa-miR-99b-5p	-0.014	0.026	0.604	0.997
hsa-miR-520b-5p	0.016	0.031	0.605	0.997
hsa-miR-34a-3p	0.036	0.069	0.605	0.997
hsa-miR-222-3p	-0.016	0.032	0.606	0.997
hsa-miR-519a-2-5p	0.016	0.031	0.606	0.997
hsa-miR-147b-5p	-0.046	0.09	0.608	0.997
hsa-miR-376b-3p	-0.025	0.05	0.611	0.997
hsa-miR-190a-5p	-0.038	0.075	0.613	0.997
hsa-miR-455-5p	-0.028	0.056	0.614	0.997
hsa-miR-2116-5p	0.076	0.151	0.614	0.997
hsa-miR-1269a	-0.095	0.189	0.616	0.997
hsa-miR-4728-3p	-0.046	0.092	0.617	0.997
hsa-miR-664a-3p	0.019	0.037	0.617	0.997
hsa-miR-4677-3p	0.05	0.1	0.617	0.997
hsa-miR-503-5p	0.017	0.034	0.619	0.997
hsa-miR-519e-3p	-0.019	0.039	0.62	0.997
hsa-miR-548t-3p	-0.038	0.076	0.621	0.997
hsa-miR-4802-5p	0.067	0.137	0.625	0.997
hsa-miR-3909	0.025	0.051	0.625	0.997
hsa-miR-371a-5p	-0.076	0.158	0.629	0.997
hsa-miR-526b-5p	0.02	0.041	0.629	0.997
hsa-miR-320c	-0.024	0.05	0.634	0.997
hsa-miR-151a-5p	0.014	0.031	0.636	0.997
hsa-let-7d-3p	0.033	0.069	0.638	0.997
hsa-miR-550a-3p	-0.035	0.075	0.639	0.997
hsa-miR-1301-3p	-0.023	0.05	0.64	0.997
hsa-miR-4521	0.048	0.105	0.643	0.997
hsa-miR-1305	-0.053	0.115	0.647	0.997
hsa-miR-619-5p	0.033	0.072	0.649	0.997
hsa-miR-1343-3p	0.065	0.142	0.649	0.997
hsa-miR-380-3p	-0.023	0.05	0.65	0.997
hsa-miR-4791	0.057	0.126	0.652	0.997
hsa-miR-181a-3p	0.02	0.044	0.652	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-15a-5p	-0.022	0.049	0.652	0.997
hsa-miR-199a-3p	-0.016	0.037	0.654	0.997
hsa-miR-3145-3p	-0.036	0.081	0.655	0.997
hsa-miR-412-3p	0.12	0.268	0.655	0.997
hsa-miR-142-5p	-0.035	0.079	0.656	0.997
hsa-miR-199b-3p	-0.016	0.037	0.656	0.997
hsa-miR-488-3p	0.06	0.134	0.657	0.997
hsa-miR-576-3p	-0.017	0.037	0.658	0.997
hsa-miR-23c	0.019	0.043	0.658	0.997
hsa-miR-136-5p	-0.017	0.04	0.664	0.997
hsa-miR-125b-5p	0.028	0.064	0.665	0.997
hsa-miR-335-3p	-0.021	0.048	0.667	0.997
hsa-miR-20b-5p	0.03	0.069	0.668	0.997
hsa-miR-1271-5p	-0.025	0.059	0.669	0.997
hsa-miR-299-3p	-0.018	0.042	0.669	0.997
hsa-miR-181b-3p	0.035	0.081	0.67	0.997
hsa-miR-1306-5p	0.027	0.064	0.67	0.997
hsa-miR-328-3p	0.021	0.049	0.671	0.997
hsa-miR-30e-5p	-0.014	0.033	0.671	0.997
hsa-miR-6501-5p	-0.036	0.086	0.673	0.997
hsa-miR-548ag	-0.06	0.141	0.673	0.997
hsa-miR-665	-0.023	0.054	0.674	0.997
hsa-miR-520f-5p	0.029	0.07	0.675	0.997
hsa-miR-3688-3p	0.029	0.068	0.675	0.997
hsa-miR-520g-3p	0.012	0.03	0.679	0.997
hsa-miR-942-5p	-0.031	0.076	0.681	0.997
hsa-miR-4443	-0.042	0.103	0.683	0.997
hsa-miR-518d-3p	-0.026	0.064	0.684	0.997
hsa-miR-3074-5p	-0.06	0.148	0.685	0.997
hsa-miR-378c	0.019	0.048	0.687	0.997
hsa-miR-148a-3p	0.023	0.057	0.687	0.997
hsa-miR-125b-1-3p	-0.026	0.065	0.688	0.997
hsa-miR-744-3p	-0.034	0.086	0.692	0.997
hsa-miR-130a-5p	0.03	0.075	0.693	0.997
hsa-miR-103a-2-5p	0.027	0.07	0.694	0.997
hsa-miR-548z	0.027	0.068	0.695	0.997
hsa-miR-130b-3p	-0.03	0.076	0.695	0.997
hsa-miR-9898	0.034	0.086	0.696	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-874-3p	-0.023	0.06	0.697	0.997
hsa-miR-425-5p	0.013	0.033	0.698	0.997
hsa-miR-548aa	-0.029	0.074	0.699	0.997
hsa-let-7g-3p	0.062	0.161	0.7	0.997
hsa-miR-330-3p	-0.017	0.044	0.703	0.997
hsa-miR-1249-3p	0.029	0.077	0.703	0.997
hsa-miR-548e-3p	-0.02	0.053	0.704	0.997
hsa-miR-92b-3p	0.018	0.046	0.705	0.997
hsa-miR-548aj-3p	-0.081	0.216	0.706	0.997
hsa-miR-218-5p	-0.018	0.049	0.706	0.997
hsa-miR-624-3p	-0.034	0.092	0.709	0.997
hsa-miR-525-5p	-0.015	0.041	0.709	0.997
hsa-miR-152-5p	0.045	0.12	0.71	0.997
hsa-miR-30c-1-3p	0.024	0.066	0.71	0.997
hsa-let-7e-3p	-0.019	0.052	0.711	0.997
hsa-miR-150-5p	0.033	0.088	0.711	0.997
hsa-miR-19b-1-5p	-0.05	0.135	0.711	0.997
hsa-miR-145-3p	0.014	0.038	0.713	0.997
hsa-miR-450a-1-3p	-0.022	0.06	0.713	0.997
hsa-miR-4684-3p	-0.06	0.162	0.713	0.997
hsa-miR-708-5p	0.052	0.143	0.715	0.997
hsa-miR-653-3p	-0.025	0.069	0.715	0.997
hsa-miR-2115-5p	-0.032	0.088	0.716	0.997
hsa-miR-513a-5p	-0.052	0.143	0.716	0.997
hsa-miR-520h	0.012	0.033	0.716	0.997
hsa-miR-7976	-0.032	0.087	0.716	0.997
hsa-miR-148b-3p	0.016	0.044	0.717	0.997
hsa-miR-143-3p	0.016	0.045	0.717	0.997
hsa-miR-369-3p	-0.014	0.039	0.719	0.997
hsa-miR-200c-5p	0.024	0.066	0.723	0.997
hsa-miR-188-3p	-0.04	0.114	0.725	0.997
hsa-miR-214-3p	-0.016	0.047	0.726	0.997
hsa-miR-99a-3p	0.041	0.118	0.727	0.997
hsa-miR-374b-5p	-0.013	0.038	0.731	0.997
hsa-miR-28-5p	-0.011	0.033	0.732	0.997
hsa-miR-135b-3p	0.04	0.118	0.734	0.997
hsa-miR-548o-5p	-0.015	0.045	0.736	0.997
hsa-miR-224-3p	-0.018	0.055	0.736	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-520b-3p	0.015	0.046	0.736	0.997
hsa-miR-374a-5p	0.02	0.06	0.738	0.997
hsa-miR-548h-3p	0.023	0.068	0.74	0.997
hsa-miR-221-3p	-0.009	0.027	0.74	0.997
hsa-miR-320e	-0.032	0.098	0.741	0.997
hsa-miR-513b-5p	0.045	0.137	0.742	0.997
hsa-miR-3188	-0.059	0.18	0.743	0.997
hsa-miR-372-3p	-0.051	0.157	0.743	0.997
hsa-miR-770-5p	-0.033	0.102	0.745	0.997
hsa-miR-548c-5p	-0.015	0.045	0.745	0.997
hsa-miR-33a-3p	0.023	0.072	0.747	0.997
hsa-miR-320d	-0.019	0.06	0.747	0.997
hsa-miR-142-3p	0.02	0.062	0.748	0.997
hsa-miR-2115-3p	-0.032	0.1	0.75	0.997
hsa-miR-1283	0.017	0.052	0.751	0.997
hsa-miR-582-3p	0.023	0.075	0.753	0.997
hsa-miR-934	0.015	0.049	0.754	0.997
hsa-miR-548l	-0.021	0.067	0.755	0.997
hsa-miR-106b-5p	0.013	0.042	0.755	0.997
hsa-miR-153-3p	0.043	0.137	0.756	0.997
hsa-miR-671-3p	-0.022	0.073	0.759	0.997
hsa-miR-589-3p	0.05	0.167	0.762	0.997
hsa-miR-548j-5p	0.029	0.097	0.763	0.997
hsa-miR-641	0.02	0.066	0.765	0.997
hsa-miR-6503-3p	0.036	0.122	0.766	0.997
hsa-miR-16-2-3p	-0.013	0.043	0.767	0.997
hsa-let-7e-5p	-0.012	0.041	0.767	0.997
hsa-miR-6511b-3p	0.027	0.092	0.77	0.997
hsa-miR-382-3p	-0.013	0.045	0.771	0.997
hsa-miR-4645-3p	-0.041	0.142	0.772	0.997
hsa-miR-3605-3p	-0.025	0.085	0.772	0.997
hsa-miR-1246	-0.078	0.271	0.773	0.997
hsa-miR-378a-5p	0.017	0.059	0.773	0.997
hsa-miR-378d	0.021	0.071	0.773	0.997
hsa-miR-548ak	0.024	0.083	0.775	0.997
hsa-miR-520g-5p	-0.021	0.076	0.778	0.997
hsa-miR-185-5p	-0.013	0.047	0.779	0.997
hsa-miR-17-3p	-0.015	0.055	0.78	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-5699-3p	0.045	0.161	0.78	0.997
hsa-miR-370-5p	-0.017	0.06	0.781	0.997
hsa-miR-548x-3p	0.202	0.732	0.783	0.997
hsa-miR-483-3p	-0.014	0.05	0.783	0.997
hsa-miR-373-3p	-0.037	0.136	0.783	0.997
hsa-miR-520a-3p	-0.012	0.044	0.784	0.997
hsa-miR-3065-3p	-0.021	0.077	0.784	0.997
hsa-miR-27b-5p	-0.01	0.038	0.785	0.997
hsa-miR-141-3p	-0.012	0.045	0.785	0.997
hsa-miR-29b-1-5p	0.024	0.09	0.787	0.997
hsa-miR-496	-0.014	0.053	0.787	0.997
hsa-miR-331-5p	0.01	0.038	0.788	0.997
hsa-miR-4775	0.027	0.102	0.79	0.997
hsa-miR-324-5p	-0.012	0.046	0.79	0.997
hsa-miR-561-3p	-0.024	0.09	0.791	0.997
hsa-miR-548az-5p	-0.039	0.148	0.791	0.997
hsa-miR-450b-5p	0.011	0.041	0.794	0.997
hsa-miR-16-1-3p	0.032	0.124	0.795	0.997
hsa-miR-323a-3p	0.01	0.04	0.796	0.997
hsa-miR-524-5p	0.008	0.032	0.797	0.997
hsa-miR-340-3p	-0.011	0.042	0.797	0.997
hsa-miR-143-5p	-0.012	0.049	0.799	0.997
hsa-let-7g-5p	0.013	0.05	0.799	0.997
hsa-miR-27b-3p	0.005	0.019	0.8	0.997
hsa-miR-450a-5p	-0.011	0.042	0.8	0.997
hsa-miR-504-5p	0.013	0.052	0.801	0.997
hsa-miR-2116-3p	0.022	0.086	0.803	0.997
hsa-miR-574-3p	-0.009	0.037	0.803	0.997
hsa-miR-136-3p	-0.009	0.038	0.803	0.997
hsa-miR-501-5p	-0.012	0.05	0.803	0.997
hsa-miR-3158-3p	-0.021	0.087	0.805	0.997
hsa-miR-486-5p	-0.022	0.089	0.806	0.997
hsa-miR-527	-0.008	0.034	0.809	0.997
hsa-miR-548ay-5p	-0.012	0.049	0.811	0.997
hsa-miR-99a-5p	0.011	0.048	0.811	0.997
hsa-miR-423-5p	-0.01	0.044	0.812	0.997
hsa-miR-548e-5p	-0.033	0.139	0.814	0.997
hsa-miR-345-5p	-0.012	0.05	0.814	0.997
hsa-miR-26a-2-3p	-0.013	0.053	0.814	0.997
hsa-miR-495-5p	0.016	0.067	0.815	0.997
hsa-miR-487b-5p	-0.023	0.1	0.817	0.997
hsa-miR-149-5p	0.009	0.038	0.818	0.997
hsa-miR-1197	-0.017	0.076	0.819	0.997
hsa-miR-509-3-5p	-0.028	0.125	0.822	0.997
hsa-miR-23b-3p	0.005	0.023	0.825	0.997
hsa-miR-519b-5p	0.008	0.038	0.827	0.997
hsa-miR-519c-5p	0.008	0.038	0.827	0.997
hsa-miR-522-5p	0.008	0.038	0.827	0.997
hsa-miR-523-5p	0.008	0.038	0.827	0.997
hsa-miR-518e-5p	0.008	0.038	0.828	0.997
hsa-miR-3664-3p	0.011	0.051	0.828	0.997
hsa-miR-518a-5p	-0.007	0.033	0.828	0.997
hsa-miR-3617-5p	0.031	0.142	0.83	0.997
hsa-miR-526b-3p	0.01	0.044	0.83	0.997
hsa-miR-331-3p	-0.009	0.042	0.83	0.997
hsa-miR-5701	-0.035	0.166	0.83	0.997
hsa-miR-652-5p	-0.016	0.078	0.834	0.997
hsa-miR-141-5p	-0.01	0.047	0.84	0.997
hsa-miR-744-5p	0.008	0.041	0.841	0.997
hsa-miR-12136	-0.018	0.09	0.844	0.997
hsa-miR-629-3p	0.016	0.083	0.845	0.997
hsa-miR-126-3p	-0.007	0.036	0.848	0.997
hsa-miR-1260a	-0.01	0.052	0.85	0.997
hsa-miR-433-5p	-0.012	0.064	0.853	0.997
hsa-miR-455-3p	0.01	0.052	0.854	0.997
hsa-miR-98-5p	0.011	0.058	0.855	0.997
hsa-miR-1910-5p	-0.026	0.141	0.856	0.997
hsa-miR-374a-3p	0.01	0.058	0.859	0.997
hsa-miR-12135	-0.02	0.114	0.863	0.997
hsa-miR-135b-5p	-0.015	0.088	0.866	0.997
hsa-miR-107	-0.008	0.045	0.867	0.997
hsa-miR-3614-5p	0.011	0.066	0.872	0.997
hsa-miR-656-3p	0.008	0.05	0.872	0.997
hsa-miR-99b-3p	-0.005	0.03	0.873	0.997
hsa-miR-30a-5p	-0.004	0.026	0.873	0.997
hsa-miR-148a-5p	-0.01	0.061	0.874	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-4639-5p	0.021	0.13	0.874	0.997
hsa-miR-103a-1-5p	0.027	0.171	0.875	0.997
hsa-miR-548q	0.014	0.087	0.876	0.997
hsa-miR-9985	0.01	0.065	0.876	0.997
hsa-miR-27a-3p	0.005	0.031	0.877	0.997
hsa-miR-516b-5p	0.007	0.048	0.877	0.997
hsa-miR-1843	-0.01	0.064	0.88	0.997
hsa-miR-889-3p	-0.008	0.052	0.883	0.997
hsa-miR-519c-3p	-0.005	0.036	0.883	0.997
hsa-miR-526a-3p	-0.008	0.058	0.883	0.997
hsa-miR-101-5p	0.011	0.079	0.884	0.997
hsa-miR-1299	0.035	0.243	0.886	0.997
hsa-miR-2110	-0.008	0.056	0.887	0.997
hsa-miR-10527-5p	0.013	0.095	0.887	0.997
hsa-miR-335-5p	0.007	0.05	0.89	0.997
hsa-miR-3179	-0.018	0.13	0.89	0.997
hsa-miR-940	0.013	0.096	0.89	0.997
hsa-miR-361-3p	-0.005	0.034	0.89	0.997
hsa-miR-423-3p	0.004	0.03	0.891	0.997
hsa-miR-144-5p	-0.013	0.097	0.891	0.997
hsa-miR-590-5p	-0.011	0.079	0.892	0.997
hsa-miR-10a-3p	0.008	0.059	0.893	0.997
hsa-miR-485-3p	-0.005	0.04	0.895	0.997
hsa-miR-154-5p	-0.007	0.05	0.895	0.997
hsa-miR-508-3p	-0.01	0.074	0.896	0.997
hsa-miR-542-3p	0.006	0.045	0.896	0.997
hsa-miR-412-5p	0.023	0.177	0.896	0.997
hsa-miR-548am-5p	-0.007	0.052	0.896	0.997
hsa-miR-519a-5p	0.005	0.038	0.898	0.997
hsa-miR-520d-5p	-0.004	0.035	0.898	0.997
hsa-miR-1304-3p	0.013	0.101	0.899	0.997
hsa-miR-205-5p	0.005	0.038	0.903	0.997
hsa-miR-30d-5p	0.004	0.036	0.904	0.997
hsa-miR-28-3p	0.004	0.037	0.905	0.997
hsa-miR-106a-5p	0.006	0.053	0.907	0.997
hsa-miR-372-5p	-0.02	0.171	0.908	0.997
hsa-miR-509-5p	0.015	0.128	0.908	0.997
hsa-miR-139-5p	0.006	0.049	0.909	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-4708-3p	0.012	0.109	0.912	0.997
hsa-miR-660-3p	0.007	0.062	0.913	0.997
hsa-miR-1296-5p	-0.005	0.049	0.913	0.997
hsa-miR-378a-3p	0.005	0.043	0.914	0.997
hsa-miR-181c-5p	0.004	0.038	0.916	0.997
hsa-miR-106a-3p	0.011	0.101	0.917	0.997
hsa-miR-133a-3p	-0.006	0.061	0.919	0.997
hsa-miR-24-3p	0.004	0.044	0.919	0.997
hsa-miR-133a-5p	-0.011	0.112	0.92	0.997
hsa-miR-15b-5p	0.006	0.057	0.92	0.997
hsa-miR-489-3p	0.007	0.072	0.921	0.997
hsa-miR-193b-3p	-0.009	0.087	0.921	0.997
hsa-miR-452-3p	0.01	0.102	0.922	0.997
hsa-miR-584-3p	-0.006	0.063	0.922	0.997
hsa-miR-130b-5p	0.009	0.093	0.923	0.997
hsa-miR-106b-3p	0.004	0.038	0.923	0.997
hsa-miR-7705	-0.007	0.074	0.925	0.997
hsa-miR-4662b	-0.013	0.143	0.927	0.997
hsa-miR-548h-5p	0.008	0.085	0.927	0.997
hsa-miR-31-3p	-0.011	0.126	0.928	0.997
hsa-miR-152-3p	0.004	0.044	0.929	0.997
hsa-miR-548d-5p	-0.004	0.049	0.932	0.997
hsa-miR-148b-5p	-0.004	0.048	0.933	0.997
hsa-miR-30d-3p	0.003	0.037	0.935	0.997
hsa-miR-532-3p	-0.004	0.054	0.936	0.997
hsa-miR-1260b	-0.004	0.052	0.937	0.997
hsa-miR-5699-5p	0.011	0.148	0.938	0.997
hsa-miR-486-3p	-0.008	0.107	0.939	0.997
hsa-miR-431-5p	-0.003	0.043	0.94	0.997
hsa-miR-6513-5p	-0.007	0.092	0.941	0.997
hsa-miR-876-3p	0.01	0.138	0.943	0.997
hsa-miR-664a-5p	-0.003	0.048	0.944	0.997
hsa-miR-1295a	-0.009	0.134	0.947	0.997
hsa-miR-373-5p	0.01	0.154	0.948	0.997
hsa-miR-1269b	0.075	1.182	0.949	0.997
hsa-miR-887-3p	-0.005	0.072	0.949	0.997
hsa-miR-25-3p	0.004	0.057	0.95	0.997
hsa-miR-5001-3p	-0.008	0.129	0.952	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-3913-5p	-0.005	0.088	0.953	0.997
hsa-miR-769-3p	-0.009	0.151	0.954	0.997
hsa-miR-498-5p	-0.003	0.046	0.956	0.997
hsa-miR-656-5p	0.008	0.14	0.956	0.997
hsa-miR-183-5p	0.003	0.052	0.957	0.997
hsa-miR-6513-3p	-0.004	0.08	0.957	0.997
hsa-miR-671-5p	0.003	0.054	0.96	0.997
hsa-miR-151a-3p	0.002	0.032	0.96	0.997
hsa-let-7i-5p	0.003	0.069	0.96	0.997
hsa-miR-4662a-3p	0.006	0.116	0.961	0.997
hsa-miR-100-3p	0.003	0.058	0.961	0.997
hsa-miR-362-3p	0.002	0.041	0.962	0.997
hsa-miR-190b-5p	0.003	0.068	0.962	0.997
hsa-miR-193a-3p	0.005	0.096	0.963	0.997
hsa-miR-525-3p	-0.002	0.035	0.965	0.997
hsa-miR-4662a-5p	-0.003	0.075	0.965	0.997
hsa-miR-342-5p	0.003	0.062	0.965	0.997
hsa-miR-5100	-0.004	0.091	0.966	0.997
hsa-miR-548b-5p	0.004	0.091	0.966	0.997
hsa-miR-548ad-5p	0.002	0.048	0.968	0.997
hsa-miR-29c-3p	0.001	0.033	0.969	0.997
hsa-miR-493-3p	0.001	0.032	0.973	0.997
hsa-miR-320b	-0.001	0.044	0.974	0.997

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-9903	-0.003	0.09	0.975	0.997
hsa-miR-204-5p	0.003	0.126	0.979	0.997
hsa-miR-139-3p	-0.002	0.075	0.98	0.997
hsa-miR-93-5p	-0.001	0.034	0.98	0.997
hsa-miR-431-3p	0.001	0.059	0.982	0.997
hsa-miR-145-5p	-0.001	0.041	0.982	0.997
hsa-miR-3614-3p	0.001	0.057	0.982	0.997
hsa-miR-421	0.001	0.037	0.983	0.997
hsa-miR-653-5p	0.001	0.075	0.985	0.997
hsa-miR-6501-3p	0.002	0.119	0.985	0.997
hsa-let-7f-1-3p	0.002	0.14	0.986	0.997
hsa-miR-5695	0.003	0.155	0.986	0.997
hsa-miR-766-3p	-0.001	0.051	0.988	0.997
hsa-miR-2355-3p	-0.001	0.088	0.988	0.997
hsa-miR-24-1-5p	0	0.038	0.99	0.997
hsa-miR-197-3p	0	0.038	0.99	0.997
hsa-miR-124-3p	-0.003	0.303	0.991	0.997
hsa-miR-3065-5p	0	0.068	0.994	0.998
hsa-miR-100-5p	0	0.054	0.995	0.998
hsa-miR-378i	0	0.07	0.996	0.998
hsa-miR-20a-3p	0	0.042	0.997	0.998
hsa-miR-21-3p	0	0.064	1	1

Table S4-2: NHBCS Cd miRNA Differential Expression Analysis Results

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-509-3p	0.273	0.067	0.00004	0.033
hsa-miR-10b-5p	-0.287	0.077	0.0002	0.054
hsa-miR-10b-3p	-0.313	0.084	0.0002	0.054
hsa-miR-506-3p	0.32	0.09	0.0004	0.072
hsa-miR-193b-5p	0.173	0.05	0.0006	0.089
hsa-miR-1248	-0.244	0.075	0.0012	0.138
hsa-miR-514a-3p	0.216	0.067	0.0012	0.138
hsa-miR-9903	0.15	0.051	0.0032	0.256
hsa-miR-365a-3p	0.118	0.04	0.0033	0.256
hsa-miR-365b-3p	0.118	0.04	0.0033	0.256
hsa-miR-95-3p	-0.24	0.084	0.0045	0.316
hsa-miR-507	0.237	0.085	0.0054	0.338
hsa-miR-549a-5p	0.191	0.069	0.0056	0.338
hsa-miR-196b-5p	-0.071	0.027	0.0081	0.449
hsa-miR-3065-3p	-0.107	0.041	0.0087	0.451
hsa-miR-514a-5p	0.188	0.073	0.0094	0.451
hsa-miR-365a-5p	0.134	0.052	0.0099	0.451
hsa-miR-30b-3p	0.061	0.024	0.0113	0.455
hsa-miR-4772-3p	-0.159	0.063	0.0123	0.455
hsa-miR-16-1-3p	-0.095	0.038	0.0129	0.455
hsa-miR-193b-3p	0.145	0.058	0.0131	0.455
hsa-miR-520a-5p	0.053	0.021	0.0132	0.455
hsa-miR-340-3p	-0.056	0.023	0.0141	0.455
hsa-miR-1323	0.058	0.023	0.0141	0.455
hsa-miR-518e-5p	0.053	0.022	0.0176	0.455
hsa-miR-519b-5p	0.053	0.022	0.0176	0.455
hsa-miR-519c-5p	0.053	0.022	0.0176	0.455
hsa-miR-522-5p	0.053	0.022	0.0176	0.455
hsa-miR-523-5p	0.053	0.022	0.0176	0.455
hsa-miR-224-3p	-0.1	0.042	0.0176	0.455
hsa-miR-301a-5p	-0.089	0.038	0.0182	0.455
hsa-miR-24-2-5p	-0.061	0.026	0.0187	0.455
hsa-miR-196b-3p	-0.079	0.034	0.0202	0.475
hsa-miR-515-5p	0.047	0.02	0.0211	0.482
hsa-miR-519a-5p	0.053	0.023	0.0223	0.485
hsa-miR-30c-5p	0.026	0.011	0.0232	0.485
hsa-miR-140-5p	-0.039	0.017	0.0237	0.485
hsa-miR-519d-5p	0.049	0.021	0.0238	0.485
hsa-miR-518f-5p	0.044	0.02	0.0257	0.485
hsa-miR-3065-5p	-0.084	0.038	0.0261	0.485
hsa-miR-519a-2-5p	0.042	0.019	0.0262	0.485
hsa-miR-520b-5p	0.042	0.019	0.0262	0.485
hsa-miR-3173-5p	0.086	0.039	0.0277	0.5
hsa-miR-30b-5p	0.041	0.019	0.0307	0.531
hsa-miR-520h	0.043	0.02	0.0307	0.531
hsa-miR-509-5p	0.171	0.08	0.0333	0.545
hsa-miR-629-3p	0.083	0.039	0.0335	0.545
hsa-miR-1275	0.103	0.049	0.0342	0.545
hsa-miR-450b-3p	-0.078	0.037	0.0344	0.545
hsa-miR-497-5p	-0.079	0.038	0.0374	0.581
hsa-miR-27a-3p	0.034	0.017	0.0385	0.587
hsa-miR-520g-3p	0.044	0.021	0.0395	0.59
hsa-miR-125b-2-3p	-0.061	0.03	0.0413	0.594
hsa-miR-143-5p	-0.059	0.029	0.042	0.594
hsa-miR-542-3p	-0.063	0.031	0.0437	0.594
hsa-miR-29b-2-5p	-0.05	0.025	0.0446	0.594
hsa-miR-548aw	0.045	0.022	0.0448	0.594
hsa-miR-525-5p	0.04	0.02	0.0449	0.594
hsa-miR-483-5p	0.079	0.04	0.0455	0.594
hsa-miR-576-5p	0.045	0.023	0.046	0.594
hsa-miR-3664-3p	0.047	0.024	0.0467	0.594
hsa-miR-195-5p	-0.088	0.045	0.0491	0.608
hsa-miR-516b-5p	0.045	0.023	0.0498	0.608
hsa-miR-340-5p	-0.045	0.023	0.0517	0.608
hsa-miR-24-3p	0.037	0.019	0.0532	0.608
hsa-miR-499a-5p	0.035	0.018	0.0537	0.608
hsa-miR-521	0.049	0.025	0.0538	0.608
hsa-miR-194-5p	-0.047	0.025	0.0546	0.608
hsa-miR-125a-5p	0.054	0.028	0.056	0.608
hsa-miR-520a-3p	0.069	0.036	0.0571	0.608
hsa-miR-5695	0.14	0.074	0.0573	0.608
hsa-miR-1307-5p	-0.045	0.024	0.0587	0.608
hsa-miR-450a-2-3p	-0.046	0.024	0.0592	0.608
hsa-miR-301a-3p	-0.039	0.021	0.0603	0.608

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-212-3p	-0.125	0.067	0.0615	0.608
hsa-miR-518d-5p	0.037	0.02	0.0618	0.608
hsa-miR-526a-5p	0.037	0.02	0.0619	0.608
hsa-miR-520f-5p	0.072	0.039	0.0622	0.608
hsa-miR-520c-5p	0.036	0.02	0.0626	0.608
hsa-miR-33a-3p	-0.059	0.032	0.0633	0.608
hsa-miR-518a-3p	0.043	0.023	0.0634	0.608
hsa-miR-6715b-3p	-0.159	0.087	0.0662	0.62
hsa-miR-296-5p	0.073	0.04	0.0662	0.62
hsa-miR-4454	-0.106	0.058	0.0682	0.62
hsa-miR-424-3p	0.046	0.025	0.0692	0.62
hsa-miR-223-5p	-0.077	0.043	0.0707	0.62
hsa-miR-524-3p	0.037	0.02	0.0718	0.62
hsa-miR-450b-5p	-0.04	0.022	0.0722	0.62
hsa-miR-519d-3p	0.033	0.019	0.0733	0.62
hsa-miR-1299	0.24	0.134	0.0738	0.62
hsa-miR-450a-5p	-0.043	0.024	0.0748	0.62
hsa-miR-518b	0.055	0.031	0.0752	0.62
hsa-miR-584-5p	-0.068	0.038	0.0758	0.62
hsa-miR-6724-5p	0.095	0.054	0.0769	0.62
hsa-miR-518e-3p	0.045	0.026	0.0785	0.62
hsa-miR-342-5p	-0.046	0.026	0.0788	0.62
hsa-miR-30d-5p	0.034	0.02	0.079	0.62
hsa-miR-3679-5p	-0.089	0.051	0.0802	0.62
hsa-miR-516a-5p	0.04	0.023	0.0807	0.62
hsa-miR-520g-5p	0.048	0.028	0.0822	0.62
hsa-miR-188-5p	-0.033	0.019	0.0832	0.62
hsa-miR-30c-1-3p	0.035	0.02	0.0836	0.62
hsa-miR-192-5p	-0.038	0.022	0.0837	0.62
hsa-miR-708-5p	-0.128	0.074	0.0842	0.62
hsa-miR-106b-5p	-0.04	0.023	0.0848	0.62
hsa-miR-548b-3p	0.061	0.036	0.0849	0.62
hsa-miR-628-5p	-0.045	0.026	0.0854	0.62
hsa-miR-3664-5p	0.069	0.04	0.0884	0.629
hsa-miR-524-5p	0.031	0.018	0.0889	0.629
hsa-miR-1305	0.054	0.032	0.0891	0.629
hsa-miR-653-3p	-0.062	0.037	0.0901	0.631
hsa-miR-31-3p	0.073	0.043	0.0917	0.636
hsa-miR-301b-3p	-0.074	0.044	0.0936	0.639
hsa-miR-498-5p	0.051	0.03	0.0937	0.639
hsa-miR-4708-3p	0.06	0.036	0.0971	0.656
hsa-miR-1284	0.062	0.038	0.1002	0.667
hsa-miR-203a-3p	0.12	0.073	0.1004	0.667
hsa-miR-27b-5p	-0.036	0.022	0.1019	0.67
hsa-miR-190a-5p	-0.068	0.042	0.1027	0.67
hsa-miR-33b-5p	-0.061	0.037	0.1034	0.67
hsa-miR-766-5p	-0.068	0.042	0.1081	0.692
hsa-let-7g-3p	-0.078	0.048	0.1086	0.692
hsa-miR-526b-5p	0.036	0.023	0.1098	0.694
hsa-miR-498-3p	0.053	0.033	0.1127	0.705
hsa-miR-2116-3p	0.069	0.044	0.1153	0.705
hsa-miR-454-3p	-0.027	0.017	0.1154	0.705
hsa-miR-1296-5p	0.043	0.028	0.1157	0.705
hsa-miR-517-5p	0.029	0.019	0.1175	0.705
hsa-miR-30c-2-3p	0.029	0.018	0.1176	0.705
hsa-miR-942-5p	-0.039	0.025	0.118	0.705
hsa-miR-2115-5p	-0.072	0.046	0.1188	0.705
hsa-miR-629-5p	0.033	0.021	0.1208	0.71
hsa-miR-653-5p	-0.059	0.038	0.1216	0.71
hsa-miR-9985	-0.034	0.022	0.1229	0.713
hsa-miR-517a-3p	0.032	0.021	0.1269	0.719
hsa-miR-517b-3p	0.032	0.021	0.1269	0.719
hsa-miR-26a-5p	0.015	0.01	0.1278	0.719
hsa-miR-6511b-3p	0.065	0.043	0.1282	0.719
hsa-miR-223-3p	-0.06	0.04	0.1286	0.719
hsa-miR-153-3p	-0.076	0.05	0.1302	0.723
hsa-miR-107	-0.044	0.03	0.1323	0.728
hsa-miR-361-5p	0.027	0.018	0.133	0.728
hsa-miR-518c-5p	0.03	0.02	0.1344	0.729
hsa-miR-483-3p	0.071	0.048	0.1351	0.729
hsa-let-7e-3p	0.029	0.02	0.1393	0.738
hsa-miR-130a-5p	-0.051	0.035	0.1397	0.738
hsa-miR-424-5p	0.038	0.026	0.141	0.738
hsa-miR-144-3p	-0.087	0.059	0.141	0.738
hsa-miR-337-3p	-0.029	0.02	0.143	0.738
hsa-miR-548d-5p	-0.042	0.029	0.1432	0.738

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-1306-5p	0.064	0.044	0.1442	0.738
hsa-miR-132-3p	-0.036	0.025	0.1443	0.738
hsa-miR-342-3p	-0.036	0.025	0.1466	0.744
hsa-miR-4802-5p	-0.041	0.028	0.1482	0.747
hsa-miR-542-5p	-0.033	0.023	0.1494	0.749
hsa-miR-186-3p	-0.041	0.028	0.1517	0.755
hsa-miR-191-5p	0.02	0.014	0.1533	0.759
hsa-miR-517c-3p	0.026	0.018	0.1552	0.763
hsa-miR-23a-3p	0.028	0.02	0.158	0.772
hsa-miR-142-5p	-0.066	0.047	0.162	0.779
hsa-miR-671-5p	-0.032	0.023	0.1625	0.779
hsa-miR-133a-5p	-0.061	0.044	0.1643	0.779
hsa-miR-4448	0.099	0.072	0.1659	0.779
hsa-miR-548ay-5p	-0.039	0.028	0.1682	0.779
hsa-miR-337-5p	-0.029	0.021	0.1683	0.779
hsa-miR-758-3p	-0.029	0.021	0.1684	0.779
hsa-miR-497-3p	-0.047	0.035	0.1699	0.779
hsa-miR-32-3p	-0.036	0.026	0.1707	0.779
hsa-miR-2114-5p	-0.075	0.055	0.1715	0.779
hsa-miR-15a-3p	-0.045	0.033	0.1729	0.779
hsa-miR-4999-3p	0.064	0.047	0.1746	0.779
hsa-miR-203b-3p	0.084	0.062	0.1747	0.779
hsa-miR-425-3p	-0.018	0.013	0.1756	0.779
hsa-miR-1246	0.08	0.059	0.1786	0.779
hsa-miR-548ad-5p	-0.037	0.027	0.1798	0.779
hsa-miR-1291	0.047	0.035	0.1826	0.779
hsa-miR-549a-3p	0.097	0.073	0.1833	0.779
hsa-miR-504-5p	-0.059	0.045	0.1842	0.779
hsa-miR-518f-3p	0.031	0.023	0.1845	0.779
hsa-miR-2355-3p	-0.056	0.042	0.1849	0.779
hsa-miR-616-3p	0.051	0.039	0.1875	0.779
hsa-miR-142-3p	-0.053	0.04	0.1883	0.779
hsa-miR-3614-5p	-0.063	0.048	0.1885	0.779
hsa-miR-548h-5p	-0.046	0.035	0.1889	0.779
hsa-miR-1304-3p	0.044	0.033	0.189	0.779
hsa-miR-145-3p	-0.031	0.024	0.1914	0.779
hsa-miR-511-3p	-0.056	0.043	0.194	0.779
hsa-miR-425-5p	-0.022	0.017	0.1944	0.779

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-15a-5p	-0.05	0.039	0.1944	0.779
hsa-miR-1255b-5p	0.052	0.04	0.1944	0.779
hsa-miR-154-3p	-0.038	0.03	0.1951	0.779
hsa-miR-590-5p	0.029	0.022	0.1954	0.779
hsa-miR-4433b-5p	0.103	0.08	0.1963	0.779
hsa-miR-500b-5p	0.022	0.017	0.1982	0.779
hsa-miR-887-3p	-0.039	0.031	0.1987	0.779
hsa-let-7f-1-3p	-0.081	0.064	0.1996	0.779
hsa-miR-3925-3p	0.058	0.045	0.2011	0.779
hsa-miR-125b-5p	0.037	0.029	0.2018	0.779
hsa-miR-518a-5p	0.027	0.021	0.2026	0.779
hsa-miR-10399-5p	0.059	0.046	0.2029	0.779
hsa-miR-1294	0.049	0.038	0.2038	0.779
hsa-miR-146b-3p	-0.072	0.056	0.204	0.779
hsa-miR-3117-3p	-0.083	0.065	0.2043	0.779
hsa-miR-1197	-0.055	0.044	0.2045	0.779
hsa-miR-421	-0.023	0.018	0.2067	0.784
hsa-miR-152-5p	-0.049	0.039	0.2111	0.794
hsa-miR-3913-5p	0.042	0.034	0.2115	0.794
hsa-miR-512-5p	0.036	0.029	0.2137	0.798
hsa-miR-652-5p	0.029	0.023	0.2156	0.801
hsa-miR-323b-3p	-0.052	0.043	0.2185	0.804
hsa-miR-496	-0.042	0.034	0.2203	0.804
hsa-miR-2276-3p	-0.055	0.045	0.2208	0.804
hsa-miR-525-3p	0.026	0.021	0.223	0.804
hsa-miR-31-5p	0.052	0.043	0.2232	0.804
hsa-miR-625-3p	0.032	0.026	0.224	0.804
hsa-miR-495-3p	-0.03	0.024	0.2254	0.804
hsa-miR-214-5p	-0.023	0.019	0.2255	0.804
hsa-miR-12135	-0.073	0.06	0.2264	0.804
hsa-miR-330-3p	-0.037	0.031	0.2266	0.804
hsa-miR-376c-3p	0.031	0.026	0.2302	0.811
hsa-miR-3179	0.055	0.046	0.2307	0.811
hsa-miR-320a-3p	0.035	0.03	0.233	0.815
hsa-miR-485-5p	0.033	0.028	0.2339	0.815
hsa-miR-1306-3p	-0.038	0.032	0.2371	0.816
hsa-miR-532-3p	0.044	0.037	0.2381	0.816
hsa-miR-1290	0.081	0.069	0.2388	0.816

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-6881-3p	-0.058	0.049	0.2402	0.816
hsa-miR-330-5p	-0.038	0.032	0.2404	0.816
hsa-miR-454-5p	-0.027	0.023	0.2407	0.816
hsa-miR-619-5p	0.077	0.066	0.2416	0.816
hsa-miR-527	0.026	0.022	0.2441	0.821
hsa-miR-642a-5p	-0.14	0.121	0.2462	0.825
hsa-miR-451a	-0.073	0.064	0.2486	0.826
hsa-miR-548e-5p	-0.034	0.029	0.2488	0.826
hsa-miR-502-3p	0.029	0.025	0.2526	0.835
hsa-miR-32-5p	-0.024	0.022	0.2587	0.852
hsa-miR-539-5p	0.043	0.039	0.2637	0.864
hsa-miR-664a-5p	0.02	0.018	0.2717	0.871
hsa-miR-423-5p	0.045	0.041	0.2717	0.871
hsa-miR-548ae-5p	-0.026	0.024	0.2725	0.871
hsa-miR-450a-1-3p	-0.023	0.021	0.2734	0.871
hsa-miR-548a-3p	-0.043	0.039	0.2737	0.871
hsa-miR-769-3p	0.041	0.037	0.2747	0.871
hsa-miR-20b-5p	-0.047	0.043	0.2767	0.871
hsa-miR-616-5p	0.044	0.04	0.2796	0.871
hsa-miR-323a-3p	0.024	0.022	0.2822	0.871
hsa-miR-585-3p	-0.058	0.054	0.2834	0.871
hsa-miR-597-5p	0.045	0.042	0.284	0.871
hsa-miR-548k	0.028	0.026	0.284	0.871
hsa-miR-151a-3p	0.017	0.016	0.2864	0.871
hsa-miR-519a-3p	0.022	0.02	0.2866	0.871
hsa-miR-34a-3p	0.037	0.035	0.2876	0.871
hsa-let-7c-5p	-0.031	0.029	0.2878	0.871
hsa-miR-570-3p	-0.042	0.039	0.2883	0.871
hsa-miR-766-3p	-0.046	0.043	0.2887	0.871
hsa-miR-148b-3p	-0.019	0.018	0.2897	0.871
hsa-miR-185-5p	-0.039	0.037	0.2903	0.871
hsa-miR-193a-3p	-0.057	0.054	0.2915	0.871
hsa-miR-3613-3p	0.041	0.039	0.2918	0.871
hsa-miR-500a-5p	0.018	0.017	0.2918	0.871
hsa-miR-520e-3p	-0.027	0.026	0.2925	0.871
hsa-miR-128-3p	-0.017	0.016	0.2955	0.872
hsa-miR-23c	0.025	0.024	0.2955	0.872
hsa-miR-20a-3p	0.015	0.015	0.2961	0.872
hsa-miR-579-3p	0.027	0.026	0.2979	0.873
hsa-miR-224-5p	-0.036	0.035	0.3005	0.877
hsa-miR-149-5p	0.032	0.031	0.3018	0.877
hsa-miR-3617-5p	-0.081	0.079	0.3039	0.877
hsa-miR-148a-3p	-0.035	0.034	0.3068	0.877
hsa-miR-374a-5p	-0.019	0.019	0.3099	0.877
hsa-miR-548b-5p	0.03	0.03	0.3103	0.877
hsa-miR-99a-3p	-0.04	0.04	0.3108	0.877
hsa-miR-545-5p	-0.026	0.026	0.312	0.877
hsa-miR-1285-3p	-0.029	0.029	0.3121	0.877
hsa-miR-433-5p	-0.043	0.043	0.3124	0.877
hsa-miR-556-3p	0.046	0.045	0.3129	0.877
hsa-miR-144-5p	-0.063	0.063	0.3148	0.877
hsa-miR-548f-5p	-0.048	0.048	0.3161	0.877
hsa-miR-1287-5p	-0.022	0.022	0.3174	0.877
hsa-miR-139-3p	0.04	0.04	0.3183	0.877
hsa-miR-4639-5p	-0.045	0.045	0.3193	0.877
hsa-miR-545-3p	-0.027	0.027	0.3196	0.877
hsa-miR-26a-2-3p	0.016	0.016	0.3199	0.877
hsa-miR-2110	0.034	0.034	0.3204	0.877
hsa-miR-590-3p	0.021	0.021	0.3252	0.886
hsa-miR-197-3p	0.029	0.03	0.3268	0.886
hsa-miR-589-5p	-0.031	0.031	0.3271	0.886
hsa-miR-515-3p	0.02	0.021	0.3318	0.892
hsa-miR-106a-3p	-0.028	0.029	0.3345	0.892
hsa-miR-143-3p	-0.027	0.028	0.3365	0.892
hsa-miR-6511a-3p	-0.033	0.035	0.338	0.892
hsa-miR-215-5p	-0.025	0.027	0.3397	0.892
hsa-miR-21-5p	-0.027	0.029	0.3404	0.892
hsa-miR-543	-0.029	0.031	0.341	0.892
hsa-miR-181c-3p	-0.021	0.022	0.3426	0.892
hsa-miR-17-5p	-0.019	0.02	0.3427	0.892
hsa-miR-181d-5p	-0.029	0.03	0.3435	0.892
hsa-miR-18a-5p	-0.031	0.033	0.3444	0.892
hsa-miR-1185-2-3p	-0.032	0.033	0.3449	0.892
hsa-miR-934	0.024	0.025	0.345	0.892
hsa-miR-374b-5p	0.018	0.019	0.3457	0.892
hsa-miR-625-5p	0.028	0.03	0.3484	0.896

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-196a-5p	-0.061	0.065	0.3495	0.896
hsa-miR-3611	-0.023	0.025	0.3536	0.898
hsa-miR-335-3p	-0.029	0.032	0.3558	0.898
hsa-miR-183-5p	0.035	0.038	0.3566	0.898
hsa-miR-10a-3p	-0.023	0.025	0.3567	0.898
hsa-miR-21-3p	-0.034	0.036	0.3572	0.898
hsa-miR-3188	0.071	0.077	0.358	0.898
hsa-miR-99a-5p	-0.032	0.035	0.3583	0.898
hsa-miR-132-5p	-0.022	0.024	0.3609	0.898
hsa-miR-518c-3p	0.02	0.022	0.3627	0.898
hsa-miR-659-5p	0.029	0.032	0.3645	0.898
hsa-miR-378i	-0.033	0.037	0.3666	0.898
hsa-miR-7-5p	-0.026	0.029	0.3668	0.898
hsa-miR-432-3p	0.031	0.035	0.3693	0.898
hsa-miR-3690	0.063	0.071	0.3699	0.898
hsa-miR-3064-5p	-0.03	0.033	0.3699	0.898
hsa-miR-2115-3p	-0.04	0.044	0.3705	0.898
hsa-miR-664b-5p	0.034	0.039	0.3711	0.898
hsa-miR-466	0.042	0.047	0.3712	0.898
hsa-miR-501-3p	0.026	0.029	0.3724	0.899
hsa-miR-200b-3p	0.03	0.034	0.3739	0.899
hsa-miR-4732-3p	-0.058	0.066	0.3777	0.9
hsa-miR-30a-5p	0.018	0.021	0.3788	0.9
hsa-miR-516a-3p	-0.058	0.066	0.3789	0.9
hsa-miR-874-5p	0.041	0.047	0.3793	0.9
hsa-miR-33a-5p	-0.026	0.03	0.3798	0.9
hsa-miR-1185-1-3p	-0.028	0.032	0.384	0.906
hsa-miR-516b-3p	-0.058	0.066	0.3857	0.906
hsa-miR-183-3p	0.049	0.057	0.3862	0.906
hsa-miR-582-5p	-0.024	0.028	0.3871	0.906
hsa-miR-544a	-0.029	0.034	0.3921	0.914
hsa-miR-500a-3p	0.016	0.019	0.3928	0.914
hsa-miR-579-5p	0.032	0.038	0.3946	0.915
hsa-miR-210-3p	0.043	0.051	0.3987	0.92
hsa-miR-99b-5p	0.014	0.017	0.3992	0.92
hsa-miR-99b-3p	0.011	0.014	0.4025	0.925
hsa-miR-16-5p	-0.029	0.035	0.4056	0.926
hsa-miR-744-5p	0.026	0.031	0.4064	0.926

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-92b-5p	0.038	0.046	0.4076	0.926
hsa-miR-889-3p	0.028	0.034	0.41	0.926
hsa-miR-2277-5p	-0.025	0.031	0.4127	0.926
hsa-miR-6513-3p	0.017	0.02	0.4131	0.926
hsa-miR-548ab	-0.035	0.043	0.4135	0.926
hsa-miR-5001-3p	0.035	0.043	0.4136	0.926
hsa-miR-1226-3p	-0.036	0.044	0.4182	0.926
hsa-miR-105-5p	-0.04	0.05	0.4187	0.926
hsa-let-7d-3p	0.046	0.057	0.4206	0.926
hsa-miR-1262	-0.025	0.032	0.4207	0.926
hsa-miR-10527-5p	0.027	0.033	0.4208	0.926
hsa-miR-155-5p	-0.062	0.078	0.4209	0.926
hsa-miR-455-5p	-0.028	0.035	0.4209	0.926
hsa-miR-423-3p	0.024	0.03	0.4228	0.928
hsa-miR-25-5p	0.023	0.029	0.426	0.931
hsa-miR-3145-3p	-0.031	0.039	0.4272	0.931
hsa-miR-502-5p	0.017	0.022	0.4289	0.931
hsa-miR-548at-5p	-0.033	0.042	0.4297	0.931
hsa-miR-296-3p	-0.037	0.047	0.4311	0.931
hsa-miR-520d-5p	0.018	0.023	0.4313	0.931
hsa-miR-30d-3p	-0.022	0.028	0.4354	0.932
hsa-miR-452-5p	-0.024	0.031	0.4363	0.932
hsa-miR-6503-3p	0.039	0.05	0.4387	0.932
hsa-miR-4742-3p	-0.024	0.032	0.4409	0.932
hsa-miR-133b	-0.037	0.049	0.4425	0.932
hsa-miR-4662a-5p	-0.025	0.032	0.4437	0.932
hsa-miR-3157-5p	0.029	0.038	0.4442	0.932
hsa-miR-100-5p	0.028	0.037	0.4454	0.932
hsa-let-7e-5p	0.012	0.016	0.447	0.932
hsa-miR-4781-3p	0.03	0.039	0.4473	0.932
hsa-miR-181a-2-3p	0.027	0.035	0.4476	0.932
hsa-miR-135b-5p	0.041	0.054	0.4482	0.932
hsa-miR-574-3p	0.025	0.033	0.4487	0.932
hsa-let-7a-3p	-0.015	0.02	0.4495	0.932
hsa-miR-3143	0.04	0.053	0.4509	0.932
hsa-miR-133a-3p	-0.033	0.043	0.4509	0.932
hsa-miR-96-5p	0.033	0.045	0.4576	0.941
hsa-miR-1271-5p	0.021	0.028	0.4578	0.941

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-146b-5p	-0.032	0.043	0.4659	0.945
hsa-miR-191-3p	-0.02	0.027	0.4677	0.945
hsa-miR-503-5p	-0.019	0.027	0.4683	0.945
hsa-miR-4732-5p	-0.058	0.08	0.4697	0.945
hsa-miR-204-5p	0.057	0.079	0.4705	0.945
hsa-miR-548ba	-0.086	0.12	0.4706	0.945
hsa-miR-18b-5p	-0.032	0.045	0.4715	0.945
hsa-miR-2116-5p	0.022	0.031	0.4747	0.945
hsa-miR-660-3p	0.016	0.023	0.4748	0.945
hsa-miR-489-3p	-0.028	0.039	0.4763	0.945
hsa-miR-98-3p	0.042	0.059	0.4804	0.945
hsa-miR-561-3p	0.026	0.037	0.4808	0.945
hsa-miR-874-3p	0.036	0.052	0.484	0.945
hsa-miR-216a-5p	-0.357	0.511	0.4844	0.945
hsa-miR-664a-3p	-0.018	0.025	0.4858	0.945
hsa-miR-345-5p	-0.017	0.025	0.486	0.945
hsa-miR-195-3p	-0.018	0.026	0.4871	0.945
hsa-miR-660-5p	0.015	0.022	0.4873	0.945
hsa-miR-519e-3p	0.015	0.022	0.4875	0.945
hsa-miR-331-5p	-0.017	0.024	0.4887	0.945
hsa-miR-654-3p	0.014	0.021	0.4904	0.945
hsa-miR-512-3p	0.021	0.031	0.4943	0.945
hsa-miR-138-5p	0.045	0.067	0.4946	0.945
hsa-miR-548i	-0.043	0.063	0.4965	0.945
hsa-miR-1260a	0.02	0.03	0.4968	0.945
hsa-miR-7706	0.02	0.029	0.4971	0.945
hsa-miR-490-3p	0.053	0.077	0.4972	0.945
hsa-miR-152-3p	-0.017	0.025	0.5	0.945
hsa-miR-769-5p	-0.012	0.018	0.5014	0.945
hsa-miR-125b-1-3p	-0.021	0.032	0.5028	0.945
hsa-miR-141-5p	0.017	0.025	0.5033	0.945
hsa-miR-154-5p	0.016	0.025	0.5049	0.945
hsa-miR-29b-1-5p	0.024	0.036	0.5053	0.945
hsa-miR-1307-3p	-0.018	0.028	0.509	0.945
hsa-miR-19a-3p	-0.02	0.03	0.5097	0.945
hsa-miR-125a-3p	0.014	0.022	0.511	0.945
hsa-miR-519c-3p	-0.013	0.02	0.5112	0.945
hsa-miR-582-3p	-0.022	0.033	0.5117	0.945

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-4659a-3p	-0.038	0.057	0.5136	0.945
hsa-miR-548t-3p	0.016	0.025	0.5144	0.945
hsa-miR-624-3p	-0.016	0.024	0.515	0.945
hsa-miR-487a-3p	-0.021	0.032	0.5158	0.945
hsa-miR-361-3p	-0.012	0.018	0.518	0.945
hsa-miR-505-3p	-0.015	0.023	0.5187	0.945
hsa-miR-378f	-0.026	0.04	0.5198	0.945
hsa-miR-376b-5p	0.018	0.028	0.5215	0.945
hsa-miR-548bc	-0.021	0.032	0.5223	0.945
hsa-miR-9-5p	0.029	0.045	0.5226	0.945
hsa-miR-196a-3p	-0.055	0.085	0.5227	0.945
hsa-miR-148b-5p	-0.012	0.019	0.5231	0.945
hsa-miR-16-2-3p	-0.02	0.031	0.5255	0.945
hsa-miR-665	-0.022	0.036	0.5268	0.945
hsa-miR-376c-5p	0.018	0.028	0.5268	0.945
hsa-miR-376a-3p	0.015	0.024	0.5274	0.945
hsa-let-7b-3p	-0.03	0.048	0.5288	0.945
hsa-miR-767-5p	-0.03	0.047	0.5293	0.945
hsa-miR-15b-3p	-0.023	0.037	0.53	0.945
hsa-miR-148a-5p	-0.024	0.039	0.5327	0.945
hsa-miR-1843	-0.014	0.022	0.5333	0.945
hsa-miR-34b-5p	-0.03	0.049	0.5334	0.945
hsa-miR-93-5p	-0.014	0.022	0.5342	0.945
hsa-miR-379-3p	-0.016	0.026	0.5362	0.945
hsa-miR-5699-3p	0.024	0.039	0.5378	0.945
hsa-miR-675-3p	0.015	0.024	0.5384	0.945
hsa-miR-324-5p	-0.013	0.021	0.5388	0.945
hsa-miR-4521	0.033	0.053	0.5408	0.945
hsa-miR-628-3p	-0.015	0.024	0.5425	0.945
hsa-miR-329-3p	0.02	0.032	0.5432	0.945
hsa-miR-1273c	-0.02	0.033	0.5442	0.945
hsa-miR-193a-5p	-0.032	0.053	0.5466	0.945
hsa-miR-522-3p	0.017	0.028	0.5496	0.945
hsa-miR-378c	-0.018	0.03	0.5509	0.945
hsa-miR-376b-3p	-0.014	0.024	0.5521	0.945
hsa-miR-431-5p	-0.02	0.033	0.5525	0.945
hsa-miR-548e-3p	-0.014	0.023	0.5529	0.945
hsa-miR-3925-5p	0.029	0.049	0.553	0.945

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-328-3p	0.025	0.042	0.5547	0.945
hsa-miR-487b-5p	0.016	0.028	0.5549	0.945
hsa-miR-651-5p	-0.015	0.026	0.5572	0.946
hsa-miR-200c-3p	0.019	0.033	0.558	0.946
hsa-miR-320b	0.016	0.027	0.5605	0.946
hsa-miR-6503-5p	0.031	0.053	0.5608	0.946
hsa-miR-3614-3p	-0.022	0.039	0.5618	0.946
hsa-miR-29c-3p	-0.014	0.024	0.564	0.946
hsa-miR-19b-3p	0.011	0.02	0.5647	0.946
hsa-miR-548n	-0.02	0.036	0.5651	0.946
hsa-miR-181b-3p	-0.018	0.032	0.5694	0.946
hsa-miR-370-5p	0.015	0.027	0.5698	0.946
hsa-miR-519e-5p	0.019	0.033	0.5716	0.946
hsa-miR-3613-5p	-0.019	0.033	0.5717	0.946
hsa-let-7g-5p	-0.02	0.036	0.5726	0.946
hsa-miR-20a-5p	0.011	0.019	0.5752	0.946
hsa-miR-9-3p	0.025	0.045	0.5764	0.946
hsa-miR-1255a	-0.035	0.064	0.5771	0.946
hsa-miR-1260b	0.017	0.03	0.5777	0.946
hsa-miR-339-5p	-0.013	0.023	0.581	0.946
hsa-miR-221-5p	0.011	0.02	0.5811	0.946
hsa-miR-3136-5p	-0.02	0.035	0.5814	0.946
hsa-miR-523-3p	0.016	0.029	0.5818	0.946
hsa-miR-493-5p	0.012	0.022	0.5825	0.946
hsa-miR-551b-3p	-0.019	0.035	0.584	0.946
hsa-miR-376a-5p	-0.014	0.026	0.5855	0.946
hsa-let-7i-3p	-0.025	0.046	0.5858	0.946
hsa-miR-941	0.015	0.027	0.5871	0.946
hsa-miR-200a-3p	-0.018	0.033	0.5879	0.946
hsa-miR-374a-3p	-0.013	0.024	0.5934	0.95
hsa-miR-23a-5p	0.029	0.056	0.5964	0.95
hsa-miR-598-3p	-0.026	0.05	0.5978	0.95
hsa-miR-3927-3p	0.066	0.126	0.5982	0.95
hsa-miR-548aa	0.013	0.024	0.6002	0.95
hsa-miR-4719	-0.033	0.063	0.6002	0.95
hsa-miR-181c-5p	0.017	0.033	0.6011	0.95
hsa-miR-501-5p	0.017	0.032	0.6017	0.95
hsa-miR-411-3p	-0.015	0.028	0.6028	0.95

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-409-5p	0.013	0.025	0.6052	0.95
hsa-miR-145-5p	-0.013	0.026	0.6069	0.95
hsa-miR-136-5p	-0.008	0.016	0.6082	0.95
hsa-miR-532-5p	0.009	0.018	0.6082	0.95
hsa-miR-455-3p	-0.017	0.034	0.6083	0.95
hsa-miR-181a-5p	0.015	0.029	0.6099	0.95
hsa-miR-7976	-0.015	0.028	0.6101	0.95
hsa-miR-199a-5p	-0.01	0.02	0.6137	0.952
hsa-miR-217-5p	-0.264	0.524	0.6142	0.952
hsa-miR-1247-5p	0.023	0.047	0.6149	0.952
hsa-miR-373-5p	0.033	0.067	0.617	0.953
hsa-miR-3200-3p	-0.029	0.058	0.6183	0.953
hsa-miR-377-3p	-0.011	0.023	0.6215	0.956
hsa-miR-181a-3p	-0.013	0.027	0.6241	0.958
hsa-miR-511-5p	-0.015	0.031	0.6264	0.96
hsa-miR-130b-5p	-0.025	0.052	0.6274	0.96
hsa-miR-372-5p	-0.036	0.074	0.6315	0.963
hsa-miR-299-3p	-0.013	0.028	0.6354	0.963
hsa-miR-4326	0.039	0.083	0.6397	0.963
hsa-miR-29a-5p	-0.012	0.025	0.6403	0.963
hsa-miR-486-3p	-0.029	0.062	0.6406	0.963
hsa-miR-190a-3p	-0.024	0.052	0.6423	0.963
hsa-miR-377-5p	-0.01	0.021	0.6426	0.963
hsa-miR-103a-2-5p	-0.019	0.04	0.6455	0.963
hsa-miR-186-5p	-0.006	0.014	0.6466	0.963
hsa-miR-4742-5p	0.017	0.038	0.6469	0.963
hsa-miR-493-3p	-0.013	0.027	0.6469	0.963
hsa-miR-222-3p	0.011	0.025	0.6489	0.963
hsa-miR-151b	-0.012	0.026	0.6492	0.963
hsa-miR-1269b	-0.331	0.729	0.6501	0.963
hsa-miR-1277-5p	-0.013	0.029	0.6523	0.963
hsa-miR-29c-5p	-0.008	0.017	0.656	0.963
hsa-miR-487b-3p	0.013	0.03	0.6563	0.963
hsa-miR-508-3p	0.104	0.235	0.6564	0.963
hsa-miR-4766-3p	-0.016	0.035	0.6573	0.963
hsa-miR-150-5p	-0.023	0.051	0.6581	0.963
hsa-miR-93-3p	0.008	0.018	0.6584	0.963
hsa-miR-19b-1-5p	0.009	0.021	0.659	0.963

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-15b-5p	-0.019	0.043	0.659	0.963
hsa-miR-550a-3p	0.016	0.037	0.6596	0.963
hsa-miR-185-3p	-0.02	0.046	0.6621	0.965
hsa-miR-23b-3p	-0.007	0.015	0.6642	0.965
hsa-miR-520b-3p	-0.012	0.029	0.6654	0.965
hsa-miR-25-3p	-0.015	0.034	0.666	0.965
hsa-miR-100-3p	-0.016	0.036	0.6686	0.965
hsa-miR-130b-3p	-0.018	0.042	0.6718	0.965
hsa-miR-9898	0.022	0.051	0.6726	0.965
hsa-miR-101-5p	0.009	0.021	0.6726	0.965
hsa-miR-548h-3p	-0.017	0.041	0.6749	0.965
hsa-miR-338-3p	-0.011	0.027	0.6751	0.965
hsa-miR-1269a	0.037	0.089	0.6754	0.965
hsa-miR-190b-5p	0.01	0.025	0.6759	0.965
hsa-miR-382-3p	-0.013	0.031	0.6783	0.965
hsa-miR-548z	-0.017	0.04	0.6811	0.965
hsa-miR-548ay-3p	-0.021	0.051	0.6814	0.965
hsa-miR-485-3p	0.016	0.04	0.6841	0.965
hsa-miR-520e-5p	-0.011	0.026	0.6842	0.965
hsa-miR-147b-5p	0.017	0.042	0.6854	0.965
hsa-miR-27b-3p	-0.006	0.014	0.6874	0.965
hsa-miR-548az-5p	0.022	0.055	0.6907	0.965
hsa-miR-202-5p	0.016	0.041	0.691	0.965
hsa-miR-3144-3p	0.027	0.068	0.6916	0.965
hsa-miR-487a-5p	0.012	0.029	0.692	0.965
hsa-miR-106b-3p	-0.009	0.023	0.6942	0.965
hsa-miR-433-3p	0.013	0.033	0.6979	0.965
hsa-miR-147b-3p	-0.019	0.049	0.6987	0.965
hsa-miR-551b-5p	-0.02	0.051	0.6992	0.965
hsa-miR-374b-3p	-0.008	0.021	0.6995	0.965
hsa-miR-326	0.009	0.022	0.6996	0.965
hsa-miR-10399-3p	-0.021	0.054	0.7002	0.965
hsa-miR-4286	0.015	0.04	0.7008	0.965
hsa-miR-1283	0.016	0.041	0.7017	0.965
hsa-miR-381-3p	0.011	0.029	0.703	0.965
hsa-miR-655-5p	0.014	0.037	0.703	0.965
hsa-miR-548g-5p	0.014	0.037	0.7046	0.966
hsa-miR-27a-5p	0.018	0.048	0.7092	0.97
hsa-miR-767-3p	-0.02	0.055	0.7109	0.97
hsa-miR-548w	-0.015	0.04	0.7149	0.97
hsa-miR-937-3p	-0.017	0.047	0.7162	0.97
hsa-miR-574-5p	0.013	0.037	0.719	0.97
hsa-miR-7-1-3p	0.009	0.024	0.7192	0.97
hsa-miR-4775	-0.015	0.042	0.7219	0.97
hsa-miR-146a-5p	-0.014	0.041	0.726	0.97
hsa-miR-449a	-0.011	0.03	0.7267	0.97
hsa-miR-4445-5p	0.087	0.25	0.7274	0.97
hsa-miR-181b-2-3p	0.016	0.046	0.7298	0.97
hsa-miR-219a-5p	-0.011	0.032	0.73	0.97
hsa-miR-490-5p	0.028	0.082	0.7301	0.97
hsa-miR-3688-3p	-0.013	0.036	0.7302	0.97
hsa-miR-410-5p	-0.024	0.069	0.7311	0.97
hsa-miR-331-3p	-0.019	0.055	0.7311	0.97
hsa-miR-3909	0.009	0.026	0.7311	0.97
hsa-miR-136-3p	0.01	0.028	0.7329	0.97
hsa-miR-765	-0.016	0.046	0.7338	0.97
hsa-miR-29a-3p	0.01	0.031	0.7341	0.97
hsa-miR-494-3p	0.009	0.027	0.7342	0.97
hsa-miR-576-3p	0.007	0.02	0.7359	0.97
hsa-miR-192-3p	-0.009	0.026	0.7363	0.97
hsa-miR-675-5p	-0.013	0.039	0.746	0.979
hsa-miR-1278	0.01	0.03	0.7474	0.979
hsa-miR-877-5p	0.013	0.042	0.7498	0.979
hsa-miR-7705	-0.01	0.03	0.7498	0.979
hsa-miR-214-3p	0.011	0.035	0.7504	0.979
hsa-miR-151a-5p	0.006	0.02	0.7519	0.979
hsa-miR-363-3p	-0.012	0.038	0.7525	0.979
hsa-miR-221-3p	0.006	0.019	0.7567	0.982
hsa-miR-369-3p	0.01	0.032	0.7579	0.982
hsa-miR-2682-3p	0.031	0.099	0.7582	0.982
hsa-miR-122-5p	-0.018	0.06	0.7613	0.983
hsa-miR-135a-5p	-0.028	0.093	0.7628	0.983
hsa-miR-770-5p	0.01	0.033	0.7652	0.983
hsa-miR-378d	-0.009	0.03	0.7688	0.983
hsa-miR-218-5p	0.009	0.031	0.7763	0.983
hsa-miR-378a-3p	-0.008	0.028	0.7783	0.983

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-98-5p	0.012	0.042	0.7784	0.983
hsa-miR-127-5p	0.007	0.025	0.7802	0.983
hsa-miR-30a-3p	0.007	0.025	0.7813	0.983
hsa-miR-138-1-3p	0.019	0.067	0.7819	0.983
hsa-miR-520d-3p	0.008	0.03	0.7826	0.983
hsa-miR-589-3p	-0.011	0.039	0.7857	0.983
hsa-miR-34a-5p	0.007	0.027	0.7876	0.983
hsa-miR-520c-3p	-0.007	0.025	0.7883	0.983
hsa-miR-182-5p	0.011	0.043	0.7895	0.983
hsa-miR-6501-5p	-0.014	0.053	0.7935	0.983
hsa-miR-362-3p	0.008	0.031	0.7938	0.983
hsa-miR-106a-5p	-0.008	0.032	0.7943	0.983
hsa-miR-526b-3p	-0.007	0.028	0.795	0.983
hsa-miR-1-3p	-0.012	0.046	0.795	0.983
hsa-miR-92a-3p	0.007	0.029	0.7955	0.983
hsa-miR-412-5p	-0.025	0.097	0.7969	0.983
hsa-miR-379-5p	0.006	0.025	0.7984	0.983
hsa-miR-581	-0.012	0.046	0.7988	0.983
hsa-let-7i-5p	-0.011	0.044	0.8008	0.983
hsa-miR-205-5p	0.007	0.029	0.8014	0.983
hsa-miR-188-3p	-0.006	0.025	0.8015	0.983
hsa-let-7b-5p	-0.01	0.041	0.8016	0.983
hsa-miR-362-5p	0.005	0.02	0.8026	0.983
hsa-miR-1295a	0.014	0.056	0.8026	0.983
hsa-miR-187-3p	-0.02	0.082	0.8033	0.983
hsa-miR-505-5p	-0.01	0.041	0.8042	0.983
hsa-miR-655-3p	0.006	0.025	0.8058	0.983
hsa-miR-140-3p	-0.004	0.017	0.8058	0.983
hsa-miR-548o-5p	0.004	0.017	0.8068	0.983
hsa-miR-486-5p	-0.014	0.058	0.8074	0.983
hsa-miR-184	0.01	0.041	0.8079	0.983
hsa-miR-211-5p	0.01	0.04	0.8081	0.983
hsa-miR-3605-3p	0.006	0.024	0.8084	0.983
hsa-miR-618	0.014	0.058	0.81	0.983
hsa-miR-758-5p	-0.008	0.033	0.8114	0.984
hsa-miR-548j-5p	-0.007	0.03	0.814	0.984
hsa-miR-30e-5p	0.005	0.023	0.8171	0.984
hsa-miR-652-3p	0.006	0.026	0.8177	0.984

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-1247-3p	0.009	0.038	0.8177	0.984
hsa-miR-4999-5p	-0.009	0.037	0.8194	0.984
hsa-miR-92b-3p	-0.008	0.037	0.8197	0.984
hsa-miR-409-3p	-0.005	0.023	0.8208	0.984
hsa-miR-432-5p	0.005	0.024	0.8238	0.986
hsa-miR-34c-3p	-0.011	0.05	0.8251	0.986
hsa-miR-548c-5p	0.004	0.017	0.827	0.986
hsa-miR-378a-5p	0.006	0.03	0.8299	0.986
hsa-miR-320c	0.006	0.029	0.8326	0.986
hsa-miR-519b-3p	0.004	0.021	0.8331	0.986
hsa-miR-4645-3p	-0.006	0.028	0.8335	0.986
hsa-miR-222-5p	0.008	0.038	0.8336	0.986
hsa-miR-539-3p	-0.008	0.037	0.8381	0.986
hsa-miR-548c-3p	-0.008	0.038	0.8397	0.986
hsa-miR-3158-3p	-0.01	0.051	0.8406	0.986
hsa-miR-1537-3p	0.007	0.035	0.8414	0.986
hsa-miR-3912-3p	0.005	0.024	0.8433	0.986
hsa-miR-488-3p	-0.013	0.067	0.8457	0.986
hsa-miR-130a-3p	-0.002	0.013	0.8465	0.986
hsa-miR-380-3p	-0.006	0.029	0.8465	0.986
hsa-miR-1180-3p	0.008	0.04	0.8472	0.986
hsa-miR-339-3p	0.003	0.016	0.8472	0.986
hsa-miR-1270	0.009	0.046	0.8481	0.986
hsa-miR-624-5p	0.004	0.022	0.8502	0.986
hsa-miR-664b-3p	-0.005	0.029	0.8509	0.986
hsa-miR-219b-5p	0.006	0.033	0.852	0.986
hsa-miR-873-5p	0.009	0.048	0.853	0.986
hsa-miR-382-5p	0.004	0.024	0.8531	0.986
hsa-miR-103a-3p	-0.002	0.013	0.8536	0.986
hsa-let-7d-5p	-0.006	0.035	0.8595	0.99
hsa-let-7f-5p	-0.007	0.037	0.8612	0.99
hsa-miR-548aq-3p	-0.008	0.047	0.8613	0.99
hsa-miR-199b-3p	-0.003	0.019	0.8637	0.99
hsa-miR-26a-1-3p	0.005	0.028	0.8684	0.99
hsa-miR-369-5p	0.004	0.022	0.8692	0.99
hsa-miR-548f-3p	-0.008	0.052	0.87	0.99
hsa-miR-199a-3p	-0.003	0.019	0.8701	0.99
hsa-miR-34c-5p	-0.008	0.048	0.871	0.99

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-548l	0.005	0.032	0.8743	0.99
hsa-miR-335-5p	-0.003	0.02	0.8744	0.99
hsa-miR-656-3p	0.006	0.035	0.8748	0.99
hsa-miR-371a-3p	-0.012	0.077	0.8761	0.99
hsa-miR-199b-5p	-0.004	0.029	0.8776	0.99
hsa-miR-5100	0.011	0.075	0.879	0.99
hsa-miR-5010-3p	-0.004	0.027	0.8793	0.99
hsa-miR-4677-3p	-0.004	0.03	0.8804	0.99
hsa-miR-671-3p	-0.005	0.032	0.8808	0.99
hsa-miR-329-5p	0.005	0.033	0.8838	0.992
hsa-miR-23b-5p	0.003	0.022	0.8866	0.993
hsa-miR-127-3p	0.004	0.028	0.8886	0.993
hsa-miR-548y	0.005	0.038	0.8889	0.993
hsa-miR-320d	0.004	0.029	0.8894	0.993
hsa-miR-18a-3p	0.005	0.04	0.898	0.994
hsa-miR-561-5p	-0.005	0.039	0.8992	0.994
hsa-miR-28-3p	0.002	0.017	0.8994	0.994
hsa-miR-6514-5p	-0.004	0.034	0.8994	0.994
hsa-miR-10a-5p	0.003	0.022	0.8997	0.994
hsa-miR-3928-3p	0.005	0.039	0.9	0.994
hsa-miR-141-3p	0.003	0.028	0.901	0.994
hsa-miR-17-3p	0.002	0.019	0.9022	0.994
hsa-miR-6513-5p	-0.005	0.04	0.9026	0.994
hsa-miR-410-3p	-0.004	0.034	0.903	0.994
hsa-miR-548am-5p	0.002	0.018	0.9087	0.994
hsa-miR-944	0.004	0.036	0.9094	0.994
hsa-miR-29b-3p	-0.003	0.026	0.9119	0.994
hsa-miR-135b-3p	0.006	0.056	0.9144	0.994
hsa-miR-548ar-5p	-0.004	0.039	0.915	0.994
hsa-miR-134-5p	-0.002	0.024	0.9185	0.994
hsa-let-7f-2-3p	-0.004	0.041	0.9193	0.994
hsa-miR-580-3p	-0.004	0.04	0.9214	0.994
hsa-miR-372-3p	-0.008	0.076	0.9214	0.994
hsa-miR-548q	0.003	0.031	0.9263	0.994
hsa-miR-373-3p	-0.006	0.061	0.9275	0.994
hsa-miR-30e-3p	0.002	0.024	0.9283	0.994
hsa-miR-381-5p	-0.002	0.025	0.9292	0.994
hsa-miR-200c-5p	0.002	0.027	0.9303	0.994

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-299-5p	0.002	0.028	0.9326	0.994
hsa-miR-548o-3p	0.002	0.031	0.9355	0.994
hsa-miR-375-3p	-0.008	0.1	0.9395	0.994
hsa-miR-503-3p	-0.002	0.033	0.9431	0.994
hsa-miR-668-3p	-0.002	0.033	0.9451	0.994
hsa-miR-548x-5p	0.003	0.052	0.9473	0.994
hsa-miR-22-3p	0.001	0.017	0.9497	0.994
hsa-miR-139-5p	0.002	0.034	0.9506	0.994
hsa-let-7a-5p	-0.001	0.016	0.9517	0.994
hsa-miR-429	0.005	0.08	0.952	0.994
hsa-miR-643	0.002	0.029	0.9526	0.994
hsa-miR-876-5p	0.003	0.058	0.9527	0.994
hsa-miR-548aj-5p	-0.003	0.046	0.9527	0.994
hsa-miR-320e	-0.002	0.032	0.9529	0.994
hsa-miR-518d-3p	0.002	0.031	0.9534	0.994
hsa-miR-1179	-0.002	0.032	0.9537	0.994
hsa-miR-491-5p	-0.001	0.026	0.9558	0.994
hsa-miR-520f-3p	0.002	0.039	0.9566	0.994
hsa-miR-22-5p	-0.001	0.022	0.9575	0.994
hsa-miR-627-5p	0.001	0.02	0.9582	0.994
hsa-miR-548au-5p	0.001	0.018	0.9587	0.994
hsa-miR-12136	0.002	0.046	0.9596	0.994
hsa-miR-484	-0.002	0.039	0.9612	0.994
hsa-miR-324-3p	0.002	0.032	0.9621	0.994
hsa-miR-1185-5p	0.001	0.027	0.9623	0.994
hsa-miR-431-3p	-0.001	0.03	0.9637	0.994
hsa-miR-370-3p	0.002	0.034	0.9637	0.994
hsa-miR-376a-2-5p	-0.001	0.027	0.9637	0.994
hsa-miR-495-5p	0.001	0.02	0.9675	0.994
hsa-miR-146a-3p	-0.004	0.098	0.9684	0.994
hsa-miR-6716-3p	-0.001	0.04	0.9699	0.994
hsa-miR-126-3p	-0.001	0.027	0.9703	0.994
hsa-miR-181b-5p	-0.001	0.027	0.9711	0.994
hsa-miR-28-5p	-0.001	0.021	0.9731	0.994
hsa-miR-137-3p	0.003	0.09	0.9734	0.994
hsa-miR-526a-3p	0.001	0.032	0.9752	0.994
hsa-miR-1277-3p	0.001	0.02	0.9756	0.994
hsa-miR-411-5p	0.001	0.028	0.976	0.994

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-641	0.001	0.025	0.9763	0.994
hsa-miR-380-5p	-0.001	0.035	0.9767	0.994
hsa-miR-205-3p	0.001	0.032	0.9776	0.994
hsa-miR-548x-3p	0.008	0.301	0.9785	0.994
hsa-miR-615-3p	0.001	0.039	0.9787	0.994
hsa-miR-26b-5p	0	0.015	0.9788	0.994
hsa-miR-6507-5p	0.002	0.057	0.9788	0.994
hsa-miR-126-5p	0.001	0.029	0.9822	0.995
hsa-miR-873-3p	0.002	0.072	0.9824	0.995
hsa-miR-5699-5p	0.001	0.04	0.9868	0.996

microRNA	log2FC	lfcSE	-log10(pval)	FDR
hsa-miR-101-2-5p	-0.001	0.047	0.987	0.996
hsa-miR-1301-3p	0.001	0.042	0.9879	0.996
hsa-miR-101-3p	0	0.027	0.991	0.996
hsa-miR-34b-3p	0.001	0.049	0.9916	0.996
hsa-miR-26b-3p	0	0.019	0.9918	0.996
hsa-miR-548ak	0	0.032	0.9933	0.996
hsa-miR-3615	0	0.035	0.9943	0.996
hsa-miR-7977	0	0.043	0.9947	0.996
hsa-miR-371a-5p	0	0.073	0.9959	0.996

Table S4-3: METAL Cd miRNA Meta-Analysis Results Summary

microRNA	log2FC	StdErr	-log10(pval)	FDR
hsa-miR-509-3p	0.1924	0.0522	0.0002	0.1128
hsa-miR-1248	-0.2395	0.0665	0.0003	0.1128
hsa-miR-193b-5p	0.1496	0.0431	0.0005	0.1229
hsa-miR-365b-3p	0.1091	0.0341	0.0014	0.1632
hsa-miR-365a-3p	0.1091	0.0341	0.0014	0.1632
hsa-miR-506-3p	0.2275	0.0711	0.0014	0.1632
hsa-miR-365a-5p	0.1415	0.0452	0.0018	0.1802
hsa-miR-514a-3p	0.1361	0.0484	0.0049	0.4405
hsa-miR-519d-5p	0.0480	0.0183	0.0086	0.5378
hsa-miR-30b-3p	0.0518	0.0208	0.0125	0.5378
hsa-miR-514a-5p	0.1467	0.0591	0.0131	0.5378
hsa-miR-1323	0.0467	0.0189	0.0135	0.5378
hsa-miR-515-5p	0.0445	0.0180	0.0136	0.5378
hsa-miR-30c-5p	0.0265	0.0107	0.0138	0.5378
hsa-miR-3173-5p	0.0928	0.0379	0.0145	0.5378
hsa-miR-3065-3p	-0.0880	0.0360	0.0145	0.5378
hsa-miR-450a-2-3p	-0.0534	0.0220	0.0152	0.5378
hsa-miR-301a-5p	-0.0764	0.0319	0.0165	0.5378
hsa-miR-30b-5p	0.0402	0.0168	0.0165	0.5378
hsa-miR-6715b-3p	-0.1685	0.0731	0.0212	0.6408
hsa-miR-340-3p	-0.0457	0.0200	0.0227	0.6510
hsa-miR-584-5p	-0.0678	0.0303	0.0256	0.6563
hsa-miR-1275	0.0966	0.0440	0.0282	0.6563
hsa-miR-520b-5p	0.0352	0.0162	0.0300	0.6563
hsa-miR-519a-2-5p	0.0352	0.0162	0.0301	0.6563
hsa-miR-518e-5p	0.0413	0.0191	0.0311	0.6563
hsa-miR-519b-5p	0.0413	0.0191	0.0311	0.6563
hsa-miR-523-5p	0.0413	0.0191	0.0311	0.6563
hsa-miR-522-5p	0.0413	0.0191	0.0311	0.6563
hsa-miR-519c-5p	0.0413	0.0191	0.0311	0.6563
hsa-miR-296-5p	0.0706	0.0336	0.0360	0.6699
hsa-miR-424-5p	0.0451	0.0215	0.0360	0.6699
hsa-miR-224-3p	-0.0697	0.0334	0.0369	0.6699
hsa-miR-125a-5p	0.0494	0.0239	0.0384	0.6699
hsa-miR-549a-3p	0.1402	0.0686	0.0411	0.6699
hsa-miR-520h	0.0345	0.0169	0.0415	0.6699
hsa-miR-181a-2-3p	0.0595	0.0293	0.0425	0.6699
hsa-miR-519a-5p	0.0398	0.0197	0.0430	0.6699
hsa-miR-337-3p	-0.0355	0.0176	0.0440	0.6699
hsa-miR-188-5p	-0.0361	0.0180	0.0448	0.6699
hsa-miR-629-3p	0.0708	0.0353	0.0448	0.6699
hsa-miR-628-5p	-0.0488	0.0243	0.0449	0.6699
hsa-miR-340-5p	-0.0400	0.0201	0.0462	0.6762
hsa-miR-200b-3p	0.0542	0.0274	0.0477	0.6839
hsa-miR-424-3p	0.0349	0.0180	0.0526	0.7233
hsa-miR-520g-3p	0.0332	0.0173	0.0550	0.7233
hsa-miR-30c-2-3p	0.0301	0.0157	0.0557	0.7233
hsa-miR-223-5p	-0.0715	0.0374	0.0562	0.7233
hsa-miR-301b-3p	-0.0772	0.0405	0.0567	0.7233
hsa-miR-3664-3p	0.0407	0.0215	0.0576	0.7233
hsa-miR-27a-3p	0.0277	0.0146	0.0585	0.7233
hsa-miR-143-5p	-0.0469	0.0251	0.0610	0.7414
hsa-miR-509-5p	0.1264	0.0679	0.0625	0.7470
hsa-miR-516b-5p	0.0380	0.0206	0.0660	0.7655
hsa-miR-520f-5p	0.0624	0.0340	0.0665	0.7655
hsa-miR-516a-5p	0.0351	0.0192	0.0673	0.7655
hsa-miR-517-5p	0.0293	0.0161	0.0690	0.7656
hsa-miR-24-3p	0.0319	0.0176	0.0694	0.7656
hsa-miR-30c-1-3p	0.0344	0.0195	0.0779	0.7972
hsa-miR-26a-5p	0.0152	0.0086	0.0787	0.7972
hsa-miR-330-5p	-0.0487	0.0278	0.0796	0.7972
hsa-miR-7-5p	-0.0427	0.0245	0.0818	0.7972
hsa-miR-31-5p	0.0618	0.0356	0.0826	0.7972
hsa-miR-337-5p	-0.0336	0.0194	0.0833	0.7972
hsa-miR-5695	0.1147	0.0665	0.0847	0.7972
hsa-miR-29a-3p	0.0433	0.0251	0.0850	0.7972
hsa-miR-10399-5p	0.0690	0.0409	0.0920	0.7972
hsa-miR-498-3p	0.0395	0.0236	0.0939	0.7972
hsa-miR-450a-5p	-0.0351	0.0210	0.0941	0.7972
hsa-miR-190a-5p	-0.0610	0.0364	0.0943	0.7972
hsa-miR-653-3p	-0.0541	0.0324	0.0957	0.7972
hsa-miR-361-5p	0.0261	0.0158	0.0974	0.7972

microRNA	log2FC	StdErr	-log10(pval)	FDR
hsa-miR-518c-5p	0.0277	0.0167	0.0978	0.7972
hsa-miR-425-3p	-0.0196	0.0119	0.0995	0.7972
hsa-miR-1299	0.1922	0.1176	0.1022	0.7972
hsa-miR-214-5p	-0.0285	0.0174	0.1024	0.7972
hsa-miR-526b-5p	0.0324	0.0199	0.1030	0.7972
hsa-miR-144-3p	-0.0840	0.0516	0.1032	0.7972
hsa-miR-454-3p	-0.0236	0.0145	0.1039	0.7972
hsa-miR-942-5p	-0.0384	0.0238	0.1067	0.7972
hsa-miR-616-3p	0.0608	0.0378	0.1074	0.7972
hsa-miR-32-3p	-0.0365	0.0226	0.1075	0.7972
hsa-miR-4708-3p	0.0555	0.0345	0.1077	0.7972
hsa-miR-524-5p	0.0252	0.0157	0.1079	0.7972
hsa-miR-30d-5p	0.0277	0.0172	0.1085	0.7972
hsa-miR-342-3p	-0.0345	0.0217	0.1116	0.7972
hsa-miR-6881-3p	-0.0724	0.0458	0.1144	0.7972
hsa-miR-23a-3p	0.0268	0.0172	0.1191	0.7972
hsa-miR-519e-5p	0.0386	0.0248	0.1196	0.7972
hsa-miR-27b-5p	-0.0294	0.0190	0.1207	0.7972
hsa-miR-2115-5p	-0.0634	0.0409	0.1209	0.7972
hsa-miR-154-3p	-0.0379	0.0246	0.1223	0.7972
hsa-miR-191-5p	0.0191	0.0125	0.1265	0.8055
hsa-miR-2276-3p	-0.0651	0.0428	0.1279	0.8055
hsa-miR-2116-3p	0.0594	0.0391	0.1292	0.8055
hsa-miR-570-3p	-0.0564	0.0373	0.1310	0.8097
hsa-miR-6511b-3p	0.0581	0.0386	0.1327	0.8112
hsa-miR-155-5p	-0.1011	0.0674	0.1335	0.8112
hsa-miR-495-3p	-0.0308	0.0206	0.1356	0.8170
hsa-miR-32-5p	-0.0271	0.0183	0.1383	0.8263
hsa-miR-105-5p	-0.0610	0.0417	0.1435	0.8503
hsa-miR-6511a-3p	-0.0477	0.0327	0.1454	0.8512
hsa-miR-1306-5p	0.0521	0.0360	0.1479	0.8512
hsa-miR-579-3p	0.0356	0.0247	0.1484	0.8512
hsa-miR-379-3p	-0.0310	0.0215	0.1500	0.8523
hsa-miR-142-5p	-0.0579	0.0405	0.1528	0.8523
hsa-miR-585-3p	-0.0703	0.0495	0.1558	0.8523
hsa-miR-767-5p	-0.0547	0.0392	0.1626	0.8523
hsa-miR-487a-3p	-0.0356	0.0257	0.1662	0.8523

microRNA	log2FC	StdErr	-log10(pval)	FDR
hsa-miR-107	-0.0334	0.0247	0.1768	0.8523
hsa-miR-4659a-3p	-0.0724	0.0537	0.1779	0.8523
hsa-miR-320a-3p	0.0319	0.0237	0.1785	0.8523
hsa-miR-451a	-0.0736	0.0547	0.1785	0.8523
hsa-miR-556-3p	0.0580	0.0431	0.1792	0.8523
hsa-miR-125b-5p	0.0353	0.0263	0.1799	0.8523
hsa-miR-548ae-5p	-0.0294	0.0219	0.1799	0.8523
hsa-miR-133a-5p	-0.0544	0.0408	0.1829	0.8523
hsa-miR-454-5p	-0.0293	0.0221	0.1856	0.8523
hsa-miR-18b-5p	-0.0544	0.0411	0.1860	0.8523
hsa-miR-548ay-5p	-0.0320	0.0244	0.1891	0.8523
hsa-miR-511-5p	-0.0351	0.0268	0.1902	0.8523
hsa-miR-466	0.0554	0.0425	0.1927	0.8538
hsa-miR-548d-5p	-0.0323	0.0248	0.1929	0.8538
hsa-miR-15a-5p	-0.0393	0.0303	0.1953	0.8560
hsa-miR-1304-3p	0.0406	0.0316	0.1981	0.8608
hsa-miR-27a-5p	0.0490	0.0383	0.2005	0.8613
hsa-miR-7706	0.0337	0.0263	0.2006	0.8613
hsa-miR-128-3p	-0.0172	0.0136	0.2061	0.8688
hsa-miR-1285-3p	-0.0336	0.0266	0.2064	0.8688
hsa-miR-1185-1-3p	-0.0339	0.0270	0.2090	0.8691
hsa-miR-183-3p	0.0634	0.0512	0.2151	0.8691
hsa-miR-411-3p	-0.0275	0.0223	0.2165	0.8691
hsa-miR-452-5p	-0.0292	0.0237	0.2179	0.8691
hsa-miR-16-5p	-0.0355	0.0289	0.2206	0.8691
hsa-miR-505-3p	-0.0238	0.0195	0.2228	0.8691
hsa-miR-1197	-0.0460	0.0379	0.2246	0.8691
hsa-miR-3064-5p	-0.0396	0.0326	0.2249	0.8691
hsa-miR-330-3p	-0.0305	0.0252	0.2254	0.8691
hsa-miR-887-3p	-0.0340	0.0282	0.2277	0.8691
hsa-miR-2355-3p	-0.0457	0.0380	0.2295	0.8691
hsa-miR-185-3p	-0.0496	0.0413	0.2302	0.8691
hsa-miR-34a-3p	0.0366	0.0310	0.2371	0.8691
hsa-miR-548e-5p	-0.0335	0.0285	0.2392	0.8691
hsa-miR-496	-0.0336	0.0285	0.2393	0.8691
hsa-miR-516b-3p	-0.0666	0.0568	0.2413	0.8691
hsa-miR-619-5p	0.0568	0.0485	0.2416	0.8691

microRNA	log2FC	StdErr	-log10(pval)	FDR
hsa-miR-19b-3p	0.0210	0.0180	0.2435	0.8691
hsa-miR-1185-2-3p	-0.0359	0.0308	0.2441	0.8691
hsa-miR-210-3p	0.0483	0.0417	0.2469	0.8691
hsa-miR-543	-0.0309	0.0267	0.2475	0.8691
hsa-miR-450a-1-3p	-0.0226	0.0196	0.2480	0.8691
hsa-miR-12135	-0.0614	0.0534	0.2503	0.8697
hsa-miR-516a-3p	-0.0644	0.0568	0.2569	0.8788
hsa-miR-23c	0.0238	0.0211	0.2592	0.8788
hsa-miR-590-3p	0.0214	0.0191	0.2619	0.8788
hsa-miR-135a-5p	-0.0894	0.0802	0.2647	0.8813
hsa-miR-589-5p	-0.0316	0.0284	0.2655	0.8813
hsa-miR-376a-5p	-0.0250	0.0227	0.2710	0.8885
hsa-miR-377-3p	-0.0218	0.0200	0.2743	0.8885
hsa-miR-18a-5p	-0.0317	0.0291	0.2764	0.8885
hsa-miR-520e-5p	-0.0240	0.0220	0.2772	0.8885
hsa-miR-548i	-0.0605	0.0560	0.2800	0.8885
hsa-miR-520c-3p	-0.0230	0.0213	0.2818	0.8885
hsa-miR-3611	-0.0263	0.0245	0.2821	0.8885
hsa-miR-323a-3p	0.0206	0.0193	0.2856	0.8885
hsa-miR-548n	-0.0365	0.0344	0.2882	0.8885
hsa-miR-548ay-3p	-0.0494	0.0466	0.2896	0.8885
hsa-miR-363-3p	-0.0323	0.0305	0.2898	0.8885
hsa-miR-3143	0.0526	0.0499	0.2919	0.8885
hsa-miR-2277-5p	-0.0314	0.0298	0.2927	0.8885
hsa-miR-221-5p	0.0178	0.0169	0.2934	0.8885
hsa-miR-1247-3p	0.0365	0.0350	0.2967	0.8885
hsa-miR-628-3p	-0.0239	0.0229	0.2968	0.8885
hsa-miR-199a-5p	-0.0171	0.0164	0.2974	0.8885
hsa-miR-9-5p	0.0398	0.0388	0.3054	0.8901
hsa-miR-377-5p	-0.0189	0.0185	0.3080	0.8901
hsa-miR-548ab	-0.0416	0.0409	0.3091	0.8901
hsa-miR-338-3p	-0.0249	0.0245	0.3091	0.8901
hsa-miR-335-3p	-0.0266	0.0264	0.3132	0.8979
hsa-miR-185-5p	-0.0292	0.0291	0.3163	0.8979
hsa-miR-200c-3p	0.0232	0.0236	0.3246	0.8979
hsa-miR-934	0.0221	0.0224	0.3259	0.8979
hsa-miR-138-5p	0.0566	0.0577	0.3263	0.8979

microRNA	log2FC	StdErr	-log10(pval)	FDR
hsa-miR-96-5p	0.0351	0.0359	0.3274	0.8979
hsa-miR-548b-5p	0.0277	0.0284	0.3284	0.8979
hsa-miR-151a-3p	0.0142	0.0146	0.3305	0.8979
hsa-miR-455-5p	-0.0281	0.0296	0.3421	0.9037
hsa-miR-2115-3p	-0.0386	0.0407	0.3431	0.9037
hsa-miR-34b-3p	0.0390	0.0413	0.3448	0.9037
hsa-miR-98-3p	0.0508	0.0539	0.3452	0.9037
hsa-miR-149-5p	0.0225	0.0239	0.3456	0.9037
hsa-miR-551b-3p	-0.0279	0.0296	0.3459	0.9037
hsa-miR-433-5p	-0.0335	0.0356	0.3470	0.9037
hsa-miR-20a-5p	0.0156	0.0167	0.3505	0.9037
hsa-let-7d-3p	0.0405	0.0440	0.3572	0.9071
hsa-miR-144-5p	-0.0482	0.0525	0.3584	0.9071
hsa-miR-3145-3p	-0.0322	0.0354	0.3631	0.9110
hsa-miR-4742-3p	-0.0275	0.0305	0.3676	0.9145
hsa-miR-548bc	-0.0272	0.0305	0.3723	0.9145
hsa-miR-125a-3p	0.0160	0.0185	0.3858	0.9190
hsa-miR-675-5p	-0.0265	0.0308	0.3897	0.9252
hsa-miR-93-3p	0.0140	0.0165	0.3961	0.9312
hsa-miR-410-3p	-0.0245	0.0291	0.3996	0.9314
hsa-miR-9-3p	0.0330	0.0392	0.4001	0.9314
hsa-miR-6503-3p	0.0383	0.0462	0.4069	0.9351
hsa-miR-3613-5p	-0.0234	0.0283	0.4095	0.9373
hsa-miR-766-3p	-0.0272	0.0330	0.4107	0.9373
hsa-miR-130a-3p	-0.0094	0.0115	0.4139	0.9373
hsa-miR-3925-5p	0.0380	0.0469	0.4186	0.9373
hsa-miR-10527-5p	0.0254	0.0316	0.4202	0.9373
hsa-miR-2116-5p	0.0245	0.0305	0.4225	0.9373
hsa-miR-548w	-0.0248	0.0314	0.4301	0.9373
hsa-miR-744-5p	0.0195	0.0248	0.4329	0.9373
hsa-miR-539-3p	-0.0236	0.0301	0.4331	0.9373
hsa-miR-125b-1-3p	-0.0222	0.0285	0.4364	0.9373
hsa-miR-183-5p	0.0239	0.0307	0.4366	0.9373
hsa-miR-138-1-3p	0.0454	0.0589	0.4405	0.9374
hsa-miR-376a-2-5p	-0.0187	0.0243	0.4411	0.9374
hsa-miR-211-5p	0.0274	0.0359	0.4454	0.9374
hsa-miR-665	-0.0226	0.0297	0.4471	0.9374

microRNA	log2FC	StdErr	-log10(pval)	FDR
hsa-miR-376b-3p	-0.0164	0.0217	0.4489	0.9374
hsa-miR-4521	0.0359	0.0475	0.4501	0.9374
hsa-miR-181a-5p	0.0170	0.0226	0.4511	0.9374
hsa-miR-1-3p	-0.0284	0.0381	0.4563	0.9374
hsa-miR-3615	-0.0217	0.0291	0.4563	0.9374
hsa-miR-345-5p	-0.0163	0.0224	0.4663	0.9411
hsa-miR-328-3p	0.0230	0.0317	0.4685	0.9411
hsa-miR-624-3p	-0.0170	0.0234	0.4685	0.9411
hsa-miR-4662a-5p	-0.0213	0.0295	0.4702	0.9411
hsa-miR-29b-1-5p	0.0238	0.0331	0.4721	0.9411
hsa-miR-660-3p	0.0153	0.0216	0.4788	0.9411
hsa-miR-126-5p	0.0156	0.0221	0.4798	0.9411
hsa-miR-137-3p	0.0516	0.0741	0.4859	0.9411
hsa-miR-548e-3p	-0.0147	0.0212	0.4868	0.9411
hsa-miR-29c-5p	-0.0110	0.0159	0.4901	0.9411
hsa-miR-16-2-3p	-0.0173	0.0252	0.4919	0.9411
hsa-miR-409-3p	-0.0131	0.0191	0.4921	0.9411
hsa-miR-34a-5p	0.0162	0.0238	0.4960	0.9411
hsa-miR-186-5p	-0.0087	0.0128	0.4974	0.9411
hsa-miR-133a-3p	-0.0238	0.0353	0.5002	0.9411
hsa-miR-324-5p	-0.0127	0.0190	0.5031	0.9411
hsa-miR-423-3p	0.0142	0.0213	0.5034	0.9411
hsa-miR-4742-5p	0.0245	0.0367	0.5041	0.9411
hsa-miR-5699-3p	0.0252	0.0379	0.5065	0.9411
hsa-miR-146a-5p	-0.0243	0.0365	0.5067	0.9411
hsa-miR-147b-3p	-0.0292	0.0448	0.5140	0.9411
hsa-miR-519c-3p	-0.0113	0.0174	0.5178	0.9411
hsa-miR-136-5p	-0.0097	0.0152	0.5227	0.9411
hsa-miR-1843	-0.0132	0.0207	0.5231	0.9411
hsa-miR-361-3p	-0.0103	0.0162	0.5255	0.9411
hsa-miR-30a-3p	0.0131	0.0207	0.5268	0.9411
hsa-miR-100-5p	0.0192	0.0303	0.5269	0.9411
hsa-miR-299-3p	-0.0146	0.0231	0.5285	0.9411
hsa-miR-204-5p	0.0417	0.0666	0.5314	0.9411
hsa-miR-148b-5p	-0.0110	0.0177	0.5318	0.9411
hsa-miR-10a-5p	0.0120	0.0192	0.5327	0.9411
hsa-miR-410-5p	-0.0397	0.0638	0.5341	0.9411

microRNA	log2FC	StdErr	-log10(pval)	FDR
hsa-miR-181b-2-3p	0.0252	0.0410	0.5394	0.9411
hsa-miR-148a-5p	-0.0201	0.0329	0.5416	0.9411
hsa-miR-767-3p	-0.0316	0.0518	0.5420	0.9411
hsa-miR-548aq-3p	-0.0258	0.0425	0.5447	0.9411
hsa-miR-7976	-0.0162	0.0271	0.5502	0.9438
hsa-miR-548g-5p	0.0201	0.0357	0.5735	0.9621
hsa-miR-9898	0.0248	0.0441	0.5737	0.9621
hsa-miR-130b-3p	-0.0204	0.0365	0.5760	0.9621
hsa-miR-668-3p	-0.0149	0.0269	0.5790	0.9621
hsa-let-7d-5p	-0.0176	0.0318	0.5806	0.9621
hsa-miR-449a	-0.0158	0.0292	0.5876	0.9621
hsa-miR-182-5p	0.0185	0.0346	0.5929	0.9621
hsa-miR-93-5p	-0.0099	0.0185	0.5931	0.9621
hsa-miR-3909	0.0122	0.0231	0.5969	0.9627
hsa-miR-199b-5p	-0.0127	0.0242	0.6000	0.9627
hsa-miR-151a-5p	0.0087	0.0167	0.6014	0.9627
hsa-miR-561-5p	-0.0180	0.0345	0.6018	0.9627
hsa-miR-431-5p	-0.0135	0.0262	0.6066	0.9627
hsa-miR-382-3p	-0.0129	0.0254	0.6124	0.9627
hsa-miR-1283	0.0160	0.0322	0.6188	0.9627
hsa-miR-491-5p	-0.0119	0.0242	0.6224	0.9627
hsa-miR-371a-3p	-0.0337	0.0693	0.6261	0.9627
hsa-miR-372-5p	-0.0332	0.0683	0.6269	0.9627
hsa-miR-373-5p	0.0297	0.0611	0.6275	0.9627
hsa-miR-505-5p	-0.0186	0.0384	0.6283	0.9627
hsa-miR-1278	0.0135	0.0283	0.6324	0.9627
hsa-miR-181c-5p	0.0116	0.0250	0.6443	0.9698
hsa-miR-222-5p	0.0165	0.0359	0.6452	0.9698
hsa-miR-145-5p	-0.0097	0.0218	0.6554	0.9716
hsa-miR-134-5p	-0.0093	0.0209	0.6554	0.9716
hsa-miR-101-5p	0.0093	0.0207	0.6555	0.9716
hsa-miR-339-3p	0.0067	0.0150	0.6562	0.9716
hsa-miR-6501-5p	-0.0200	0.0450	0.6568	0.9716
hsa-miR-486-3p	-0.0238	0.0540	0.6586	0.9716
hsa-miR-873-5p	0.0189	0.0440	0.6677	0.9766
hsa-miR-548au-5p	0.0070	0.0167	0.6753	0.9766
hsa-miR-190b-5p	0.0096	0.0235	0.6827	0.9828

microRNA	log2FC	StdErr	-log10(pval)	FDR
hsa-miR-548x-5p	0.0200	0.0494	0.6865	0.9828
hsa-miR-380-3p	-0.0099	0.0249	0.6922	0.9828
hsa-miR-381-5p	-0.0091	0.0234	0.6986	0.9831
hsa-miR-331-3p	-0.0126	0.0333	0.7049	0.9831
hsa-miR-7977	-0.0129	0.0355	0.7151	0.9842
hsa-miR-199b-3p	-0.0059	0.0167	0.7223	0.9842
hsa-miR-199a-3p	-0.0059	0.0167	0.7264	0.9842
hsa-miR-30e-3p	0.0073	0.0208	0.7270	0.9842
hsa-miR-23b-5p	0.0071	0.0207	0.7327	0.9842
hsa-miR-486-5p	-0.0165	0.0486	0.7348	0.9842
hsa-miR-98-5p	0.0113	0.0338	0.7374	0.9842
hsa-miR-26a-1-3p	0.0090	0.0270	0.7395	0.9842
hsa-miR-7705	-0.0092	0.0278	0.7408	0.9842
hsa-miR-378a-5p	0.0086	0.0266	0.7470	0.9842
hsa-miR-188-3p	-0.0078	0.0243	0.7485	0.9842
hsa-miR-6514-5p	-0.0100	0.0327	0.7607	0.9842
hsa-miR-3158-3p	-0.0132	0.0440	0.7652	0.9842
hsa-miR-205-5p	0.0063	0.0229	0.7834	0.9842
hsa-miR-4645-3p	-0.0072	0.0274	0.7932	0.9842
hsa-miR-671-3p	-0.0076	0.0293	0.7944	0.9842
hsa-miR-380-5p	-0.0087	0.0336	0.7968	0.9842
hsa-miR-135b-3p	0.0122	0.0504	0.8089	0.9842
hsa-miR-362-3p	0.0059	0.0249	0.8131	0.9842
hsa-miR-372-3p	-0.0160	0.0688	0.8164	0.9842
hsa-miR-656-3p	0.0063	0.0286	0.8246	0.9842
hsa-miR-200c-5p	0.0053	0.0248	0.8310	0.9842
hsa-miR-28-5p	-0.0037	0.0176	0.8337	0.9842
hsa-miR-373-3p	-0.0108	0.0553	0.8454	0.9842
hsa-miR-28-3p	0.0025	0.0154	0.8693	0.9843
hsa-miR-320e	-0.0049	0.0306	0.8735	0.9843
hsa-miR-126-3p	-0.0031	0.0215	0.8854	0.9852
hsa-miR-6513-5p	-0.0052	0.0368	0.8874	0.9852
hsa-miR-548q	0.0041	0.0296	0.8884	0.9852
hsa-miR-641	0.0031	0.0236	0.8936	0.9852
hsa-miR-548x-3p	0.0362	0.2783	0.8966	0.9852
hsa-miR-139-5p	0.0033	0.0281	0.9071	0.9852
hsa-miR-548ak	0.0033	0.0298	0.9116	0.9852
hsa-miR-495-5p	0.0021	0.0193	0.9152	0.9852
hsa-miR-5699-5p	0.0014	0.0386	0.9712	0.9864

Table S4-4: miRDIP Output of predicted Targets

mRNA Target	MicroRNA
STK39	hsa-miR-10b-3p
KCNJ3	hsa-miR-10b-3p
C11orf87	hsa-miR-10b-3p
ANKRD12	hsa-miR-10b-3p
PICALM	hsa-miR-10b-3p
SALL1	hsa-miR-10b-3p
CCDC117	hsa-miR-10b-3p
MAX	hsa-miR-10b-3p
RAB4A	hsa-miR-10b-3p
TRIB2	hsa-miR-10b-3p
API5	hsa-miR-10b-3p
ADCY9	hsa-miR-10b-3p
PTP4A2	hsa-miR-10b-3p
KPNA3	hsa-miR-10b-3p
PUM1	hsa-miR-10b-3p
SATB2	hsa-miR-10b-3p
GTDC1	hsa-miR-10b-3p
SC5D	hsa-miR-10b-3p
MPPED2	hsa-miR-10b-3p
PNN	hsa-miR-10b-3p
EYA4	hsa-miR-10b-3p
GLS	hsa-miR-10b-3p
CNIH1	hsa-miR-10b-3p
DLAT	hsa-miR-10b-3p
ERBB4	hsa-miR-10b-3p
RGPD8	hsa-miR-10b-3p
RAP2B	hsa-miR-10b-3p
PPP3CC	hsa-miR-10b-3p
VASH2	hsa-miR-10b-3p
GSK3B	hsa-miR-10b-3p
YPEL2	hsa-miR-10b-3p
ADAMTS5	hsa-miR-10b-3p
WWTR1	hsa-miR-10b-3p
NCOA1	hsa-miR-10b-3p
YWHAE	hsa-miR-10b-3p
ACVR2B	hsa-miR-10b-3p
HSPA12A	hsa-miR-10b-3p
KCNIP4	hsa-miR-10b-3p
ZNF248	hsa-miR-10b-3p
TNKS2	hsa-miR-10b-3p
TTC33	hsa-miR-10b-3p
FGF13	hsa-miR-10b-3p
MTDH	hsa-miR-10b-3p
NUP160	hsa-miR-10b-3p
RALA	hsa-miR-10b-3p
HLA-B	hsa-miR-10b-3p
GLI2	hsa-miR-10b-3p
METTL16	hsa-miR-10b-3p
FMR1	hsa-miR-10b-3p
TIAM2	hsa-miR-10b-3p
SYT1	hsa-miR-10b-3p
SEMA6D	hsa-miR-10b-3p
BCAT1	hsa-miR-10b-3p
UBR3	hsa-miR-10b-3p
TM9SF3	hsa-miR-10b-3p
ZNF474	hsa-miR-10b-3p
MLLT10	hsa-miR-10b-3p
DNM1L	hsa-miR-10b-3p
SLC39A10	hsa-miR-10b-3p
CALD1	hsa-miR-10b-3p
PCDH17	hsa-miR-10b-3p
CREBRF	hsa-miR-10b-3p
UNC5D	hsa-miR-10b-3p
COPB1	hsa-miR-10b-3p
RSPO2	hsa-miR-10b-3p
MYOZ3	hsa-miR-10b-3p
PHLPP2	hsa-miR-10b-3p
CRISPLD1	hsa-miR-10b-3p
NAV1	hsa-miR-10b-3p
GRIN2A	hsa-miR-10b-3p
ZNF140	hsa-miR-10b-3p
ZNF148	hsa-miR-10b-3p
RBM12B	hsa-miR-10b-3p
RB1	hsa-miR-10b-3p
ARFIP1	hsa-miR-10b-3p
MAGI2	hsa-miR-10b-3p
CAB39	hsa-miR-10b-3p
EYA3	hsa-miR-10b-3p
SESN3	hsa-miR-10b-3p
ZC3H12C	hsa-miR-10b-3p
AHCYL2	hsa-miR-10b-3p
CYP27B1	hsa-miR-10b-3p
METAP1	hsa-miR-10b-3p
HLA-G	hsa-miR-10b-3p
NRXN1	hsa-miR-10b-3p
PAM	hsa-miR-10b-3p
LCORL	hsa-miR-10b-3p
RGPD5	hsa-miR-10b-3p
RNF139	hsa-miR-10b-3p
AP3B1	hsa-miR-10b-3p
DAZL	hsa-miR-10b-3p
MFAP5	hsa-miR-10b-3p
LANCL3	hsa-miR-10b-3p
CNTN3	hsa-miR-10b-3p
TRIM14	hsa-miR-10b-3p
CACNA1E	hsa-miR-10b-3p
LRRTM1	hsa-miR-10b-3p
BTBD3	hsa-miR-10b-3p
FOXO3	hsa-miR-10b-3p
RMND5A	hsa-miR-10b-3p
ATRX	hsa-miR-10b-3p
KIAA2026	hsa-miR-10b-3p
SLC16A4	hsa-miR-10b-3p
RGPD6	hsa-miR-10b-3p
BCL9	hsa-miR-10b-3p
MCTP1	hsa-miR-10b-3p
NBR1	hsa-miR-10b-3p
CNOT6	hsa-miR-10b-3p
BACH1	hsa-miR-10b-3p
U2SURP	hsa-miR-10b-3p
TXLNG	hsa-miR-10b-3p

mRNA Target	MicroRNA
MTF1	hsa-miR-10b-3p
EXOG	hsa-miR-10b-3p
ITGAV	hsa-miR-10b-3p
TLR10	hsa-miR-10b-3p
SH3D19	hsa-miR-10b-3p
KRTAP4-3	hsa-miR-10b-3p
PAPOLA	hsa-miR-10b-3p
SOD2	hsa-miR-10b-3p
SCN1A	hsa-miR-10b-3p
CEP120	hsa-miR-10b-3p
MED13L	hsa-miR-10b-3p
WDR37	hsa-miR-10b-3p
ZIC2	hsa-miR-10b-3p
HOXD1	hsa-miR-10b-3p
FZD3	hsa-miR-10b-3p
ETV5	hsa-miR-10b-3p
GPR155	hsa-miR-10b-3p
APPBP2	hsa-miR-10b-3p
ARIH1	hsa-miR-10b-3p
CTPS2	hsa-miR-10b-3p
ZBTB26	hsa-miR-10b-3p
HFM1	hsa-miR-10b-3p
GREM1	hsa-miR-10b-3p
SKP1	hsa-miR-10b-3p
VPS13A	hsa-miR-10b-3p
TNS1	hsa-miR-10b-3p
PRAME	hsa-miR-10b-3p
ARPP21	hsa-miR-10b-3p
MAPK1	hsa-miR-10b-3p
GNAT2	hsa-miR-10b-3p
MTSS1	hsa-miR-10b-3p
WTAP	hsa-miR-10b-3p
MDM2	hsa-miR-10b-3p
SIX1	hsa-miR-10b-3p
RTCA	hsa-miR-10b-3p
CCDC6	hsa-miR-10b-3p
TMCC1	hsa-miR-10b-3p
LMNB1	hsa-miR-10b-3p
SOX6	hsa-miR-10b-3p
CLIC5	hsa-miR-10b-3p
KCNA1	hsa-miR-10b-3p
SLC48A1	hsa-miR-10b-3p
KCNS1	hsa-miR-10b-3p
TFAP2C	hsa-miR-10b-5p
FIGN	hsa-miR-10b-5p
GALNT1	hsa-miR-10b-5p
CRLF3	hsa-miR-10b-5p
NCOR2	hsa-miR-10b-5p
KLHL29	hsa-miR-10b-5p
BDNF	hsa-miR-10b-5p
GATA6	hsa-miR-10b-5p
SOBP	hsa-miR-10b-5p
CADM2	hsa-miR-10b-5p
HOXA3	hsa-miR-10b-5p
RORA	hsa-miR-10b-5p
KLF11	hsa-miR-10b-5p
HCN1	hsa-miR-10b-5p
DAZAP1	hsa-miR-10b-5p
RPRD1A	hsa-miR-10b-5p
SMTNL2	hsa-miR-10b-5p
HNRNPK	hsa-miR-10b-5p
HOXB3	hsa-miR-10b-5p
ZMYND11	hsa-miR-10b-5p
CELF2	hsa-miR-10b-5p
GTF2H1	hsa-miR-10b-5p
TRIM2	hsa-miR-10b-5p
UBE2I	hsa-miR-10b-5p
BAZ1B	hsa-miR-10b-5p
USP46	hsa-miR-10b-5p
GOLGA3	hsa-miR-10b-5p
MAP3K7	hsa-miR-10b-5p
ARSJ	hsa-miR-10b-5p
CREB1	hsa-miR-10b-5p
TBX5	hsa-miR-10b-5p
CYTH1	hsa-miR-10b-5p
TFRC	hsa-miR-10b-5p
IGDCC4	hsa-miR-10b-5p
SDC1	hsa-miR-10b-5p
RAP2A	hsa-miR-10b-5p
SON	hsa-miR-10b-5p
ELOVL2	hsa-miR-10b-5p
NPAS3	hsa-miR-10b-5p
ZNF367	hsa-miR-10b-5p
SMAP1	hsa-miR-10b-5p
BBX	hsa-miR-10b-5p
FNBP1L	hsa-miR-10b-5p
MTF1	hsa-miR-10b-5p
EPHA5	hsa-miR-10b-5p
RB1CC1	hsa-miR-10b-5p
ELAVL2	hsa-miR-10b-5p
NEDD4	hsa-miR-10b-5p
GATA3	hsa-miR-10b-5p
SNX18	hsa-miR-10b-5p
BAZ2B	hsa-miR-10b-5p
FBXO30	hsa-miR-10b-5p
WDR26	hsa-miR-10b-5p
E2F3	hsa-miR-10b-5p
BCL6	hsa-miR-10b-5p
CTNNBIP1	hsa-miR-10b-5p
CNOT6	hsa-miR-10b-5p
DOCK11	hsa-miR-10b-5p
WNK3	hsa-miR-10b-5p
PIK3CA	hsa-miR-10b-5p
ESRRG	hsa-miR-10b-5p
NCOA6	hsa-miR-10b-5p
LRRC8B	hsa-miR-10b-5p
WWC2	hsa-miR-10b-5p
SLC38A2	hsa-miR-10b-5p
XRN1	hsa-miR-10b-5p
ANKFY1	hsa-miR-10b-5p
TNRC6B	hsa-miR-10b-5p
KCTD16	hsa-miR-10b-5p
PDE7A	hsa-miR-10b-5p
NR4A3	hsa-miR-10b-5p

mRNA Target	MicroRNA
TMEM170B	hsa-miR-10b-5p
TENM2	hsa-miR-10b-5p
RNF186	hsa-miR-10b-5p
MDGA2	hsa-miR-10b-5p
SSX2IP	hsa-miR-10b-5p
SRSF1	hsa-miR-10b-5p
HOXA1	hsa-miR-10b-5p
SPAG9	hsa-miR-10b-5p
CSRNP3	hsa-miR-10b-5p
NR2C2	hsa-miR-10b-5p
GABRB2	hsa-miR-10b-5p
FRS2	hsa-miR-10b-5p
MTMR3	hsa-miR-10b-5p
NFAT5	hsa-miR-10b-5p
CDK6	hsa-miR-10b-5p
TIAM1	hsa-miR-10b-5p
PTPN4	hsa-miR-10b-5p
JARID2	hsa-miR-10b-5p
ITSN1	hsa-miR-10b-5p
KLHDC10	hsa-miR-10b-5p
CBX5	hsa-miR-10b-5p
NR6A1	hsa-miR-10b-5p
MIEF1	hsa-miR-10b-5p
RNF165	hsa-miR-10b-5p
ERI3	hsa-miR-10b-5p
PRRT3	hsa-miR-10b-5p
USP25	hsa-miR-10b-5p
PURG	hsa-miR-10b-5p
AFF4	hsa-miR-10b-5p
BACH2	hsa-miR-10b-5p
E2F7	hsa-miR-10b-5p
KCNA6	hsa-miR-10b-5p
HOXD10	hsa-miR-10b-5p
CSMD1	hsa-miR-10b-5p
BCL2L11	hsa-miR-10b-5p
MTF2	hsa-miR-10b-5p
TMEM183A	hsa-miR-10b-5p
SH3D19	hsa-miR-10b-5p

mRNA Target	MicroRNA
ANK1	hsa-miR-10b-5p
RBM27	hsa-miR-10b-5p
IGSF1	hsa-miR-10b-5p
BTRC	hsa-miR-10b-5p
NONO	hsa-miR-10b-5p
PTEN	hsa-miR-10b-5p
PAFAH1B1	hsa-miR-10b-5p
L3MBTL3	hsa-miR-10b-5p
DLG5	hsa-miR-10b-5p
ITGB8	hsa-miR-10b-5p
CNNM4	hsa-miR-10b-5p
TPP2	hsa-miR-10b-5p
EBF2	hsa-miR-10b-5p
ATXN7	hsa-miR-10b-5p
CLCC1	hsa-miR-10b-5p
TMEM167B	hsa-miR-10b-5p
CHL1	hsa-miR-10b-5p
MYT1L	hsa-miR-10b-5p
CALCR	hsa-miR-10b-5p
ZNF608	hsa-miR-10b-5p
SCN3A	hsa-miR-10b-5p
CAMK2B	hsa-miR-10b-5p
IFFO2	hsa-miR-10b-5p
TBC1D22B	hsa-miR-10b-5p
PHF20L1	hsa-miR-10b-5p
EPHA4	hsa-miR-10b-5p
RTN4R	hsa-miR-10b-5p
HAS3	hsa-miR-10b-5p
INO80D	hsa-miR-10b-5p
NR5A2	hsa-miR-10b-5p
MYBL1	hsa-miR-10b-5p
FLRT2	hsa-miR-10b-5p
TMOD1	hsa-miR-10b-5p
KPNA5	hsa-miR-10b-5p
MAPRE1	hsa-miR-10b-5p
SH3KBP1	hsa-miR-193b-5p
ARL8B	hsa-miR-193b-5p
LTN1	hsa-miR-193b-5p

mRNA Target	MicroRNA
ZFP36L1	hsa-miR-193b-5p
FHOD3	hsa-miR-193b-5p
PI4KB	hsa-miR-193b-5p
SORCS1	hsa-miR-193b-5p
C3orf38	hsa-miR-193b-5p
ETV1	hsa-miR-193b-5p
PHF20L1	hsa-miR-193b-5p
POU2F2	hsa-miR-193b-5p
MARCKSL1	hsa-miR-193b-5p
CCDC173	hsa-miR-193b-5p
FBXL20	hsa-miR-193b-5p
BRI3BP	hsa-miR-193b-5p
PIK3R2	hsa-miR-193b-5p
SMG1	hsa-miR-193b-5p
TNFRSF11B	hsa-miR-193b-5p
PCDH17	hsa-miR-193b-5p
DUSP3	hsa-miR-193b-5p
YY1AP1	hsa-miR-193b-5p
TMEM214	hsa-miR-193b-5p
RASAL2	hsa-miR-193b-5p
DLX3	hsa-miR-193b-5p
PIGF	hsa-miR-193b-5p
AIF1L	hsa-miR-193b-5p
CYP20A1	hsa-miR-193b-5p
KDSR	hsa-miR-193b-5p
GRIK5	hsa-miR-193b-5p
PDCD4	hsa-miR-193b-5p
GINS4	hsa-miR-193b-5p
MTURN	hsa-miR-193b-5p
CNOT2	hsa-miR-193b-5p
KIAA0930	hsa-miR-193b-5p
CLIP3	hsa-miR-193b-5p
ACVR2A	hsa-miR-193b-5p
CHN1	hsa-miR-193b-5p
EIF1AD	hsa-miR-193b-5p
CS	hsa-miR-193b-5p
MAVS	hsa-miR-193b-5p
MAP2K7	hsa-miR-193b-5p

mRNA Target	MicroRNA
SLC4A7	hsa-miR-193b-5p
UTP23	hsa-miR-193b-5p
SDC4	hsa-miR-193b-5p
DMD	hsa-miR-193b-5p
EIF4G3	hsa-miR-193b-5p
SMAP1	hsa-miR-193b-5p
TRAM2	hsa-miR-193b-5p
RSL1D1	hsa-miR-193b-5p
SEPHS2	hsa-miR-193b-5p
ENAH	hsa-miR-193b-5p
ELOVL5	hsa-miR-193b-5p
UBE2W	hsa-miR-193b-5p
GMPPA	hsa-miR-193b-5p
SULF2	hsa-miR-193b-5p
LYRM7	hsa-miR-193b-5p
GSE1	hsa-miR-193b-5p
ZNF714	hsa-miR-193b-5p
EFCAB2	hsa-miR-193b-5p
POLH	hsa-miR-193b-5p
COPS2	hsa-miR-193b-5p
ABL2	hsa-miR-193b-5p
TAOK1	hsa-miR-193b-5p
HELZ	hsa-miR-193b-5p
RERE	hsa-miR-193b-5p
TTPAL	hsa-miR-193b-5p
DPH6	hsa-miR-193b-5p
PPP1R12B	hsa-miR-193b-5p
DAG1	hsa-miR-193b-5p
CYP26B1	hsa-miR-193b-5p
EPG5	hsa-miR-193b-5p
PLXDC1	hsa-miR-193b-5p
IFI44L	hsa-miR-193b-5p
RAB11B	hsa-miR-193b-5p
ZNF701	hsa-miR-193b-5p
SCN3B	hsa-miR-193b-5p
XIAP	hsa-miR-193b-5p
DENND5B	hsa-miR-193b-5p
ABCB8	hsa-miR-193b-5p

mRNA Target	MicroRNA
TMEM183A	hsa-miR-193b-5p
DLX1	hsa-miR-193b-5p
C5orf22	hsa-miR-193b-5p
CLN8	hsa-miR-193b-5p
LSMEM1	hsa-miR-193b-5p
ACER3	hsa-miR-193b-5p
ILF2	hsa-miR-193b-5p
OPA3	hsa-miR-193b-5p
ZNF138	hsa-miR-193b-5p
INTS7	hsa-miR-193b-5p
TANC2	hsa-miR-193b-5p
RNF150	hsa-miR-193b-5p
JARID2	hsa-miR-193b-5p
GNA13	hsa-miR-193b-5p
UFL1	hsa-miR-193b-5p
HOOK3	hsa-miR-193b-5p
TNFRSF1B	hsa-miR-193b-5p
AAK1	hsa-miR-193b-5p
LARP1	hsa-miR-193b-5p
SIX4	hsa-miR-193b-5p
ADCY1	hsa-miR-193b-5p
XAF1	hsa-miR-193b-5p
C5orf51	hsa-miR-193b-5p
ZNF780B	hsa-miR-193b-5p
WIPF2	hsa-miR-193b-5p
CASP3	hsa-miR-193b-5p
ABCE1	hsa-miR-193b-5p
IQSEC1	hsa-miR-193b-5p
ST3GAL1	hsa-miR-193b-5p
UBN2	hsa-miR-193b-5p
ASB6	hsa-miR-193b-5p
PEG10	hsa-miR-193b-5p
CLEC16A	hsa-miR-193b-5p
SYN1	hsa-miR-193b-5p
FMO1	hsa-miR-193b-5p
GLUL	hsa-miR-193b-5p
ADAMTS6	hsa-miR-193b-5p
RBPJ	hsa-miR-193b-5p

mRNA Target	MicroRNA
CORO2A	hsa-miR-193b-5p
TBC1D5	hsa-miR-193b-5p
TMED5	hsa-miR-193b-5p
CFLAR	hsa-miR-193b-5p
FOXP2	hsa-miR-193b-5p
ZFHX3	hsa-miR-193b-5p
GPC6	hsa-miR-193b-5p
SNRK	hsa-miR-193b-5p
FGF11	hsa-miR-193b-5p
TRIB1	hsa-miR-193b-5p
RORC	hsa-miR-193b-5p
IGSF3	hsa-miR-193b-5p
MSL3	hsa-miR-193b-5p
HOXC8	hsa-miR-193b-5p
SLC35B4	hsa-miR-193b-5p
KAT6A	hsa-miR-193b-5p
ZNF431	hsa-miR-193b-5p
RAD23A	hsa-miR-193b-5p
TSHZ2	hsa-miR-193b-5p
FZD4	hsa-miR-193b-5p
ZBTB8A	hsa-miR-193b-5p
LCORL	hsa-miR-193b-5p
TGOLN2	hsa-miR-193b-5p
IMPG1	hsa-miR-193b-5p
EPHB2	hsa-miR-193b-5p
TPP1	hsa-miR-193b-5p
MEX3B	hsa-miR-193b-5p
DDIT4L	hsa-miR-193b-5p
LRP6	hsa-miR-193b-5p
ENTPD1	hsa-miR-193b-5p
ITSN1	hsa-miR-193b-5p
YBX3	hsa-miR-193b-5p
IQCE	hsa-miR-193b-5p
KPNA6	hsa-miR-193b-5p
GNAS	hsa-miR-193b-5p
ZNF793	hsa-miR-193b-5p
FAM81A	hsa-miR-193b-5p
RORA	hsa-miR-193b-5p

mRNA Target	MicroRNA
CIC	hsa-miR-193b-5p
FOXK1	hsa-miR-193b-5p
NUP50	hsa-miR-193b-5p
DPYSL5	hsa-miR-193b-5p
TNFSF15	hsa-miR-193b-5p
SLC31A1	hsa-miR-193b-5p
CAMTA1	hsa-miR-193b-5p
UBR5	hsa-miR-193b-5p
LMO4	hsa-miR-193b-5p
GATAD1	hsa-miR-193b-5p
TTYH3	hsa-miR-193b-5p
TMEM135	hsa-miR-193b-5p
C1orf21	hsa-miR-193b-5p
SLC14A1	hsa-miR-193b-5p
TMEM87A	hsa-miR-193b-5p
KLF7	hsa-miR-193b-5p
VPS36	hsa-miR-193b-5p
VPS53	hsa-miR-193b-5p
EHF	hsa-miR-193b-5p
PNPT1	hsa-miR-193b-5p
PMP22	hsa-miR-193b-5p
EDEM3	hsa-miR-193b-5p
SNAP29	hsa-miR-193b-5p
CD164	hsa-miR-506-3p
MAGT1	hsa-miR-506-3p
VAMP3	hsa-miR-506-3p
LRRC58	hsa-miR-506-3p
PTPN12	hsa-miR-506-3p
SPOPL	hsa-miR-506-3p
RHOG	hsa-miR-506-3p
FLOT2	hsa-miR-506-3p
PIK3C2A	hsa-miR-506-3p
LAMC1	hsa-miR-506-3p
EYA4	hsa-miR-506-3p
SIX4	hsa-miR-506-3p
CTDSP1	hsa-miR-506-3p
BMP6	hsa-miR-506-3p
PTBP3	hsa-miR-506-3p

mRNA Target	MicroRNA
SLC16A1	hsa-miR-506-3p
PTBP2	hsa-miR-506-3p
B4GALT1	hsa-miR-506-3p
LRRC1	hsa-miR-506-3p
QKI	hsa-miR-506-3p
CHSY1	hsa-miR-506-3p
KLHL24	hsa-miR-506-3p
OSBPL3	hsa-miR-506-3p
NR3C1	hsa-miR-506-3p
RHOQ	hsa-miR-506-3p
SNAI2	hsa-miR-506-3p
TUB	hsa-miR-506-3p
CHIC1	hsa-miR-506-3p
PTPN9	hsa-miR-506-3p
TEAD1	hsa-miR-506-3p
PRRX1	hsa-miR-506-3p
MITF	hsa-miR-506-3p
FAR1	hsa-miR-506-3p
SLC16A13	hsa-miR-506-3p
ANTXR2	hsa-miR-506-3p
C1GALT1	hsa-miR-506-3p
TMEM134	hsa-miR-506-3p
RAB27A	hsa-miR-506-3p
NFIB	hsa-miR-506-3p
HIPK3	hsa-miR-506-3p
TRIM45	hsa-miR-506-3p
IQGAP1	hsa-miR-506-3p
NR3C2	hsa-miR-506-3p
CREBRF	hsa-miR-506-3p
TARBP1	hsa-miR-506-3p
SERP1	hsa-miR-506-3p
ELK3	hsa-miR-506-3p
JAG1	hsa-miR-506-3p
WIPF2	hsa-miR-506-3p
ATP7A	hsa-miR-506-3p
G3BP1	hsa-miR-506-3p
KCNK10	hsa-miR-506-3p
PLEKHM3	hsa-miR-506-3p

mRNA Target	MicroRNA
RCOR1	hsa-miR-506-3p
PTBP1	hsa-miR-506-3p
ATMIN	hsa-miR-506-3p
SLC10A7	hsa-miR-506-3p
LRRC57	hsa-miR-506-3p
ESRP1	hsa-miR-506-3p
PI4K2B	hsa-miR-506-3p
DNAJC1	hsa-miR-506-3p
QSER1	hsa-miR-506-3p
ITGB1	hsa-miR-506-3p
XYLT1	hsa-miR-506-3p
SMARCAD1	hsa-miR-506-3p
ELOVL5	hsa-miR-506-3p
TMED1	hsa-miR-506-3p
FRMD8	hsa-miR-506-3p
MYO10	hsa-miR-506-3p
RSRC2	hsa-miR-506-3p
SP1	hsa-miR-506-3p
RBMS1	hsa-miR-506-3p
PDCD6	hsa-miR-506-3p
ROCK1	hsa-miR-506-3p
PARP16	hsa-miR-506-3p
TMEM109	hsa-miR-506-3p
MBOAT2	hsa-miR-506-3p
XPO4	hsa-miR-506-3p
TOR3A	hsa-miR-506-3p
SERTAD4	hsa-miR-506-3p
RYR3	hsa-miR-506-3p
MYLIP	hsa-miR-506-3p
RAB34	hsa-miR-506-3p
ZNF608	hsa-miR-506-3p
RAD17	hsa-miR-506-3p
SLC31A2	hsa-miR-506-3p
PLCXD3	hsa-miR-506-3p
FRMD4B	hsa-miR-506-3p
FUT10	hsa-miR-506-3p
STT3A	hsa-miR-506-3p
PGM2	hsa-miR-506-3p

mRNA Target	MicroRNA
AMOTL1	hsa-miR-506-3p
ANXA7	hsa-miR-506-3p
LYSMD3	hsa-miR-506-3p
PALLD	hsa-miR-506-3p
GLI3	hsa-miR-506-3p
RNPEPL1	hsa-miR-506-3p
SLC39A9	hsa-miR-506-3p
KATNA1	hsa-miR-506-3p
ELL2	hsa-miR-506-3p
THAP2	hsa-miR-506-3p
SCAMP2	hsa-miR-506-3p
ATF7IP	hsa-miR-506-3p
CTDSPL	hsa-miR-506-3p
HIPK1	hsa-miR-506-3p
SNTB2	hsa-miR-506-3p
FAM199X	hsa-miR-506-3p
RAVER1	hsa-miR-506-3p
GRIA2	hsa-miR-506-3p
RBM24	hsa-miR-506-3p
FAM177A1	hsa-miR-506-3p
ZNF449	hsa-miR-506-3p
ATP6V0A2	hsa-miR-506-3p
RFX4	hsa-miR-506-3p
SURF4	hsa-miR-506-3p
CBLN4	hsa-miR-506-3p
NFATC1	hsa-miR-506-3p
CREB3L2	hsa-miR-506-3p
PTPRD	hsa-miR-506-3p
CDK4	hsa-miR-506-3p
SUCLG2	hsa-miR-506-3p
KCNK2	hsa-miR-506-3p
ACAA2	hsa-miR-506-3p
FOXQ1	hsa-miR-506-3p
RELA	hsa-miR-506-3p
TTL	hsa-miR-506-3p
SLC35F5	hsa-miR-506-3p
PLEKHH1	hsa-miR-506-3p
BLOC1S6	hsa-miR-506-3p

mRNA Target	MicroRNA
SERTAD3	hsa-miR-506-3p
LHX2	hsa-miR-506-3p
LITAF	hsa-miR-506-3p
PCDH8	hsa-miR-506-3p
RNF128	hsa-miR-506-3p
LPP	hsa-miR-506-3p
AIDA	hsa-miR-506-3p
CHODL	hsa-miR-506-3p
GXYLT1	hsa-miR-506-3p
VSNL1	hsa-miR-506-3p
OSBPL11	hsa-miR-506-3p
SNX18	hsa-miR-506-3p
PITPNA	hsa-miR-506-3p
PLEKHF2	hsa-miR-506-3p
BCAT1	hsa-miR-506-3p
PRKAG2	hsa-miR-506-3p
PAPSS2	hsa-miR-506-3p
CHP1	hsa-miR-506-3p
KLF4	hsa-miR-506-3p
PLXNB2	hsa-miR-506-3p
PPFIBP2	hsa-miR-506-3p
KCNJ6	hsa-miR-506-3p
ALG2	hsa-miR-506-3p
CPT1A	hsa-miR-506-3p
VPS37C	hsa-miR-506-3p
PHF6	hsa-miR-506-3p
PNN	hsa-miR-506-3p
FAM222B	hsa-miR-506-3p
ASPA	hsa-miR-506-3p
PRKD1	hsa-miR-506-3p
CNN3	hsa-miR-506-3p
SERTAD2	hsa-miR-506-3p
AHR	hsa-miR-506-3p
DDAH1	hsa-miR-509-3p
OSBP	hsa-miR-509-3p
TCF7L2	hsa-miR-509-3p
PBX3	hsa-miR-509-3p
ST3GAL2	hsa-miR-509-3p

mRNA Target	MicroRNA
TP53INP1	hsa-miR-509-3p
LARP4	hsa-miR-509-3p
YAP1	hsa-miR-509-3p
VEZF1	hsa-miR-509-3p
KATNBL1	hsa-miR-509-3p
PLP1	hsa-miR-509-3p
RAB5C	hsa-miR-509-3p
SLC37A2	hsa-miR-509-3p
PHLPP2	hsa-miR-509-3p
PTEN	hsa-miR-509-3p
RNF130	hsa-miR-509-3p
CES3	hsa-miR-509-3p
USP47	hsa-miR-509-3p
SNX13	hsa-miR-509-3p
KCNMA1	hsa-miR-509-3p
NLK	hsa-miR-509-3p
ENPP2	hsa-miR-509-3p
MMD2	hsa-miR-509-3p
LCORL	hsa-miR-509-3p
SCG3	hsa-miR-509-3p
HCN1	hsa-miR-509-3p
RYBP	hsa-miR-509-3p
MYOCD	hsa-miR-509-3p
SF3B4	hsa-miR-509-3p
ZNF423	hsa-miR-509-3p
KLF6	hsa-miR-509-3p
ERLIN2	hsa-miR-509-3p
LRRTM1	hsa-miR-509-3p
PRKACB	hsa-miR-509-3p
TTC17	hsa-miR-509-3p
NR1D2	hsa-miR-509-3p
CRK	hsa-miR-509-3p
STAC	hsa-miR-509-3p
CACNB4	hsa-miR-509-3p
SFPQ	hsa-miR-509-3p
ARHGAP1	hsa-miR-509-3p
OSCAR	hsa-miR-509-3p
ACVR2A	hsa-miR-509-3p

mRNA Target	MicroRNA
IL1A	hsa-miR-509-3p
AMOT	hsa-miR-509-3p
KIF3B	hsa-miR-509-3p
RC3H1	hsa-miR-509-3p
PCDHA4	hsa-miR-509-3p
KCNJ3	hsa-miR-509-3p
CD164	hsa-miR-509-3p
PCDH7	hsa-miR-509-3p
MEIS1	hsa-miR-509-3p
CTSC	hsa-miR-509-3p
UNC13B	hsa-miR-509-3p
MAP3K8	hsa-miR-509-3p
MLF1	hsa-miR-509-3p
PCDHAC1	hsa-miR-509-3p
ARID5B	hsa-miR-509-3p
ZNF345	hsa-miR-509-3p
GOLPH3	hsa-miR-509-3p
TRPA1	hsa-miR-509-3p
PIK3C2A	hsa-miR-509-3p
KLK7	hsa-miR-509-3p
NAV1	hsa-miR-509-3p
WLS	hsa-miR-509-3p
EIF4E	hsa-miR-509-3p
APOD	hsa-miR-509-3p
BRDT	hsa-miR-509-3p
MCFD2	hsa-miR-509-3p
BICD2	hsa-miR-509-3p
CHD9	hsa-miR-509-3p
CMTM6	hsa-miR-509-3p
ZIC3	hsa-miR-509-3p
NPAS2	hsa-miR-509-3p
AHCYL1	hsa-miR-509-3p
SGCB	hsa-miR-509-3p
C4orf46	hsa-miR-509-3p
BTBD7	hsa-miR-509-3p
DEDD	hsa-miR-509-3p
SEMA5A	hsa-miR-509-3p
CDK17	hsa-miR-509-3p

mRNA Target	MicroRNA
DCLK1	hsa-miR-509-3p
RAC1	hsa-miR-509-3p
ATXN1	hsa-miR-509-3p
ZMAT3	hsa-miR-509-3p
SLC46A1	hsa-miR-509-3p
TRIO	hsa-miR-509-3p
HABP4	hsa-miR-509-3p
JADE1	hsa-miR-509-3p
ZNF536	hsa-miR-509-3p
WDR5B	hsa-miR-509-3p
ATXN7	hsa-miR-509-3p
BEND6	hsa-miR-509-3p
IGF2BP2	hsa-miR-509-3p
MMGT1	hsa-miR-509-3p
KIAA1328	hsa-miR-509-3p
MEX3C	hsa-miR-509-3p
PTPN13	hsa-miR-509-3p
NETO2	hsa-miR-509-3p
PCDH19	hsa-miR-509-3p
PDCD6IP	hsa-miR-509-3p
INSIG1	hsa-miR-509-3p
MAP3K1	hsa-miR-509-3p
MTMR3	hsa-miR-509-3p
NCALD	hsa-miR-509-3p
PCDHA2	hsa-miR-509-3p
HDAC9	hsa-miR-509-3p
PCDH8	hsa-miR-509-3p
PKIA	hsa-miR-509-3p
COCH	hsa-miR-509-3p
ARID1A	hsa-miR-509-3p
EHD3	hsa-miR-509-3p
ZFAND3	hsa-miR-509-3p
ANKRD40	hsa-miR-509-3p
KAT6B	hsa-miR-509-3p
NECAP1	hsa-miR-509-3p
ANKH	hsa-miR-509-3p
PCDHA11	hsa-miR-509-3p
BRWD3	hsa-miR-509-3p

mRNA Target	MicroRNA
OTX2	hsa-miR-509-3p
SERPINB9	hsa-miR-509-3p
FLI1	hsa-miR-509-3p
IRAK3	hsa-miR-509-3p
WNK1	hsa-miR-509-3p
USP42	hsa-miR-509-3p
COG5	hsa-miR-509-3p
IL13RA1	hsa-miR-509-3p
ELAVL1	hsa-miR-509-3p
TAOK3	hsa-miR-509-3p
PSD3	hsa-miR-509-3p
CALB1	hsa-miR-509-3p
ZNF107	hsa-miR-509-3p
TET1	hsa-miR-509-3p
GOSR1	hsa-miR-509-3p
BDH2	hsa-miR-509-3p
PBLD	hsa-miR-509-3p
ZBTB10	hsa-miR-509-3p
DMRT3	hsa-miR-509-3p
VGLL4	hsa-miR-509-3p
PJA1	hsa-miR-509-3p
ABCB10	hsa-miR-509-3p
XPR1	hsa-miR-509-3p
NTRK3	hsa-miR-509-3p
CNKSR2	hsa-miR-509-3p
ST8SIA3	hsa-miR-509-3p
PPP2R5C	hsa-miR-509-3p
PHF20L1	hsa-miR-509-3p
ADAM10	hsa-miR-509-3p
PELO	hsa-miR-509-3p
PCDHA6	hsa-miR-509-3p
TYRP1	hsa-miR-509-3p
APOBEC2	hsa-miR-509-3p
NRN1	hsa-miR-509-3p
PCDHA1	hsa-miR-509-3p
PCDHA3	hsa-miR-509-3p
PCDHA13	hsa-miR-509-3p
DAZL	hsa-miR-509-3p

mRNA Target	MicroRNA
PCDHA10	hsa-miR-509-3p
ANO5	hsa-miR-509-3p
PCDHA12	hsa-miR-509-3p
NAV2	hsa-miR-509-3p

mRNA Target	MicroRNA
TMPRSS11E	hsa-miR-509-3p
GULP1	hsa-miR-509-3p
APOL6	hsa-miR-509-3p
NECAB1	hsa-miR-509-3p

mRNA Target	MicroRNA
IFIT1	hsa-miR-509-3p
SCUBE3	hsa-miR-509-3p
CCNJ	hsa-miR-509-3p

Table S4-5: miR-509-3p Predicted Target Pathway Enrichment Analysis

Enriched Pathway	Enriched Targets	p-Value	q-Value
homophilic cell adhesion via plasma membrane adhesion molecules	PCDH8; PCDHA3; PCDHA1; PCDHA6; PCDHA4; PCDH19; PCDH7; PCDHAC1; PCDHA2; PCDHA10; PCDHA11; PCDHA12; PCDHA13	4.91E-09	1.67E-06
cell-cell adhesion via plasma-membrane adhesion molecules	PCDH8; PCDHA3; PCDHA1; PCDHA6; PCDHA4; PCDH19; WNK1; CD164; PCDH7; PCDHAC1; PCDHA2; PCDHA10; PCDHA11; PCDHA12; PCDHA13	3.37E-08	1.56E-05
multicellular organism development	ANKH; DMRT3; NRN1; HDAC9; WLS; DCLK1; SGCB; ADAM10; PCDHA10; MYOCD; CRK; IL1A; NR1D2; OTX2; MLF1; APOD; NAV2; OSCAR; RC3H1; NPAS2; MEIS1; NTRK3; NAV1; KLF6; PELO; PCDHAC1; LRRTM1; ZIC3; RYBP; MEX3C; TAOK3; PLP1; VGLL4; DAZL; BEND6; ACVR2A; TRIO; ZNF423; NECAB1; RAC1; TET1; FLI1; CTSC; ENPP2; ZNF536; CALB1; VEZF1; PIK3C2A; PCDHA1; PBLD; INSIG1; EIF4E; PCDHA11; IGF2BP2; KIF3B; PBX3; YAP1; PCDH8; PCDHA3; PCDHA2; PCDHA6; PCDHA4; SEMA5A; ARID5B; HCN1; ARID1A; CD164; TCF7L2; MMD2; PTEN; WNK1; IRAK3; PCDH19; PRKACB; BTBD7; AMOT; DDAH1; ATXN1	8.18E-07	4.78E-05
anatomical structure development	ANKH; DMRT3; NRN1; HDAC9; ZNF423; KLK7; DCLK1; SGCB; ADAM10; PCDHA10; MYOCD; CRK; IL1A; NR1D2; OTX2; MLF1; APOD; AMOT; NAV2; BDH2; RC3H1; NPAS2; MEIS1; NTRK3; NAV1; KLF6; PELO; PCDHAC1; LRRTM1; ZIC3; RYBP; MEX3C; TAOK3; PLP1; BRWD3; VGLL4; COCH; BEND6; ACVR2A; TRIO; WLS; LARP4; NECAB1; RAC1; TET1; FLI1; CTSC; ENPP2; ZNF536; CALB1; VEZF1; PIK3C2A; PCDHA1; PBLD; INSIG1; EIF4E; PCDHA11; IGF2BP2; KIF3B; PBX3; YAP1; PCDH8; PCDHA3; PCDHA2; PCDHA6; PCDHA4; SEMA5A; ARID5B; HCN1; OSCAR; ARID1A; CD164; TCF7L2; MMD2; PTEN; WNK1; IRAK3; PCDH19; PRKACB; BTBD7; DAZL; DDAH1; ATXN1	8.69E-07	4.78E-05
nervous system development	DMRT3; NRN1; HDAC9; DCLK1; ADAM10; PCDHA10; CRK; PLP1; OTX2; APOD; NAV2; NPAS2; MEIS1; NTRK3; NAV1; PCDHAC1; LRRTM1; ZIC3; TAOK3; BEND6; TRIO; WNK1; RAC1; CTSC; MMD2; ZNF536; EIF4E; PCDHA11; IGF2BP2; PBX3; YAP1; PCDHA2; PCDHA3; PCDHA1; PCDHA6; PCDHA4; SEMA5A; HCN1; ARID1A; PTEN; ZNF423; PRKACB; PCDH19; ATXN1	4.88E-06	1.13E-03
system development	ANKH; DMRT3; NRN1; HDAC9; DCLK1; SGCB; ADAM10; PCDHA10; MYOCD; CRK; IL1A; NR1D2; OTX2; MLF1; APOD; NAV2; OSCAR; RC3H1; NPAS2; MEIS1; NTRK3; NAV1; KLF6; PCDHAC1; LRRTM1; ZIC3; IRAK3; MEX3C; TAOK3; PLP1; VGLL4; VEZF1; BEND6; ACVR2A; TRIO; WNK1; RAC1; FLI1; CTSC; ENPP2; ZNF536; CALB1; PIK3C2A; PBLD; INSIG1; EIF4E; PCDHA11; IGF2BP2; PBX3; YAP1; PCDHA2; PCDHA3; PCDHA1; PCDHA6; PCDHA4; SEMA5A; ARID5B; HCN1; ARID1A; CD164; TCF7L2; MMD2; PTEN; ZNF423; PCDH19; PRKACB; BTBD7; AMOT; DDAH1; ATXN1	5.37E-06	1.42E-03
regulation of developmental process	DMRT3; ELAVL1; HDAC9; ADAM10; MMD2; MYOCD; CRK; IL1A; NR1D2; OTX2; ZNF536; MEIS1; NTRK3; ANKH; LRRTM1; VEZF1; IRAK3; BRWD3; VGLL4; COCH; BEND6; ACVR2A; TRIO; WNK1; LARP4; RAC1; CTSC; ENPP2; PBLD; PIK3C2A; TP53INP1; INSIG1; EIF4E; MEX3C; YAP1; RC3H1; SEMA5A; TCF7L2; PTEN; ZNF423; PRKACB; BTBD7; DDAH1; AMOT	1.03E-04	1.37E-02
regulation of striated muscle tissue development	HDAC9; MEIS1; PTEN; MYOCD; NR1D2; VGLL4; YAP1	2.23E-04	2.69E-02
regulation of muscle tissue development	HDAC9; MEIS1; PTEN; MYOCD; NR1D2; VGLL4; YAP1	2.37E-04	2.94E-02
regulation of muscle organ development	HDAC9; MEIS1; PTEN; MYOCD; NR1D2; VGLL4; YAP1	2.37E-04	2.69E-02
regulation of multicellular organismal development	DMRT3; HDAC9; ADAM10; MMD2; MYOCD; IL1A; CRK; NR1D2; OTX2; ZNF536; MEIS1; NTRK3; ANKH; LRRTM1; VEZF1; IRAK3; VGLL4; BEND6; ACVR2A; WNK1; RAC1; CTSC; ENPP2; PBLD; PIK3C2A; EIF4E; YAP1; RC3H1; SEMA5A; TCF7L2; PTEN; ZNF423; PRKACB; BTBD7; DDAH1; AMOT	2.55E-04	2.94E-02
cell-cell adhesion	PCDH8; PCDHA3; MAP3K8; PCDHA1; PCDHA6; PCDHA4; RAC1; GOLPH3; CD164; PCDH7; RC3H1; WNK1; PCDHAC1; PCDHA2; PCDH19; PCDHA11; PCDHA10; IL1A; PCDHA12; PCDHA13	3.55E-04	3.14E-02
regulation of cardiac muscle cell proliferation	PTEN; VGLL4; MEIS1; YAP1	6.71E-04	4.76E-02

positive regulation of biosynthetic process	ELAVL1; TYRP1; HABP4; MYOCD; IL1A; NR1D2; JADE1; NPAS2; MEIS1; OTX2; KLF6; VEZF1; ZNF345; BRDT; RYBP; ZNF107; ZIC3; ACVR2A; LARP4; RAC1; TET1; FLI1; SFPQ; TP53INP1; INSIG1; YAP1; ARID5B; ERLIN2; ARID1A; TCF7L2; ZNF423; KAT6B; DAZL; DDAH1	7.87E-04	4.76E-02
regulation of RNA metabolic process	RYBP; DMRT3; ELAVL1; HDAC9; SF3B4; NPAS2; RC3H1; MYOCD; CRK; IL1A; NR1D2; JADE1; MLF1; ZNF536; ZBTB10; AHCYL1; USP47; CDK17; MEIS1; OTX2; KLF6; PELO; VEZF1; ZNF345; BRDT; IRAK3; NLK; BRWD3; VGLL4; ZIC3; BEND6; ACVR2A; TET1; FLI1; SFPQ; TP53INP1; INSIG1; IGF2BP2; PBX3; YAP1; HABP4; ARID5B; ERLIN2; ARID1A; PKIA; TCF7L2; PTEN; ZNF423; KAT6B; PHF20L1; DAZL; ZNF107; LCORL; ATXN1	9.42E-04	4.76E-02
regulation of biological process	WLS; CDK17; OTX2; MAP3K8; AHCYL1; MAP3K1; NTRK3; PSD3; BRDT; IRAK3; TAOK3; MTMR3; NECAB1; VEZF1; TYRP1; LARP4; RAB5C; CTSC; ENPP2; SERPINB9; PIK3C2A; KLK7; ARID5B; PTPN13; ARID1A; PKIA; TCF7L2; PTEN; NETO2; DDAH1; CCNJ; DMRT3; ELAVL1; KATNBL1; DCLK1; RC3H1; STAC; PLP1; CRK; ARHGAP1; IFIT1; APOD; CHD9; OSCAR; USP47; GOLPH3; KCNMA1; MEIS1; USP42; LRRTM1; ZIC3; NLK; SFPQ; TP53INP1; INSIG1; EIF4E; KIF3B; SCUBE3; IL13RA1; ERLIN2; BICD2; ZNF423; ATXN7; BTBD7; GOSR1; LCORL; ATXN1; EHD3; HDAC9; MMD2; IL1A; CNKSR2; MLF1; ZNF536; ZBTB10; SNX13; CACNB4; ZNF345; BRWD3; MEX3C; VGLL4; COCH; BEND6; ACVR2A; TRIO; TET1; CALB1; UNC13B; PHLPP2; IGF2BP2; ZNF107; YAP1; KCNJ3; HABP4; SEMA5A; PRKACB; HCN1; PHF20L1; DAZL; DEDD; AMOT; ANKH; SF3B4; CD164; ADAM10; ZMAT3; MYOCD; TRPA1; NR1D2; NPAS2; KLF6; PELO; JADE1; RYBP; XPR1; WNK1; RAC1; FLI1; CES3; PBLD; PBX3; PCDH8; PDCD6IP; KAT6B; PPP2R5C	9.64E-04	3.53E-02

Table S4-6: miR-193b-5p Predicted Target Pathway Enrichment Analysis

Enriched Pathway	**Enriched Targets**	**q-Value**	**q-Value**
nervous system development	FOXP2; CIC; UFL1; COPS2; LMO4; ENAH; JARID2; ZFHX3; CHN1; IQSEC1; ABL2; RERE; ACER3; FZD4; ITSN1; RBPJ; SULF2; RORA; KLF7; CFLAR; HOOK3; FGF11; DLX1; PLXDC1; CLN8; EPHB2; DPYSL5; TPP1; ZFP36L1; TANC2; DAG1; GPC6; TNFRSF1B; TAOK1; ADCY1; ETV1; PMP22; LRP6; CASP3; SDC4; SLC4A7; SH3KBP1; MARCKSL1; SIX4; PCDH17; SCN3B; SYN1	6.49E-07	3.08E-04
generation of neurons	UFL1; COPS2; SDC4; ENAH; ZFHX3; CHN1; IQSEC1; ABL2; RERE; FZD4; ITSN1; RBPJ; RORA; KLF7; CFLAR; DLX1; CLN8; EPHB2; DPYSL5; HOOK3; TANC2; DAG1; TNFRSF1B; TAOK1; CASP3; ETV1; LRP6; ADCY1; LMO4; SLC4A7; SH3KBP1; SIX4; SYN1	8.41E-06	3.20E-03
neurogenesis	UFL1; COPS2; SDC4; ENAH; ZFHX3; CHN1; IQSEC1; ABL2; RERE; FZD4; ITSN1; RBPJ; RORA; KLF7; CFLAR; DLX1; CLN8; EPHB2; DPYSL5; HOOK3; TANC2; DAG1; TNFRSF1B; TAOK1; CASP3; ETV1; LRP6; ADCY1; LMO4; SLC4A7; SH3KBP1; SIX4; SYN1	3.55E-05	7.53E-03
neuron differentiation	COPS2; SDC4; ENAH; ZFHX3; CHN1; IQSEC1; ABL2; RERE; FZD4; ITSN1; RBPJ; RORA; KLF7; CFLAR; DLX1; CLN8; EPHB2; DPYSL5; TANC2; DAG1; TAOK1; CASP3; ETV1; LRP6; ADCY1; LMO4; SLC4A7; SH3KBP1; SYN1	4.75E-05	7.53E-03
multicellular organism development	FOXP2; HOXC8; CIC; DMD; GPC6; FOXK1; COPS2; LMO4; PNPT1; JARID2; ZFHX3; IGSF3; UFL1; CHN1; PCDH17; TRIB1; SMAP1; IQSEC1; SLC4A7; ABL2; IQCE; RERE; CYP26B1; ADAMTS6; FZD4; ITSN1; RBPJ; RORC; SULF2; RORA; KLF7; CFLAR; HOOK3; CNOT2; FGF11; DLX1; PLXDC1; DLX3; EPHB2; ACVR2A; ST3GAL1; DPYSL5; ACER3; TSHZ2; TPP1; ENAH; PDCD4; ZFP36L1; TANC2; EHF; DAG1; TNFRSF11B; TNFRSF1B; TAOK1; CASP3; ETV1; PMP22; FHOD3; LRP6; ADCY1; GINS4; GNAS; MTURN; SNRK; SDC4; GLUL; SH3KBP1; MARCKSL1; SIX4; YBX3; KAT6A; CLN8; SCN3B; SYN1	5.08E-05	5.43E-03
system development	FOXP2; CIC; DMD; GPC6; FOXK1; COPS2; LMO4; PNPT1; JARID2; ZFHX3; IGSF3; UFL1; CHN1; PCDH17; TRIB1; SMAP1; IQSEC1; SLC4A7; ABL2; RERE; CYP26B1; ADAMTS6; FZD4; ITSN1; RBPJ; RORC; SULF2; RORA; KLF7; CFLAR; HOOK3; FGF11; DLX1; PLXDC1; DLX3; EPHB2; ACVR2A; ST3GAL1; DPYSL5; ACER3; TPP1; ENAH; PDCD4; ZFP36L1; TANC2; DAG1; TNFRSF11B; TNFRSF1B; TAOK1; CASP3; ETV1; PMP22; FHOD3; LRP6; ADCY1; GNAS; MTURN; SNRK; SDC4; GLUL; SH3KBP1; MARCKSL1; SIX4; YBX3; KAT6A; CLN8; SCN3B; SYN1	6.39E-05	1.85E-02
cellular response to sterol	RORC; LRP6; DAG1; RORA	8.19E-05	1.56E-02
cell differentiation	UFL1; DMD; FOXK1; COPS2; LMO4; ENAH; JARID2; ZFHX3; CHN1; TRIB1; IQSEC1; ABL2; PEG10; RERE; CYP26B1; FZD4; ITSN1; RBPJ; RORC; SULF2; RORA; KLF7; CFLAR; CLIP3; ZNF431; HOOK3; CNOT2; PDCD4; DLX1; DLX3; EPHB2; ACVR2A; ST3GAL1; DPYSL5; SMAP1; TPP1; ZFP36L1; TANC2; EHF; RSL1D1; DAG1; TNFRSF1B; TAOK1; CASP3; ETV1; FHOD3; LRP6; ADCY1; GNAS; MTURN; SNRK; SDC4; SLC4A7; SH3KBP1; SIX4; YY1AP1; KAT6A; CLN8; SYN1	1.47E-04	2.13E-02
central nervous system development	CIC; FOXP2; JARID2; ZFHX3; RERE; FZD4; ITSN1; RBPJ; RORA; HOOK3; DLX1; PLXDC1; CLN8; EPHB2; TPP1; DAG1; TNFRSF1B; CASP3; LRP6; ADCY1; LMO4; MARCKSL1	1.52E-04	1.80E-02
cellular developmental process	UFL1; DMD; FOXK1; COPS2; LMO4; PNPT1; JARID2; ZFHX3; CHN1; TRIB1; IQSEC1; ABL2; PEG10; RERE; CYP26B1; FZD4; ITSN1; RBPJ; RORC; SULF2; RORA; KLF7; CFLAR; CLIP3; ZNF431; HOOK3; CNOT2; PDCD4; DLX1; DLX3; EPHB2; ACVR2A; ST3GAL1; DPYSL5; SMAP1; TPP1; ZFP36L1; TANC2; EHF; RSL1D1; DAG1; ENAH; TNFRSF1B; TAOK1; CASP3; ETV1; PMP22; FHOD3; LRP6; ADCY1; GNAS; MTURN; SNRK; SDC4; SLC4A7; SH3KBP1; SIX4; YY1AP1; KAT6A; CLN8; SYN1	1.74E-04	9.32E-03
cellular response to lipid	UFL1; CNOT2; LRP6; ADCY1; RORC; ZFP36L1; RORA; CYP26B1; CFLAR; DAG1; FZD4; TNFRSF1B; PDCD4; ABL2; UBR5; TRIB1	1.85E-04	2.35E-02
chordate embryonic development	ACVR2A; LRP6; CASP3; GINS4; GNAS; COPS2; LMO4; RBPJ; SDC4; ZFP36L1; SULF2; SIX4; CNOT2; TANC2; DLX1; YBX3	2.75E-04	2.61E-02
response to sterol	RORC; LRP6; DAG1; RORA	3.43E-04	3.02E-02
muscle structure development	FHOD3; DMD; CASP3; FOXK1; SIX4; COPS2; RBPJ; RORA; JARID2; ZFP36L1; ZFHX3; CYP26B1; CFLAR; DAG1; PDCD4; YBX3	3.82E-04	3.69E-02
embryo development ending in birth or egg hatching	ACVR2A; LRP6; CASP3; GINS4; GNAS; COPS2; LMO4; RBPJ; SDC4; ZFP36L1; SULF2; SIX4; CNOT2; TANC2; DLX1; YBX3	3.82E-04	3.02E-02

acid-ammonia (or amide) ligase activity	GLUL; DPH6	4.71E-04	3.39E-02
cellular response to organic cyclic compound	UFL1; LARP1; LRP6; CASP3; RORC; ZFP36L1; RORA; EPG5; CFLAR; DAG1; CNOT2; MAVS; UBR5; ADCY1	5.65E-04	3.56E-02
animal organ development	FOXP2; CIC; DMD; GPC6; FOXK1; COPS2; LMO4; PNPT1; JARID2; ZFHX3; IGSF3; UFL1; SLC4A7; TRIB1; RERE; CYP26B1; ADAMTS6; FZD4; ITSN1; RBPJ; RORC; SULF2; RORA; KLF7; CFLAR; PDCD4; DLX1; PLXDC1; DLX3; EPHB2; ACVR2A; ST3GAL1; SMAP1; HOOK3; ZFP36L1; DAG1; TNFRSF11B; TNFRSF1B; ADCY1; FHOD3; LRP6; CASP3; GNAS; MTURN; SNRK; SDC4; SIX4; KAT6A; CLN8; YBX3	5.69E-04	4.12E-02
anatomical structure development	FOXP2; HOXC8; CIC; DMD; GPC6; FOXK1; TMEM135; COPS2; LMO4; PNPT1; JARID2; ZFHX3; IGSF3; UFL1; CHN1; PCDH17; TRIB1; SMAP1; IQSEC1; SLC4A7; ABL2; IQCE; RERE; CYP26B1; ADAMTS6; FZD4; ITSN1; RBPJ; RORC; SULF2; RORA; KLF7; CFLAR; HOOK3; CNOT2; FGF11; DLX1; PLXDC1; DLX3; EPHB2; ACVR2A; ST3GAL1; DPYSL5; ACER3; TSHZ2; TPP1; ENAH; PDCD4; ZFP36L1; TANC2; EHF; DAG1; TNFRSF11B; TNFRSF1B; TAOK1; CASP3; ETV1; PMP22; FHOD3; LRP6; ADCY1; GINS4; GNAS; MTURN; SNRK; SDC4; GLUL; SH3KBP1; MARCKSL1; SIX4; YBX3; KAT6A; CLN8; SCN3B; SYN1	6.03E-04	2.15E-02
regulation of RNA metabolic process	FOXP2; HOXC8; CIC; FOXK1; MSL3; COPS2; PNPT1; JARID2; ZFHX3; XIAP; MAP2K7; TRIB1; ZNF780B; RERE; FZD4; LARP1; SIX4; RBPJ; RORC; ZBTB8A; RORA; KLF7; CFLAR; YY1AP1; ZNF431; PIK3R2; CAMTA1; CNOT2; PDCD4; DLX1; DLX3; UFL1; ACVR2A; TSHZ2; ZFP36L1; EHF; PHF20L1; TNFRSF1B; GATAD1; ETV1; MAVS; LRP6; ADCY1; ZNF714; MTURN; LMO4; ZNF138; KPNA6; ZNF701; ZNF793; KAT6A; ABCE1; POU2F2; LCORL; YBX3; ILF2	6.55E-04	0.035623
regulation of nucleobase-containing compound metabolic process	FOXP2; HOXC8; CIC; FOXK1; MSL3; COPS2; PNPT1; JARID2; ZFHX3; XIAP; MAP2K7; TRIB1; ZNF780B; POLH; RERE; SMG1; LARP1; SIX4; RBPJ; RORC; ZBTB8A; RORA; KLF7; CFLAR; YY1AP1; ZNF431; PIK3R2; CAMTA1; CNOT2; PDCD4; DLX1; DLX3; UFL1; ACVR2A; TSHZ2; ZNF793; ZFP36L1; EHF; NUP50; PHF20L1; TNFRSF1B; GATAD1; UBR5; ETV1; MAVS; LRP6; ADCY1; ZNF714; MTURN; LMO4; ZNF138; KPNA6; ZNF701; FZD4; KAT6A; ABCE1; POU2F2; LCORL; YBX3; ILF2	6.56E-04	3.56E-02
muscle organ development	DMD; FOXK1; SIX4; COPS2; RBPJ; JARID2; ZFHX3; CYP26B1; CFLAR; DAG1; YBX3	8.84E-04	5.70E-02
skeletal muscle fiber differentiation	SIX4; CYP26B1	9.35E-04	4.44E-02
response to lipid	FOXP2; CNOT2; FMO1; LRP6; CASP3; UFL1; RORC; ZFP36L1; RORA; TRIB1; CFLAR; DAG1; FZD4; TNFRSF1B; CYP26B1; ABL2; PDCD4; UBR5; ADCY1	9.61E-04	5.70E-02

Table S4-7: Nervous System Development mRNA Targets

Target	Ensmbl ID	miRNA	Target	Ensmbl ID	miRNA
FOXP2	ENSG00000128573	miR-193b-3p	CASP3	ENSG00000164305	miR-193b-3p
CIC	ENSG00000079432	miR-193b-3p	SDC4	ENSG00000124145	miR-193b-3p
UFL1	ENSG00000014123	miR-193b-3p	SLC4A7	ENSG00000033867	miR-193b-3p
COPS2	ENSG00000166200	miR-193b-3p	SH3KBP1	ENSG00000147010	miR-193b-3p
LMO4	ENSG00000143013	miR-193b-3p	MARCKSL1	ENSG00000175130	miR-193b-3p
ENAH	ENSG00000154380	miR-193b-3p	SIX4	ENSG00000100625	miR-193b-3p
JARID2	ENSG00000008083	miR-193b-3p	PCDH17	ENSG00000118946	miR-193b-3p
ZFHX3	ENSG00000140836	miR-193b-3p	SCN3B	ENSG00000166257	miR-193b-3p
CHN1	ENSG00000128656	miR-193b-3p	SYN1	ENSG00000008056	miR-193b-3p
IQSEC1	ENSG00000144711	miR-193b-3p	DMRT3	ENSG00000064218	miR-509-3p
ABL2	ENSG00000143322	miR-193b-3p	NRN1	ENSG00000124785	miR-509-3p
RERE	ENSG00000142599	miR-193b-3p	HDAC9	ENSG00000048052	miR-509-3p
ACER3	ENSG00000078124	miR-193b-3p	DCLK1	ENSG00000133083	miR-509-3p
FZD4	ENSG00000174804	miR-193b-3p	ADAM10	ENSG00000137845	miR-509-3p
ITSN1	ENSG00000205726	miR-193b-3p	PCDHA10	ENSG00000250120	miR-509-3p
RBPJ	ENSG00000168214	miR-193b-3p	CRK	ENSG00000167193	miR-509-3p
SULF2	ENSG00000196562	miR-193b-3p	PLP1	ENSG00000123560	miR-509-3p
RORA	ENSG00000069667	miR-193b-3p	OTX2	ENSG00000165588	miR-509-3p
KLF7	ENSG00000118263	miR-193b-3p	APOD	ENSG00000189058	miR-509-3p
CFLAR	ENSG00000003402	miR-193b-3p	NAV2	ENSG00000166833	miR-509-3p
HOOK3	ENSG00000168172	miR-193b-3p	NPAS2	ENSG00000170485	miR-509-3p
FGF11	ENSG00000161958	miR-193b-3p	MEIS1	ENSG00000143995	miR-509-3p
DLX1	ENSG00000144355	miR-193b-3p	NTRK3	ENSG00000140538	miR-509-3p
PLXDC1	ENSG00000161381	miR-193b-3p	NAV1	ENSG00000134369	miR-509-3p
CLN8	ENSG00000182372	miR-193b-3p	PCDHAC1	ENSG00000248383	miR-509-3p
EPHB2	ENSG00000133216	miR-193b-3p	LRRTM1	ENSG00000162951	miR-509-3p
DPYSL5	ENSG00000157851	miR-193b-3p	ZIC3	ENSG00000156925	miR-509-3p
TPP1	ENSG00000166340	miR-193b-3p	TAOK3	ENSG00000135090	miR-509-3p
ZFP36L1	ENSG00000185650	miR-193b-3p	BEND6	ENSG00000151917	miR-509-3p
TANC2	ENSG00000170921	miR-193b-3p	TRIO	ENSG00000038382	miR-509-3p
DAG1	ENSG00000173402	miR-193b-3p	WNK1	ENSG00000060237	miR-509-3p
GPC6	ENSG00000183098	miR-193b-3p	RAC1	ENSG00000136238	miR-509-3p
TNFRSF1B	ENSG00000028137	miR-193b-3p	CTSC	ENSG00000109861	miR-509-3p
TAOK1	ENSG00000160551	miR-193b-3p	MMD2	ENSG00000136297	miR-509-3p
ADCY1	ENSG00000164742	miR-193b-3p	ZNF536	ENSG00000198597	miR-509-3p
ETV1	ENSG00000006468	miR-193b-3p	EIF4E	ENSG00000151247	miR-509-3p
PMP22	ENSG00000109099	miR-193b-3p	PCDHA11	ENSG00000249158	miR-509-3p
LRP6	ENSG00000070018	miR-193b-3p	IGF2BP2	ENSG00000073792	miR-509-3p

Target	Ensmbl ID	miRNA
PBX3	ENSG00000167081	miR-509-3p
YAP1	ENSG00000137693	miR-509-3p
PCDHA2	ENSG00000204969	miR-509-3p
PCDHA3	ENSG00000255408	miR-509-3p
PCDHA1	ENSG00000204970	miR-509-3p
PCDHA6	ENSG00000081842	miR-509-3p
PCDHA4	ENSG00000204967	miR-509-3p
SEMA5A	ENSG00000112902	miR-509-3p
HCN1	ENSG00000164588	miR-509-3p
ARID1A	ENSG00000117713	miR-509-3p
PTEN	ENSG00000171862	miR-509-3p
ZNF423	ENSG00000102935	miR-509-3p
PRKACB	ENSG00000142875	miR-509-3p
PCDH19	ENSG00000165194	miR-509-3p
ATXN1	ENSG00000124788	miR-509-3p

Table S4-8: Simple linear regression of summary scores of NNNS metrics and Cd-associated miRNA transcript abundances; effect sizes ± 95% CI, and p-values (n=114)

	miR-509-3p	**miR-193b-5p**
Arousal	**β**= 0.039 ± 0.378 **p** = 0.84	**β** = 0.141 ± 0.283 **p** = 0.33
Quality of movement	**β** = -0.47 ± 0.38 **p** = 0.017 (**)	**β** = -0.278 ± 0.287 **p** = 0.06 (*)
Excitability	**β** = 0.223 ± 0.403 **p =** 0.28	**β** = 0.27 ± 0.3 **p =** 0.09 (*)
Self Regulaton	**β** = -0.110 ± 0.402 **p =** 0.59	**β** = -0.237 ± 0.296 **p =** 0.12
Stress Abstinence	**β** = 0.111±0.344 **p =** 0.53	**β** = 0.040 ± 0.258 **p =** 0.76

$^*p \leq 0.1$; $^{**}p \leq 0.05$; $^{***}p \leq 0.001$

SUPPLEMENTARY FIGURES

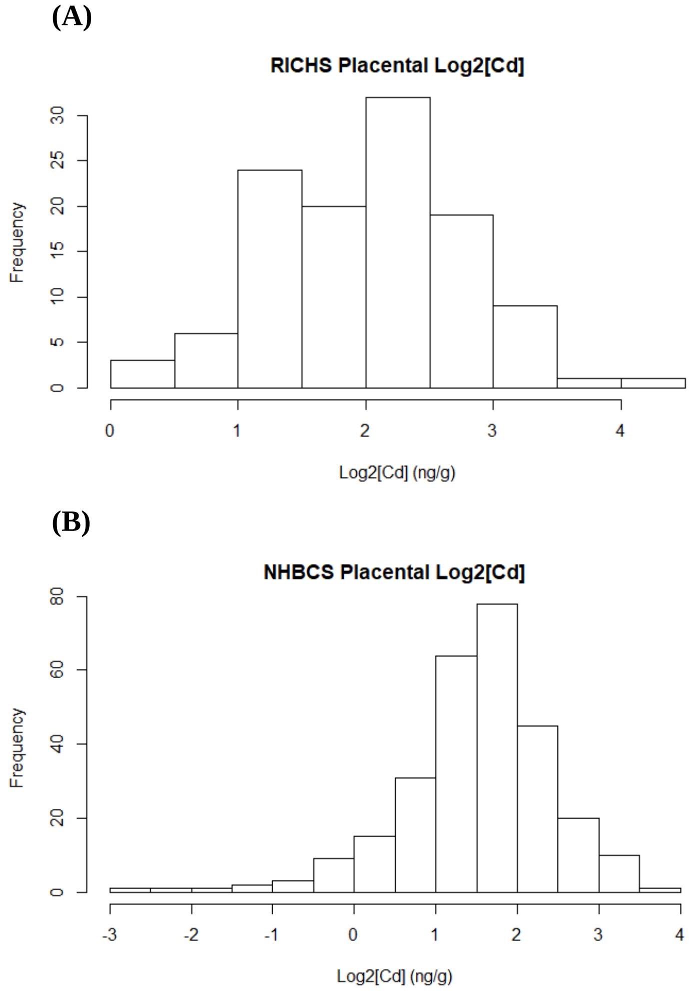


Figure S4-1 – Log2 transformed placental Cd in RICHS and NHBCS. Histogram depicting each individual cohort's distribution of log2 transformed placental cadmium concentrations. RICHS (A) exhibits a mean concentration of 4.39 ng/g with a standard deviation of 2.52 ng/g. NHBCS (B) exhibits a mean concentration of 2.93 ng/g with a standard deviation of 1.99 ng/g.

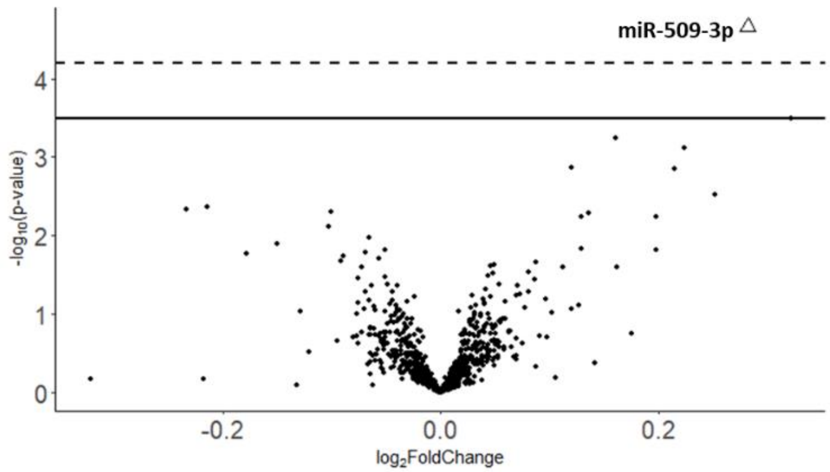
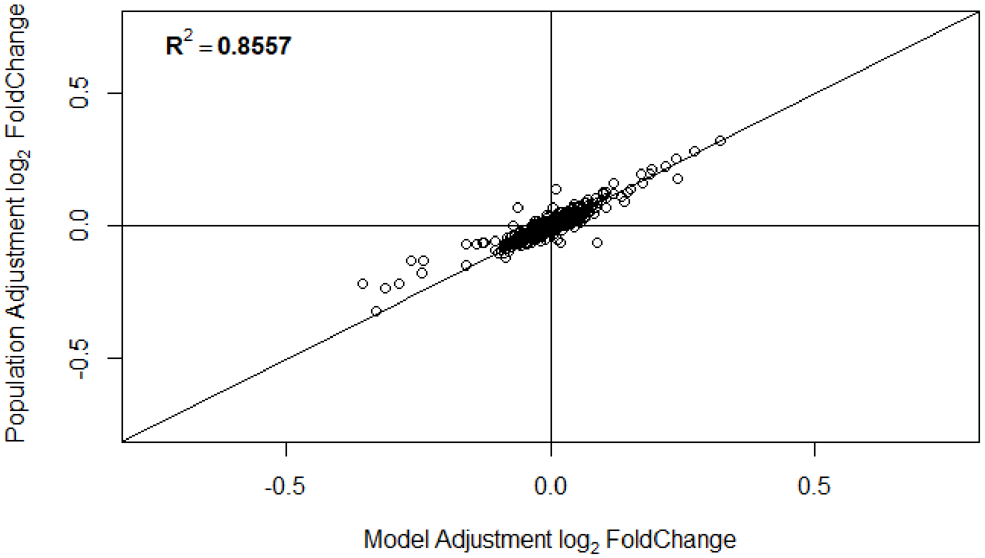
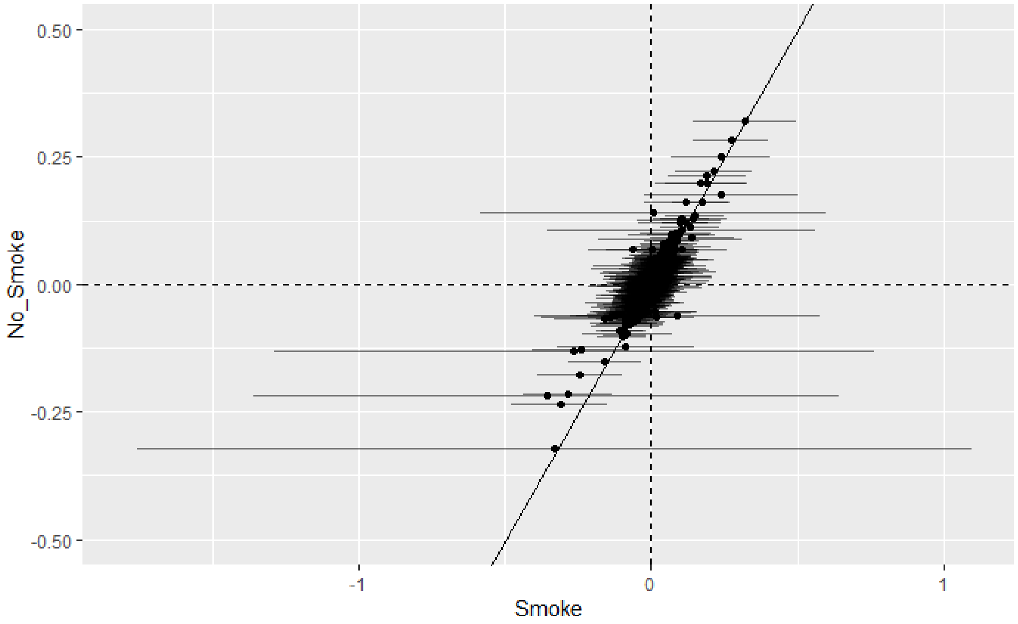


Figure S4-2: Placental miRNA associates with placental cadmium concentrations in a population excluding self-reported smokers. Volcano plot representing the results of the NHBCS differential expression analysis while excluding mothers who self-reported to smoking during any point of their pregnancy. The y-axis shows the $-\log_{10}$(p-values) in the association of each miRNA with $\log_2$-transformed placental cadmium concentrations. The x-axis displays the effect estimates in units of $\log_2$ fold change in each miRNA's transcript abundance per doubling of placental cadmium. 1 miRNA is significantly (FDR <0.1) associated with placental cadmium accumulation and remains significant following Bonferroni correction (p-value < 6.23e-05).

(A)


$R^2 = 0.8557$
Population Adjustment $\log_2$ FoldChange
Model Adjustment $\log_2$ FoldChange
-0.5
0.0
0.5
-0.5
0.0
0.5

(B)


0.50
0.25
0.00
-0.25
-0.50
No_Smoke
-1
0
1
Smoke

(C)

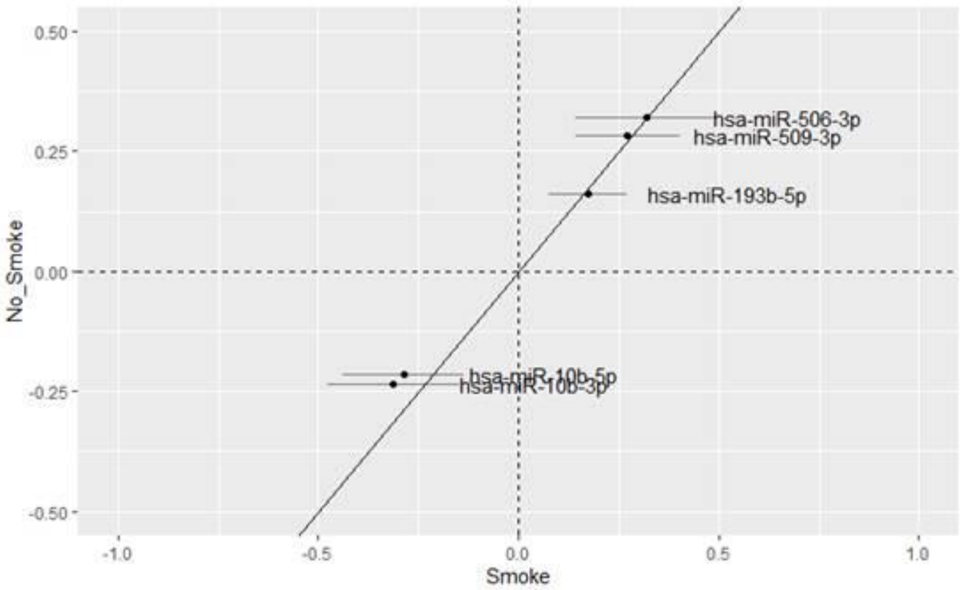


Figure S4-3: Effect size estimates of placental miRNAs are highly robust on a transcriptome-wide scale to the exclusion of self-reported smokers. **(A)** Scatter plot displaying the coefficient of determination (R^2) to emphasize the relationship between the estimates produced by the original NHBCS model, which adjusts for maternal smoking, and one which excludes self-reported smokers. **(B)** Forest plot representing all miRNA effect size estimates compared between the original NHBCS model (x-axis), and the self-reported smoker exclusionary model (y-axis). Error bars represent the estimated 95% confidence interval from the NHBCS original model. **(C)** Forest plot representing only miRNAs found to be differentially expressed with respect to gestational Cd in the NHBCS original model, comparing effect sizes between the original NHBCS model (x-axis) and the self-reported smoker exclusionary model (y-axis). Error bars represent the estimated 95% confidence interval from the NHBCS original model.

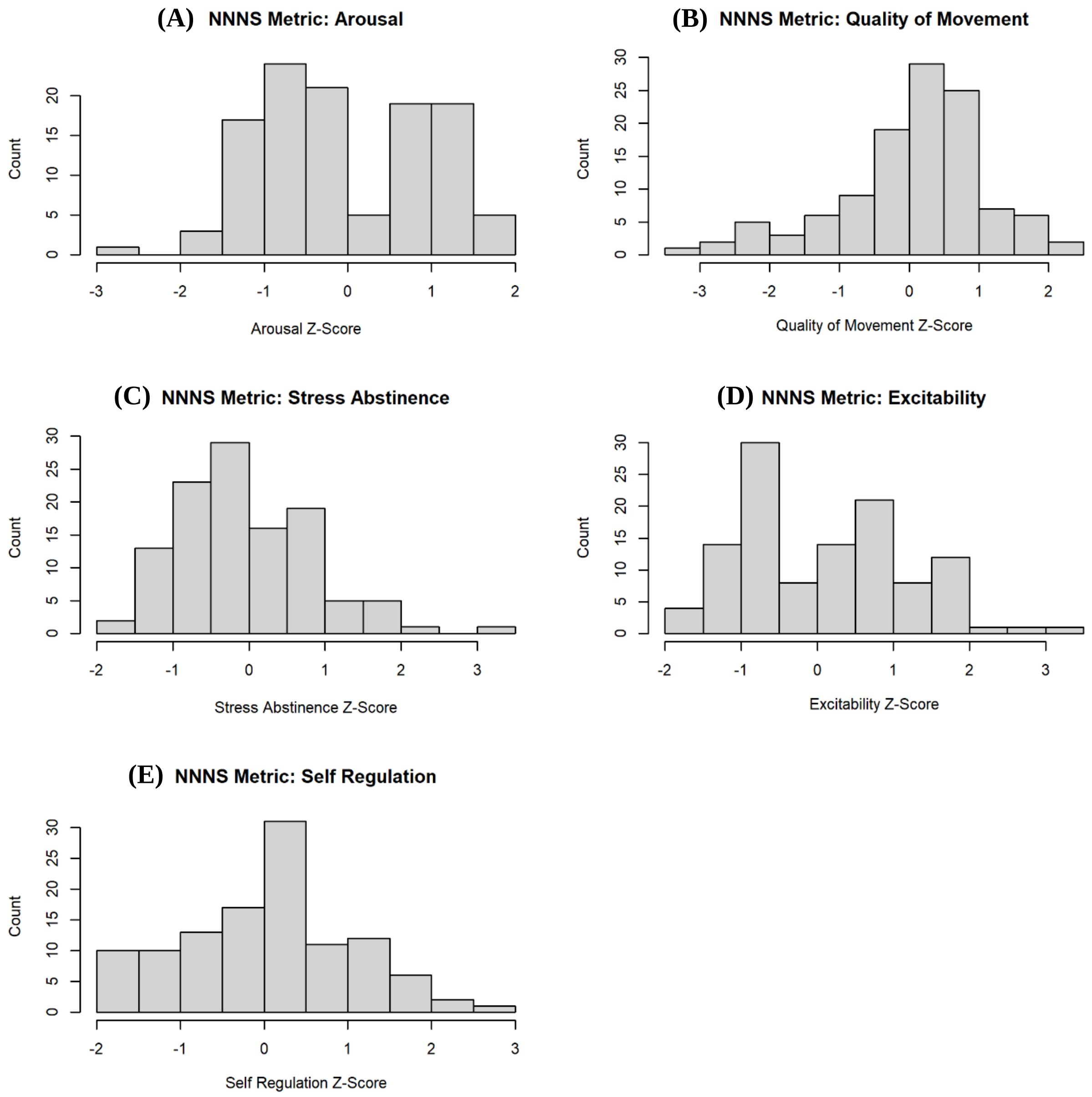


Figure S4-4: Histogram depicting the distribution of z-transformed NNNS metrics that are highly variable across atypical vs neuro-typical profiles in RICHS infants (n=114). **(A)** Arousal **(B)** Quality of movement **(C)** Stress abstinence, **(D)** Excitability **(E)** Self-Regulation.

REFERENCES

1. WHO. EXPOSURE TO CADMIUM : A MAJOR PUBLIC HEALTH CONCERN2010.
2. Jarup L, Akesson A. Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol. 2009;238(3):201-8. Epub 2009/05/05. doi: 10.1016/j.taap.2009.04.020. PubMed PMID: 19409405.
3. Adams SV, Passarelli MN, Newcomb PA. Cadmium exposure and cancer mortality in the Third National Health and Nutrition Examination Survey cohort. Occup Environ Med. 2012;69(2):153-6. Epub 2011/11/10. doi: 10.1136/oemed-2011-100111. PubMed PMID: 22068173; PMCID: PMC3289533.
4. Peters JL, Perlstein TS, Perry MJ, McNeely E, Weuve J. Cadmium exposure in association with history of stroke and heart failure. Environ Res. 2010;110(2):199-206. Epub 2010/01/12. doi: 10.1016/j.envres.2009.12.004. PubMed PMID: 20060521; PMCID: PMC3031174.
5. Suwazono Y, Sand S, Vahter M, Filipsson AF, Skerfving S, Lidfeldt J, Akesson A. Benchmark dose for cadmium-induced renal effects in humans. Environ Health Perspect. 2006;114(7):1072-6. Epub 2006/07/13. doi: 10.1289/ehp.9028. PubMed PMID: 16835061; PMCID: PMC1513341.
6. Punshon T, Li Z, Jackson BP, Parks WT, Romano M, Conway D, Baker ER, Karagas MR. Placental metal concentrations in relation to placental growth, efficiency and birth weight. Environ Int. 2019;126:533-42. Epub 2019/03/10. doi: 10.1016/j.envint.2019.01.063. PubMed PMID: 30851484; PMCID: PMC6475117.
7. Cross JC, Baczyk D, Dobric N, Hemberger M, Hughes M, Simmons DG, Yamamoto H, Kingdom JC. Genes, development and evolution of the placenta. Placenta. 2003;24(2-3):123-30. Epub 2003/02/25. doi: 10.1053/plac.2002.0887. PubMed PMID: 12596737.
8. Hussey MR, Burt A, Deyssenroth MA, Jackson BP, Hao K, Peng S, Chen J, Marsit CJ, Everson TM. Placental lncRNA expression associated with placental cadmium concentrations and birth weight. Environ Epigenet. 2020;6(1):dvaa003. Epub 2020/05/16. doi: 10.1093/eep/dvaa003. PubMed PMID: 32411397; PMCID: PMC7211362.
9. Laine JE, Ray P, Bodnar W, Cable PH, Boggess K, Offenbacher S, Fry RC. Placental Cadmium Levels Are Associated with Increased Preeclampsia Risk. PLoS One. 2015;10(9):e0139341. Epub 2015/10/01. doi: 10.1371/journal.pone.0139341. PubMed PMID: 26422011; PMCID: PMC4589375.
10. Hudson KM, Shiver E, Yu J, Mehta S, Jima DD, Kane MA, Patisaul HB, Cowley M. Transcriptomic, proteomic, and metabolomic analyses identify candidate pathways linking maternal cadmium exposure to altered neurodevelopment and behavior. Scientific Reports. 2021;11(1). doi: 10.1038/s41598-021-95630-2.
11. Liu J, Martin LJ, Dinu I, Field CJ, Dewey D, Martin JW. Interaction of prenatal bisphenols, maternal nutrients, and toxic metal exposures on neurodevelopment of 2-year-olds in the APrON cohort. Environ Int. 2021;155:106601. Epub 2021/05/08. doi: 10.1016/j.envint.2021.106601. PubMed PMID: 33962233.
12. Tian LL, Zhao YC, Wang XC, Gu JL, Sun ZJ, Zhang YL, Wang JX. Effects of gestational cadmium exposure on pregnancy outcome and development in the offspring at age 4.5 years. Biol Trace Elem Res. 2009;132(1-3):51-9. Epub 2009/05/01. doi: 10.1007/s12011-009-8391-0. PubMed PMID: 19404590.

13. Wang Y, Chen L, Gao Y, Zhang Y, Wang C, Zhou Y, Hu Y, Shi R, Tian Y. Effects of prenatal exposure to cadmium on neurodevelopment of infants in Shandong, China. Environ Pollut. 2016;211:67-73. Epub 2016/01/07. doi: 10.1016/j.envpol.2015.12.038. PubMed PMID: 26736057.
14. Tung PW, Burt A, Karagas M, Jackson BP, Punshon T, Lester B, Marsit CJ. Association between placental toxic metal exposure and NICU Network Neurobehavioral Scales (NNNS) profiles in the Rhode Island Child Health Study (RICHS). Environ Res. 2021;204(Pt A):111939. Epub 2021/08/31. doi: 10.1016/j.envres.2021.111939. PubMed PMID: 34461121.
15. Lester BM, Marsit CJ. Epigenetic mechanisms in the placenta related to infant neurodevelopment. Epigenomics. 2018;10(3):321-33. Epub 2018/01/31. doi: 10.2217/epi-2016-0171. PubMed PMID: 29381081; PMCID: PMC6219448.
16. Rosenfeld CS. The placenta-brain-axis. J Neurosci Res. 2021;99(1):271-83. Epub 2020/02/29. doi: 10.1002/jnr.24603. PubMed PMID: 32108381; PMCID: PMC7483131.
17. Shallie PD, Naicker T. The placenta as a window to the brain: A review on the role of placental markers in prenatal programming of neurodevelopment. Int J Dev Neurosci. 2019;73:41-9. Epub 2019/01/12. doi: 10.1016/j.ijdevneu.2019.01.003. PubMed PMID: 30634053.
18. Vilahur N, Vahter M, Broberg K. The Epigenetic Effects of Prenatal Cadmium Exposure. Curr Environ Health Rep. 2015;2(2):195-203. Epub 2015/05/12. doi: 10.1007/s40572-015-0049-9. PubMed PMID: 25960943; PMCID: PMC4417128.
19. Gu S, Dai J, Qu T, He Z. Emerging Roles of MicroRNAs and Long Noncoding RNAs in Cadmium Toxicity. Biol Trace Elem Res. 2020;195(2):481-90. Epub 2019/08/20. doi: 10.1007/s12011-019-01859-4. PubMed PMID: 31422539.
20. Cowley M, Skaar DA, Jima DD, Maguire RL, Hudson KM, Park SS, Sorrow P, Hoyo C. Effects of Cadmium Exposure on DNA Methylation at Imprinting Control Regions and Genome-Wide in Mothers and Newborn Children. Environ Health Perspect. 2018;126(3):037003. Epub 2018/03/13. doi: 10.1289/EHP2085. PubMed PMID: 29529597; PMCID: PMC6071808.
21. Everson TM, Punshon T, Jackson BP, Hao K, Lambertini L, Chen J, Karagas MR, Marsit CJ. Cadmium-Associated Differential Methylation throughout the Placental Genome: Epigenome-Wide Association Study of Two U.S. Birth Cohorts. Environ Health Perspect. 2018;126(1):017010. Epub 2018/01/27. doi: 10.1289/EHP2192. PubMed PMID: 29373860; PMCID: PMC6014712.
22. Appleton AA, Jackson BP, Karagas M, Marsit CJ. Prenatal exposure to neurotoxic metals is associated with increased placental glucocorticoid receptor DNA methylation. Epigenetics. 2017;12(8):607-15. Epub 2017/05/27. doi: 10.1080/15592294.2017.1320637. PubMed PMID: 28548590; PMCID: PMC5687337.
23. Wang D, Na Q, Song WW, Song GY. Altered Expression of miR-518b and miR-519a in the placenta is associated with low fetal birth weight. Am J Perinatol. 2014;31(9):729-34. Epub 2014/04/01. doi: 10.1055/s-0033-1361832. PubMed PMID: 24683074.
24. Thamotharan S, Chu A, Kempf K, Janzen C, Grogan T, Elashoff DA, Devaskar SU. Differential microRNA expression in human placentas of term intra-uterine growth restriction that regulates target genes mediating angiogenesis and amino acid transport. PLOS ONE. 2017;12(5):e0176493. doi: 10.1371/journal.pone.0176493.

25. Lesseur C, Armstrong DA, Paquette AG, Koestler DC, Padbury JF, Marsit CJ. Tissue-specific Leptin promoter DNA methylation is associated with maternal and infant perinatal factors. Mol Cell Endocrinol. 2013;381(1-2):160-7. Epub 2013/08/06. doi: 10.1016/j.mce.2013.07.024. PubMed PMID: 23911897; PMCID: PMC3795868.
26. Higashijima A, Miura K, Mishima H, Kinoshita A, Jo O, Abe S, Hasegawa Y, Miura S, Yamasaki K, Yoshida A, Yoshiura K, Masuzaki H. Characterization of placenta-specific microRNAs in fetal growth restriction pregnancy. Prenat Diagn. 2013;33(3):214-22. Epub 2013/01/29. doi: 10.1002/pd.4045. PubMed PMID: 23354729.
27. Awamleh Z, Gloor GB, Han VKM. Placental microRNAs in pregnancies with early onset intrauterine growth restriction and preeclampsia: potential impact on gene expression and pathophysiology. BMC Medical Genomics. 2019;12(1):91. doi: 10.1186/s12920-019-0548-x.
28. Östling H, Kruse R, Helenius G, Lodefalk M. Placental expression of microRNAs in infants born small for gestational age. Placenta. 2019;81:46-53. Epub 2019/05/30. doi: 10.1016/j.placenta.2019.05.001. PubMed PMID: 31138431.
29. Meng M, Cheng YKY, Wu L, Chaemsaithong P, Leung MBW, Chim SSC, Sahota DS, Li W, Poon LCY, Wang CC, Leung TY. Whole genome miRNA profiling revealed miR-199a as potential placental pathogenesis of selective fetal growth restriction in monochorionic twin pregnancies. Placenta. 2020;92:44-53. Epub 2020/02/18. doi: 10.1016/j.placenta.2020.02.002. PubMed PMID: 32063549.
30. Leek JT. svaseq: removing batch effects and other unwanted noise from sequencing data. Nucleic Acids Res. 2014;42(21). Epub 2014/10/09. doi: 10.1093/nar/gku864. PubMed PMID: 25294822; PMCID: PMC4245966.
31. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biology. 2014;15(12):550. doi: 10.1186/s13059-014-0550-8.
32. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010;26(17):2190-1. doi: 10.1093/bioinformatics/btq340.
33. Tokar T, Pastrello C, Rossos AEM, Abovsky M, Hauschild A-C, Tsay M, Lu R, Jurisica I. mirDIP 4.1-integrative database of human microRNA target predictions. Nucleic acids research. 2018;46(D1):D360-D70. doi: 10.1093/nar/gkx1144. PubMed PMID: 29194489.
34. Kamburov A, Pentchev K, Galicka H, Wierling C, Lehrach H, Herwig R. ConsensusPathDB: toward a more complete picture of cell biology. Nucleic Acids Res. 2011;39(Database issue):D712-7. Epub 2010/11/13. doi: 10.1093/nar/gkq1156. PubMed PMID: 21071422; PMCID: PMC3013724.
35. Kamburov A, Wierling C, Lehrach H, Herwig R. ConsensusPathDB--a database for integrating human functional interaction networks. Nucleic Acids Res. 2009;37(Database issue):D623-8. Epub 2008/10/23. doi: 10.1093/nar/gkn698. PubMed PMID: 18940869; PMCID: PMC2686562.
36. Esteban-Vasallo MD, Aragonés N, Pollan M, López-Abente G, Perez-Gomez B. Mercury, cadmium, and lead levels in human placenta: a systematic review. Environmental health perspectives. 2012;120(10):1369-77. Epub 2012/05/16. doi: 10.1289/ehp.1204952. PubMed PMID: 22591711.

37. Ahir BK, Elias NM, Lakka SS. SPARC overexpression alters microRNA expression profiles involved in tumor progression. Genes Cancer. 2017;8(1-2):453-71. Epub 2017/04/25. doi: 10.18632/genesandcancer.130. PubMed PMID: 28435518; PMCID: PMC5396623.
38. Su Z, Chen D, Zhang E, Li Y, Yu Z, Shi M, Jiang Z, Ni L, Yang S, Gui Y, Ye J, Lai Y. MicroRNA-509-3p inhibits cancer cell proliferation and migration by targeting the mitogen-activated protein kinase kinase kinase 8 oncogene in renal cell carcinoma. Mol Med Rep. 2015;12(1):1535-43. doi: 10.3892/mmr.2015.3498.
39. Pan Y, Robertson G, Pedersen L, Lim E, Hernandez-Herrera A, Rowat AC, Patil SL, Chan CK, Wen Y, Zhang X, Basu-Roy U, Mansukhani A, Chu A, Sipahimalani P, Bowlby R, Brooks D, Thiessen N, Coarfa C, Ma Y, Moore RA, Schein JE, Mungall AJ, Liu J, Pecot CV, Sood AK, Jones SJM, Marra MA, Gunaratne PH. miR-509-3p is clinically significant and strongly attenuates cellular migration and multi-cellular spheroids in ovarian cancer. Oncotarget. 2016;7(18):25930-48. doi: 10.18632/oncotarget.8412. PubMed PMID: 27036018.
40. Daoud G, Amyot M, Rassart E, Masse A, Simoneau L, Lafond J. ERK1/2 and p38 regulate trophoblasts differentiation in human term placenta. J Physiol. 2005;566(Pt 2):409-23. Epub 2005/05/12. doi: 10.1113/jphysiol.2005.089326. PubMed PMID: 15890698.
41. Wang K, Zheng J. Signaling regulation of fetoplacental angiogenesis. J Endocrinol. 2012;212(3):243-55. Epub 2011/11/23. doi: 10.1530/JOE-11-0296. PubMed PMID: 22106098; PMCID: PMC3288248.
42. Hu H, Li S, Liu J, Ni B. MicroRNA-193b modulates proliferation, migration, and invasion of non-small cell lung cancer cells. Acta Biochimica et Biophysica Sinica. 2012;44(5):424-30. doi: 10.1093/abbs/gms018.
43. Hulin J-A, Tommasi S, Elliot D, Hu DG, Lewis BC, Mangoni AA. MiR-193b regulates breast cancer cell migration and vasculogenic mimicry by targeting dimethylarginine dimethylaminohydrolase 1. Scientific Reports. 2017;7(1):13996. doi: 10.1038/s41598-017-14454-1.
44. Shin CH, Lee H, Kim HR, Choi KH, Joung J-G, Kim HH. Regulation of PLK1 through competition between hnRNPK, miR-149-3p and miR-193b-5p. Cell Death & Differentiation. 2017;24(11):1861-71. doi: 10.1038/cdd.2017.106.
45. Pineles BL, Romero R, Montenegro D, Tarca AL, Han YM, Kim YM, Draghici S, Espinoza J, Kusanovic JP, Mittal P, Hassan SS, Kim CJ. Distinct subsets of microRNAs are expressed differentially in the human placentas of patients with preeclampsia. Am J Obstet Gynecol. 2007;196(3):261 e1-6. Epub 2007/03/10. doi: 10.1016/j.ajog.2007.01.008. PubMed PMID: 17346547.
46. Awamleh Z, Gloor GB, Han VKM. Placental microRNAs in pregnancies with early onset intrauterine growth restriction and preeclampsia: potential impact on gene expression and pathophysiology. BMC Med Genomics. 2019;12(1):91. Epub 2019/06/30. doi: 10.1186/s12920-019-0548-x. PubMed PMID: 31248403; PMCID: PMC6598374.
47. Zhou X, Li Q, Xu J, Zhang X, Zhang H, Xiang Y, Fang C, Wang T, Xia S, Zhang Q, Xing Q, He L, Wang L, Xu M, Zhao X. The aberrantly expressed miR-193b-3p contributes to preeclampsia through regulating transforming growth factor-β signaling. Scientific Reports. 2016;6(1):19910. doi: 10.1038/srep19910.

48. Awamleh Z, Han VKM. Potential pathophysiological role of microRNA 193b-5p in human placentae from pregnancies complicated by preeclampsia and intrauterine growth restriction. Molecular Biology Reports. 2020;47(9):6531-44. doi: 10.1007/s11033-020-05705-y.
49. Rosenfeld CS. Placental serotonin signaling, pregnancy outcomes, and regulation of fetal brain development†. Biol Reprod. 2020;102(3):532-8. Epub 2019/11/12. doi: 10.1093/biolre/ioz204. PubMed PMID: 31711155; PMCID: PMC7443348.
50. Figueras F, Oros D, Cruz-Martinez R, Padilla N, Hernandez-Andrade E, Botet F, Costas-Moragas C, Gratacos E. Neurobehavior in term, small-for-gestational age infants with normal placental function. Pediatrics. 2009;124(5):e934-41. Epub 2009/10/28. doi: 10.1542/peds.2008-3346. PubMed PMID: 19858151.
51. Maccani MA, Padbury JF, Lester BM, Knopik VS, Marsit CJ. Placental miRNA expression profiles are associated with measures of infant neurobehavioral outcomes. Pediatr Res. 2013;74(3):272-8. Epub 2013/06/21. doi: 10.1038/pr.2013.102. PubMed PMID: 23783433; PMCID: PMC3766495.
52. Lester BM, Tronick EZ, Brazelton TB. The Neonatal Intensive Care Unit Network Neurobehavioral Scale procedures. Pediatrics. 2004;113(3 Pt 2):641-67. Epub 2004/03/03. PubMed PMID: 14993524.
53. Boukydis CF, Bigsby R, Lester BM. Clinical use of the Neonatal Intensive Care Unit Network Neurobehavioral Scale. Pediatrics. 2004;113(3 Pt 2):679-89. Epub 2004/03/03. PubMed PMID: 14993527.
54. Liu J, Bann C, Lester B, Tronick E, Das A, Lagasse L, Bauer C, Shankaran S, Bada H. Neonatal neurobehavior predicts medical and behavioral outcome. Pediatrics. 2010;125(1):e90-8. Epub 2009/12/09. doi: 10.1542/peds.2009-0204. PubMed PMID: 19969621; PMCID: PMC2873896.
55. Sucharew H, Khoury JC, Xu Y, Succop P, Yolton K. NICU Network Neurobehavioral Scale profiles predict developmental outcomes in a low-risk sample. Paediatr Perinat Epidemiol. 2012;26(4):344-52. Epub 2012/06/13. doi: 10.1111/j.1365-3016.2012.01288.x. PubMed PMID: 22686386.
56. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59. Epub 2013/04/23. doi: 10.1186/1471-2431-13-59. PubMed PMID: 23601190; PMCID: PMC3637477.
57. Punshon T, Li Z, Marsit CJ, Jackson BP, Baker ER, Karagas MR. Placental Metal Concentrations in Relation to Maternal and Infant Toenails in a U.S. Cohort. Environ Sci Technol. 2016;50(3):1587-94. Epub 2016/01/15. doi: 10.1021/acs.est.5b05316. PubMed PMID: 26727403.
58. Kennedy EM, Hermetz K, Burt A, Everson TM, Deyssenroth M, Hao K, Chen J, Karagas MR, Pei D, Koestler DC, Marsit CJ. Placental microRNA expression associates with birthweight through control of adipokines: results from two independent cohorts. Epigenetics. 2020:1-13. Epub 2020/10/06. doi: 10.1080/15592294.2020.1827704. PubMed PMID: 33016211.
59. Friedlander MR, Mackowiak SD, Li N, Chen W, Rajewsky N. miRDeep2 accurately identifies known and hundreds of novel microRNA genes in seven animal clades. Nucleic Acids Res. 2012;40(1):37-52. Epub 2011/09/14. doi: 10.1093/nar/gkr688. PubMed PMID: 21911355; PMCID: PMC3245920.

60. Langmead B, Trapnell C, Pop M, Salzberg SL. Ultrafast and memory-efficient alignment of short DNA sequences to the human genome. Genome Biol. 2009;10(3):R25. Epub 2009/03/06. doi: 10.1186/gb-2009-10-3-r25. PubMed PMID: 19261174; PMCID: PMC2690996.
61. Griffiths-Jones S, Saini HK, van Dongen S, Enright AJ. miRBase: tools for microRNA genomics. Nucleic Acids Res. 2008;36(Database issue):D154-8. Epub 2007/11/10. doi: 10.1093/nar/gkm952. PubMed PMID: 17991681; PMCID: PMC2238936.
62. Anders S, Huber W. Differential expression analysis for sequence count data. Genome Biology. 2010;11(10):R106. doi: 10.1186/gb-2010-11-10-r106.
63. Huang R, Jaritz M, Guenzl P, Vlatkovic I, Sommer A, Tamir IM, Marks H, Klampfl T, Kralovics R, Stunnenberg HG, Barlow DP, Pauler FM. An RNA-Seq strategy to detect the complete coding and non-coding transcriptome including full-length imprinted macro ncRNAs. PLoS One. 2011;6(11):e27288. Epub 2011/11/22. doi: 10.1371/journal.pone.0027288. PubMed PMID: 22102886; PMCID: PMC3213133.
64. Bentley DR, Balasubramanian S, Swerdlow HP, Smith GP, Milton J, Brown CG, Hall KP, Evers DJ, Barnes CL, Bignell HR, Boutell JM, Bryant J, Carter RJ, Keira Cheetham R, Cox AJ, Ellis DJ, Flatbush MR, Gormley NA, Humphray SJ, Irving LJ, Karbelashvili MS, Kirk SM, Li H, Liu X, Maisinger KS, Murray LJ, Obradovic B, Ost T, Parkinson ML, Pratt MR, Rasolonjatovo IM, Reed MT, Rigatti R, Rodighiero C, Ross MT, Sabot A, Sankar SV, Scally A, Schroth GP, Smith ME, Smith VP, Spiridou A, Torrance PE, Tzonev SS, Vermaas EH, Walter K, Wu X, Zhang L, Alam MD, Anastasi C, Aniebo IC, Bailey DM, Bancarz IR, Banerjee S, Barbour SG, Baybayan PA, Benoit VA, Benson KF, Bevis C, Black PJ, Boodhun A, Brennan JS, Bridgham JA, Brown RC, Brown AA, Buermann DH, Bundu AA, Burrows JC, Carter NP, Castillo N, Chiara ECM, Chang S, Neil Cooley R, Crake NR, Dada OO, Diakoumakos KD, Dominguez-Fernandez B, Earnshaw DJ, Egbujor UC, Elmore DW, Etchin SS, Ewan MR, Fedurco M, Fraser LJ, Fuentes Fajardo KV, Scott Furey W, George D, Gietzen KJ, Goddard CP, Golda GS, Granieri PA, Green DE, Gustafson DL, Hansen NF, Harnish K, Haudenschild CD, Heyer NI, Hims MM, Ho JT, Horgan AM, Hoschler K, Hurwitz S, Ivanov DV, Johnson MQ, James T, Huw Jones TA, Kang GD, Kerelska TH, Kersey AD, Khrebtukova I, Kindwall AP, Kingsbury Z, Kokko-Gonzales PI, Kumar A, Laurent MA, Lawley CT, Lee SE, Lee X, Liao AK, Loch JA, Lok M, Luo S, Mammen RM, Martin JW, McCauley PG, McNitt P, Mehta P, Moon KW, Mullens JW, Newington T, Ning Z, Ling Ng B, Novo SM, O'Neill MJ, Osborne MA, Osnowski A, Ostadan O, Paraschos LL, Pickering L, Pike AC, Pike AC, Chris Pinkard D, Pliskin DP, Podhasky J, Quijano VJ, Raczy C, Rae VH, Rawlings SR, Chiva Rodriguez A, Roe PM, Rogers J, Rogert Bacigalupo MC, Romanov N, Romieu A, Roth RK, Rourke NJ, Ruediger ST, Rusman E, Sanches-Kuiper RM, Schenker MR, Seoane JM, Shaw RJ, Shiver MK, Short SW, Sizto NL, Sluis JP, Smith MA, Ernest Sohna Sohna J, Spence EJ, Stevens K, Sutton N, Szajkowski L, Tregidgo CL, Turcatti G, Vandevondele S, Verhovsky Y, Virk SM, Wakelin S, Walcott GC, Wang J, Worsley GJ, Yan J, Yau L, Zuerlein M, Rogers J, Mullikin JC, Hurles ME, McCooke NJ, West JS, Oaks FL, Lundberg PL, Klenerman D, Durbin R, Smith AJ. Accurate whole human genome sequencing using reversible terminator chemistry. Nature. 2008;456(7218):53-9. Epub 2008/11/07. doi: 10.1038/nature07517. PubMed PMID: 18987734; PMCID: PMC2581791.
65. Dobin A, Davis CA, Schlesinger F, Drenkow J, Zaleski C, Jha S, Batut P, Chaisson M, Gingeras TR. STAR: ultrafast universal RNA-seq aligner. Bioinformatics. 2013;29(1):15-21.

Epub 2012/10/30. doi: 10.1093/bioinformatics/bts635. PubMed PMID: 23104886; PMCID: PMC3530905.

Chapter 5 - Summary, Limitations, Future Directions and Conclusions

SUMMARY

Investigating the role of placental miRNA in the developmental origins of lifelong health outcomes may lead to insight into how various genetic and environmental influences *in utero* alter the overall health trajectory and risk of chronic disease in offspring. Maternal cardiometabolic conditions and environmental exposures during pregnancy have been implicated in placental insufficiencies. However, clinical placental pathologies remain rare within the general population, and are unable to account for the increasing prevalence of the gestational outcomes that are potentially developmentally programmed. Minor alterations in the functional capacity of the placenta that occur in response to gestational conditions may, in part, be responsible for this developmental programming of long term health outcomes in offspring. This work addresses how genetic and environmental influences relevant to cardiovascular disease, (CVD) associate with placental miRNA expression.

In chapter two, we show that a maternal family history of CVD is associated with altered expression of specific placental miRNAs. This clinical variable, estimating both genetic and environmental influences of CVD, associated with miRNAs that oversee TGFβ and VEGF signaling within the placenta. In addition, these miRNAs regulate overall endothelial cellular function and maintenance, so their dysregulation may result in abnormal placental physiology and may contribute to the developmental programming of chronic disease risk. These results were shown to be robust to various environmental and biological confounders, including maternal smoking status, infant sex and birth weight. The effect size and significance of these results were also robust to the addition of various technical covariates measured through the RNA isolation and sequencing process into the model. The overall consistency of the models constructed within chapter two increase the overall confidence in the relevance and validity of our findings.

In chapter three, we go on to isolate the genetic influences of CVD through the calculation of a polygenic risk score for CVD based on previous GWAS data. This analysis identified unique miRNAs from those characterized in chapter two, suggesting those associated with a maternal family history of CVD may ultimately result from environmental variation and are distinct from the risks posed by genetic predisposition to CVD. Placental miRNAs that associated with this genetic predisposition of CVD were implicated in pathways relevant to metabolic programming, specifically genes relevant to the peroxisome proliferator pathways that oversee metabolic functions involved in mitochondrial biogenesis, fatty acid oxidation, and cellular respiration. Other miRNAs whose expression associates with this CVD polygenic risk score were implicated in overall trophoblast and endothelial function and maintenance, specifically in cell cycle regulation and hypoxic response pathways.

In chapter four, we explore the role of gestational cadmium exposure in the dysregulation of placental miRNA expression. Cadmium is a toxic metal found in tobacco products, air, food and drinking water. It serves no known biological role in humans, and may function to initiate endothelial dysfunction and atherosclerogenesis as a result of exposure, thus serving as a risk factor for the development of CVD (1). This analysis revealed a significant association between gestational cadmium exposure and placental miRNA expression, several of which were predicted to regulate mRNAs participating in various facets of fetal neurodevelopment. The abnormal expression patterns of these miRNAs were also identified to trend with adverse neurobehaviors measured during very early postnatal life. These deficiencies in neurobehavioral performance at birth is consistent with previous work from independent cohorts of infants born from high risk pregnancies and amongst children born small for gestational age (2). This relationship between gestational Cd exposure and abnormal neurobehavioral outcomes at birth suggests dysregulation of placental miRNA expression may serve as a mechanism of developmental programming of adverse newborn health outcomes. While the cadmium levels measured within the RICHS and NHBCS cohort are relatively low compared to the general population, these data show that subtle, chronic exposure to cadmium may initiate adverse developmental programming of long-term neurobehavioral outcomes (3).

This work adds to a growing body of scientific literature that suggests placental miRNA expression is a mechanism by which long term health outcomes are developmentally programmed *in utero* in response to both genetic and environmental insults faced by the fetus throughout gestation. Previous work within this field have found that various environmental perturbations can explain functional deficits within placental-based cell lines *in vitro*; however, the integration of multi-omics technology and extension of this work into large cohorts of human tissue samples is still lacking (4-8). While other studies have shown that placental miRNA expression is sensitive to environmental and genetic sources of variation, this is the first study to characterize these associations with respect to cardiovascular disease predispositions (4-9). Additionally, while cadmium-related changes in DNA methylation in developmentally relevant tissues in human cohort studies has been well characterized, this same level of characterization is unique to this study of miRNA expression (10-12). This work also highlights the relationship between cadmium-associated dysregulation of placental miRNA expression and early life neurobehavioral outcomes.

The functional annotation performed throughout this body of work highlights, fundamentally, placental miRNA's dysregulated in response to genetic and environmental sources are largely influencing endothelial processes critical to proper placental functionality. As a central vascular organ which oversees multiple facets of *in utero* growth and development, proper function of the placenta remains essential to successful gestational outcomes. Perturbations to the basic cellular processes of its endothelial origins may manifest as placental insufficiencies through the accumulation of minor insults throughout the developmental circulatory system. Considering that placental development and fetal heart development occur concurrently, disruptions to either organ may adversely impact its counterpart. Both cardiovascular disease predispositions and gestational cadmium exposure (i.e, the sources of variation outlined in this study) are considered to be common exposures within the general population, and do not represent a specific acutely-exposed group of individuals. The findings are potentially much more applicable to the larger population.

Given the association of placental miRNA with various facets that challenge the overall gestational environment, and the strong relationship between placental efficiency and lifelong risk of chronic disease, this suggests placental miRNA expression may ultimately serve as a molecular mechanism of developmental programming of chronic disease. Finally, this work contributes to the broader field of clinical biomarker discovery through the detection of molecular pathologies present at birth within the placenta. Considering these changes are detectable at birth, this may allow for the development of early interventional methods to mitigate long-term developmental defects, and/or lifelong risk of chronic disease.

OVERALL LIMITATIONS

Placental tissue samples are limited to term placenta, which presents unique challenges in characterizing genetic and epigenetic associations that are most prevalent during early development, yet still influence newborn health outcomes. Given the nature of placenta-based studies, and existing federal policies and medical practice, tissue collected at term is often the only avenue by which to ethically study molecular hallmarks of fetal growth and metabolism.

The placenta is a highly complex tissue composed of various cell-types, and associations may be cell-type specific. To overcome this, Surrogate Variable Analysis (SVA) was widely used, which allows for the construction of placeholder variables to estimate variation from unknown sources, such as cell-type heterogeneity, and was included within each model. There also may be environmental factors, such as maternal behaviors or unmeasured social determinants of health that influence the expression of placental miRNA, ultimately confounding these relationships.

Considering our lack of access to protein quantifications within the samples utilized in this work, our understanding of how dysregulation of placental miRNAs broadly influences downstream cellular functions is limited to *in vitro* validation in the current literature, and pathway enrichment analysis of predicted mRNA targets of these miRNAs. Stringent filtering, and parallel mRNA sequencing libraries were utilized throughout these analyses to predict robust miRNA:mRNA interactions, as well as to highlight relevant biological processes potentially influenced by abnormal miRNA expression.

While proper measures were taken to account for potential cell-type biases, recent single-cell sequencing studies within the placenta have shown large representation of trophoblasts in their results (13). Our group has shown using DNA methylation-based cellular estimation methods from

RICHS samples, that more than 90% of the cells in the samples are cytrotrophoblasts and synctiotrophoblasts (14). Finally, the RICHS cohort is comprised of predominantly mothers of European descent (72%), while NHBCS is comprised of only mothers of European descent (100%). Results produced from this work which are based on genetic risks are severely limited in their generalizability to the ancestral backgrounds studied here.

FUTURE DIRECTIONS

Placental miRNAs are critical molecules in post-transcriptional gene regulation. Their regulatory activities have been linked to overall physiology and function of the placenta throughout gestation and offspring developmental outcomes, marking them as essential to successful gestational outcomes. Here we have identified the abundance of various miRNAs to be associated with placental cadmium accumulation and cardiovascular disease predispositions. Targets of these miRNAs are predicted to be involved in endothelial cell function and maintenance, overall cell cycle regulation, and broad aspects of neurodevelopment. These placental miRNAs may influence neurobehavioral outcomes at birth through their role in overseeing placental physiology throughout gestation, allowing for them to serve as early life indicators of long-term health outcomes and lifelong risk of chronic disease.

In order to further progress our understanding of the developmental origins of health and disease, more work is needed to characterize the relationships between changes in placental miRNA expression and early life health outcomes, such as cardiometabolic traits, including blood pressure, BMI and adiposity, as well as neurobehavior throughout childhood and into adulthood. Conducting studies on larger sample sizes would also allow for sufficient statistical power ideal for casual mediation analyses to better understand the role of molecular hallmarks, such as miRNA or mRNA expression, as causal mediators in developmental outcomes. Larger cohort sample sizes would also promote a higher level of diversity and representation of racial and ethnic backgrounds to better understand how each may interact with genetic and environmental sources of variation throughout gestation in relation to their influence toward placental miRNA expression.

Additional work will also be needed within *in vitro* systems to functionally validate the role of placental miRNAs. The opportunity to implement genetic modifications into placental-based cell lines through the utilization of genome editing technologies, such as those offered by the CRISPR-Cas9 system, would allow for the potential identification of causal genetic variants in their ability to disrupt normal placental function. Imposing specific environmental challenges *in vitro*, such as toxic metal exposures or hypoxic conditions, in combination with specific genetic modifications may also prove useful in distinguishing causality, and/or interactions between genetic and environmental sources of variation outlined in cohort-based studies.

CONCLUSIONS

MiRNAs are critical molecules in post-transcriptional gene regulation that play a central role in regulating overall physiology and function of the placenta, marking them as essential to successful gestational outcomes. Dysregulation of placental miRNA expression is implicated in adverse pregnancy outcomes, such as preeclampsia and fetal growth restriction, highlighting their potential role as a mechanism in the developmental programming of lifelong health outcomes. Here, we have characterized robust associations between the expression of placental miRNAs and genetic and environmental risk factors of cardiovascular disease. Bioinformatically predicted targets of these miRNAs are enriched across various biological pathways relevant to gestational development, including endothelial function and maintenance, metabolic programming, and nervous system development. The expression of these specific miRNAs also proved to be predictive of neurobehavioral outcomes at birth, further emphasizing their potential as surveillance molecules by which to assess gestational conditions postpartum. Considering these changes in miRNA expression are detectable at birth, this may allow for the development of early interventional methods to mitigate long-term developmental deficits, offering an extremely promising avenue by which to combat the globally increasing prevalence of chronic disease.

REFERENCES

1. Tellez-Plaza M, Jones MR, Dominguez-Lucas A, Guallar E, Navas-Acien A. Cadmium exposure and clinical cardiovascular disease: a systematic review. Curr Atheroscler Rep. 2013;15(10):356. Epub 2013/08/21. doi: 10.1007/s11883-013-0356-2. PubMed PMID: 23955722; PMCID: PMC3858820.
2. Figueras F, Oros D, Cruz-Martinez R, Padilla N, Hernandez-Andrade E, Botet F, Costas-Moragas C, Gratacos E. Neurobehavior in term, small-for-gestational age infants with normal placental function. Pediatrics. 2009;124(5):e934-41. Epub 2009/10/28. doi: 10.1542/peds.2008-3346. PubMed PMID: 19858151.
3. Esteban-Vasallo MD, Aragonés N, Pollan M, López-Abente G, Perez-Gomez B. Mercury, cadmium, and lead levels in human placenta: a systematic review. Environmental health perspectives. 2012;120(10):1369-77. Epub 2012/05/16. doi: 10.1289/ehp.1204952. PubMed PMID: 22591711.
4. Ostling H, Kruse R, Helenius G, Lodefalk M. Placental expression of microRNAs in infants born small for gestational age. Placenta. 2019;81:46-53. Epub 2019/05/30. doi: 10.1016/j.placenta.2019.05.001. PubMed PMID: 31138431.
5. Thamotharan S, Chu A, Kempf K, Janzen C, Grogan T, Elashoff DA, Devaskar SU. Differential microRNA expression in human placentas of term intra-uterine growth restriction that regulates target genes mediating angiogenesis and amino acid transport. PLoS One. 2017;12(5):e0176493. Epub 2017/05/04. doi: 10.1371/journal.pone.0176493. PubMed PMID: 28463968; PMCID: PMC5413012.
6. Meng M, Cheng YKY, Wu L, Chaemsaithong P, Leung MBW, Chim SSC, Sahota DS, Li W, Poon LCY, Wang CC, Leung TY. Whole genome miRNA profiling revealed miR-199a as potential placental pathogenesis of selective fetal growth restriction in monochorionic twin pregnancies. Placenta. 2020;92:44-53. Epub 2020/02/18. doi: 10.1016/j.placenta.2020.02.002. PubMed PMID: 32063549.
7. Wang D, Na Q, Song WW, Song GY. Altered Expression of miR-518b and miR-519a in the placenta is associated with low fetal birth weight. Am J Perinatol. 2014;31(9):729-34. Epub 2014/04/01. doi: 10.1055/s-0033-1361832. PubMed PMID: 24683074.
8. Higashijima A, Miura K, Mishima H, Kinoshita A, Jo O, Abe S, Hasegawa Y, Miura S, Yamasaki K, Yoshida A, Yoshiura K, Masuzaki H. Characterization of placenta-specific microRNAs in fetal growth restriction pregnancy. Prenat Diagn. 2013;33(3):214-22. Epub 2013/01/29. doi: 10.1002/pd.4045. PubMed PMID: 23354729.
9. Awamleh Z, Gloor GB, Han VKM. Placental microRNAs in pregnancies with early onset intrauterine growth restriction and preeclampsia: potential impact on gene expression and pathophysiology. BMC Med Genomics. 2019;12(1):91. Epub 2019/06/30. doi: 10.1186/s12920-019-0548-x. PubMed PMID: 31248403; PMCID: PMC6598374.
10. Appleton AA, Jackson BP, Karagas M, Marsit CJ. Prenatal exposure to neurotoxic metals is associated with increased placental glucocorticoid receptor DNA methylation. Epigenetics. 2017;12(8):607-15. Epub 2017/05/27. doi: 10.1080/15592294.2017.1320637. PubMed PMID: 28548590; PMCID: PMC5687337.
11. Cowley M, Skaar DA, Jima DD, Maguire RL, Hudson KM, Park SS, Sorrow P, Hoyo C. Effects of Cadmium Exposure on DNA Methylation at Imprinting Control Regions and Genome-

Wide in Mothers and Newborn Children. Environ Health Perspect. 2018;126(3):037003. Epub 2018/03/13. doi: 10.1289/EHP2085. PubMed PMID: 29529597; PMCID: PMC6071808.

12. Everson TM, Punshon T, Jackson BP, Hao K, Lambertini L, Chen J, Karagas MR, Marsit CJ. Cadmium-Associated Differential Methylation throughout the Placental Genome: Epigenome-Wide Association Study of Two U.S. Birth Cohorts. Environ Health Perspect. 2018;126(1):017010. Epub 2018/01/27. doi: 10.1289/EHP2192. PubMed PMID: 29373860; PMCID: PMC6014712.

13. Pique-Regi R, Romero R, Tarca AL, Sendler ED, Xu Y, Garcia-Flores V, Leng Y, Luca F, Hassan SS, Gomez-Lopez N. Single cell transcriptional signatures of the human placenta in term and preterm parturition. Elife. 2019;8. Epub 2019/12/13. doi: 10.7554/eLife.52004. PubMed PMID: 31829938; PMCID: PMC6949028.

14. Song S, Jiang W, Hou L, Zhao H. Leveraging effect size distributions to improve polygenic risk scores derived from summary statistics of genome-wide association studies. PLOS Computational Biology. 2020;16(2):e1007565. doi: 10.1371/journal.pcbi.1007565.