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Anqi Dai Date

Heritability Analysis of individual-level pathway scores in GTEx samples

By

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Master of Science in Public Health

Biostatistics and Bioinformatics

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2019

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Abstract

Heritability Analysis of individual-level pathway scores in GTEx samples

By Anqi Dai

Background: QTL analysis plays an important role in exploring the functional impact of genetic variants, and further providing opportunities to understand complex diseases. Most QTL analyses are conducted one feature at a time due to computational cost and the need for controlling false positives, which omits the pleiotropic effect. Studies based on the aggregation of genetic variants, especially the pathway-based method can provide a more stable and effective way for assessing the biological impact of genetic variants. To ensure the feasibility of pathway-based QTL, heritability analysis for individual-level pathway expression scores is needed.

Method: After obtaining pathway expression scores from gene expression data using four methods, namely GSVA, Z-score, PLAGE, and ssGSEA, we used mixed model analysis to quantify the heritability of individual-level pathway scores for 186 KEGG Pathways, 196 PID Pathways, and 289 BIOCARTA Pathways across 49 tissues in the GTEx data via GCTA software. Based on the estimated heritability, analyses of value and significance of the heritability of pathway scores across tissues or pathways were conducted. A list of pathway/tissue combinations with the highest heritability was also identified.

Results: We found that in most tissues or pathways, regardless of scoring algorithms and pathway types, the genetic relationship matrix contributed significantly to explain the differences in individual-level pathway scores in at least one pair of tissue/pathway, and Whole Blood had the greatest number of pathways with significant heritability. Heritability estimates for different score methods were consistent with each other. We identified that KEGG Leishmania Infection, PID Aurora-A Pathway, and BIOCARTA CSK Pathway have the highest mean heritability. Brain Amygdala, Brain Spinal cord cervical c-1, Brain Frontal Cortex BA9, Small Intestine Terminal Ileum, and Whole Blood have higher mean heritability of GSVA scores, and this finding was consistent among three different types of pathways.

Conclusion: This heritability analysis strongly proved that the individual-level pathway expression scores are heritable. The findings from this study also provided a theoretical basis for future studies using pathway expression and QTL analysis based on pathway level.

Keywords: Heritability, Pathway, Mixed model analysis, GCTA

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Table of Contents

1. Introduction

Exploring the functional impact of genetic variants is a fundamental objective in human genetics. The rapid advance of the next-generation sequencing technologies has ushered in a wave of high throughput genome-wide profiling assays to give us a comprehensive and multi-factorial view of the genomic and epigenomic patterns across tissue types, sometimes down to the single-cell resolution. Also, large consortia such as GTEx[1] and GEUVADIS[2] have been established to produce transcriptome data at the population–level. Multi-omics data such as DNA methylation, histone modification, and protein expression are on their way. The integration of genetics and genomics has produced a slew of new findings including expression quantitative trait loci (eQTL), protein quantitative trait loci (pQTL), methylation quantitative trait loci (meQTL), and histone quantitative trait loci (hQTL). The arrival of the new data types and findings offers unprecedented opportunities to understand complex diseases such as Alzheimer's Disease (AD).

It has been repeatedly demonstrated in the literature that the knowledge of eQTL greatly facilitates the identification of the target genes of GWAS-identified variants[3-5]. Other types of QTL also contributed important clues for complex disease studies[6]. However, despite significant findings, existing QTL analyses are limited in at least three areas. Considering the sheer number of the features, not all features/variant combinations were tested due to consideration for computational cost, necessity, and the need for controlling false positives. First, most QTL analyses are conducted one feature at a time with the feature being a gene, peak or locus. These methods do not consider the function of the gene combination, nor do they consider the pleiotropic effect. Second, most QTL analyses only focus on cis effects

and usually do not consider trans-eQTL. Third, there are false positives caused by the noise of high throughput technologies and batch effects in QTL studies.

The introduction of gene set enrichment analysis (GSEA) approach[7] revolutionized how scientists analyze high throughput omics data. Pathway-based analyses such as DAVID[8] and GSEA become indispensable analysis tools in omic studies. Similar to what GSEA has done to differential expression (DE) analysis, we tried to extend single gene eQTL to the pathway level to overcome the limitations mentioned above. Analyses based on pathways from databases such as Kyoto Encyclopedia of Genes and Genomes (KEGG)[9], NCI-Nature Pathway Interaction Database (PID)[10], and BIOCARTA[11] will produce more stable, intuitive, and interpretable results, compared with single gene-based methods. Given that multiple genes are always connected to a single biological pathway, diseases usually involve entire groups of genes, and small changes cannot be detected in the expression of single genes, this pathway-based method can provide a more stable and effective way for assessing the biological impact of genetic variants.

In this study, we aim to use mixed-model analysis to quantify the heritability of individual-level pathway expression scores across tissues in the GTEx dataset, analyze the heritability of pathway scores and identify a list of pathway/tissue combinations with the highest heritability. In order to ensure the feasibility of pathway-based QTL, heritability analysis for pathway scores is needed. Only when the individual-level pathway scores are hereditary, the genome-wide QTL analysis using these pathway scores will be meaningful. Besides, many disease-related genes tend to converge on multiple pathways. For example, multiple pathways have been involved in AD, including amyloid precursor processing, cholesterol metabolism, neuroinflammation, cellular immunity, and endocytosis

pathways[12]. In-depth evaluation of pathway heritability may help to direct the research field towards novel biological targets for therapeutic intervention.

2. Method

2.1 Genetic and transcriptomic data

GTEx dataset. We obtained RNA-seq gene expression levels from 17,382 tissue samples (54 unique tissue types) from 948 unique donors in the Genotype-Tissue Expression (GTEx) data released on 06/05/2017 (GTEx Analysis v8)[13]. Among all donors, genotypes were available for 838 individuals. While all 15,253 tissue samples were obtained with genotype, we used the 49 tissues with sample sizes ($n > 70$) when calculating. 69,763,935 single nucleotide polymorphisms (SNPs) from 22 pairs of autosomes were extracted using PLINK (v1.90b6.12) for subsequent analyses of heritability.

2.2 Calculation of pathway scores

After separating the gene expression data based on tissue sources and gene sets, i.e. pathways, four different methods were applied to calculate pathway scores: Gene Set Variation Analysis (GSVA)[14], combined Z-score method[15], Pathway Level Analysis of Gene Expression (PLAGE)[16], and single sample Gene Set Enrichment Analysis (ssGSEA)[17]. All these are unsupervised single sample enrichment methods that yield the enrichment score per individual sample and gene set, which allows us to assess the variation in the activity of a set of genes, such as a pathway. PLAGE standardizes each gene expression level for each sample and then defines the coefficients of the first right-

singular vector from the Singular Value Decomposition (SVD) of the gene set matrix as the pathway activity profiles[16]. Like PLAGE, the combined z-score method also standardizes gene expression profiles into z-scores over each sample, but the pathway activity estimation is given by the combination of the individual gene z-scores per sample[15]. In ssGSEA, the enrichment statistic for each sample is defined as the normalized difference in empirical cumulative distribution functions (ECDF) of gene expression ranks both inside and outside the gene set of interest[17]. GSVA first calculates an expression statistic with the kernel estimation of the ECDF over the samples and then yields the enrichment score based on the Kolmogorov-Smirnov (KS) like random walk statistics[14]. The R package "GSVA"[18] was used to generate the four types of pathway-level enrichment score data based on gene-level expression data.

2.3 Heritability of individual-level pathway scores

To estimate the heritability of individual-level pathway scores across 49 different tissues using all the SNPs autosomes in the GTEx dataset, for every pathway in each tissue, we calculated the proportion of the variance (narrow-sense heritability) explained by all the SNPs using the following mixed linear model (MLM):

$$Y = X\beta + Wu + \epsilon$$

Where Y is an $n \times 1$ vector of pathway scores with n being the sample size for the specific tissue; X is a $n \times p$ matrix of the p predictor variables; β is a $p \times 1$ vector of fixed effects such as sex, age, and/or one or more eigenvectors from principal component analysis (PCA); u is a $N \times 1$ vector of SNP effects with $u \sim N(0, I\sigma_u^2)$ with N being the number

of SNPs, I is an $N \times N$ identity matrix; ϵ is a vector of residual effects with $\epsilon \sim N(0, I\sigma_\epsilon^2)$; W is a $n \times N$ standardized genotype matrix with the ij^{th} element:

$$w_{ij} = \left(x_{ij} - 2p_j\right) / \sqrt{2p_j(1-p_j)}$$

where x_{ij} is the number of copies of the reference allele for the j^{th} SNP of the i^{th} individual and p_j is the frequency of the reference allele.

We define $A = WW'/N$ and define σ_g^2 as the residual explained by all the SNPs, i.e. $\sigma_g^2 = N\sigma_u^2$, with N being the number of SNPs, then we get:

$$var(y) = V = W\sigma_u^2 W' + I\sigma_\epsilon^2 = A\sigma_g^2 + I\sigma_\epsilon^2$$

where A is interpreted as the genetic relationship matrix (GRM) between individuals. The estimation of heritability is given by $h^2 = \sigma_g^2 / \left(\sigma_\epsilon^2 + \sigma_g^2\right)$, ranging from 0 to 1.

From the SNPs extracted before, GCTA software (v1.93.2beta)[19] was used to calculate the GRM for each autosome from the SNPs, and then merge the 22 matrixes into one GRM as A for the following analysis. We estimated σ_g^2, σ_ϵ^2 and heritability by the restricted maximum likelihood (REML) approach as implemented in the GCTA software for each of the pathways across 49 tissues, relying on the GRM. Software R (v 4.0.2) was used for data pre-processing and heritability analysis.

3. Results

3.1 Heritability Analysis for KEGG Pathways

First, we estimated heritability for each of the 186 KEGG pathways across 49 tissues using all 69,763,935 SNPs presented in the GTEx dataset. Four different individual-level

pathway scores were used: GSVA, Z-score, PLAGE, and ssGSEA. Our analysis generates a total of 36,456 heritability estimates.

3.1.1 Correlation among different pathway score methods

Figure 1 is a heatmap showing four heritability estimates from all 186 pathways across 49 tissues. The heatmap showed a similar pattern among the four different types of pathway scores, especially for GSVA score, Z-score, and ssGSEA. The Pearson correlations among the four complete sets of heritability estimates are summarized in Table 1. All the Pearson correlations are significantly different from zero, indicating that the heritability estimates were consistent among the four types of pathway scores. The Pearson correlations of heritability values between PLAGE and the other three scores are all less than 0.5 (0.288 for GSVA, 0.321 for ssGSEA, and 0.488 for Z-score), while Pearson correlations among GSVA score, Z-score, and ssGSEA were all greater than 0.7 (0.830 for GSVA vs ssGSEA, 0.734 for GSVA vs Z-score, and 0.760 for ssGSEA vs Z-score). The Pearson correlations across tissues or pathways between four score methods also showed a similar pattern, which means each score method's heritability estimates were consistent with each other. Given their similarity, we only use GSVA pathway scores for all subsequent heritability analyses of KEGG pathways.

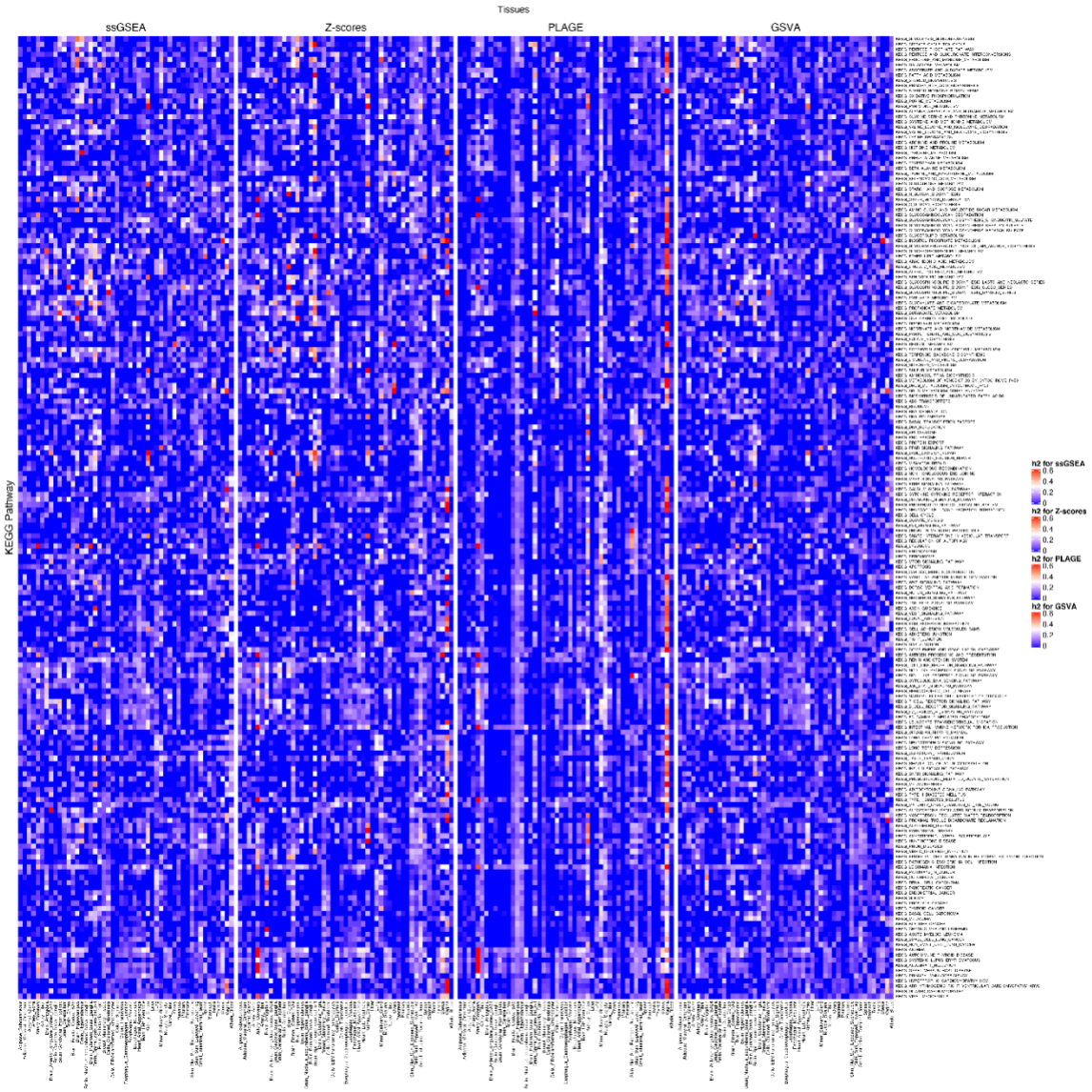

Figure 1. Heatmap of KEGG pathway score heritability for GSVA, Z-score, PLAGE, and ssGSEA.

Table 1. Pearson correlation with 95% CI among four different pathway score heritability. All the Pearson correlations are significantly different from zero with p-value $< 2.2 \times 10^{-16}$.

	PLAGE	**GSVA**	**ssGSEA**	**Z-scores**
PLAGE	1	0.288 (0.269, 0.306)	0.321 (0.303, 0.340)	0.488 (0.472, 0.504)
GSVA	0.288 (0.269, 0.306)	1	0.830 (0.823, 0.836)	0.734 (0.725, 0.743)
ssGSEA	0.321 (0.303, 0.340)	0.830 (0.823, 0.836)	1	0.760 (0.751, 0.768)
Z-scores	0.488 (0.472, 0.504)	0.734 (0.725, 0.743)	0.760 (0.751, 0.768)	1

3.1.2 Relationship between heritability and sample size

The number of available samples for different tissues varies, we draw a scatter plot and calculated the Pearson correlation between sample sizes and heritability estimates to see if they are correlated. The scatter plots of mean heritability values vs. sample numbers across 49 tissues didn't show any obvious relationship (Figure 2). However, the Pearson correlation test showed a significant $\rho = -0.326$ (p-value = 0.022) with 95% CI: [-0.556, -0.050].

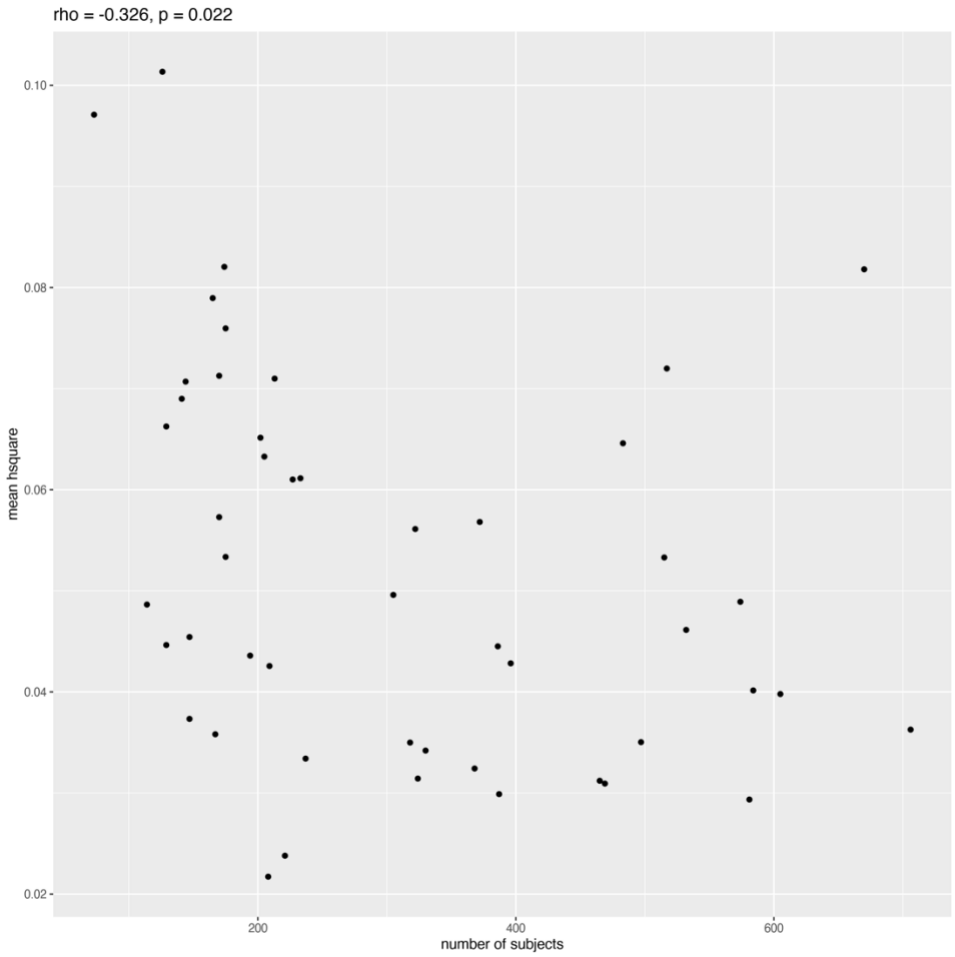

Figure 2. Scatter plots between mean heritability values and sample numbers for GSVA scores in KEGG Pathways.

3.1.3 Summary of heritability across tissues

Table A1 summarizes the heritability estimate results across all tissues. The number of KEGG pathways with significant heritability ($p<0.05$) and with estimates greater than threshold 0.25 and 0.5 in each tissue are also reported. Figure 3 shows a side-by-side violin plot of heritability from 186 KEGG pathways that demonstrates the distribution of heritability estimate results across tissues, rank from high to low. The red points in this figure represent the mean heritability values across pathways. The mean heritability

estimates across all tissues range from 0.022 to 0.101. Brain Spinal cord cervical c-1 has the highest mean heritability value of 0.101 (SE=0.127) with 26 KEGG pathways' h2 estimates greater than 0.25 and 1 KEGG pathway's h2 estimates greater than 0.5, followed by Kidney Cortex (h2=0.097, SE=0.119) and Small Intestine Terminal Ileum (h2=0.082, SE=0.071).

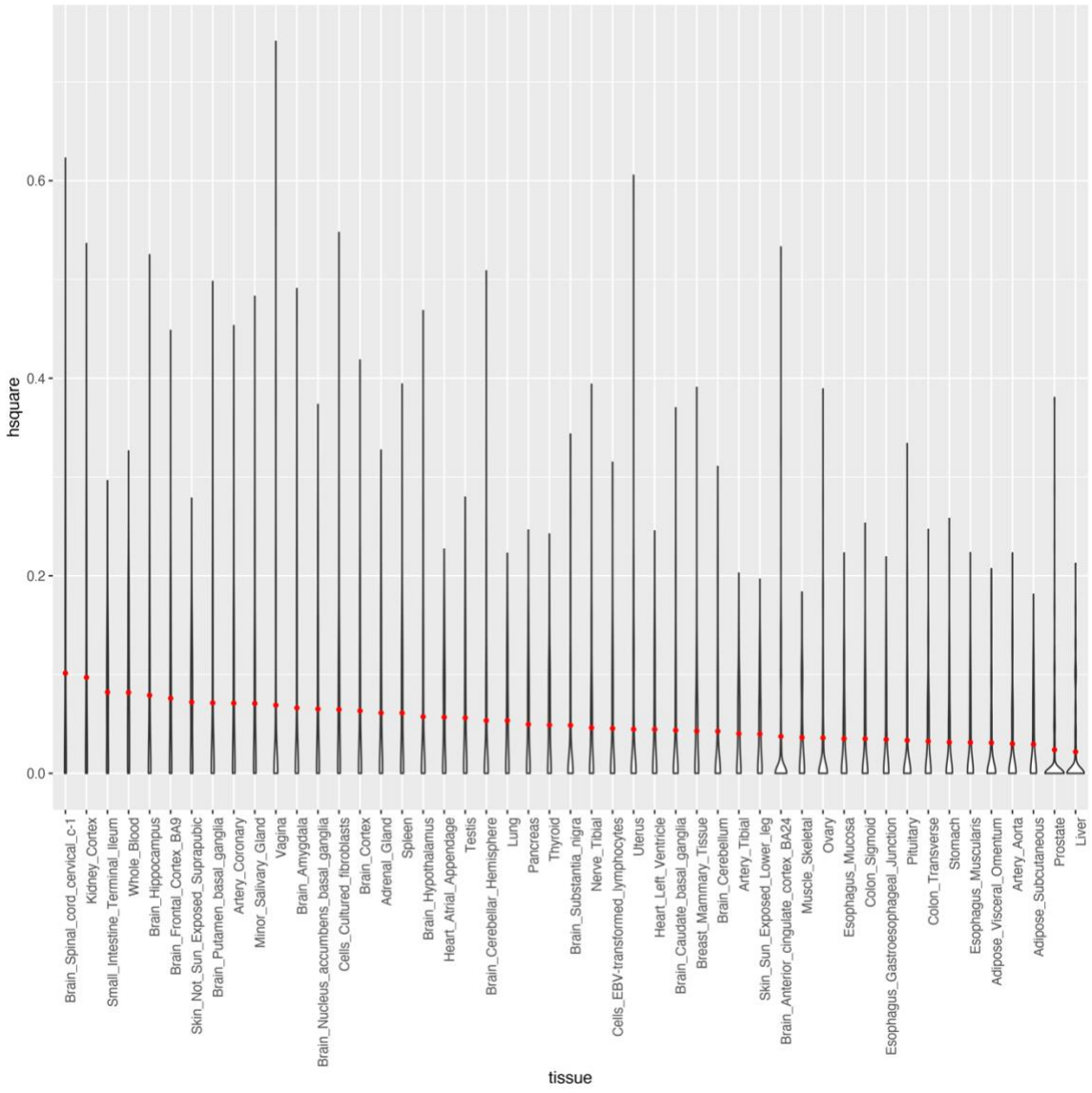

Figure 3. Violin plot of heritability values from 186 KEGG pathways across all 49 tissues for GSVA scores. Red points in each bar represent the mean heritability values across that tissue.

3.1.4 Summary of heritability across KEGG pathways

Table A2 summarizes the heritability estimates across all KEGG pathways. The number of tissues with significant heritability estimates and with h2 estimates greater than 0.25 and 0.5 were also reported. We also draw the side-by-side violin plots of heritability values, ranking from high to low (Figure 4). This violin plot from 49 tissues across all pathways shows the top 20 pathways with the higher mean heritability values and red points stand for the mean heritability values. The mean heritability estimates across all KEGG Pathways range from 0.022 to 0.092. KEGG Pathway Leishmania Infection has the highest mean heritability value of 0.092 (SE=0.080) with only one tissue Artery Coronary's h2 estimates greater than 0.25, followed by KEGG Pathway Asthma (h2=0.088, SE=0.082) and KEGG Pathway Glycosphingolipid Biosynthesis Globo Series (h2=0.081, SE=0.088).

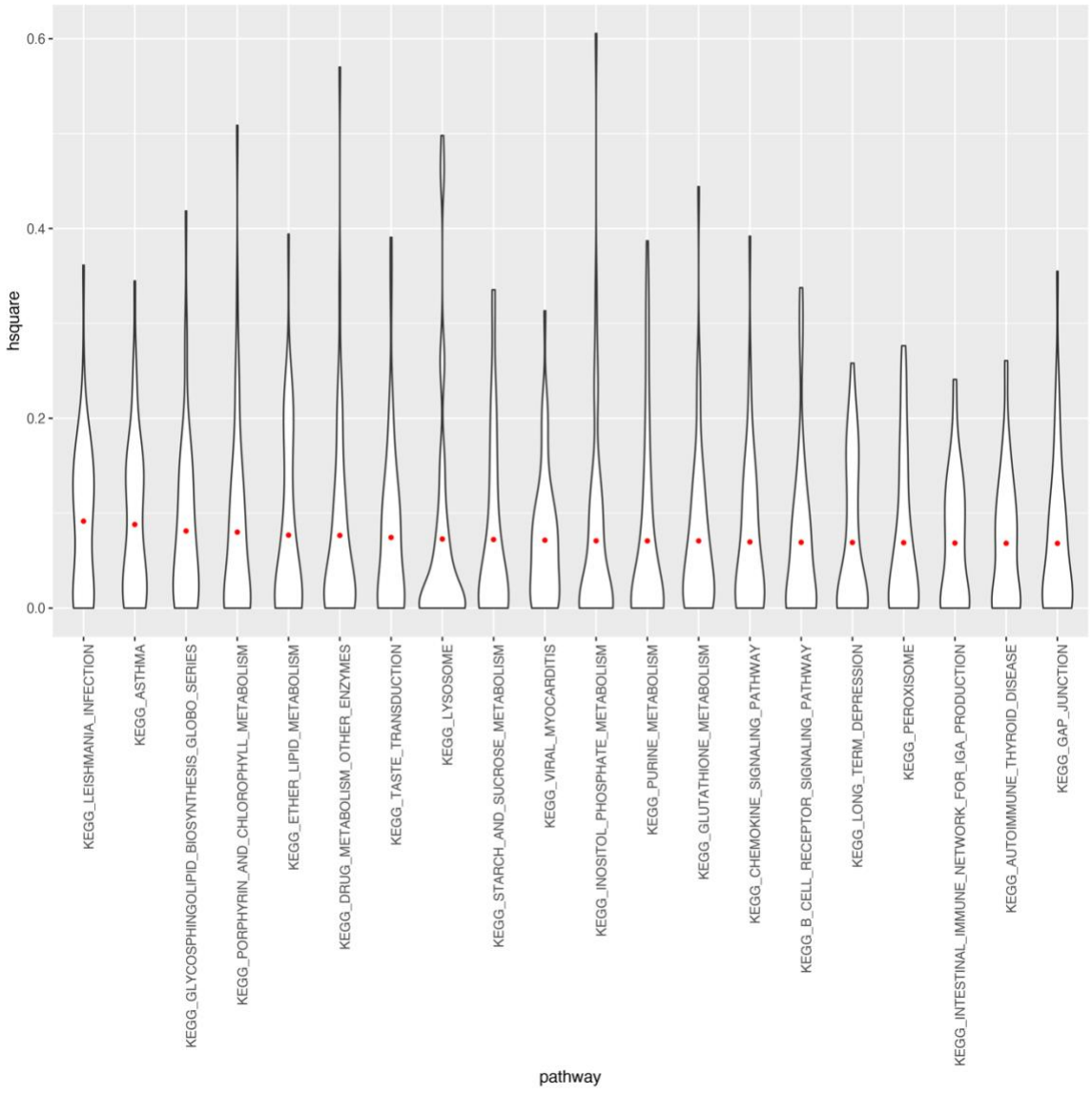

Figure 4. Violin plot of top 20 heritability values from 49 tissues across KEGG pathways for GSVA scores. Red points in each bar represent the mean heritability values across that KEGG pathways.

3.1.5 Summary of heritability for KEGG pathway/tissue combination

Table 2 demonstrates the top 20 combinations of KEGG pathways and tissues that have the highest heritability values. The Proximal Tubule Bicarbonate pathway in Vagina has

the highest estimated heritability (h2=0.741, p=0.005), followed by Glycerolipid Metabolism pathway in Brain Spinal cord cervical c-1 (h2=0.623, p=0.043) and Inositol Phosphate Metabolism pathway in Uterus (h2=0.606, p=0.010).

Table 2. Top 20 KEGG pathway/tissue combinations with the highest heritability for GSVA scores.

tissue	pathway	h2	P
Vagina	KEGG PROXIMAL TUBULE BICARBONATE RECLAMATION	0.741	0.005
Brain Spinal cord cervical c-1	KEGG GLYCEROLIPID METABOLISM	0.623	0.043
Uterus	KEGG INOSITOL PHOSPHATE METABOLISM	0.606	0.010
Vagina	KEGG DRUG METABOLISM OTHER ENZYMES	0.570	0.006
Cells Cultured fibroblasts	KEGG GLYCOSPHINGOLIPID BIOSYNTHESIS GANGLIO SERIES	0.548	0.000
Kidney Cortex	KEGG BASE EXCISION REPAIR	0.536	0.054
Brain Anterior cingulate cortex BA24	KEGG ALDOSTERONE REGULATED SODIUM REABSORPTION	0.533	0.024
Kidney Cortex	KEGG PYRIMIDINE METABOLISM	0.529	0.062
Brain Hippocampus	KEGG GLYOXYLATE AND DICARBOXYLATE METABOLISM	0.525	0.017
Brain Cerebellar Hemisphere	KEGG PORPHYRIN AND CHLOROPHYLL METABOLISM	0.509	0.021
Brain Putamen basal ganglia	KEGG LYSOSOME	0.498	0.008
Brain Spinal cord cervical c-1	KEGG ERBB SIGNALING PATHWAY	0.496	0.036
Brain Amygdala	KEGG COLORECTAL CANCER	0.491	0.056
Minor Salivary Gland	KEGG PPAR SIGNALING PATHWAY	0.483	0.008
Brain Amygdala	KEGG DORSO VENTRAL AXIS FORMATION	0.477	0.082
Brain Hippocampus	KEGG PENTOSE PHOSPHATE PATHWAY	0.476	0.040
Brain Hypothalamus	KEGG STEROID HORMONE BIOSYNTHESIS	0.468	0.023
Kidney Cortex	KEGG SULFUR METABOLISM	0.466	0.025
Brain Hippocampus	KEGG LYSOSOME	0.461	0.010
Brain Hippocampus	KEGG FRUCTOSE AND MANNOSE METABOLISM	0.455	0.023

Out of 9,114 combinations of KEGG pathways and tissue types, we observed 479 pairs (5.26%) with significant heritability estimations ($p<0.05$), ranging from 0.070 to 0.741. Among these significant combinations, 47 tissues have significant heritability in at least one of the 186 KEGG pathways. Whole Blood has 59 KEGG pathways with significant

heritability, which is the most in these tissues (Table A1). For pathway level, 171 KEGG pathways have significant heritability in at least one tissue. KEGG Ether Lipid Metabolism has the most combinations with heritability significant in 10 tissues (Table A2).

3.2 Heritability Analysis for PID Pathways and BIOCARTA Pathways

We replicated the analysis on KEGG Pathways to PID Pathways and BIOCARTA Pathways. Heritability of individual-level GSVA pathway scores were estimated for 196 PID Pathways and 289 BIOCARTA Pathways across 49 tissues using the same method we described earlier. After summarizing the heritability values, we draw heatmaps of heritability for PID Pathways and BIOCARTA Pathways (Figure 5).

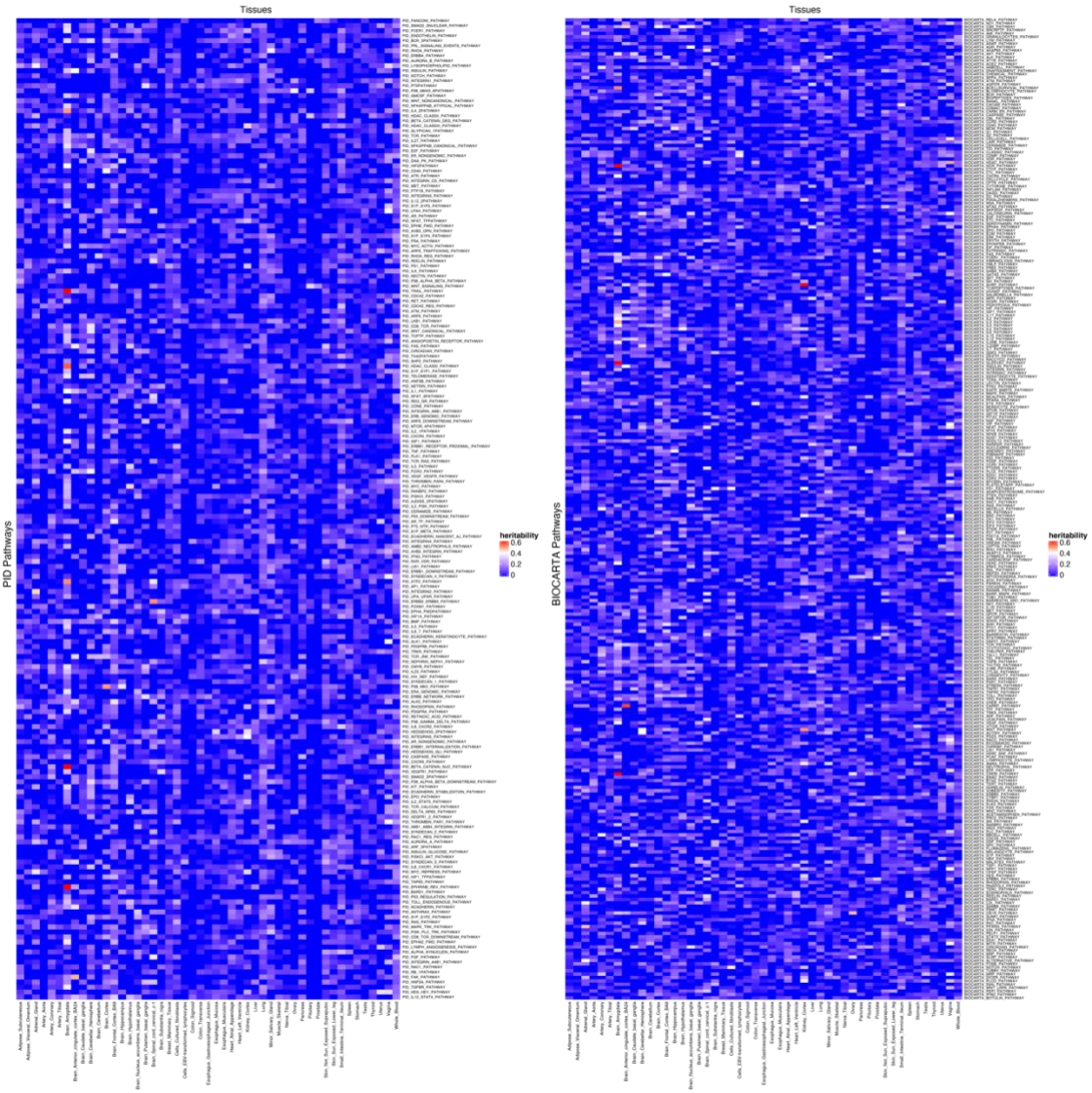

Figure 5. Heatmaps of GSVA Heritability for PID Pathways and BIOCARTA Pathways.

3.2.1 Relationship between heritability and sample size

Scatter plots and Pearson correlations were demonstrated to analyze whether sample numbers affect the estimated heritability values. We found that the mean heritability values are not correlated with sample sizes across the 49 tissue types either for PID Pathways

(Figure 6a) or BIOCARTA Pathways (Figure 6b), consistent with the Pearson correlation tests. For PID Pathways, the Pearson correlation $\rho = -0.061$ (95% CI: [-0.337, 0.224], p-value = 0.675). For BIOCARTA Pathways, the Pearson correlation $\rho = -0.210$ (95% CI: [-0.464, 0.076], p-value = 0.148).

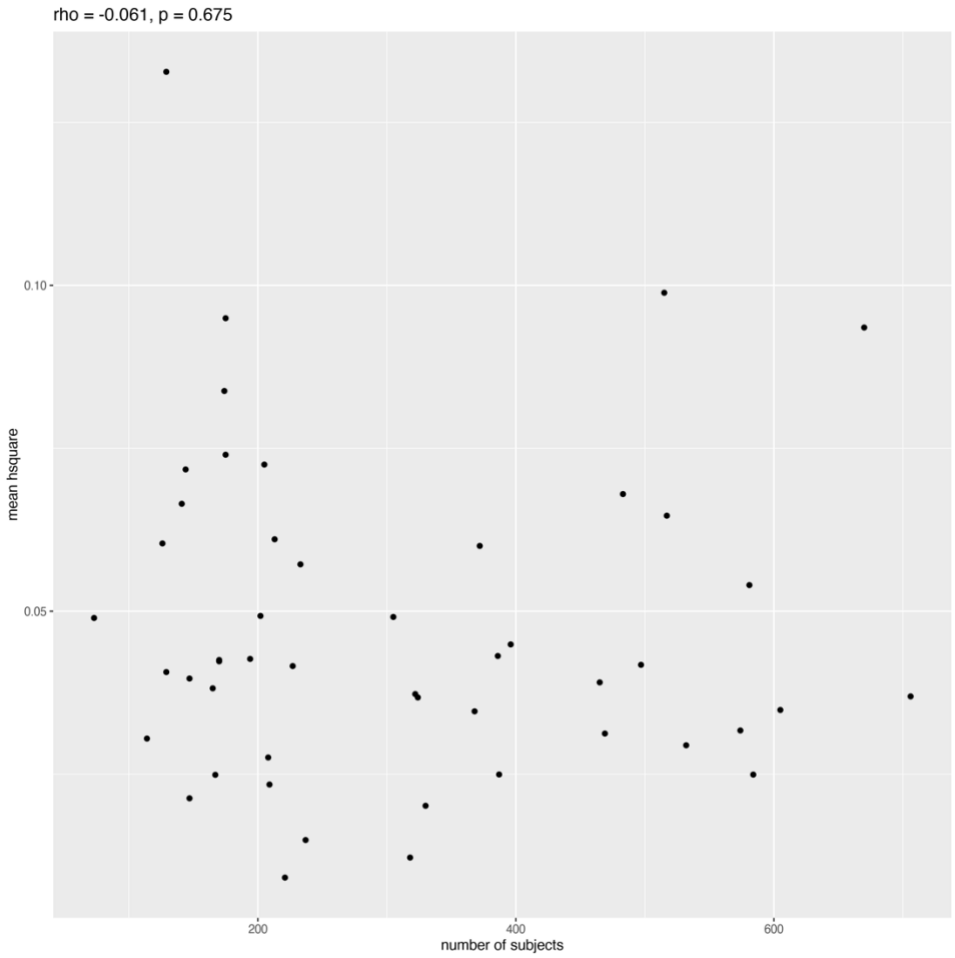

Figure 6a. Scatter plots between mean heritability values and sample numbers for GSVA scores for PID Pathways.

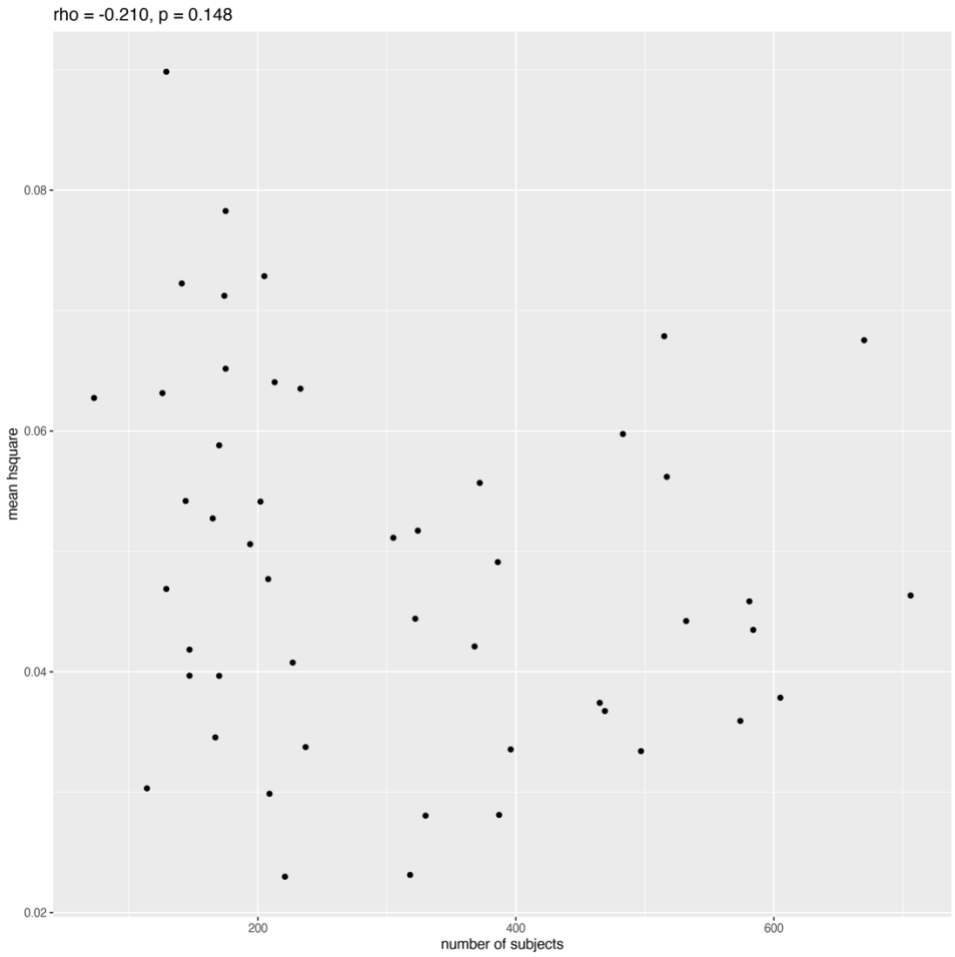

Figure 6b. Scatter plots between mean heritability values and sample numbers for GSVA scores for BIOCARTA Pathways.

3.2.2 Summary of heritability across tissues

The heritability estimate results across all tissues were summarized for PID pathways (Table A3) and BIOCARTA pathways (Table A4). Side-by-side violin plots of heritability from 196 PID Pathways (Figure 7) and 289 BIOCARTA Pathways (Figure 8) demonstrates the distribution of heritability estimate results across tissues, rank from high to low. The red points in this figure represent the mean heritability values across pathways.

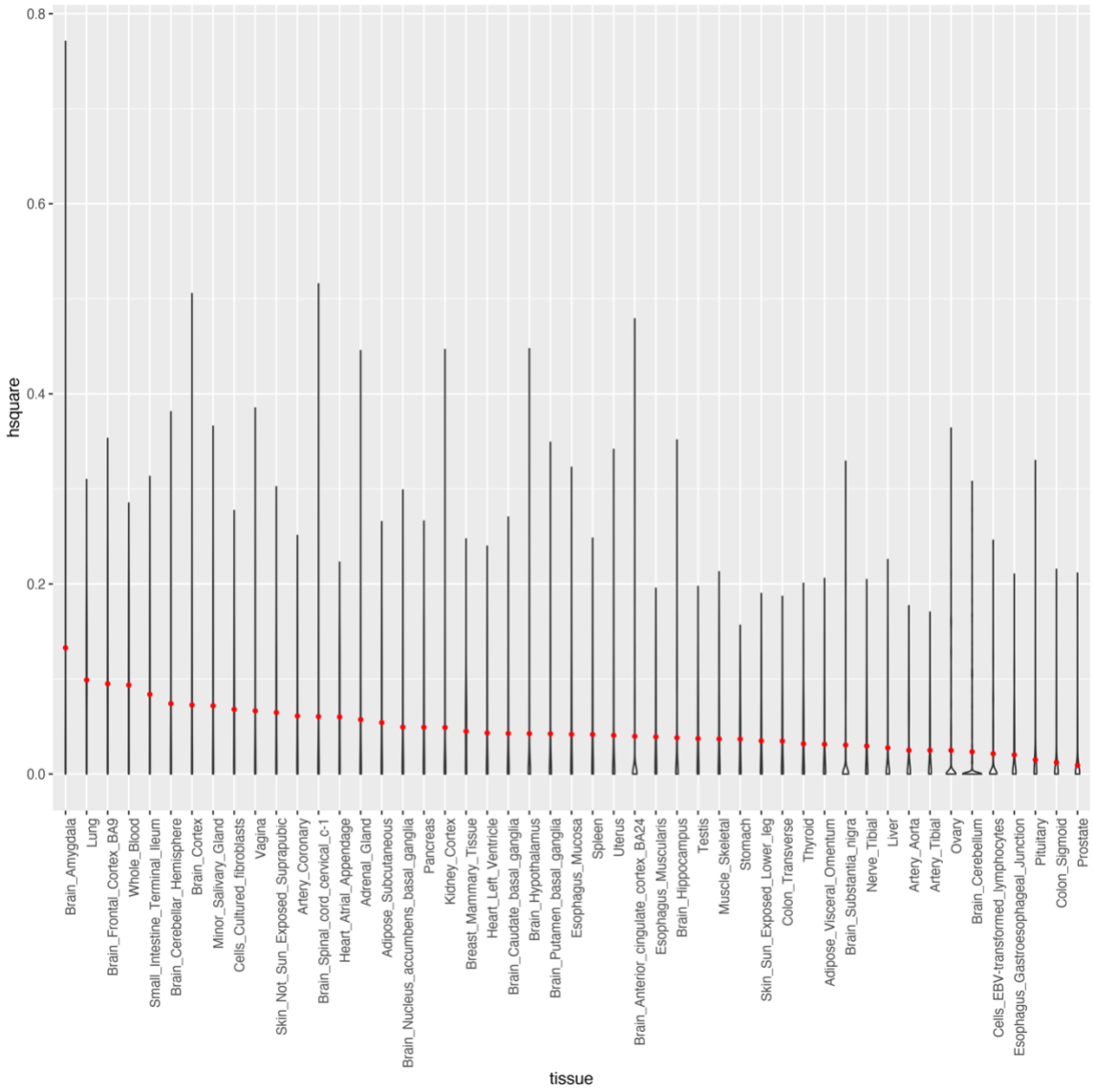

Figure 7. Violin plot of heritability values from 196 PID pathways across all 49 tissues for GSVA scores. Red points in each bar represent the mean heritability values across that tissue.

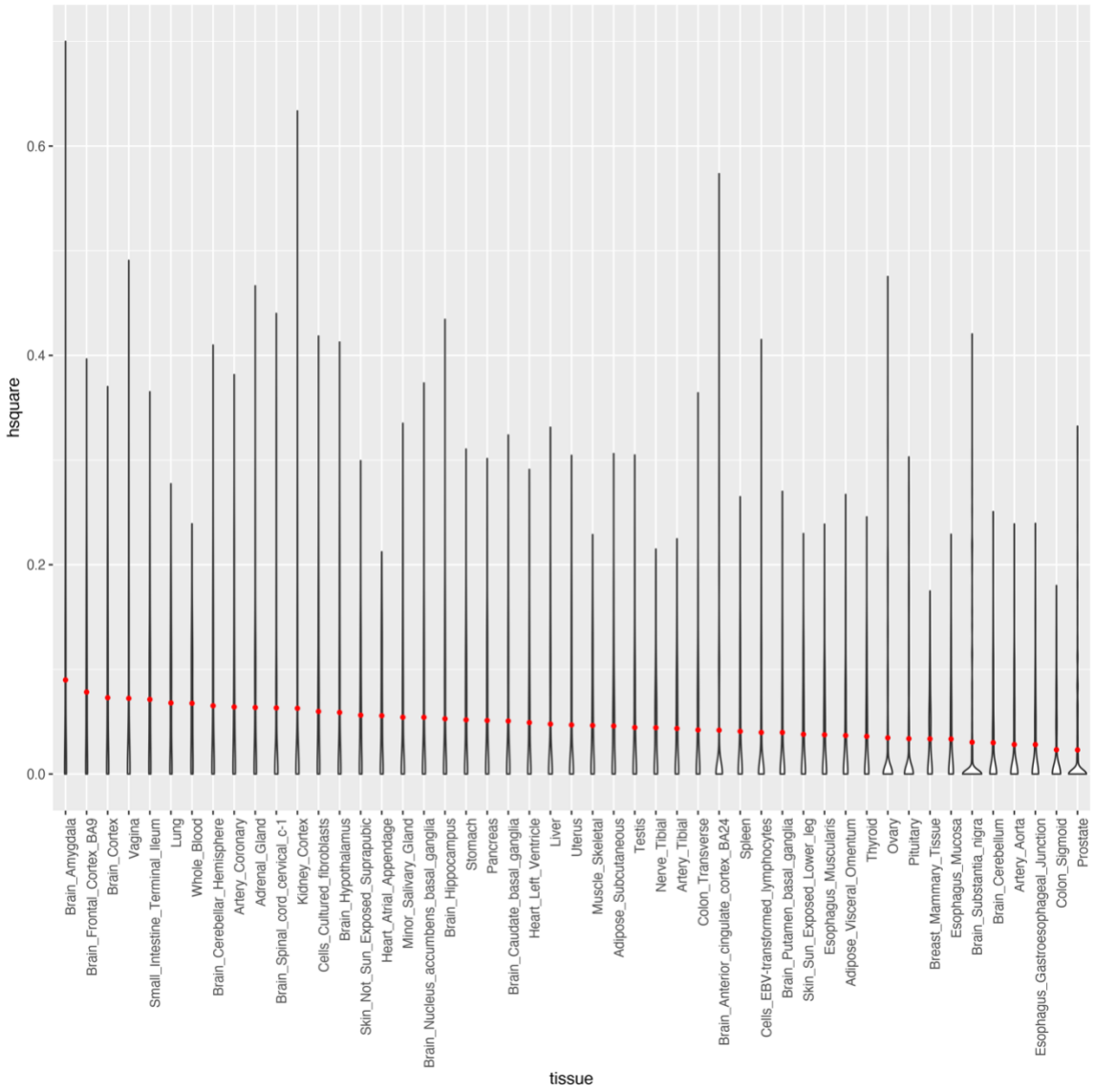

Figure 8. Violin plot of heritability values from 289 BIOCARTA pathways across all 49 tissues for GSVA scores. Red points in each bar represent the mean heritability values across that tissue.

For PID Pathways, the mean heritability estimates across all tissues range from 0.009 to 0.133. Brain Amygdala has the highest mean heritability value of 0.608 (SE=0.154) with 50 pathways' h2 estimates greater than 0.25 and 6 pathways' h2 estimates greater than 0.5,

followed by Lung (h2=0.099, SE=0.065) and Brain Frontal Cortex BA9 (h2=0.095, SE=0.085).

For BIOCARTA Pathways, the mean heritability estimates across all tissues range from 0.023 to 0.090. Brain Amygdala has the highest mean heritability value of 0.090 (SE=0.124) with 28 pathways' h2 estimates greater than 0.25 and 4 pathways' h2 estimates greater than 0.5, followed by Brain Frontal Cortex BA9 (h2=0.078, SE=0.080) and Brain Cortex (h2=0.073, SE=0.083).

3.2.3 Summary of heritability across pathways

We summarized the heritability estimate results across all 196 PID Pathways (Table A5) and 289 BIOCARTA Pathways (Table A6). The numbers of tissues with significant heritability and with h2 estimates greater than 0.25 and 0.5 in each pathway are also reported. Also, we draw the side-by-side violin plots of heritability values, ranking from high to low (Figure 9 for PID Pathway, Figure 10 for BIOCARTA Pathway). These violin plots from 49 tissues across all pathways show the top 20 pathways with the higher mean heritability values.

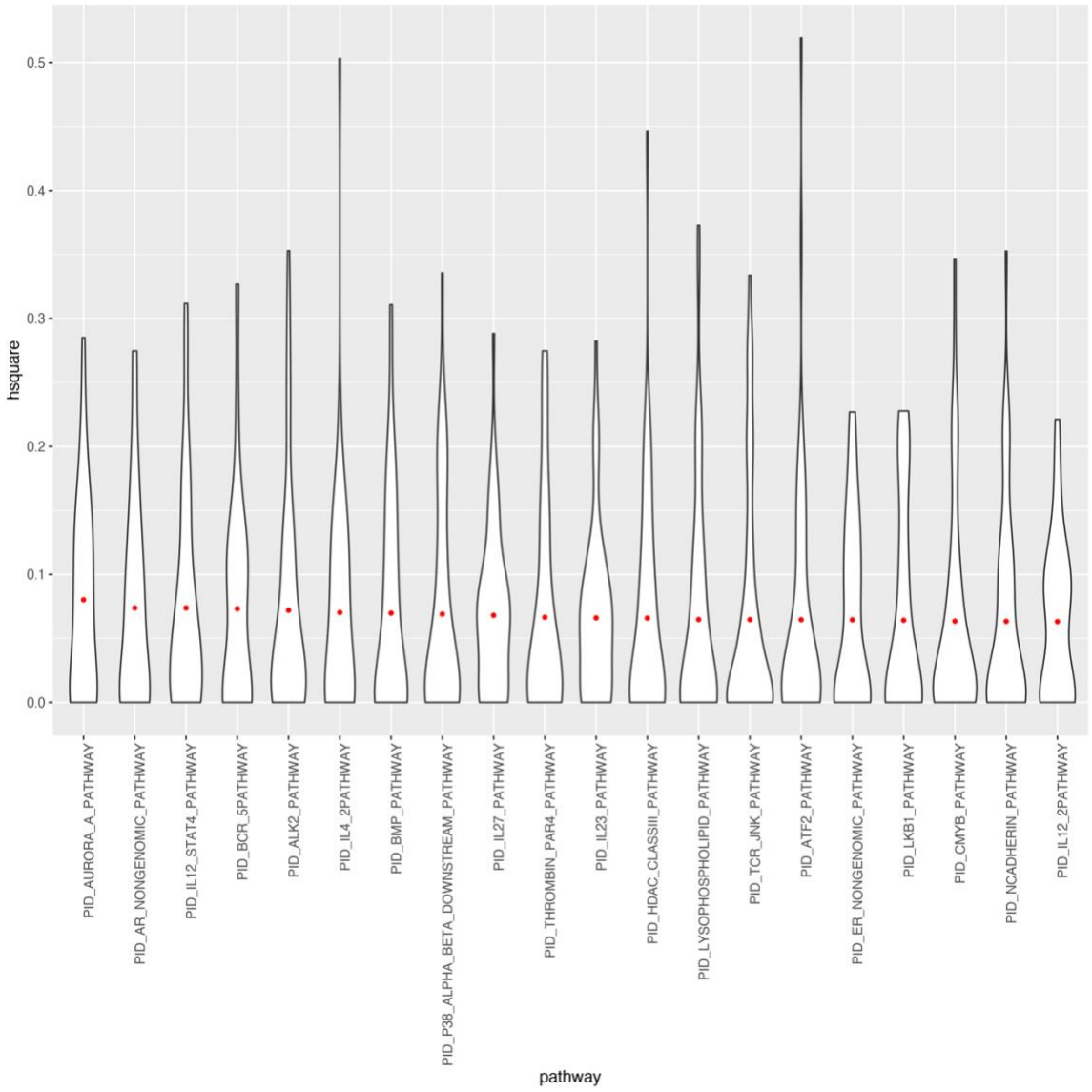

Figure 9. Violin plot of top 20 heritability values from 49 tissues across PID pathways for GSVA scores. Red points in each bar represent the mean heritability values across that KEGG pathways.

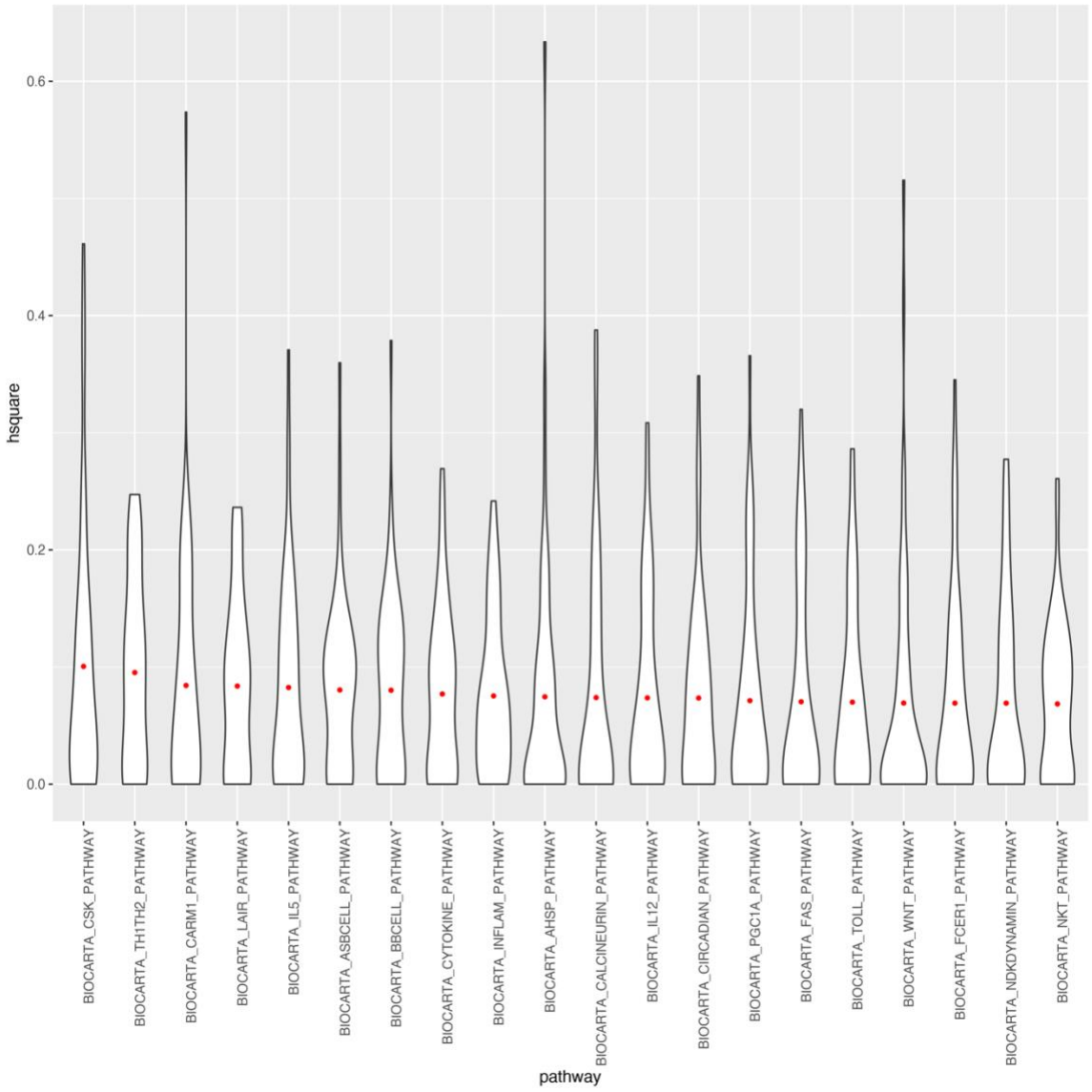

Figure 10. Violin plot of top 20 heritability values from 49 tissues across BIOCARTA pathways for GSVA scores. Red points in each bar represent the mean heritability values across that KEGG pathways.

The mean heritability estimates across all PID Pathways range from 0.013 to 0.080. PID Aurora-A Pathway has the highest mean heritability value of 0.080 (SE=0.078) with 2

tissues' h2 estimates greater than 0.25, followed by PID AR NONGENOMIC Pathway (h2=0.074, SE=0.081) and PID IL12 STAT4 Pathway (h2=0.074, SE=0.084).

The mean heritability estimates for GSVA scores across all BIOCARTA Pathways range from 0.021 to 0.100. BIOCARTA CSK Pathway has the highest mean heritability value of 0.100 (SE=0.116) with 5 tissues' h2 estimates greater than 0.25, followed by BIOCARTA TH1TH2 Pathway (h2=0.095, SE=0.081), BIOCARTA carm1 Pathway (h2=0.084, SE=0.105) and BIOCARTA LAIR Pathway (h2=0.084, SE=0.075).

3.2.4 Summary of heritability for pathway/tissue combination

Table 3 demonstrates the top 20 combinations of PID pathways and tissues that have the highest heritability values. The PID pathway/tissue pair Ephrinb Rev Pathway / Brain Amygdala has the highest estimated heritability (h2=0.771, p=0.016), followed by Beta Catenin Nuc Pathway in Brain Amygdala (h2=0.745, p=0.007) and Trail Pathway in Brain Amygdala (h2=0.600, p=0.041). GSVA scores for the PID pathway has relatively stronger heritability in the tissue Brain Amygdala with 10 pathways ranked in the top 20.

Table 3. Top 20 PID pathway/tissue combinations with the highest heritability for GSVA scores.

tissue	pathway	h2	P
Brain Amygdala	PID EPHRINB REV PATHWAY	0.771	0.016
Brain Amygdala	PID BETA CATENIN NUC PATHWAY	0.745	0.007
Brain Amygdala	PID TRAIL PATHWAY	0.600	0.041
Brain Amygdala	PID HDAC CLASSI PATHWAY	0.558	0.060
Brain Amygdala	PID ATF2 PATHWAY	0.519	0.036
Brain Spinal cord cervical c-1	PID ERBB2 ERBB3 PATHWAY	0.516	0.050
Brain Cortex	PID P38 MK2 PATHWAY	0.506	0.005
Brain Amygdala	PID IL4 2PATHWAY	0.503	0.055

Brain Anterior cingulate cortex BA24	PID FAK PATHWAY	0.479	0.079
Brain Hypothalamus	PID MYC PATHWAY	0.447	0.079
Kidney Cortex	PID HDAC CLASSIII PATHWAY	0.447	0.035
Adrenal Gland	PID INTEGRIN2 PATHWAY	0.445	0.005
Brain Amygdala	PID IGF1 PATHWAY	0.426	0.095
Brain Amygdala	PID REG GR PATHWAY	0.426	0.107
Brain Amygdala	PID EPHA2 FWD PATHWAY	0.424	0.101
Brain Spinal cord cervical c-1	PID FGF PATHWAY	0.421	0.058
Brain Anterior cingulate cortex BA24	PID FAS PATHWAY	0.420	0.066
Kidney Cortex	PID INTEGRIN5 PATHWAY	0.402	0.113
Brain Anterior cingulate cortex BA24	PID INSULIN PATHWAY	0.400	0.076
Brain Amygdala	PID HIF2PATHWAY	0.394	0.088

Out of 9,604 combinations of PID pathways and tissue types, we observed 449 pairs (4.68%) with significant heritability estimations ($p<0.05$), ranging from 0.073 to 0.771. Among these significant combinations, 40 tissues have significant heritability in at least one of the 196 PID pathways. Whole Blood has 82 PID pathways with significant heritability, which is the most in these tissues (Table A3). Among all 196 PID pathways, we observed that 178 pathways have significant heritability in at least one tissue and PID SYNDECAN 4 pathway has the most combinations with heritability significant in 8 tissues (Table A5).

Table 4 shows the top 20 combinations of BIOCATRA pathways and tissues for GSVA scores. The BIOCATRA Gleevec Pathway in Brain Amygdala has the highest heritability ($h2=0.700$, $p=0.052$), followed by CREM Pathway in Brain Amygdala ($h2=0.689$, $p=0.010$) and GCR Pathway in Brain Amygdala ($h2=0.643$, $p=0.012$).

Table 4. Top 20 BIOCATRA pathway/tissue combinations with the highest heritability for GSVA scores.

tissue	**pathway**	**h2**	**P**
Brain Amygdala	BIOCARTA GLEEVEC PATHWAY	0.700	0.052

Brain Amygdala	BIOCARTA CREM PATHWAY	0.689	0.010
Brain Amygdala	BIOCARTA GCR PATHWAY	0.643	0.012
Kidney Cortex	BIOCARTA AHSP PATHWAY	0.634	0.049
Brain Anterior cingulate cortex BA24	BIOCARTA CARM1 PATHWAY	0.574	0.035
Brain Amygdala	BIOCARTA BCELLSURVIVAL PATHWAY	0.524	0.039
Kidney Cortex	BIOCARTA WNT PATHWAY	0.516	0.029
Brain Amygdala	BIOCARTA IL3 PATHWAY	0.492	0.038
Vagina	BIOCARTA HDAC PATHWAY	0.491	0.008
Ovary	BIOCARTA CB1R PATHWAY	0.475	0.001
Adrenal Gland	BIOCARTA PPARG PATHWAY	0.466	0.001
Brain Anterior cingulate cortex BA24	BIOCARTA CSK PATHWAY	0.461	0.044
Vagina	BIOCARTA NOS1 PATHWAY	0.455	0.011
Vagina	BIOCARTA CELL2CELL PATHWAY	0.445	0.019
Brain Spinal cord cervical c-1	BIOCARTA AKAP95 PATHWAY	0.440	0.081
Brain Amygdala	BIOCARTA AKT PATHWAY	0.438	0.133
Brain Hippocampus	BIOCARTA MCM PATHWAY	0.434	0.035
Brain Amygdala	BIOCARTA IL2RB PATHWAY	0.424	0.083
Brain Substantia nigra	BIOCARTA PS1 PATHWAY	0.420	0.027
Kidney Cortex	BIOCARTA AMAN PATHWAY	0.420	0.060

Out of 14,161 pathway/tissue combinations of BIOCARTA pathways, there are 653 pairs (4.61%) with significant heritability estimations ($p<0.05$), ranging from 0.061 to 0.689. Among these significant combinations, 46 tissues have significant heritability in at least one of the 289 BIOCARTA pathways. Like the result from KEGG and PID pathways, Whole Blood also has the greatest number of significant pathways with 87 BIOCARTA pathways having significant heritability (Table A4). 252 BIOCARTA pathways have significant heritability in at least one tissue and 7 BIOCARTA pathways have the most combinations with heritability significant in 7 tissues (Table A6).

4. Discussion

Motivated by the important use of pathway expression scores in QTL analysis, we have performed heritability analysis to individual-level pathway scores in GTEx samples. The heritability of GSVA scores, PLAGE scores, Z-scores, and ssGSEA scores for 186 KEGG Pathways, 196 PID Pathways, and 289 BIOCARTA Pathways were calculated across 49 tissues. We found that in most tissues or pathways, no matter which scoring method and pathway type were used, GRM contributed significantly to explain the differences in individual-level pathway scores in at least one pair of tissue/pathway. This finding strongly proved that the individual-level pathway expression scores are heritable, especially in Whole Blood.

By comparing heritability estimate results of GSVA scores, PLAGE scores, Z-scores, and ssGSEA scores for KEGG Pathways, we showed that heritability estimates for different score methods were consistent with each other, especially for GSVA scores, Z-scores, and ssGSEA scores. Both the pattern of heatmaps and the significant Pearson correlations indicated the similarity between different score methods when estimating the heritability of individual-level pathway expression.

In the heritability analysis across pathways, we identified that KEGG Leishmania Infection, PID Aurora-A Pathway, and BIOCARTA CSK Pathway have the highest mean heritability of GSVA scores for KEGG Pathways, PID Pathways, and BIOCATRA Pathways, respectively. When comparing the heritability across tissues for these 3 different types of pathways, we found that Brain Amygdala, Brain Spinal cord cervical c-1, Brain Frontal Cortex BA9, Small Intestine Terminal Ileum, and Whole Blood have higher mean heritability of GSVA scores, no matter in KEGG, PID or BIOCATRA Pathways. The

analysis results across tissues for PID Pathways are quite consistent with the results for BIOCATRA Pathways, and Brain Amygdala is the tissue with the highest mean heritability value in both kinds of pathways.

Concerning limitations and further research, first, sample sizes are different in different tissues when using GTEx data. This may have influenced the accuracy and comparability of heritability estimates across tissues, with a potential negative correlation between mean heritability and sample size in KEGG Pathways. Besides, the terms of the fixed effects are commonly dropped from the analysis from the GCTA analysis and the effects of demographic variables on pathway expression scores are still unknown. Future directions for increasing the understanding could include adding more fixed effects in the mixed linear model and testing their influences on heritability estimates.

In this paper, we quantitate the individual-level pathway expression using different score methods across different types of pathways and tissues. We show that the heritability of pathway expression scores can be accurately estimated across pathways and tissues, and most of them are significant, indicating the heritability for individual-level pathway expression scores. Furthermore, the heritability estimate results are consistent in different score algorithms and pathway types. The analysis conducted in this study of heritability for pathway expression also provided a theoretical basis for future studies using pathway expression and proved the feasibility of QTL analysis based on pathway level.

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Appendix

Table A1. Heritability estimate results for GSVA scores across tissues for KEGG Pathways. Rank by mean heritability from high to low.

	Mean	SE	num h2>0.25	num h2>0.5	num p<0.05
Brain Spinal cord cervical c-1	0.101	0.127	26	1	7
Kidney Cortex	0.097	0.119	22	2	1
Small Intestine Terminal Ileum	0.082	0.071	6	0	7
Whole Blood	0.082	0.068	1	0	59
Brain Hippocampus	0.079	0.112	13	1	10
Brain Frontal Cortex BA9	0.076	0.082	6	0	3
Skin Not Sun Exposed Suprapubic	0.072	0.061	2	0	58
Artery Coronary	0.071	0.094	11	0	10
Brain Putamen basal ganglia	0.071	0.106	14	0	10
Minor Salivary Gland	0.071	0.089	10	0	6
Vagina	0.069	0.121	16	2	8
Brain Amygdala	0.066	0.101	13	0	0
Brain Nucleus accumbens basal ganglia	0.065	0.084	8	0	2
Cells Cultured fibroblasts	0.065	0.079	5	1	23
Brain Cortex	0.063	0.089	8	0	6
Adrenal Gland	0.061	0.077	5	0	10
Spleen	0.061	0.071	4	0	11
Brain Hypothalamus	0.057	0.091	12	0	7
Heart Atrial Appendage	0.057	0.058	0	0	28
Testis	0.056	0.067	2	0	16
Brain Cerebellar Hemisphere	0.053	0.086	7	1	3
Lung	0.053	0.056	0	0	20
Pancreas	0.050	0.055	0	0	11
Brain Substantia nigra	0.049	0.082	10	0	0
Thyroid	0.049	0.052	0	0	23
Nerve Tibial	0.046	0.062	2	0	12
Cells EBV-transformed lymphocytes	0.045	0.066	5	0	5
Heart Left Ventricle	0.045	0.059	0	0	11
Uterus	0.045	0.079	3	1	1
Brain Caudate basal ganglia	0.044	0.069	4	0	2
Brain Cerebellum	0.043	0.070	4	0	2
Breast Mammary Tissue	0.043	0.051	1	0	11
Artery Tibial	0.040	0.043	0	0	15
Skin Sun Exposed Lower leg	0.040	0.043	0	0	26
Brain Anterior cingulate cortex BA24	0.037	0.078	6	1	1

Muscle Skeletal	0.036	0.047	0	0	11
Ovary	0.036	0.068	4	0	4
Colon Sigmoid	0.035	0.053	2	0	3
Esophagus Mucosa	0.035	0.048	0	0	9
Esophagus Gastroesophageal Junction	0.034	0.049	0	0	7
Pituitary	0.033	0.059	2	0	2
Colon Transverse	0.032	0.044	0	0	4
Adipose Visceral Omentum	0.031	0.053	0	0	10
Esophagus Muscularis	0.031	0.045	0	0	10
Stomach	0.031	0.047	1	0	3
Artery Aorta	0.030	0.049	0	0	1
Adipose Subcutaneous	0.029	0.041	0	0	4
Prostate	0.024	0.054	2	0	3
Liver	0.022	0.043	0	0	1

Table A2. Heritability estimate results across KEGG pathways for GSVA scores.

Rank by mean heritability from high to low.

	Mean	SE	num h2>0.25	num h2>0.5	num p<0.05
KEGG LEISHMANIA INFECTION	0.092	0.080	1	0	9
KEGG ASTHMA	0.088	0.082	1	0	9
KEGG GLYCOSPHINGOLIPID BIOSYNTHESIS GLOBO SERIES	0.081	0.088	3	0	5
KEGG PORPHYRIN AND CHLOROPHYLL METABOLISM	0.080	0.103	3	1	3
KEGG ETHER LIPID METABOLISM	0.077	0.094	1	0	10
KEGG DRUG METABOLISM OTHER ENZYMES	0.077	0.107	2	1	2
KEGG TASTE TRANSDUCTION	0.074	0.087	2	0	6
KEGG LYSOSOME	0.073	0.125	6	0	5
KEGG STARCH AND SUCROSE METABOLISM	0.072	0.095	3	0	5
KEGG VIRAL MYOCARDITIS	0.072	0.070	1	0	4
KEGG INOSITOL PHOSPHATE METABOLISM	0.071	0.114	3	1	2
KEGG PURINE METABOLISM	0.071	0.101	5	0	2
KEGG GLUTATHIONE METABOLISM	0.071	0.086	2	0	4
KEGG CHEMOKINE SIGNALING PATHWAY	0.070	0.082	2	0	1
KEGG B CELL RECEPTOR SIGNALING PATHWAY	0.069	0.088	4	0	2
KEGG LONG TERM DEPRESSION	0.069	0.079	1	0	5
KEGG PEROXISOME	0.069	0.083	2	0	3
KEGG INTESTINAL IMMUNE NETWORK FOR IGA PRODUCTION	0.069	0.068	0	0	3
KEGG AUTOIMMUNE THYROID DISEASE	0.068	0.069	2	0	1

KEGG GAP JUNCTION	0.068	0.079	1	0	3
KEGG T CELL RECEPTOR SIGNALING PATHWAY	0.068	0.083	3	0	2
KEGG ALDOSTERONE REGULATED SODIUM REABSORPTION	0.068	0.099	2	1	3
KEGG PROXIMAL TUBULE BICARBONATE RECLAMATION	0.067	0.120	2	1	3
KEGG NOD LIKE RECEPTOR SIGNALING PATHWAY	0.067	0.064	0	0	2
KEGG TYPE I DIABETES MELLITUS	0.067	0.058	0	0	2
KEGG BUTANOATE METABOLISM	0.066	0.091	2	0	3
KEGG GLYCOSPHINGOLIPID BIOSYNTHESIS LACTO AND NEOLACTO SERIES	0.066	0.073	2	0	4
KEGG PENTOSE PHOSPHATE PATHWAY	0.066	0.101	4	0	6
KEGG GLYOXYLATE AND DICARBOXYLATE METABOLISM	0.065	0.109	3	1	4
KEGG GLYCEROPHOSPHOLIPID METABOLISM	0.065	0.073	1	0	2
KEGG TOLL LIKE RECEPTOR SIGNALING PATHWAY	0.065	0.074	1	0	2
KEGG RENIN ANGIOTENSIN SYSTEM	0.065	0.071	0	0	5
KEGG ANTIGEN PROCESSING AND PRESENTATION	0.064	0.078	2	0	2
KEGG GLYCOSAMINOGLYCAN BIOSYNTHESIS CHONDROITIN SULFATE	0.064	0.078	1	0	5
KEGG BASE EXCISION REPAIR	0.064	0.109	3	1	0
KEGG PPAR SIGNALING PATHWAY	0.063	0.101	4	0	4
KEGG HEMATOPOIETIC CELL LINEAGE	0.063	0.069	1	0	1
KEGG NITROGEN METABOLISM	0.063	0.078	0	0	7
KEGG HUNTINGTONS DISEASE	0.063	0.086	2	0	3
KEGG JAK STAT SIGNALING PATHWAY	0.063	0.073	2	0	3
KEGG GLYCINE SERINE AND THREONINE METABOLISM	0.063	0.080	3	0	5
KEGG AMINO SUGAR AND NUCLEOTIDE SUGAR METABOLISM	0.063	0.087	2	0	3
KEGG GALACTOSE METABOLISM	0.062	0.087	1	0	5
KEGG FATTY ACID METABOLISM	0.061	0.074	1	0	3
KEGG CELL ADHESION MOLECULES CAMS	0.061	0.077	1	0	2
KEGG PYRUVATE METABOLISM	0.061	0.069	1	0	2
KEGG ALLOGRAFT REJECTION	0.061	0.056	0	0	2
KEGG OTHER GLYCAN DEGRADATION	0.061	0.086	2	0	3
KEGG WNT SIGNALING PATHWAY	0.061	0.087	2	0	3
KEGG DORSO VENTRAL AXIS FORMATION	0.060	0.098	3	0	1
KEGG SPHINGOLIPID METABOLISM	0.060	0.094	4	0	4
KEGG TAURINE AND HYPOTAURINE METABOLISM	0.059	0.080	2	0	4
KEGG RNA POLYMERASE	0.059	0.074	0	0	5
KEGG N GLYCAN BIOSYNTHESIS	0.059	0.077	1	0	3
KEGG ALPHA LINOLENIC ACID METABOLISM	0.058	0.080	1	0	0

KEGG PENTOSE AND GLUCURONATE INTERCONVERSIONS	0.058	0.071	1	0	3
KEGG FRUCTOSE AND MANNOSE METABOLISM	0.058	0.100	3	0	6
KEGG STEROID HORMONE BIOSYNTHESIS	0.058	0.091	2	0	5
KEGG NATURAL KILLER CELL MEDIATED CYTOTOXICITY	0.058	0.075	2	0	5
KEGG GLYCOSPHINGOLIPID BIOSYNTHESIS GANGLIO SERIES	0.058	0.100	2	1	3
KEGG ONE CARBON POOL BY FOLATE	0.058	0.086	2	0	4
KEGG CYSTEINE AND METHIONINE METABOLISM	0.058	0.093	3	0	5
KEGG SELENOAMINO ACID METABOLISM	0.057	0.087	2	0	3
KEGG TERPENOID BACKBONE BIOSYNTHESIS	0.057	0.078	1	0	0
KEGG PYRIMIDINE METABOLISM	0.057	0.102	3	1	4
KEGG TIGHT JUNCTION	0.057	0.085	3	0	4
KEGG TYPE II DIABETES MELLITUS	0.057	0.088	3	0	2
KEGG CYTOKINE CYTOKINE RECEPTOR INTERACTION	0.057	0.052	0	0	4
KEGG FC EPSILON RI SIGNALING PATHWAY	0.057	0.075	1	0	5
KEGG LINOLEIC ACID METABOLISM	0.057	0.088	3	0	2
KEGG PANTOTHENATE AND COA BIOSYNTHESIS	0.057	0.080	2	0	5
KEGG PARKINSONS DISEASE	0.057	0.074	2	0	2
KEGG RNA DEGRADATION	0.057	0.075	1	0	0
KEGG ALZHEIMERS DISEASE	0.056	0.076	2	0	4
KEGG PROPANOATE METABOLISM	0.056	0.079	2	0	2
KEGG GNRH SIGNALING PATHWAY	0.056	0.093	2	0	4
KEGG ARACHIDONIC ACID METABOLISM	0.056	0.070	0	0	3
KEGG FOLATE BIOSYNTHESIS	0.056	0.066	0	0	2
KEGG PRION DISEASES	0.056	0.064	0	0	3
KEGG RIG I LIKE RECEPTOR SIGNALING PATHWAY	0.056	0.061	0	0	2
KEGG GRAFT VERSUS HOST DISEASE	0.056	0.058	1	0	2
KEGG VEGF SIGNALING PATHWAY	0.055	0.072	0	0	4
KEGG BIOSYNTHESIS OF UNSATURATED FATTY ACIDS	0.055	0.073	1	0	2
KEGG MAPK SIGNALING PATHWAY	0.055	0.068	0	0	3
KEGG CITRATE CYCLE TCA CYCLE	0.055	0.071	2	0	0
KEGG VASCULAR SMOOTH MUSCLE CONTRACTION	0.055	0.078	1	0	3
KEGG GLYCOSYLPHOSPHATIDYLINOSITOL GPI ANCHOR BIOSYNTHESIS	0.055	0.077	2	0	4
KEGG OXIDATIVE PHOSPHORYLATION	0.055	0.069	1	0	2
KEGG TRYPTOPHAN METABOLISM	0.054	0.062	0	0	2
KEGG FC GAMMA R MEDIATED PHAGOCYTOSIS	0.054	0.070	2	0	2
KEGG GLYCEROLIPID METABOLISM	0.054	0.111	2	1	4
KEGG CARDIAC MUSCLE CONTRACTION	0.054	0.062	1	0	2

KEGG LIMONENE AND PINENE DEGRADATION	0.054	0.068	2	0	1
KEGG MELANOMA	0.053	0.092	3	0	4
KEGG GLIOMA	0.053	0.073	2	0	1
KEGG GLYCOSAMINOGLYCAN DEGRADATION	0.053	0.069	1	0	2
KEGG RIBOFLAVIN METABOLISM	0.053	0.085	2	0	4
KEGG GLYCOSAMINOGLYCAN BIOSYNTHESIS HEPARAN SULFATE	0.052	0.071	1	0	6
KEGG ECM RECEPTOR INTERACTION	0.052	0.069	0	0	3
KEGG GLYCOLYSIS GLUCONEOGENESIS	0.052	0.084	2	0	4
KEGG ENDOMETRIAL CANCER	0.052	0.079	3	0	2
KEGG OOCYTE MEIOSIS	0.051	0.061	0	0	1
KEGG HYPERTROPHIC CARDIOMYOPATHY HCM	0.051	0.071	1	0	1
KEGG SULFUR METABOLISM	0.051	0.086	2	0	4
KEGG PRIMARY IMMUNODEFICIENCY	0.051	0.056	0	0	2
KEGG MELANOGENESIS	0.049	0.068	0	0	2
KEGG CYTOSOLIC DNA SENSING PATHWAY	0.049	0.058	1	0	3
KEGG AMYOTROPHIC LATERAL SCLEROSIS ALS	0.049	0.069	0	0	6
KEGG DILATED CARDIOMYOPATHY	0.049	0.076	1	0	2
KEGG RETINOL METABOLISM	0.048	0.092	2	0	3
KEGG ERBB SIGNALING PATHWAY	0.048	0.103	3	0	3
KEGG STEROID BIOSYNTHESIS	0.048	0.063	0	0	0
KEGG AMINOACYL TRNA BIOSYNTHESIS	0.048	0.073	1	0	1
KEGG LEUKOCYTE TRANSENDOTHELIAL MIGRATION	0.048	0.060	0	0	2
KEGG PHOSPHATIDYLINOSITOL SIGNALING SYSTEM	0.048	0.081	2	0	1
KEGG MTOR SIGNALING PATHWAY	0.047	0.086	3	0	3
KEGG ARGININE AND PROLINE METABOLISM	0.047	0.070	2	0	2
KEGG SNARE INTERACTIONS IN VESICULAR TRANSPORT	0.047	0.078	2	0	1
KEGG VALINE LEUCINE AND ISOLEUCINE DEGRADATION	0.047	0.066	1	0	1
KEGG ENDOCYTOSIS	0.047	0.066	0	0	2
KEGG ABC TRANSPORTERS	0.047	0.062	0	0	2
KEGG LONG TERM POTENTIATION	0.047	0.063	0	0	3
KEGG VIBRIO CHOLERAE INFECTION	0.046	0.075	1	0	2
KEGG MATURITY ONSET DIABETES OF THE YOUNG	0.046	0.067	1	0	1
KEGG VALINE LEUCINE AND ISOLEUCINE BIOSYNTHESIS	0.046	0.065	1	0	0
KEGG GLYCOSAMINOGLYCAN BIOSYNTHESIS KERATAN SULFATE	0.046	0.076	3	0	5
KEGG NUCLEOTIDE EXCISION REPAIR	0.046	0.090	3	0	1
KEGG SYSTEMIC LUPUS ERYTHEMATOSUS	0.046	0.050	0	0	3
KEGG LYSINE DEGRADATION	0.045	0.058	0	0	3
KEGG DRUG METABOLISM CYTOCHROME P450	0.045	0.072	1	0	2

KEGG FOCAL ADHESION	0.044	0.068	1	0	3
KEGG COLORECTAL CANCER	0.044	0.083	1	0	2
KEGG NOTCH SIGNALING PATHWAY	0.044	0.060	0	0	2
KEGG HISTIDINE METABOLISM	0.044	0.063	0	0	1
KEGG VASOPRESSIN REGULATED WATER REABSORPTION	0.044	0.061	1	0	2
KEGG AXON GUIDANCE	0.044	0.068	1	0	3
KEGG PROGESTERONE MEDIATED OOCYTE MATURATION	0.043	0.058	0	0	1
KEGG COMPLEMENT AND COAGULATION CASCADES	0.043	0.070	2	0	1
KEGG TGF BETA SIGNALING PATHWAY	0.043	0.079	1	0	5
KEGG SMALL CELL LUNG CANCER	0.042	0.060	1	0	4
KEGG NON SMALL CELL LUNG CANCER	0.041	0.067	0	0	1
KEGG ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY ARVC	0.041	0.070	1	0	2
KEGG REGULATION OF ACTIN CYTOSKELETON	0.041	0.052	0	0	2
KEGG THYROID CANCER	0.041	0.080	2	0	3
KEGG ACUTE MYELOID LEUKEMIA	0.041	0.062	0	0	2
KEGG APOPTOSIS	0.040	0.052	0	0	0
KEGG BASAL CELL CARCINOMA	0.040	0.060	0	0	0
KEGG PATHWAYS IN CANCER	0.040	0.061	0	0	3
KEGG ASCORBATE AND ALDARATE METABOLISM	0.040	0.052	0	0	3
KEGG CALCIUM SIGNALING PATHWAY	0.040	0.077	1	0	2
KEGG PROSTATE CANCER	0.040	0.054	0	0	2
KEGG RENAL CELL CARCINOMA	0.040	0.065	1	0	2
KEGG PRIMARY BILE ACID BIOSYNTHESIS	0.039	0.068	1	0	2
KEGG P53 SIGNALING PATHWAY	0.039	0.055	0	0	5
KEGG PROTEASOME	0.039	0.054	0	0	2
KEGG NEUROACTIVE LIGAND RECEPTOR INTERACTION	0.039	0.078	3	0	1
KEGG BETA ALANINE METABOLISM	0.039	0.058	0	0	1
KEGG CIRCADIAN RHYTHM MAMMAL	0.038	0.050	0	0	2
KEGG METABOLISM OF XENOBIOTICS BY CYTOCHROME P450	0.038	0.075	2	0	5
KEGG RIBOSOME	0.038	0.042	0	0	1
KEGG PATHOGENIC ESCHERICHIA COLI INFECTION	0.038	0.055	1	0	2
KEGG PHENYLALANINE METABOLISM	0.038	0.074	1	0	4
KEGG EPITHELIAL CELL SIGNALING IN HELICOBACTER PYLORI INFECTION	0.037	0.073	1	0	4
KEGG BLADDER CANCER	0.036	0.055	0	0	2
KEGG REGULATION OF AUTOPHAGY	0.036	0.064	1	0	3
KEGG O GLYCAN BIOSYNTHESIS	0.035	0.054	0	0	2
KEGG ALANINE ASPARTATE AND GLUTAMATE METABOLISM	0.034	0.059	0	0	1

KEGG ADHERENS JUNCTION	0.034	0.052	0	0	2
KEGG PANCREATIC CANCER	0.034	0.072	1	0	4
KEGG PROTEIN EXPORT	0.034	0.061	1	0	0
KEGG TYROSINE METABOLISM	0.033	0.058	0	0	3
KEGG HEDGEHOG SIGNALING PATHWAY	0.032	0.057	0	0	1
KEGG SPLICEOSOME	0.032	0.058	1	0	0
KEGG NEUROTROPHIN SIGNALING PATHWAY	0.031	0.044	0	0	1
KEGG CHRONIC MYELOID LEUKEMIA	0.031	0.059	1	0	1
KEGG INSULIN SIGNALING PATHWAY	0.029	0.053	0	0	1
KEGG NICOTINATE AND NICOTINAMIDE METABOLISM	0.028	0.055	1	0	2
KEGG MISMATCH REPAIR	0.028	0.061	1	0	0
KEGG HOMOLOGOUS RECOMBINATION	0.027	0.041	0	0	0
KEGG CELL CYCLE	0.027	0.046	0	0	0
KEGG UBIQUITIN MEDIATED PROTEOLYSIS	0.027	0.044	0	0	1
KEGG OLFACTORY TRANSDUCTION	0.026	0.048	0	0	1
KEGG ADIPOCYTOKINE SIGNALING PATHWAY	0.025	0.037	0	0	1
KEGG NON HOMOLOGOUS END JOINING	0.024	0.055	1	0	1
KEGG BASAL TRANSCRIPTION FACTORS	0.023	0.040	0	0	2
KEGG DNA REPLICATION	0.022	0.054	1	0	0

Table A3. Heritability estimate results for GSVA scores across tissues for PID Pathways. Rank by mean heritability from high to low.

	Mean	SE	num h2>0.25	num h2>0.5	num p<0.05
Brain Amygdala	0.133	0.154	50	6	4
Lung	0.099	0.065	2	0	65
Brain Frontal Cortex BA9	0.095	0.085	8	0	4
Whole Blood	0.094	0.071	3	0	82
Small Intestine Terminal Ileum	0.084	0.074	4	0	6
Brain Cerebellar Hemisphere	0.074	0.097	14	0	6
Brain Cortex	0.073	0.084	7	1	3
Minor Salivary Gland	0.072	0.082	4	0	1
Cells Cultured fibroblasts	0.068	0.064	3	0	20
Vagina	0.066	0.096	12	0	4
Skin Not Sun Exposed Suprapubic	0.065	0.067	3	0	55
Artery Coronary	0.061	0.067	1	0	4
Brain Spinal cord cervical c-1	0.060	0.093	11	1	1
Heart Atrial Appendage	0.060	0.055	0	0	24
Adrenal Gland	0.057	0.082	7	0	8

Adipose Subcutaneous	0.054	0.063	1	0	26
Brain Nucleus accumbens basal ganglia	0.049	0.069	2	0	0
Pancreas	0.049	0.056	1	0	19
Kidney Cortex	0.049	0.083	9	0	1
Breast Mammary Tissue	0.045	0.039	0	0	7
Heart Left Ventricle	0.043	0.057	0	0	9
Brain Caudate basal ganglia	0.043	0.062	1	0	0
Brain Hypothalamus	0.043	0.077	7	0	3
Brain Putamen basal ganglia	0.042	0.072	5	0	2
Esophagus Mucosa	0.042	0.054	2	0	13
Spleen	0.042	0.055	0	0	4
Uterus	0.041	0.067	4	0	1
Brain Anterior cingulate cortex BA24	0.040	0.088	10	0	0
Esophagus Muscularis	0.039	0.048	0	0	6
Brain Hippocampus	0.038	0.067	4	0	1
Testis	0.037	0.044	0	0	0
Muscle Skeletal	0.037	0.050	0	0	13
Stomach	0.037	0.040	0	0	0
Skin Sun Exposed Lower leg	0.035	0.043	0	0	24
Colon Transverse	0.035	0.045	0	0	3
Thyroid	0.032	0.038	0	0	7
Adipose Visceral Omentum	0.031	0.047	0	0	6
Brain Substantia nigra	0.030	0.063	3	0	0
Nerve Tibial	0.029	0.040	0	0	3
Liver	0.028	0.048	0	0	0
Artery Aorta	0.025	0.043	0	0	1
Artery Tibial	0.025	0.038	0	0	8
Ovary	0.025	0.056	1	0	1
Brain Cerebellum	0.023	0.054	3	0	1
Cells EBV-transformed lymphocytes	0.021	0.045	0	0	0
Esophagus Gastroesophageal Junction	0.020	0.032	0	0	1
Pituitary	0.015	0.047	3	0	1
Colon Sigmoid	0.012	0.032	0	0	1
Prostate	0.009	0.028	0	0	0

Table A4. Heritability estimate results for GSVA scores across tissues for BIOCARTA Pathways. Rank by mean heritability from high to low.

	Mean	SE	num h2>0.25	num h2>0.5	num p<0.05
Brain Amygdala	0.090	0.124	28	4	4

Brain Frontal Cortex BA9	0.078	0.080	10	0	5
Brain Cortex	0.073	0.083	11	0	5
Vagina	0.072	0.109	27	0	12
Small Intestine Terminal Ileum	0.071	0.071	4	0	6
Lung	0.068	0.065	1	0	55
Whole Blood	0.068	0.059	0	0	87
Brain Cerebellar Hemisphere	0.065	0.083	10	0	5
Artery Coronary	0.064	0.081	9	0	11
Adrenal Gland	0.064	0.081	12	0	12
Brain Spinal cord cervical c-1	0.063	0.095	23	0	2
Kidney Cortex	0.063	0.102	18	2	3
Cells Cultured fibroblasts	0.060	0.069	2	0	22
Brain Hypothalamus	0.059	0.078	4	0	2
Skin Not Sun Exposed Suprapubic	0.056	0.064	5	0	64
Heart Atrial Appendage	0.056	0.058	0	0	32
Minor Salivary Gland	0.054	0.074	8	0	1
Brain Nucleus accumbens basal ganglia	0.054	0.078	11	0	3
Brain Hippocampus	0.053	0.071	4	0	1
Stomach	0.052	0.058	1	0	12
Pancreas	0.051	0.062	2	0	19
Brain Caudate basal ganglia	0.051	0.073	7	0	5
Heart Left Ventricle	0.049	0.065	5	0	23
Liver	0.048	0.075	9	0	5
Uterus	0.047	0.069	5	0	0
Muscle Skeletal	0.046	0.055	0	0	37
Adipose Subcutaneous	0.046	0.051	1	0	16
Testis	0.044	0.059	2	0	11
Nerve Tibial	0.044	0.049	0	0	17
Artery Tibial	0.043	0.050	0	0	35
Colon Transverse	0.042	0.055	2	0	5
Brain Anterior cingulate cortex BA24	0.042	0.085	12	1	2
Spleen	0.041	0.057	1	0	7
Cells EBV-transformed lymphocytes	0.040	0.069	7	0	4
Brain Putamen basal ganglia	0.040	0.061	3	0	1
Skin Sun Exposed Lower leg	0.038	0.046	0	0	35
Esophagus Muscularis	0.037	0.046	0	0	12
Adipose Visceral Omentum	0.037	0.051	1	0	11
Thyroid	0.036	0.045	0	0	17
Ovary	0.035	0.070	6	0	7
Pituitary	0.034	0.064	4	0	0
Breast Mammary Tissue	0.034	0.040	0	0	10
Esophagus Mucosa	0.033	0.046	0	0	14
Brain Substantia nigra	0.030	0.068	8	0	1

Brain Cerebellum	0.030	0.049	1	0	1
Artery Aorta	0.028	0.048	0	0	4
Esophagus Gastroesophageal Junction	0.028	0.044	0	0	7
Colon Sigmoid	0.023	0.040	0	0	0
Prostate	0.023	0.051	3	0	3

Table A5. Heritability estimate results across PID pathways for GSVA scores. Rank by mean heritability from high to low.

	Mean	SE	num h2>0.25	num h2>0.5	num p<0.05
PID AURORA A PATHWAY	0.080	0.078	2	0	7
PID AR NONGENOMIC PATHWAY	0.074	0.081	3	0	1
PID IL12 STAT4 PATHWAY	0.074	0.084	3	0	3
PID BCR 5PATHWAY	0.073	0.084	2	0	2
PID ALK2 PATHWAY	0.072	0.090	4	0	4
PID IL4 2PATHWAY	0.070	0.089	1	1	3
PID BMP PATHWAY	0.070	0.084	2	0	3
PID P38 ALPHA BETA DOWNSTREAM PATHWAY	0.069	0.085	1	0	5
PID IL27 PATHWAY	0.068	0.064	1	0	1
PID THROMBIN PAR4 PATHWAY	0.066	0.083	3	0	3
PID IL23 PATHWAY	0.066	0.066	1	0	2
PID HDAC CLASSIII PATHWAY	0.066	0.088	1	0	4
PID LYSOPHOSPHOLIPID PATHWAY	0.065	0.091	2	0	6
PID TCR JNK PATHWAY	0.065	0.092	4	0	4
PID ATF2 PATHWAY	0.065	0.101	2	1	3
PID ER NONGENOMIC PATHWAY	0.064	0.072	0	0	1
PID LKB1 PATHWAY	0.064	0.081	0	0	4
PID CMYB PATHWAY	0.063	0.085	2	0	2
PID NCADHERIN PATHWAY	0.063	0.082	1	0	2
PID IL12 2PATHWAY	0.063	0.063	0	0	2
PID TCR PATHWAY	0.063	0.072	1	0	2
PID S1P S1P2 PATHWAY	0.063	0.072	0	0	3
PID MYC REPRESS PATHWAY	0.062	0.084	2	0	5
PID ERBB NETWORK PATHWAY	0.062	0.077	1	0	4
PID S1P S1P4 PATHWAY	0.061	0.067	0	0	4
PID EPHA FWDPATHWAY	0.061	0.075	2	0	1
PID FCER1 PATHWAY	0.061	0.079	2	0	2
PID HDAC CLASSII PATHWAY	0.061	0.079	2	0	5
PID CD8 TCR PATHWAY	0.060	0.076	2	0	3
PID P73PATHWAY	0.060	0.070	1	0	5

PID CD8 TCR DOWNSTREAM PATHWAY	0.060	0.067	1	0	4
PID IL8 CXCR2 PATHWAY	0.060	0.069	1	0	3
PID HNF3A PATHWAY	0.059	0.080	2	0	3
PID HES HEY PATHWAY	0.058	0.082	2	0	3
PID INTEGRIN4 PATHWAY	0.058	0.073	0	0	2
PID CASPASE PATHWAY	0.058	0.072	1	0	2
PID SMAD2 3NUCLEAR PATHWAY	0.058	0.076	1	0	3
PID DELTA NP63 PATHWAY	0.058	0.074	1	0	4
PID ALPHA SYNUCLEIN PATHWAY	0.058	0.076	1	0	4
PID TOLL ENDOGENOUS PATHWAY	0.058	0.079	3	0	4
PID NFAT TFPATHWAY	0.058	0.073	1	0	5
PID AMB2 NEUTROPHILS PATHWAY	0.058	0.073	1	0	4
PID ILK PATHWAY	0.057	0.075	1	0	5
PID FOXO PATHWAY	0.057	0.089	3	0	4
PID ARF6 DOWNSTREAM PATHWAY	0.057	0.080	1	0	5
PID FAS PATHWAY	0.057	0.091	3	0	1
PID THROMBIN PAR1 PATHWAY	0.056	0.082	1	0	6
PID RETINOIC ACID PATHWAY	0.056	0.074	1	0	4
PID BETA CATENIN NUC PATHWAY	0.056	0.119	1	1	2
PID HDAC CLASSI PATHWAY	0.056	0.096	1	1	4
PID INTEGRIN5 PATHWAY	0.055	0.079	1	0	4
PID ANTHRAX PATHWAY	0.055	0.076	1	0	3
PID AR TF PATHWAY	0.054	0.081	2	0	4
PID FOXM1 PATHWAY	0.054	0.067	1	0	5
PID P38 MK2 PATHWAY	0.054	0.095	2	1	3
PID SYNDECAN 4 PATHWAY	0.054	0.073	1	0	8
PID REELIN PATHWAY	0.053	0.072	1	0	1
PID MAPK TRK PATHWAY	0.053	0.067	0	0	0
PID IL6 7 PATHWAY	0.053	0.067	1	0	2
PID HEDGEHOG 2PATHWAY	0.053	0.084	2	0	2
PID EPHRINB REV PATHWAY	0.053	0.120	1	1	2
PID NETRIN PATHWAY	0.053	0.064	0	0	3
PID CIRCADIAN PATHWAY	0.053	0.069	1	0	2
PID INTEGRIN2 PATHWAY	0.053	0.083	1	0	4
PID RHODOPSIN PATHWAY	0.053	0.071	1	0	2
PID AVB3 INTEGRIN PATHWAY	0.053	0.065	1	0	3
PID NFKAPPAB CANONICAL PATHWAY	0.052	0.070	1	0	2
PID ANGIOPOIETIN RECEPTOR PATHWAY	0.052	0.069	2	0	1
PID RXR VDR PATHWAY	0.052	0.072	2	0	4
PID PDGFRA PATHWAY	0.051	0.075	1	0	4
PID IL1 PATHWAY	0.051	0.079	2	0	1
PID IL8 CXCR1 PATHWAY	0.051	0.067	1	0	1
PID RET PATHWAY	0.050	0.068	1	0	2

PID VEGFR1 PATHWAY	0.050	0.083	2	0	2
PID AP1 PATHWAY	0.050	0.061	0	0	1
PID NFAT 3PATHWAY	0.050	0.073	1	0	3
PID IL2 STAT5 PATHWAY	0.050	0.070	2	0	3
PID REG GR PATHWAY	0.050	0.086	2	0	5
PID RHOA PATHWAY	0.050	0.072	1	0	4
PID RHOA REG PATHWAY	0.050	0.069	1	0	3
PID LIS1 PATHWAY	0.050	0.065	1	0	3
PID RAC1 PATHWAY	0.050	0.058	1	0	1
PID INTEGRIN1 PATHWAY	0.049	0.069	0	0	4
PID KIT PATHWAY	0.049	0.073	1	0	1
PID INSULIN PATHWAY	0.049	0.085	2	0	1
PID TELOMERASE PATHWAY	0.049	0.080	3	0	2
PID TRKR PATHWAY	0.049	0.064	0	0	0
PID ERBB2 ERBB3 PATHWAY	0.049	0.087	1	1	1
PID CXCR3 PATHWAY	0.049	0.060	0	0	1
PID MYC PATHWAY	0.049	0.087	2	0	1
PID PI3KCI PATHWAY	0.048	0.064	1	0	1
PID PI3K PLC TRK PATHWAY	0.048	0.073	2	0	1
PID FAK PATHWAY	0.048	0.085	1	0	2
PID ECADHERIN KERATINOCYTE PATHWAY	0.048	0.055	0	0	3
PID AVB3 OPN PATHWAY	0.048	0.068	1	0	1
PID HNF3B PATHWAY	0.048	0.065	0	0	3
PID TRAIL PATHWAY	0.048	0.094	1	1	1
PID CDC42 REG PATHWAY	0.048	0.066	1	0	4
PID CD40 PATHWAY	0.048	0.067	1	0	4
PID HIF1A PATHWAY	0.048	0.072	1	0	2
PID PS1 PATHWAY	0.048	0.075	1	0	4
PID FRA PATHWAY	0.047	0.058	0	0	2
PID S1P S1P3 PATHWAY	0.047	0.072	2	0	4
PID EPO PATHWAY	0.047	0.070	1	0	1
PID CXCR4 PATHWAY	0.047	0.055	0	0	1
PID P38 MKK3 6PATHWAY	0.047	0.081	2	0	4
PID WNT CANONICAL PATHWAY	0.047	0.071	1	0	0
PID DNA PK PATHWAY	0.047	0.074	1	0	0
PID EPHA2 FWD PATHWAY	0.047	0.082	2	0	2
PID LPA4 PATHWAY	0.047	0.080	2	0	2
PID CDC42 PATHWAY	0.046	0.060	0	0	3
PID HIF1 TFPATHWAY	0.046	0.071	2	0	3
PID TXA2PATHWAY	0.046	0.064	1	0	6
PID IL5 PATHWAY	0.046	0.070	2	0	1
PID TCR CALCIUM PATHWAY	0.046	0.059	0	0	1
PID SYNDECAN 3 PATHWAY	0.046	0.086	3	0	3

PID SHP2 PATHWAY	0.046	0.061	0	0	2
PID INSULIN GLUCOSE PATHWAY	0.045	0.065	0	0	2
PID IL2 1PATHWAY	0.045	0.073	1	0	1
PID RAC1 REG PATHWAY	0.045	0.051	0	0	2
PID ENDOTHELIN PATHWAY	0.044	0.054	0	0	3
PID INTEGRIN CS PATHWAY	0.043	0.055	0	0	1
PID S1P S1P1 PATHWAY	0.043	0.064	1	0	2
PID ERBB1 DOWNSTREAM PATHWAY	0.043	0.064	0	0	0
PID S1P META PATHWAY	0.043	0.055	0	0	2
PID SMAD2 3PATHWAY	0.043	0.066	1	0	4
PID NFKAPPAB ATYPICAL PATHWAY	0.042	0.062	1	0	1
PID FGF PATHWAY	0.042	0.081	2	0	4
PID MYC ACTIV PATHWAY	0.042	0.069	1	0	0
PID TCR RAS PATHWAY	0.042	0.053	0	0	1
PID ERBB4 PATHWAY	0.042	0.067	1	0	2
PID HIF2PATHWAY	0.042	0.081	2	0	3
PID PI3KCI AKT PATHWAY	0.042	0.061	1	0	3
PID NEPHRIN NEPH1 PATHWAY	0.042	0.063	1	0	2
PID P53 DOWNSTREAM PATHWAY	0.041	0.049	0	0	2
PID GLYPICAN 1PATHWAY	0.041	0.068	1	0	4
PID WNT SIGNALING PATHWAY	0.041	0.071	1	0	1
PID TGFBR PATHWAY	0.041	0.067	1	0	2
PID A6B1 A6B4 INTEGRIN PATHWAY	0.041	0.064	0	0	2
PID MET PATHWAY	0.040	0.071	2	0	1
PID UPA UPAR PATHWAY	0.040	0.052	0	0	2
PID HEDGEHOG GLI PATHWAY	0.040	0.057	0	0	1
PID INTEGRIN3 PATHWAY	0.040	0.053	0	0	3
PID RANBP2 PATHWAY	0.040	0.059	1	0	2
PID ARF 3PATHWAY	0.040	0.060	0	0	3
PID ERBB1 RECEPTOR PROXIMAL PATHWAY	0.039	0.064	1	0	2
PID AJDISS 2PATHWAY	0.039	0.055	0	0	3
PID SYNDECAN 1 PATHWAY	0.039	0.049	0	0	1
PID ECADHERIN NASCENT AJ PATHWAY	0.039	0.061	0	0	1
PID PTP1B PATHWAY	0.039	0.051	0	0	0
PID AURORA B PATHWAY	0.039	0.057	1	0	0
PID INTEGRIN A4B1 PATHWAY	0.039	0.061	1	0	2
PID TAP63 PATHWAY	0.038	0.058	0	0	2
PID TCPTP PATHWAY	0.038	0.059	1	0	2
PID WNT NONCANONICAL PATHWAY	0.038	0.056	0	0	2
PID ERA GENOMIC PATHWAY	0.038	0.069	2	0	2
PID ECADHERIN STABILIZATION PATHWAY	0.038	0.066	0	0	2
PID GMCSF PATHWAY	0.037	0.059	1	0	0
PID RB 1PATHWAY	0.037	0.048	0	0	2

PID ARF6 TRAFFICKING PATHWAY	0.037	0.060	1	0	1
PID RAS PATHWAY	0.037	0.061	1	0	2
PID SYNDECAN 2 PATHWAY	0.037	0.055	1	0	1
PID CONE PATHWAY	0.037	0.058	0	0	1
PID ALK1 PATHWAY	0.036	0.069	1	0	3
PID PDGFRB PATHWAY	0.036	0.058	0	0	1
PID HIV NEF PATHWAY	0.036	0.054	0	0	0
PID ARF6 PATHWAY	0.035	0.052	0	0	2
PID IL2 PI3K PATHWAY	0.035	0.063	1	0	3
PID EPHB FWD PATHWAY	0.035	0.050	0	0	1
PID P38 ALPHA BETA PATHWAY	0.034	0.051	0	0	2
PID P75 NTR PATHWAY	0.034	0.047	0	0	1
PID P53 REGULATION PATHWAY	0.033	0.054	0	0	1
PID ERB GENOMIC PATHWAY	0.033	0.049	0	0	0
PID LYMPH ANGIOGENESIS PATHWAY	0.033	0.059	1	0	3
PID P38 GAMMA DELTA PATHWAY	0.033	0.050	0	0	3
PID MTOR 4PATHWAY	0.033	0.055	0	0	1
PID TNF PATHWAY	0.032	0.045	0	0	1
PID IFNG PATHWAY	0.032	0.047	0	0	0
PID PLK1 PATHWAY	0.031	0.051	0	0	2
PID ERBB1 INTERNALIZATION PATHWAY	0.030	0.052	0	0	2
PID INTEGRIN A9B1 PATHWAY	0.030	0.044	0	0	2
PID AR PATHWAY	0.029	0.049	0	0	0
PID VEGFR1 2 PATHWAY	0.029	0.049	0	0	1
PID NECTIN PATHWAY	0.029	0.045	0	0	1
PID NOTCH PATHWAY	0.029	0.047	0	0	1
PID E2F PATHWAY	0.029	0.062	1	0	2
PID VEGF VEGFR PATHWAY	0.028	0.051	0	0	2
PID PRL SIGNALING EVENTS PATHWAY	0.028	0.046	0	0	0
PID IL3 PATHWAY	0.028	0.052	1	0	0
PID IGF1 PATHWAY	0.027	0.069	1	0	1
PID ATM PATHWAY	0.027	0.045	0	0	1
PID CERAMIDE PATHWAY	0.025	0.051	0	0	0
PID BARD1 PATHWAY	0.024	0.048	0	0	0
PID BETA CATENIN DEG PATHWAY	0.023	0.047	0	0	1
PID FANCONI PATHWAY	0.016	0.038	0	0	1
PID ATR PATHWAY	0.013	0.032	0	0	0

Table A6. Heritability estimate results across BIOCARTA pathways for GSVA scores. Rank by mean heritability from high to low.

	Mean	SE	num h2>0.25	num h2>0.5	num p<0.05
BIOCARTA CSK PATHWAY	0.100	0.116	5	0	7
BIOCARTA TH1TH2 PATHWAY	0.095	0.081	0	0	7
BIOCARTA CARM1 PATHWAY	0.084	0.105	1	1	4
BIOCARTA LAIR PATHWAY	0.084	0.075	0	0	4
BIOCARTA IL5 PATHWAY	0.082	0.087	3	0	7
BIOCARTA ASBCELL PATHWAY	0.080	0.075	2	0	6
BIOCARTA BBCELL PATHWAY	0.080	0.079	1	0	7
BIOCARTA CYTOKINE PATHWAY	0.077	0.072	1	0	5
BIOCARTA INFLAM PATHWAY	0.075	0.068	0	0	6
BIOCARTA AHSP PATHWAY	0.075	0.113	3	1	2
BIOCARTA CALCINEURIN PATHWAY	0.074	0.104	3	0	4
BIOCARTA IL12 PATHWAY	0.074	0.084	2	0	5
BIOCARTA CIRCADIAN PATHWAY	0.074	0.083	3	0	4
BIOCARTA PGC1A PATHWAY	0.071	0.088	1	0	5
BIOCARTA FAS PATHWAY	0.070	0.091	3	0	3
BIOCARTA TOLL PATHWAY	0.070	0.081	2	0	5
BIOCARTA WNT PATHWAY	0.069	0.110	4	1	5
BIOCARTA FCER1 PATHWAY	0.069	0.087	3	0	3
BIOCARTA NDKDYNAMIN PATHWAY	0.069	0.082	3	0	5
BIOCARTA NKT PATHWAY	0.068	0.065	1	0	4
BIOCARTA TCR PATHWAY	0.068	0.086	3	0	2
BIOCARTA MYOSIN PATHWAY	0.068	0.089	4	0	4
BIOCARTA HDAC PATHWAY	0.068	0.101	3	0	5
BIOCARTA PS1 PATHWAY	0.068	0.107	3	0	3
BIOCARTA PAR1 PATHWAY	0.067	0.084	2	0	7
BIOCARTA AMAN PATHWAY	0.067	0.095	2	0	6
BIOCARTA CREM PATHWAY	0.066	0.117	2	1	4
BIOCARTA EOSINOPHILS PATHWAY	0.066	0.073	1	0	5
BIOCARTA STATHMIN PATHWAY	0.066	0.079	2	0	3
BIOCARTA NFAT PATHWAY	0.065	0.095	3	0	3
BIOCARTA CB1R PATHWAY	0.065	0.094	3	0	4
BIOCARTA CTBP1 PATHWAY	0.065	0.069	0	0	3
BIOCARTA TSP1 PATHWAY	0.064	0.073	2	0	7
BIOCARTA GATA3 PATHWAY	0.064	0.084	1	0	4
BIOCARTA FMLP PATHWAY	0.064	0.055	0	0	1
BIOCARTA RHO PATHWAY	0.064	0.073	1	0	3
BIOCARTA BLYMPHOCYTE PATHWAY	0.064	0.068	0	0	3
BIOCARTA DREAM PATHWAY	0.063	0.073	1	0	3
BIOCARTA TNFR1 PATHWAY	0.063	0.079	1	0	4
BIOCARTA BAD PATHWAY	0.063	0.094	2	0	4
BIOCARTA ETS PATHWAY	0.062	0.083	2	0	2

BIOCARTA RANKL PATHWAY	0.062	0.062	0	0	3
BIOCARTA ERBB4 PATHWAY	0.062	0.085	3	0	3
BIOCARTA GPCR PATHWAY	0.062	0.082	3	0	3
BIOCARTA COMP PATHWAY	0.062	0.085	1	0	4
BIOCARTA IL2 PATHWAY	0.061	0.082	2	0	3
BIOCARTA MRP PATHWAY	0.061	0.086	4	0	4
BIOCARTA ERYTH PATHWAY	0.061	0.070	1	0	1
BIOCARTA LYM PATHWAY	0.061	0.066	0	0	2
BIOCARTA BARRESTIN PATHWAY	0.060	0.076	2	0	3
BIOCARTA AGPCR PATHWAY	0.060	0.083	2	0	1
BIOCARTA CTLA4 PATHWAY	0.059	0.077	2	0	2
BIOCARTA CLASSIC PATHWAY	0.059	0.074	1	0	5
BIOCARTA SPRY PATHWAY	0.059	0.079	3	0	1
BIOCARTA ALK PATHWAY	0.059	0.084	2	0	3
BIOCARTA TCYTOTOXIC PATHWAY	0.059	0.072	1	0	5
BIOCARTA P38MAPK PATHWAY	0.058	0.065	0	0	2
BIOCARTA IL4 PATHWAY	0.058	0.087	1	0	4
BIOCARTA FLUMAZENIL PATHWAY	0.058	0.059	0	0	1
BIOCARTA DSP PATHWAY	0.058	0.074	2	0	3
BIOCARTA IL1R PATHWAY	0.058	0.064	0	0	3
BIOCARTA ATM PATHWAY	0.058	0.065	0	0	3
BIOCARTA NKCELLS PATHWAY	0.057	0.082	1	0	4
BIOCARTA LECTIN PATHWAY	0.057	0.076	2	0	4
BIOCARTA THELPER PATHWAY	0.057	0.066	0	0	4
BIOCARTA GCR PATHWAY	0.057	0.105	1	1	2
BIOCARTA NO1 PATHWAY	0.057	0.078	2	0	2
BIOCARTA PKC PATHWAY	0.057	0.077	1	0	5
BIOCARTA P53HYPOXIA PATHWAY	0.057	0.070	0	0	5
BIOCARTA PEPI PATHWAY	0.057	0.081	2	0	3
BIOCARTA ACH PATHWAY	0.057	0.071	1	0	1
BIOCARTA LDL PATHWAY	0.056	0.077	2	0	4
BIOCARTA NO2IL12 PATHWAY	0.056	0.069	1	0	2
BIOCARTA P35ALZHEIMERS PATHWAY	0.056	0.074	1	0	4
BIOCARTA BCR PATHWAY	0.056	0.066	1	0	1
BIOCARTA EPHA4 PATHWAY	0.056	0.082	3	0	3
BIOCARTA STEM PATHWAY	0.056	0.063	0	0	2
BIOCARTA BCELLSURVIVAL PATHWAY	0.056	0.088	1	1	2
BIOCARTA AKAPCENTROSOME PATHWAY	0.055	0.064	1	0	1
BIOCARTA VIP PATHWAY	0.055	0.084	1	0	2
BIOCARTA AGR PATHWAY	0.055	0.073	1	0	4
BIOCARTA AKAP13 PATHWAY	0.055	0.074	2	0	3
BIOCARTA SAM68 PATHWAY	0.055	0.067	0	0	0
BIOCARTA FREE PATHWAY	0.055	0.064	0	0	3

BIOCARTA MPR PATHWAY	0.054	0.080	2	0	4
BIOCARTA EICOSANOID PATHWAY	0.054	0.070	1	0	2
BIOCARTA ARENRF2 PATHWAY	0.054	0.078	2	0	1
BIOCARTA TGFB PATHWAY	0.054	0.074	1	0	1
BIOCARTA NTHI PATHWAY	0.054	0.062	0	0	1
BIOCARTA ETC PATHWAY	0.054	0.066	0	0	1
BIOCARTA NPP1 PATHWAY	0.054	0.081	1	0	4
BIOCARTA MALATEX PATHWAY	0.054	0.077	3	0	0
BIOCARTA TPO PATHWAY	0.053	0.070	1	0	2
BIOCARTA CD40 PATHWAY	0.053	0.059	0	0	1
BIOCARTA IL2RB PATHWAY	0.053	0.075	1	0	2
BIOCARTA GRANULOCYTES PATHWAY	0.052	0.059	0	0	2
BIOCARTA CARM ER PATHWAY	0.052	0.065	0	0	2
BIOCARTA REELIN PATHWAY	0.052	0.085	3	0	7
BIOCARTA IL10 PATHWAY	0.052	0.056	0	0	3
BIOCARTA MITOCHONDRIA PATHWAY	0.052	0.077	2	0	4
BIOCARTA PLCD PATHWAY	0.052	0.086	2	0	2
BIOCARTA INTRINSIC PATHWAY	0.052	0.069	1	0	3
BIOCARTA AKT PATHWAY	0.052	0.091	2	0	3
BIOCARTA BARR MAPK PATHWAY	0.052	0.084	2	0	5
BIOCARTA NOS1 PATHWAY	0.052	0.081	1	0	1
BIOCARTA CCR5 PATHWAY	0.052	0.072	0	0	2
BIOCARTA MEF2D PATHWAY	0.052	0.066	1	0	2
BIOCARTA PARKIN PATHWAY	0.052	0.071	1	0	3
BIOCARTA RACC PATHWAY	0.051	0.080	1	0	1
BIOCARTA MHC PATHWAY	0.051	0.060	0	0	5
BIOCARTA CK1 PATHWAY	0.051	0.070	0	0	3
BIOCARTA IL17 PATHWAY	0.051	0.071	2	0	2
BIOCARTA BARRESTIN SRC PATHWAY	0.051	0.078	2	0	4
BIOCARTA PRC2 PATHWAY	0.051	0.059	0	0	1
BIOCARTA CCR3 PATHWAY	0.051	0.068	1	0	1
BIOCARTA PRION PATHWAY	0.051	0.070	1	0	3
BIOCARTA DICER PATHWAY	0.051	0.071	2	0	4
BIOCARTA CACAM PATHWAY	0.051	0.072	1	0	2
BIOCARTA PPARG PATHWAY	0.051	0.077	1	0	2
BIOCARTA CDK5 PATHWAY	0.051	0.060	0	0	3
BIOCARTA HIF PATHWAY	0.050	0.068	1	0	2
BIOCARTA TCRA PATHWAY	0.050	0.055	0	0	1
BIOCARTA TERT PATHWAY	0.050	0.074	1	0	4
BIOCARTA BIOPEPTIDES PATHWAY	0.050	0.077	2	0	1
BIOCARTA ALTERNATIVE PATHWAY	0.050	0.078	1	0	2
BIOCARTA IGF1 PATHWAY	0.050	0.073	1	0	2
BIOCARTA TFF PATHWAY	0.050	0.065	0	0	3

BIOCARTA CASPASE PATHWAY	0.050	0.058	0	0	2
BIOCARTA PITX2 PATHWAY	0.050	0.070	1	0	2
BIOCARTA DC PATHWAY	0.050	0.060	0	0	2
BIOCARTA UCALPAIN PATHWAY	0.050	0.071	1	0	2
BIOCARTA SRCRPTP PATHWAY	0.050	0.064	0	0	4
BIOCARTA MCALPAIN PATHWAY	0.050	0.079	2	0	4
BIOCARTA ACE2 PATHWAY	0.049	0.074	1	0	3
BIOCARTA CELL2CELL PATHWAY	0.049	0.084	2	0	3
BIOCARTA ACTINY PATHWAY	0.049	0.078	2	0	3
BIOCARTA PELP1 PATHWAY	0.049	0.064	0	0	3
BIOCARTA SHH PATHWAY	0.049	0.074	1	0	2
BIOCARTA VOBESITY PATHWAY	0.049	0.072	2	0	2
BIOCARTA DEATH PATHWAY	0.049	0.063	0	0	5
BIOCARTA CTL PATHWAY	0.049	0.056	0	0	1
BIOCARTA BTG2 PATHWAY	0.049	0.060	0	0	2
BIOCARTA MONOCYTE PATHWAY	0.049	0.056	0	0	1
BIOCARTA LYMPHOCYTE PATHWAY	0.048	0.050	0	0	0
BIOCARTA IL22BP PATHWAY	0.048	0.071	1	0	3
BIOCARTA HSP27 PATHWAY	0.048	0.056	0	0	3
BIOCARTA PDZS PATHWAY	0.048	0.073	1	0	1
BIOCARTA MITR PATHWAY	0.048	0.073	2	0	2
BIOCARTA LIS1 PATHWAY	0.048	0.059	0	0	3
BIOCARTA ACETAMINOPHEN PATHWAY	0.047	0.062	0	0	5
BIOCARTA BOTULIN PATHWAY	0.047	0.049	0	0	2
BIOCARTA IL3 PATHWAY	0.047	0.084	1	0	2
BIOCARTA RAS PATHWAY	0.047	0.074	1	0	1
BIOCARTA LEPTIN PATHWAY	0.047	0.067	1	0	3
BIOCARTA STRESS PATHWAY	0.047	0.060	1	0	0
BIOCARTA MET PATHWAY	0.047	0.071	1	0	0
BIOCARTA EFP PATHWAY	0.047	0.072	1	0	1
BIOCARTA MCM PATHWAY	0.047	0.090	2	0	1
BIOCARTA MTA3 PATHWAY	0.047	0.063	1	0	4
BIOCARTA TCAPOPTOSIS PATHWAY	0.047	0.061	1	0	1
BIOCARTA CARDIACEGF PATHWAY	0.047	0.051	0	0	1
BIOCARTA MELANOCYTE PATHWAY	0.047	0.057	0	0	1
BIOCARTA GABA PATHWAY	0.046	0.054	0	0	1
BIOCARTA CXCR4 PATHWAY	0.046	0.080	1	0	3
BIOCARTA MAL PATHWAY	0.046	0.064	0	0	1
BIOCARTA PTEN PATHWAY	0.046	0.070	1	0	1
BIOCARTA PPARA PATHWAY	0.046	0.058	0	0	1
BIOCARTA SPPA PATHWAY	0.046	0.062	1	0	1
BIOCARTA CDC25 PATHWAY	0.046	0.069	1	0	4
BIOCARTA PML PATHWAY	0.046	0.061	0	0	3

BIOCARTA TALL1 PATHWAY	0.046	0.064	1	0	2
BIOCARTA PLATELETAPP PATHWAY	0.045	0.053	0	0	1
BIOCARTA FOSB PATHWAY	0.045	0.064	0	0	0
BIOCARTA GLEEVEC PATHWAY	0.045	0.106	1	1	0
BIOCARTA INSULIN PATHWAY	0.045	0.077	1	0	3
BIOCARTA HIVNEF PATHWAY	0.045	0.052	0	0	0
BIOCARTA RHODOPSIN PATHWAY	0.045	0.055	0	0	0
BIOCARTA RANBP2 PATHWAY	0.045	0.070	1	0	0
BIOCARTA PTDINS PATHWAY	0.045	0.077	1	0	4
BIOCARTA ERAD PATHWAY	0.045	0.056	0	0	3
BIOCARTA SALMONELLA PATHWAY	0.045	0.062	0	0	2
BIOCARTA ERBB3 PATHWAY	0.045	0.068	0	0	2
BIOCARTA P27 PATHWAY	0.045	0.080	2	0	3
BIOCARTA DNAFRAGMENT PATHWAY	0.045	0.072	1	0	3
BIOCARTA 41BB PATHWAY	0.045	0.054	0	0	3
BIOCARTA EDG1 PATHWAY	0.044	0.061	1	0	2
BIOCARTA CHEMICAL PATHWAY	0.044	0.067	1	0	2
BIOCARTA TID PATHWAY	0.044	0.056	0	0	1
BIOCARTA RECK PATHWAY	0.044	0.061	1	0	3
BIOCARTA D4GDI PATHWAY	0.044	0.052	0	0	2
BIOCARTA SKP2E2F PATHWAY	0.044	0.069	1	0	1
BIOCARTA RACCYCD PATHWAY	0.044	0.062	0	0	3
BIOCARTA NGF PATHWAY	0.044	0.073	1	0	3
BIOCARTA RARRXR PATHWAY	0.044	0.066	1	0	2
BIOCARTA PLCE PATHWAY	0.044	0.061	1	0	1
BIOCARTA ERK5 PATHWAY	0.044	0.060	1	0	1
BIOCARTA RB PATHWAY	0.044	0.059	0	0	2
BIOCARTA G2 PATHWAY	0.044	0.057	0	0	1
BIOCARTA EPO PATHWAY	0.043	0.058	0	0	2
BIOCARTA MSP PATHWAY	0.043	0.052	0	0	0
BIOCARTA CDMAC PATHWAY	0.043	0.060	1	0	2
BIOCARTA SLRP PATHWAY	0.043	0.063	1	0	2
BIOCARTA RELA PATHWAY	0.043	0.057	0	0	1
BIOCARTA IL7 PATHWAY	0.042	0.066	1	0	1
BIOCARTA EPONFKB PATHWAY	0.042	0.061	0	0	3
BIOCARTA AT1R PATHWAY	0.042	0.059	1	0	1
BIOCARTA VITCB PATHWAY	0.042	0.062	1	0	4
BIOCARTA AMI PATHWAY	0.042	0.061	1	0	2
BIOCARTA SET PATHWAY	0.042	0.061	0	0	5
BIOCARTA PYK2 PATHWAY	0.041	0.056	0	0	0
BIOCARTA SODD PATHWAY	0.041	0.047	0	0	0
BIOCARTA VEGF PATHWAY	0.041	0.079	2	0	1
BIOCARTA RAB PATHWAY	0.040	0.062	1	0	2

BIOCARTA CREB PATHWAY	0.040	0.056	0	0	1
BIOCARTA HER2 PATHWAY	0.040	0.071	1	0	1
BIOCARTA NFKB PATHWAY	0.040	0.053	0	0	1
BIOCARTA CHREBP PATHWAY	0.040	0.051	0	0	0
BIOCARTA PLC PATHWAY	0.040	0.062	1	0	0
BIOCARTA STAT3 PATHWAY	0.039	0.050	0	0	1
BIOCARTA NEUTROPHIL PATHWAY	0.039	0.048	0	0	1
BIOCARTA PLK3 PATHWAY	0.039	0.068	1	0	4
BIOCARTA TEL PATHWAY	0.039	0.058	0	0	1
BIOCARTA MAPK PATHWAY	0.039	0.051	0	0	1
BIOCARTA GSK3 PATHWAY	0.039	0.061	1	0	1
BIOCARTA SM PATHWAY	0.039	0.072	2	0	0
BIOCARTA HBX PATHWAY	0.038	0.064	1	0	0
BIOCARTA HES PATHWAY	0.038	0.069	1	0	1
BIOCARTA NUCLEARRS PATHWAY	0.038	0.066	1	0	2
BIOCARTA NOTCH PATHWAY	0.038	0.075	2	0	1
BIOCARTA ECM PATHWAY	0.038	0.060	1	0	2
BIOCARTA PDGF PATHWAY	0.038	0.053	0	0	2
BIOCARTA CELLCYCLE PATHWAY	0.038	0.051	0	0	2
BIOCARTA HCMV PATHWAY	0.038	0.079	2	0	0
BIOCARTA TNFR2 PATHWAY	0.038	0.046	0	0	0
BIOCARTA EEA1 PATHWAY	0.038	0.054	0	0	2
BIOCARTA EGF PATHWAY	0.038	0.055	0	0	2
BIOCARTA INTEGRIN PATHWAY	0.038	0.068	1	0	2
BIOCARTA LONGEVITY PATHWAY	0.038	0.052	0	0	1
BIOCARTA PCAF PATHWAY	0.037	0.055	1	0	0
BIOCARTA PTC1 PATHWAY	0.037	0.059	0	0	2
BIOCARTA ATRBRCA PATHWAY	0.037	0.055	0	0	1
BIOCARTA SUMO PATHWAY	0.037	0.049	0	0	0
BIOCARTA IFNG PATHWAY	0.037	0.055	0	0	3
BIOCARTA SARS PATHWAY	0.036	0.056	1	0	3
BIOCARTA IGF1R PATHWAY	0.036	0.061	1	0	2
BIOCARTA CPSF PATHWAY	0.036	0.047	0	0	4
BIOCARTA CDC42RAC PATHWAY	0.036	0.053	0	0	2
BIOCARTA RNAPOL3 PATHWAY	0.036	0.065	1	0	1
BIOCARTA CFTR PATHWAY	0.036	0.059	0	0	2
BIOCARTA IL6 PATHWAY	0.036	0.047	0	0	2
BIOCARTA RNA PATHWAY	0.036	0.061	1	0	0
BIOCARTA BARD1 PATHWAY	0.036	0.056	1	0	1
BIOCARTA CBL PATHWAY	0.036	0.062	0	0	1
BIOCARTA TOB1 PATHWAY	0.036	0.060	1	0	1
BIOCARTA TERC PATHWAY	0.035	0.062	1	0	2
BIOCARTA GH PATHWAY	0.035	0.056	0	0	1

BIOCARTA IGF1MTOR PATHWAY	0.035	0.067	1	0	0
BIOCARTA P53 PATHWAY	0.035	0.062	2	0	0
BIOCARTA WNT LRP6 PATHWAY	0.035	0.054	1	0	0
BIOCARTA EXTRINSIC PATHWAY	0.034	0.064	1	0	2
BIOCARTA CTCF PATHWAY	0.034	0.048	0	0	0
BIOCARTA GHRELIN PATHWAY	0.034	0.052	0	0	1
BIOCARTA TRKA PATHWAY	0.034	0.050	0	0	1
BIOCARTA TUBBY PATHWAY	0.034	0.049	0	0	2
BIOCARTA IFNA PATHWAY	0.034	0.057	0	0	1
BIOCARTA KERATINOCYTE PATHWAY	0.033	0.050	0	0	0
BIOCARTA FIBRINOLYSIS PATHWAY	0.033	0.066	1	0	1
BIOCARTA ARAP PATHWAY	0.032	0.056	0	0	3
BIOCARTA G1 PATHWAY	0.032	0.051	0	0	0
BIOCARTA NPC PATHWAY	0.032	0.063	2	0	1
BIOCARTA ERK PATHWAY	0.032	0.053	0	0	4
BIOCARTA EIF4 PATHWAY	0.031	0.049	0	0	2
BIOCARTA FBW7 PATHWAY	0.031	0.050	0	0	1
BIOCARTA VDR PATHWAY	0.031	0.040	0	0	0
BIOCARTA EIF2 PATHWAY	0.030	0.053	0	0	0
BIOCARTA EGFR SMRTE PATHWAY	0.029	0.054	0	0	0
BIOCARTA RAN PATHWAY	0.029	0.050	1	0	0
BIOCARTA MTOR PATHWAY	0.028	0.050	0	0	1
BIOCARTA ION PATHWAY	0.026	0.043	0	0	0
BIOCARTA RANMS PATHWAY	0.026	0.042	0	0	0
BIOCARTA RAC1 PATHWAY	0.025	0.038	0	0	1
BIOCARTA ARF PATHWAY	0.024	0.051	1	0	2
BIOCARTA CERAMIDE PATHWAY	0.024	0.056	1	0	1
BIOCARTA S1P PATHWAY	0.024	0.046	0	0	0
BIOCARTA FXR PATHWAY	0.024	0.040	0	0	2
BIOCARTA HSWI SNF PATHWAY	0.023	0.047	0	0	0
BIOCARTA IRES PATHWAY	0.022	0.041	0	0	1
BIOCARTA AKAP95 PATHWAY	0.021	0.067	1	0	0
BIOCARTA EIF PATHWAY	0.021	0.035	0	0	1