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Taylor Lane Chambers Date

Effects of Low Calcium, Immune, and Endocrine Factors on Maladaptive Behavioral Problems in Patients with 22q11 Deletion Syndrome

By

Taylor Lane Chambers

MPH

Epidemiology

_____

Bradley Pearce, PhD

Faculty Thesis Advisor

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By

Taylor Lane Chambers

B.S.P.H.

Tulane University

2014

Faculty Thesis Advisor: Bradley Pearce, PhD

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ABSTRACT

Effects of Low Calcium, Immune, and Endocrine Factors on Maladaptive Behavioral Problems in Patients with 22q11 Deletion Syndrome

By Taylor Chambers

Background: 22q11DS is a common chromosomal abnormality associated with a large number of somatic manifestations and cognitive delays. Dysgenesis of the parathyroid gland is a common complication that leads to hypocalcaemia. Previous studies suggest that low calcium during brain development can negatively impact behavioral outcomes. However, the association has not been well studied and often does not account for possible confounding by other common abnormalities. The impact of immune and endocrine factors will be studied in combination with the effect of calcium of behavioral outcomes.

Methods: A retrospective cohort study was conducted utilizing information from Children's Healthcare of Atlanta 22q11 clinic and information maintained separately in a REDCap database. Immune, endocrine, and serum albumin-adjusted calcium values were pulled from CHOA in August 2015. This information was combined with select psychological assessments within REDCap.

Results and Discussion: Inverse correlations were found between calcium and Aberrant Behavior Checklist Irritability subscale ($F=4.86$, $p=0.0474$) and the Aberrant Behavior Checklist Stereotypy subscale ($F=4.36$, $p=0.0580$). No other significant relationships were found. Small sample sizes limited analyses.

Conclusions: In this sample of children with 22q11 deletion syndrome, lower calcium levels were associated with a greater number of problems in the areas of irritability and stereotypy. Further analysis is needed in order to determine the tease out specific relationships. Future studies with greater sample sizes may be more conclusive to confounding effects of various immune and endocrine factors not able to be seen in this analysis.

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INTRODUCTION

Chromosome 22q11.2 deletion syndrome, also known as 22q11DS, DiGeorge syndrome, and velocardiofacial syndrome is a chromosomal abnormality occurring in approximately 1 in 2000 to 1 in 4000 live births, making it fairly common (Robin & Shprintzen, 2005 and McDonald-McGinn & Sullivan, 2011). 22q11DS is associated with a range of somatic manifestations, cognitive delays, and an increasing number of psychiatric and behavioral problems (McDonald-McGinn & Sullivan, 2011). While the exact mechanism for why those with 22q11DS have apparent higher rates of maladaptive behavioral problems is unknown, speculation and research point to prenatal and neonatal calcium deficiencies among other endocrine and immune abnormalities as a possible reason why.

Dysgenesis of the parathyroid gland is a common complication that leads to hypocalcaemia (Hay, 2007). Low calcium levels can have an adverse effect on early brain development (Freitas de Mattos et al., 2014). The connection between these calcium regulatory abnormalities and behavioral outcomes has not been well studied. Association analyses suggest that the severity of hypocalcaemia in these patients is a predictor of social communication deficits, but it is unknown whether this is a causal relationship (Hay, 2007). Specifically, the association between hypocalcaemia and behavioral symptoms may be confounded by other somatic illnesses in 22q11DS (thymus hypoplasia, thyroid abnormalities) that can co-occur with the parathyroid hormone deficiency and could also influence brain development and behavior.

Understanding the interaction between calcium, immune, and endocrine factors in relation to Autism Spectrum Disorders (ASD), prodromal psychosis, and maladaptive behavioral problems can be looked at to help understand the mechanisms of disease of these deficiencies overall, in addition to better understanding behavior in patients with 22q11DS.

BACKGROUND

22q11 Deletion Syndrome

22q11DS is a common deletion caused by mispairing of the low copy number repeats and unequal crossing over in blocks A-D (McDonald-McGinn & Sullivan, 2011). There are no known differences in the deletion affecting various ethnic groups or genders differently; however, the incidence of the deletion is suspected to rise as half of all children of affected adults will have the same deletion (McDonald-McGinn & Sullivan, 2011). The true prevalence of 22q11DS is impossible to know as the only way to diagnose is through screenings not routinely done (Oskarsdottir, Vujic & Fasth, 2003). Prevalence information would have to be obtained using population level screenings, which is impractical. Current prevalence estimates fluctuate so greatly as a result of greater area knowledge in some cases and ignorance in others as to the deletion, rather than actual changes in prevalence (Oskarsdottir, Vujic & Fasth, 2003).

Before modern technology, prenatal ultrasounds, kayotyping via microscopy, and examination of physical characterizations after birth could be reviewed to diagnose DiGeorge syndrome. However, this deletion is usually submicroscopic, and not all anomalies are present in all cases, so utilization of Fluorescence in situ hybridization (FISH) is the modern day gold standard and only way to confirm 22q11DS (Antshel et al., 2005).

Somatic Symptoms of 22q11DS

22q11DS is commonly known for the clinical manifestations seen. Such physical ailments include palate, craniofacial, and cardiac malformations, low calcium levels, kidney problems, difficulty fighting infections, velopharyngeal insufficiencies, feeding difficulties, and hearing loss (Robin & Shprintzen, 2005 and Antshel et al., 2005). Over 75% of people with 22q11DS have any cardiac anomaly, the most common of which include ventricular septal

defects, interrupted aortic arch, and tetralogy of fallot. Around half of this population also experience some sort of palatal defect, and over 75% have an immune deficiency (McDonald-McGinn & Sullivan, 2011). However, not all people with 22q11DS have these physical anomalies nor does everyone with some combination of these symptoms have 22q11DS. While DiGeorge syndrome can be diagnosed clinically, one must have the chromosomal deletion in order to be diagnosed with 22q11DS (Yakut et al., 2006).

The only way to measure the deletion is to perform FISH (Robin & Shprintzen, 2005). While used interchangeably in this thesis, it's possible that some people with DiGeorge syndrome do not have this deletion (Scrambler, 2000; Yakut, 2006). Additionally, previous research often groups them together and uses them interchangeably. It is beyond the scope of this thesis to differentiate between the two. Since 22q11DS can only be diagnosed with a specialized molecular test, to better understand the nuances between DiGeorge syndrome and 22q11DS, more molecular testing would need to be done.

This study aims to examine the role of low calcium levels, problems with the thyroid, and thymus deficiencies. Hypocalcaemia occurs in nearly 75% of children with 22q11DS (McDonald-McGinn & Sullivan, 2011). Calcium is regulated through three main hormones - calcitonin, vitamin D, and parathyroid hormone (PTH) (Fong & Khan, 2012). In order to diagnose hypocalcemia, a value corrected for albumin levels must first be obtained, then the corrected serum calcium levels must be less than 2.12 mmol/L (Fong & Khan, 2012). Hypoparathyroidism is indicated by parathyroid hormone of less than 10 pg/ml (Choi et al., 2004).

Maladaptive Behavioral Problems of 22q11DS

22q11DS has been associated with a higher prevalence than the general population for a number of psychiatric and behavioral problems. These range from psychosis to ASD. ASD references a group of developmental disorders that reference a spectrum of delays and problems impacting ability social communication. Such diagnoses that fall under this spectrum include Autistic Disorder, Asperger's syndrome, and other pervasive developmental disorders not otherwise specified (NIMH, 2016). The Centers for Disease Control and Prevention estimate that approximately 1 in 68 children have been diagnosed with ASD, and note that a higher prevalence seems to occur in people with genetic or chromosomal conditions (Data & Statistics, 2016). ASD and Attention Deficit Hyperactivity Disorder (AD/HD) have a prevalence of around 20-50% in people with the deletion (Vorstman et al., 2006 and McDonald-McGinn & Sullivan, 2011).

In a study of 60 children conducted by Vorstman et al. (2006), 2/3 of the population had been diagnosed with any type of psychiatric disorder (including ASD and AD/HD). Psychosis was found to be the second leading psychiatric condition (after ASD), and became more prominent when investigators examined symptoms of psychosis outside of a strict diagnosis. According to McDonald-McGinn and Sullivan (2011), as high as 25% of people with this deletion may be living with schizophrenia. While this statistic may be an overestimation, compared to the general population where prevalence is less than 1%, it is especially alarming (Radoeva et al., 2016). More research needs to be done to establish differences from the population without such a deletion to highlight where cognitive and behavioral problems are most prominent; therefore, better understanding mental illness itself and lining up a future better able to manage symptoms within this cohort.

Importance of Current Project and Hypotheses

Little research has been conducted to determine if there is a correlation between hypoparathyroidism (as manifested by low levels of parathyroid hormone or hypocalcaemia) and thymus hypoplasia (as manifested by T cell lymphopenia). Moreover, the relationship between parathyroid hormone deficiency and thyroid abnormalities in 22q11DS has received little specific consideration. The overall goal of this thesis is to clarify the relationships between parathyroid abnormalities, hypocalcaemia, thymus and thyroid abnormalities, and behavioral outcomes in persons with 22q11DS.

Given the role of calcium and parathyroid hormone in brain development and function, as well as the known effects of thyroid hormone and immune responses on neuropsychiatric morbidity, the 22q11DS serves as an important disorder to examine the relationship of these somatic morbidities to ASD-like behaviors and prodromal psychosis. This leads to the following hypotheses to consider:

Primary: From a subcohort with endocrine or immune factors data available, examine the correlation with behavioral outcomes including ASD-like, prodromal psychosis, and maladaptive behavioral measures.

Secondary: Test the hypothesis that hypoparathyroidism and hypocalcaemia are associated with a greater likelihood to have thymic defects or low levels of thyroid hormones.

METHODS

Recruitment and the SERPh22 Database

The Children's Healthcare of Atlanta (CHOA) formed a specialty clinic in 1995 to better serve patients with DiGeorge syndrome. Recruitment for the cohort was done through this specialty clinic and its various components. The specialty clinic is comprised of the Marcus and Emory Autism Centers, Sibley Heart Center, Emory Department of Genetics, Children's Healthcare of Atlanta, and the Emory Children's Center. Recruitment was completed by Opal Ousley, PhD, Joseph Cubells, MD, PhD, Samuel Fernandez-Caribba, PhD, Matthew Oster, MD, MPH, Karlene Coleman, RN, MN, CGC, and Lisa Kobrynski, MD, MPH, respectively with both Dr. Cubells and Ms. Coleman recruiting through the Department of Genetics. The REDCap (Research Electronic Data Capture) database containing the SERPh22 information was created by Dr. Brad Pearce and maintained in part by the aforementioned individuals and other various graduate students.

Data Mining

In partnership with CHOA, electronic medical records were mined to obtain more information about the cohort. Such information included additional calcium levels, albumin, other immunologic and endocrine data, and information on cardiac surgeries and scans noting thymus development where available. Keywords were tabulated for values of interest and additional data was pulled where medical records were available (appendix 1). This would not have been possible without Tal Senior, RN and Craig Buchanan. Of the 709 individuals in the SERPh22 database, medical records were available for 621 patients (87.6%).

SERPh22 Database Information

The SERPh22 database is housed within the Emory REDCap system and confidentially maintains all information on study participants. As of early Fall 2015 when data were abstracted, there was data on 709 individuals. Gender distribution is roughly equal with 340 females, 346 males, and 23 without information on gender. The cohort is predominantly made up of white (n = 215) participants followed by black or African American (n = 107) participants. Two participants reported being American Indian or Alaskan Native, 19 were Asian, one was Native Hawaiian or other Pacific Islander, and 43 people identified as Hispanic – two of whom also identified as black or African American, and 1 who also identified as Asian. Race is unknown on 343 people. Of the 709 subjects, 663 are considered to be currently living based on available data. Of those, the average age 13.8 years old with a minimum age of 0 years old and a maximum age of 59 years old.

Calcium homeostasis

Calcium and albumin results were obtained through the data mining of electronic medical records. Albumin levels were obtained as an indication of protein levels within the blood. Previous studies have shown that low protein may erroneously cause calcium levels to look low (Takano et al., 2012). Corrected calcium levels were available for 355 individuals out of 419 total people for whom calcium alone was available (Calcium Correction for Hypoalbuminemia Medical Calculator, 2012). The lowest calcium for which an albumin value was available was chosen for each individual for further analysis.

Other Immune Factors

As part of better understanding the interrelationship between thyroid and thymic abnormalities with hypocalcaemia and behavioral outcomes, part of the data pull from medical records included information on these various endocrine and immune factors. Of the 249 IgG

values found, 208 were also linked to a corrected calcium level; 177 of the 214 IgA values linked, 188 of the 224 IgM levels linked, 100 of the 140 PTH results linked, 183 of the 228 T4 values linked, 248 of the 291 phosphorous results linked, and 14 of the 16 TSH values could be linked to a patient that also had a corrected calcium value calculated.

Information on thymus was obtained through screening of medical records looking for surgical encounters related to the heart and imaging of the area. Notes that mentioned thymus and misspellings of thymus were captured. Notes were then combed through and thymus status was coded as currently having thymus, never having thymus, and thymus was removed during surgery. Of the cohort, only 80 patients had information from thymus obtained, 72 of those also had information available on corrected calcium values. In cases where thymus information was discrepant, date of encounter and type (surgery vs. image alone) was taken into account (n = 24).

While the intent of this thesis is to be able to examine corrected calcium with PTH, TSH, and the aforementioned immune values, low sample sizes of available data may prevent in-depth data analysis.

Neuropsychological Assessments

Psychological, cognitive, and developmental assessments were administered at the Marcus and Emory Autism Centers through trained professionals under the guide of Dr. Ousley and Dr. Fernandez-Carriba. Assessments included clinical evaluation, other-report questionnaires and checklists (completed by parents or guardian), and interviews of caretakers. Assessments related to behavioral outcomes have been included as primary outcome variables of interest. Subscales of assessments will be broken out in order to best understand nuances in associations. Complete information on assessments administered to the cohort and specifics of assessments included in this analysis can be found in Tables 2 and 3, respectively.

Abberrant Behavior Checklist (ABC)

This checklist includes five-factor scales for 58 items under the categories of 1) Irritability, Agitation, Crying; 2) Lethargy, Social Withdrawal; 3) Stereotypic Behavior; 4) Hyperactivity, Noncompliance; and 5) Inappropriate Speech. It is validated for people aged 6-54 years old, and should be administered by a parent, guardian, or other adult who knows the child or person well.

Adaptive Behavior Assessment System (ABAS)

This assessment is designed specifically for children as early as birth through persons 89 years of age. The kit assesses conceptual, social, and practical areas of adaptive behavior. It looks how individuals respond to daily demands and how they may benefit from treatment. This system should be administered by parents, teachers, or other caregivers.

Autism Diagnostic Interview-Revised (ADI-R)

This interview is validated for diagnosing Autism and distinguishing it from other developmental disorders. It can be used for children or adults with a mental age above 2 years old. A clinical interviewer asks questions of a parent or care taker to obtain necessary information. The 93 interview questions focus on 1) language and communication; 2) reciprocal social interactions; and 3) restricted, repetitive, and stereotyped behaviors and interests.

Autism Diagnostic Observation Schedule (ADOS)

ADOS is a semi-structured assessment of communication, social interaction, and play. It is intended to evaluate those suspected of having autism or other pervasive developmental disorders. Clinicians observe children in 30-45 minute sessions and record their behavior and interests.

Child Behavior Checklist (CBCL)

This is also a parent-report questionnaire. It looks at rating a child aged 2 to 18 years of age on maladaptive behavioral and emotional problems. It assesses both internalizing problems such as anxious, depressive, and overcontrolled, and externalizing problems such as aggressive, hyperactive, noncompliant, and undercontrolled.

Prodromal Questionnaire - Brief (PQ-B)

The Prodromal Questionnaire is a brief screener intended to look for psychosis and risk syndromes. It is a self-report screener valid for adolescents and young adults. It is composed of 92 items and is highly sensitive but lacks specificity. With measuring prodromal symptoms, it's important to note that not all warning signs will lead to psychosis and it's not a measure of future risk.

Study Population

While previous research has highlighted clinical problems among infants, toddlers, and younger children, little research has been done in the area of adolescence and adulthood. Since this cohort is recruited from children in the Southeast, adults are not routinely followed up.. Additionally, many of the assessments and data collection measures have started in more recent

years, thus making it unavailable for those over 18. The purpose of this study is to better examine outcomes in adolescents.

While the database has a wealth of information on patient demographics, diagnoses, family history of 22q11DS, clinical, and psychological outcomes, limits to the sample size for this thesis were made upon obtainment of medical record to link to immune and endocrine outcomes and then the availability of the data within the electronic medical record (Figure 1).

Statistical Methods

All analyses were conducted using SAS version 9.4. Initial data exploration began with looking at sample sizes for all variables of interest, frequency distributions of categorical variables, and mean analysis of continuous variables to assess normality assumptions for model building (Tables 1, 4-14). Only those who had a valid medical record number and albumin adjusted calcium value were included in further analyses. However, initial normality was obtained without included values to ensure there wasn't selection bias in these values.

A correlation model was next run to explore potential confounding between covariates and psychological outcomes (Tables 15-17). P-values of ≤ 0.10 in crude correlation analyses between outcomes and predictors and potential covariates were selected for further examination in regression models. Confounders considered included gender, race, and age at blood draw. In addition, the values for calcium, PTH, phosphorous, TSH, T4, IgG, IgA, IgM, CD4, and CD8 were also considered as predictors and covariates.

Data Analyses

Primary analysis

The primary hypothesis is to determine if any of the various endocrine and immune factors collected from this population have any correlation with behavioral outcomes. Analysis

of covariance (ANCOVA) will be performed to determine variability in models given predictors that correlate highly with outcome variables.

From a subcohort with endocrine or immune factors data available, examine the correlation with behavioral outcomes including ASD-like, prodromal psychosis, and maladaptive behavioral measures.

Ethics

The Institutional Review Board at Emory University of Atlanta, Georgia approved the amendment adding me to the study and the pursuit of additional data collection (IRB00045086).

RESULTS

Descriptive Analysis

Predictor Variables

The SERPh22 database included 709 unique patients with 22q11DS. 621 of those individuals also had a medical record in REDCap associated with their unique study identification. Information on predictor variables was only obtained for those who had an electronic medical record number and albumin adjusted calcium value available. Initial demographics were obtained for those with a medical record number (Table 1). The average age for those with a medical record is 13.5 (SD: 9.04, Range: 0-57).

There were calcium values for 419 individuals, but only 355 had an albumin drawn at the same time and were thus able to calculate an albumin adjusted calcium value. The average value for albumin adjusted calcium was 7.83mg/dL (SD: 1.21, Range: 3.3-10.9). This compares to an average of 7.9mg/dL (SD: 1.30, Range: 3.3-10.9) for unadjusted calcium values. The average age for those with adjusted calcium values is 3.37 (SD: 5.45, Range: 0-29)

Of those with corrected calcium values available, 223 had information on IgG, 188 had IgA, 199 had IgM, 108 had PTH, 190 had T4, 263 had phosphorous, and 16 had TSH values available (Table 1). The average IgG value was 575.94mg/dL (SD: 337.76, Range: 48.0-2374.0). The average IgM was 48.98mg/dL (SD: 34.56, Range: 5.0-180.0). The average IgA was 65.57mg/dL (SD: 64.76, Range: 6.9-459.0). The average PTH was 24.03pg/mL (SD: 13.87, Range: 2.0-89.0). The average T4 was 2.90ug/dl (SD: 3.37, Range: 0.36-15.1). The average phosphorous value was 4.35mg/dL (SD: 1.30, Range: 1.4-9.3). The average TSH was 2.67mIU/L (SD: 2.38, Range: 0.57-8.15). This information is summarized in Table 1.

Outcome Variables

Information on various psychological assessments have been collected and stored within REDCap. The full list of assessments captured in REDCap can be found in Table 2 of the appendix. Including assessments was based off of relevance to hypothesis (not looking at cognitive function), age appropriateness for adolescents, and having at least 10 reports on unique patients. All subscales of the ABCs assessment were evaluated and each had a sample size of 28 individuals. The irritability raw score had a mean of 10.07 (SD: 9.23; Range: 0-30), the lethargy raw score had a mean of 3.75 (SD: 4.77; Range: 0-17), stereotypy raw score had a mean of 1.57 (SD: 1.97; Range: 0-5), hyperactivity score had a mean of 14.46 (SD: 13.39; Range: 0-41), and inappropriate speech had a mean of 2.64 (SD: 2.45; Range: 0-9).

Only the social and communication scores of ABAS were assessed due to small sample sizes. Communication and Social sub scales both had a sample of 12. The average communication score was 57.33 (SD: 17.52; Range: 8-73). The average social score was 54.42 (SD: 16.88; Range: 15-69). All subscales of the ADI-R were also examined. 61 patients had information on these scores (except for nonverbal communication, n = 19). The average social score was 8.7 (SD: 6.14; Range: 0-25), the average communication score was 6.15 (SD: 4.80; Range: 0-18), the average nonverbal communication score was 2.84 (SD: 3.10; Range: 0-12), the average restrictive and repetitive behaviors score was 2.95 (SD: 2.68; Range: 0-12), and the average developmental score was 3.46 (SD: 1.42, Range: 0-6).

The total ADOS score combining the subscales was examined. It had a sample of 28 with a mean of 6.64 (SD: 4.73; Range: 0-19). The total CBCL score was examined as well and had a sample size of 41 with a mean of 47.71 (SD: 25.65; Range: 7-97). In addition, the affective, internalizing, and externalizing problems scores were addressed. The affective problems mean was 3.68 (SD: 2.7; Range: 0-9; n = 28), the externalizing problems mean was 10.59 (SD: 9.44;

Range: 0-35), and the internalizing problems score was 11.66 (SD: 7.23; Range: 2-27). The final assessment considered was the PQ-B. The subscales addressing negative and disorganized symptoms were examined (n = 27). The average number of negative symptoms was 4.33 (SD: 3.29; Range: 0-14), and the average number of disorganized symptoms was 3.15 (SD: 2.64; Range: 0-9).

Initial Primary Analysis

Using univariate statistical analysis, basic information was gathered on all potential predictors and covariates with the outcomes of interest. For the purpose of these analyses, only individuals who had both a medical record number and adjusted calcium value available were selected. Pearson's Correlation coefficients were established for all possible predictors and covariates with the outcomes of interest (Tables 15-17).

At an alpha significance level of 0.10, significant relationships were seen between age of T4 draw and ABAS Social score (p = 0.0140), age of TSH draw and ABC Irritability score (p = 0.0833), ABC Lethargy score with age of T4, PTH, IgG, IgM, and Calcium draw (p = 0.0894, 0.0618, 0.0358, 0.0503, and 0.0605, respectively), age at TSH draw and ABC Stereotypy score (p = 00394), age at calcium draw and ABC Inappropriate Speech score (p = 0.0467), age at TSH draw CBCL Externalizing Problems score (p = 0.0971), Phosphorous result and ABC Lethargy score (p = 0.0143), CD4 count and ABC stereotypy score (p = 0.0053), Phosphorous result and ADI Social score (p = 0.0399), ADI Com score with CD8 count and sex (p = 0.0066 and 0.0673, respectively), ADI RRB Score and sex (p = 0.0761), ADI Dev score and sex (p = 0.0757), ADOS Total and race (p = 0.0111), CBCL Affective Problems score and race (p = 0.0202), CBCL Externalizing Problems score and CD4 count (p = 0.0120), PQ-B Negative Symptoms score and race (p = 0.0099), T4 result and ABAS Communication score (p = 0.0191), calcium

and ABAS Communication score (p = 0.0725), IgA result and ABAS Social score (p = 0.03367), ABC Irritability score and PTH, TSH, and calcium results (p = 0.0121, 0.833, and 0.0138, respectively), ABC Lethargy score and IgG, IgA, and IgM results (p = 0.0038, 0.0740, and 0.0004, respectively), ABC Stereotypy score and PTH, TSH, and calcium results (p = 0.0321, 0.0394, and 0.0210, respectively), ABC Hyperactivity score and PTH, IgG, IgM, and calcium results (p = 0.0117, 0.0336, 0.0802, and 0.0317, respectively), ABC inappropriate speech and IgG, IgA, and IgM results (p = 0.0066, 0.0427, and 0.0161, respectively), ADI Social and PTH and IgM results (p = 0.0356 and 0.0326, respectively), CBCL Total score and IgM result (p = 0.0664), CBCL Externalizing Problems score and TSH and IgM result (p = 0.0971 and 0.0367, respectively), and CBCL Internalizing Problems Score and IgG (p = 0.0751).

. Criteria for further analysis included sample size ≥ 10 and alpha ≤ 0.01. Unfortunately, age at which assessment was administered was not able to be used as a covariate of interest as dates at which tests were administered were missing or absent from the REDCap database.

Secondary Analysis

PROC GLM was used to analyze variance of various thymus status (always missing, removed, intact) with calcium results. Via the means procedure, no statistical differences existed in the mean calcium result dependent on thymus status when controlling for age at calcium draw, race and sex (n = 48, F-value = 0.35, P-value = 0.8819). Mean PTH result dependent on thymus status when controlling for age at PTH draw, race, and sex was also not significant at the 0.10 alpha level (n = 16, F-value = 0.39, P-value = 0.8431).

Regression Analysis

Regression analysis was only completed on predictor variables that had samples greater than or equal to 10 and covariate correlations with *alpha* ≤ 0.01 and $n \geq 10$. Sex was forced into

the model regardless to account for known differences between genders. Models not hierarchically well formulated were not evaluated. Unfortunately, when limiting analysis to those whom had data available for adjusted calcium values, no multivariable analyses were available.

The model for ABC Irritability containing calcium result and sex had an F-value of 4.86 that was significant at the alpha = 0.10 level (P-value = 0.0474). 58.1% of the variance of this score can be explained by the model with the calcium result being the most significant (P-value = 0.0470). The model for ABC Stereotypy containing calcium result and sex had an F-value of 4.39 that was significant at the alpha = 0.10 level (P-value = 0.0580). 55.7% of the variance of this score can be explained by the model with the calcium result being the most significant (P-value = 0.0221).

The model for ABC Hyperactivity containing calcium result and sex was not significant at the 0.10 alpha level (F-value = 2.97, P-value = 0.1166). The model for ADI Social containing IgM result and sex was not significant at the 0.10 alpha level (F-value = 0.37, P-value = 0.6934). The model for CBCL total score containing IgM result and sex was not significant at the 0.10 alpha level (F-value = 1.01, P-value = 0.3887). The model for CBCL Externalizing Problems score containing IgM result and sex was not significant at the 0.10 alpha level (F-value = 2.38, P-value = 0.1286). The model for CBCL Internalizing Problems score containing IgG result and sex was not significant at the 0.10 alpha level (F-value = 0.76, P-value = 0.4848).

DISCUSSION

The purpose of this study was to examine the impact of various immune factors on hypocalcaemia in addition to examining calcium and immune factors in conjunction while looking at psychological and behavioral measures. Unfortunately, limiting analyses to only those for which calcium was available limited sample sizes and prevented further in-depth analyses.

While the primary hypothesis intended to look at immune and endocrine interaction in assessing behavioral outcomes, correlations run did not point to any new information in these areas. Two of the subscales for the Aberrant Behavior Checklist scores were significant after performing a regression analysis (PROC GLM). The calcium value explained 58.1% of the variability within the ABC Irritability subscale and the calcium value explained 55.7% of the variability within the ABC Stereotypy subscale. However, both of these regressions only included 10 subjects in the sample size, so conclusions are limited here. None of the other regressions run based on hierarchically well formulated models were significant at the 0.10 alpha level.

While my secondary hypothesis suggested that PTH and calcium may be dependent on thymus status, there were no differences in these means when controlling for age of draw, race, and sex among the three thymus statuses. Because the overall sample sizes were small here (as few as 16 for PTH results), this result should not be considered conclusive and should continue to be looked at as the database grows.

Limitations

One limitation of this study is spotty data available for the entire cohort. While some of this cohort has been followed for over 20 years, complete immune, endocrine, behavioral, and

clinical factors were not completely available. Part of this is in part to maintaining a separate database outside of the medical record that is responsible for hosting this information. Uploading this information is inconsistent and has led to incomplete information on members of the cohort.

Future Directions

While examining correlations and prevalence of disease in 22q11DS alone and in the general population alone have been examined, future studies should seek to examine differences in prevalence and correlations between populations. While 22q11DS is genetic, comparing siblings with and without the deletion may help us better understand psychiatric illness and Autism spectrum disorders. Finally, updated maintenance of the REDCap database should occur in order to have the most complete information on cohort decades old. Specifically within this cohort, a greater number of evaluations measuring prodromal and adult onset psychosis should be administered to patients to better understand the effects of 22q11DS in combination with hypocalcaemia on psychiatric outcomes.

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TABLES

Table 1: Description of Predictors and Sample.

Variable	**n (%)**				
Male	157 (52.5)				
Female	142 (47.5)				
	n	**Mean**	**SD**	**Min**	**Max**
Age	355	9.97	6.42	0	38
Predictors					
Calcium, adjusted	355	7.83	1.21	3.3	10.9
Calcium, raw	419	7.90	1.30	3.3	10.9
IgG	223	575.94	337.76	48.0	2374.0
IgA	188	65.57	64.76	6.9	459.0
IgM	199	48.98	34.56	5.0	180.0
PTH	108	24.03	13.87	2.0	89.0
T4	190	2.90	3.37	0.4	15.1
TSH	16	2.66	2.38	0.6	8.2
Phosphorous	263	4.35	1.30	1.4	9.3
CD4 count	159	1095	766	1	4921.
CD8 count	159	495	403	1	2137.

*Descriptions of predictor variables represents only those for which a medical record and an adjusted calcium value was available. See results section for units. CD4 and CD8 cell count units are cells per uL.

Table 2: Psychological Assessments in RedCap.

Assessment	**n**	**What the Measure Examines**	**Is Evaluation Appropriate?**
ABAS	91	Assesses cognitive, development & behavioral problems	Yes
ABC	23	Assess behavioral problems	Yes
ABCL	23	Adult behavioral checklist	No
ADI	57	Autism assessment	Yes
ADOS	57	Autism assessment	Yes
ASR	20	Adult behavioral	No
CAARS	33	Adult ADHD assessment	No
CBCL	37	Assess behavioral problems	Yes
CDIP	71	Assesses Development & behavioral problems	Yes

Controlled Oral Word Assessment	33	Verbal fluency test	No
CSBS	72	Measures Early communication	Yes
CTOPP	13	Word Assessment	No
CVLT	34	Verbal fluency test	No
DAS	36	Identify strengths and weaknesses	No
Facial Recognition	1	Facial recognition	No
Grooved Pegboard Assessment	34	Fine motor skill assessment	No
Handedness Assessment	1	Fine motor skills assessment	No
MCST	15	Communication assessment for people with aphasia	No
MINI	34	Measures DSM-IV	No
MWCST	33	Cognitive Function	No
NEPSY	13	Cognitive Function	No
OWLS	13	Oral & Written language assessment	No
Pegs Assessment	14	How well to children with disabilities perform	No
PPVT	36	Vocab assessment	No
PPVT III	34	Vocab assessment	No
PQ-B	45	Assesses Prodromal psychosis	Yes
Rey O Assessment	32	Cognitive Assessment	No
SCID	28	Measures DSM-5	No
SIPS	32	Assesses Prodromal psychosis	No
SRS	23	Autism social assessment	No
Stroop Evaluation	32	Color and word test	No
Trails Assessment	34	Literacy Assessment	No
Vineland	23	Diagnose special needs	No
WAIS	50	Adult IQ test	No
WIAT	23	Achievement test	No
WISC	3	IQ Test	No
WMS	33	Memory Assessment	No
Woodcock Johnson Evaluation	47	Cognitive Assessment	No
WRAVMA	32	Visual motor ability	No
YSR	15	Assess emotional and behavioral problems	No

Table 3: Descriptions of Selected Psychological Assessments.

Child Assessments	**Test**	**Scoring**	**Result**
Adaptive Behavior Assessment System (ABAS)	Complete assessment of adaptive skills given to parent/primary caregiver or teacher for persons aged 0 to 89. Evaluates functioning, mental retardation, strengths and weaknesses.	Raw scores in a number of skill areas are translated into composite scores in four areas based on age.	Higher scores indicates better functioning. Average composite scores are 8-12 with lower scores signaling below average functioning than what is typical in the age range.
Aberrant Behavior Checklist (ABC)	Caregiver independently completes the form to capture specific behavioral problems of children or adults with mental retardation.	The form includes 58 items and 5 subscales in irritability, lethargy, stereotypy, hyperactivity/noncompliance, and inappropriate speech.	Higher scores indicate greater number of problems within the subscale. Used as an indicator of problems but should not be used alone to diagnose.
Autism Diagnostic Interview (ADI)	Semi-structured interview given by a clinician to caregivers of children and adults. Contains 93 items assessing three domains: quality of social interaction, communication/language, and repetitive, restricted, and stereotyped interests.	Score of 0 is given when behavior of the type specified in the coding is not present; 1 specified behavior present but not severe/frequent; 2 definite abnormal in specified behavior; 3 “extreme severity” of the specified behavior.	Higher scores indicates greater ASD behavior. Cutoff for communication and language domain is >=8 for verbal subjects and >=7 for nonverbal subjects. Cutoff for the social interaction >=10, and the cutoff for restricted and repetitive behaviors is >= 3.
Autism Diagnostic Observation Schedule (ADOS)	Semi-structured play sessions to evaluate communication, social interaction, and play.	Module and scoring algorithm depend on language level/age	Higher scores indicates greater ASD behavior
Child Behavior Checklist (CBCL)	Parent questionnaire to evaluate childhood behavior. 112 items that assess behavior.	Scores are summed to assess behavioral problems.	Higher scores suggest more behavioral problems.
Prodromal Questionnaire – Brief (PQ-B)	Self-report screening measure for psychosis risk symptoms for adolescents and young adults.	Items are broken down into modules and scores are summed to assess psychosis risk, but they don’t suggest actual diagnosis of psychosis.	Higher scores suggest greater risk with score cutoffs at >=6 for validated greatest risk.

Table 4: Description of Outcomes.

Outcome	N	Mean	SD	Min	Max	Skewness	Kurtosis
ABAS Communication Score	12	57.3	17.52	8	73	-2.25	6.12
ABAS Social Score	12	54.4	16.88	15	69	-1.25	1.22
ABCs – Irritability	28	10.1	9.23	0	30	0.99	0.17
ABCs – Lethargy	28	3.8	4.77	0	17	1.29	0.74
ABCs – Stereotypy	28	1.6	1.97	0	5	0.87	-1.00
ABCs – Hyperactivity	28	14.5	13.39	0	41	0.89	-0.63
ABCs – Inappropriate Speech	28	2.6	2.45	0	9	0.76	0.10
ADI Social	61	8.9	6.14	0	25	6.14	0.25
ADI Com	60	6.2	4.80	0	18	1.11	0.64
ADI Comvv	19	2.8	3.10	0	12	1.65	3.30
ADI RRB	61	3.0	2.68	0	12	1.26	1.46
ADI Dev	59	3.5	1.42	0	6	-0.53	-0.20
ADOS Total	28	6.6	4.73	0	19	0.63	0.17
CBCL Total	41	47.7	26.65	7	97	0.18	-1.15
CBCL Affective Problems Score	28	3.7	2.74	0	9	0.46	-0.71
CBCL Externalizing Problems Score	41	10.6	9.44	0	35	0.74	-0.44
CBCL Internalizing Problems Score	41	11.7	7.23	2	27	0.27	-1.11
PQ-B Negative Symptoms	27	4.3	3.29	0	14	1.55	2.97
PQ-B Disorganized Symptoms	27	3.1	2.64	0	9	0.83	-0.36

Table 5: Psychological Assessment Descriptive Statistics with MRN and Corrected Calcium Value.

Assessment	N	Mean	SD	Min	Max	Skewness	Kurtosis
ABAS Communication Score	4	-	-	-	-	-	-
ABAS Social Score	4	-	-	-	-	-	-
ABCs – Irritability	10	18	10.07	2	30	-0.96	2.47
ABCs – Lethargy	10	3.8	4.82	0	12	1.75	3.15
ABCs – Stereotypy	10	2.2	2.59	0	5	0.50	-3.21
ABCs – Hyperactivity	10	27.6	15.01	1	36	-2.14	4.62
ABCs – Inappropriate Speech	10	5.0	3.54	0	9	-0.57	-0.69
ADI Social	17	10.9	6.69	1	22	0.15	-0.12
ADI Com	16	7.3	5.70	2	18	1.13	0.29
ADI Comv	5	6.0	2.83	4	8	-	-
ADI RRB	17	3.6	2.26	1	8	0.82	1.17
ADI Dev	17	4.4	1.19	2	6	-0.97	1.87
ADOS Total	10	11.4	4.98	6	19	0.82	0.78
CBCL Total	14	60.8	22.92	22	87	-0.85	1.06
CBCL Affective Problems Score	10	5.0	1.41	3	7	0	2
CBCL Externalizing Problems Score	14	17.8	11.63	1	35	0	0.31
CBCL Internalizing Problems Score	14	9.2	5.31	5	19	1.61	2.56
PQ-B Negative Symptoms	6	4	2.83	2	6	-	-
PQ-B Disorganized Symptoms	6	2	2.83	0	4	-	-

Table 6: Psychological Assessment Descriptive Statistics for IgG with MRN and Adjusted Calcium Value.

Assessment	N	Mean	SD	Min	Max	Skewness	Kurtosis
ABAS Communication Score	3	41.0	29.10	8	63	-1.48	-
ABAS Social Score	3	40.7	22.68	15	58	-1.43	-
ABCs – Irritability	8	14.9	8.74	3	30	0.38	-0.28
ABCs – Lethargy	8	6.0	5.78	0	17	1.17	0.55
ABCs – Stereotypy	8	2.1	2.23	0	5	0.41	-1.97
ABCs – Hyperactivity	8	24.9	11.64	9	36	-0.54	-1.89
ABCs – Inappropriate Speech	8	5.4	2.07	3	9	0.50	-0.25
ADI Social	10	11.8	7.41	1	25	0.53	-0.07
ADI Com	9	6.9	5.40	2	18	1.23	0.89
ADI Comvv	1	12	-	12	12	-	-
ADI RRB	10	4	2.94	0	8	0.20	-1.39
ADI Dev	10	3.9	0.88	3	5	0.22	-1.73
ADOS Total	8	7.9	3.94	1	12	-0.71	-0.52
CBCL Total	10	65.6	15.93	32	87	-0.85	1.05
CBCL Affective Problems Score	8	5.6	1.92	3	8	-0.41	-1.44
CBCL Externalizing Problems Score	10	16.3	9.44	0	35	0.36	1.12
CBCL Internalizing Problems Score	10	13.6	7.49	5	27	0.57	-0.82
PQ-B Negative Symptoms	2	3.5	3.54	1	6	-	-
PQ-B Disorganized Symptoms	2	2.5	2.12	1	4	-	-

Table 7: Psychological Assessment Descriptive Statistics for IgA with MRN and Adjusted Calcium Value.

Assessment	N	Mean	SD	Min	Max	Skewness	Kurtosis
ABAS Communication Score	3	41.0	29.10	8	63	-1.46	-
ABAS Social Score	3	40.7	22.68	15	58	-1.43	-
ABCs – Irritability	8	14.9	8.74	3	30	0.38	-0.28
ABCs – Lethargy	8	6.0	5.78	0	17	1.17	0.55
ABCs – Stereotypy	8	2.1	2.23	0	5	0.41	-1.97
ABCs – Hyperactivity	8	24.9	11.64	9	36	-0.54	-1.89
ABCs – Inappropriate Speech	8	5.4	2.07	3	9	0.50	-0.25
ADI Social	10	11.8	7.41	1	25	0.53	-0.07
ADI Com	9	6.9	5.40	2	18	1.23	0.89
ADI Comvv	1	12	-	12	12	-	-
ADI RRB	10	4.0	2.94	0	8	0.20	-1.39
ADI Dev	10	3.9	0.88	3	5	0.22	-1.73
ADOS Total	8	7.9	3.94	1	12	-0.71	-0.52
CBCL Total	10	65.6	15.93	32	87	-0.85	1.05
CBCL Affective Problems Score	8	5.6	1.92	3	8	-0.41	-1.44
CBCL Externalizing Problems Score	10	16.3	9.44	0	35	0.36	1.12
CBCL Internalizing Problems Score	10	13.6	7.49	5	27	0.57	-0.82
PQ-B Negative Symptoms	2	3.5	3.54	1	6	-	-
PQ-B Disorganized Symptoms	2	2.5	2.12	1	4	-	-

Table 8: Psychological Assessment Descriptive Statistics for IgM with MRN and Adjusted Calcium Value.

Assessment	N	Mean	SD	Min	Max	Skewness	Kurtosis
ABAS Communication Score	3	41.0	29.10	8	63	-1.46	-
ABAS Social Score	3	40.7	22.68	15	58	-1.43	-
ABCs – Irritability	8	14.9	8.74	3	30	0.38	-0.28
ABCs – Lethargy	8	6.0	5.78	0	17	1.14	0.55
ABCs – Stereotypy	8	2.1	2.23	0	5	0.41	-1.97
ABCs – Hyperactivity	8	24.9	11.64	9	36	-0.54	-1.89
ABCs – Inappropriate Speech	8	5.4	2.07	3	9	0.50	-0.25
ADI Social	10	11.8	7.41	1	25	0.53	-0.07
ADI Com	9	6.9	5.40	2	18	1.23	0.89
ADI Comvv	1	12.0	-	12	12	-	-
ADI RRB	10	4.0	2.94	0	8	0.20	-1.39
ADI Dev	10	3.9	0.88	3	5	0.88	-1.74
ADOS Total	8	7.9	3.94	1	12	-0.71	-0.52
CBCL Total	10	65.6	15.93	32	87	-0.85	1.05
CBCL Affective Problems Score	8	5.6	1.92	3	8	-0.41	-1.44
CBCL Externalizing Problems Score	10	16.3	9.44	0	35	0.36	1.12
CBCL Internalizing Problems Score	10	13.6	7.49	5	27	0.57	-0.82
PQ-B Negative Symptoms	2	3.5	3.53	1	6	-	-
PQ-B Disorganized Symptoms	2	2.5	2.12	1	4	-	-

Table 9: Psychological Assessment Descriptive Statistics for T4 with MRN and Adjusted Calcium Value.

Assessment	N	Mean	SD	Min	Max	Skewness	Kurtosis
ABAS Communication Score	4	47.3	26.85	8	66	-1.72	2.91
ABAS Social Score	4	47.8	23.31	15	69	-1.29	1.90
ABCs – Irritability	6	15.7	10.65	3	30	-0.24	-1.12
ABCs – Lethargy	6	4.5	4.37	0	12	1.13	0.83
ABCs – Stereotypy	6	1.8	2.48	0	5	0.87	-1.92
ABCs – Hyperactivity	6	25.0	14.53	4	36	-0.95	-1.59
ABCs – Inappropriate Speech	6	4.8	3.19	0	9	-0.33	-0.27
ADI Social	8	13.4	7.63	4	25	0.42	-1.38
ADI Com	7	9.1	5.81	2	18	0.35	-0.76
ADI Comvv	1	12	-	12	12	-	-
ADI RRB	8	5.3	4.13	0	12	0.30	-0.97
ADI Dev	8	4.3	0.89	3	5	-0.62	-1.48
ADOS Total	6	7.7	4.13	1	12	-0.59	0.21
CBCL Total	8	53.1	20.30	19	80	-0.50	-0.42
CBCL Affective Problems Score	6	4.7	2.88	0	8	-0.71	0.26
CBCL Externalizing Problems Score	8	12.3	8.08	0	23	-0.22	-0.92
CBCL Internalizing Problems Score	8	8.9	5.94	3	22	1.77	3.74
PQ-B Negative Symptoms	2	4.0	4.24	1	7	-	-
PQ-B Disorganized Symptoms	2	3.0	2.83	1	5	-	-

Table 10: Psychological Assessment Descriptive Statistics for Phosphorous with MRN and Adjusted Calcium Value.

Assessment	N	Mean	SD	Min	Max	Skewness	Kurtosis
ABAS Communication Score	2	64.5	2.12	63	66	-	-
ABAS Social Score	2	59.0	14.14	49	69	-	-
ABCs – Irritability	5	15.8	10.85	3	30	0.06	-1.33
ABCs – Lethargy	5	3.6	4.77	0	12	2.04	4.42
ABCs – Stereotypy	5	3.0	2.35	0	5	-0.58	-2.63
ABCs – Hyperactivity	5	27.6	13.59	4	36	-1.94	3.78
ABCs – Inappropriate Speech	6	4.8	3.42	0	9	-0.40	-0.18
ADI Social	6	10.3	7.09	1	22	0.66	1.07
ADI Com	6	7.5	5.96	2	18	1.23	1.33
ADI Comvv	0	-	-	-	-	-	-
ADI RRB	6	2.2	3.06	0	8	1.84	3.37
ADI Dev	6	4.3	0.82	3	5	-0.86	-0.30
ADOS Total	5	7.4	2.97	4	12	0.88	1.45
CBCL Total	6	64.7	24.70	19	87	-1.55	2.59
CBCL Affective Problems Score	5	4.8	2.86	0	7	-1.58	2.74
CBCL Externalizing Problems Score	6	20.0	10.33	3	35	-0.42	1.99
CBCL Internalizing Problems Score	6	10.7	6.65	3	19	0.33	-1.87
PQ-B Negative Symptoms	1	6	-	6	6	-	-
PQ-B Disorganized Symptoms	1	4	-	4	4	-	-

Table 11: Psychological Assessment Descriptive Statistics for PTH with MRN and Adjusted Calcium Value.

Assessment	N	Mean	SD	Min	Max	Skewness	Kurtosis
ABAS Communication Score	3	49.0	30.27	8	66	-1.32	-
ABAS Social Score	3	47.3	28.54	15	69	-1.45	-
ABCs – Irritability	5	15.0	11.77	3	30	0.03	-1.94
ABCs – Lethargy	5	4.6	4.88	0	12	1.03	-0.12
ABCs – Stereotypy	5	2.2	2.59	0	5	0.50	-3.21
ABCs – Hyperactivity	5	23.8	15.91	4	36	-0.65	-2.99
ABCs – Inappropriate Speech	5	4.4	3.36	0	9	0.15	0.15
ADI Social	6	14.2	7.68	7	25	0.67	-1.75
ADI Com	5	9.2	5.72	2	18	0.68	2.15
ADI Comvv	1	12	-	12	12	-	-
ADI RRB	6	4.5	3.62	0	8	-0.23	-2.56
ADI Dev	6	4.5	0.84	3	5	-1.54	1.43
ADOS Total	5	6.8	3.96	1	12	-0.36	1.46
CBCL Total	6	54.3	23.77	19	80	-0.71	-1.11
CBCL Affective Problems Score	5	5.0	3.08	0	8	-1.28	2.00
CBCL Externalizing Problems Score	6	12.5	9.50	0	23	-0.33	-1.93
CBCL Internalizing Problems Score	6	9.8	6.68	3	22	1.38	2.44
PQ-B Negative Symptoms	1	1	-	1	1	-	-
PQ-B Disorganized Symptoms	1	1	-	1	1	-	-

Table 12: Psychological Assessment Descriptive Statistics for TSH with MRN and Adjusted Calcium Value.

Assessment	N	Mean	SD	Min	Max	Skewness	Kurtosis
ABAS Communication Score	3	41.0	29.10	8	63	-1.46	-
ABAS Social Score	3	40.7	22.68	15	58	-1.43	-
ABCs – Irritability	3	14.7	10.05	3	30	0.11	-1.06
ABCs – Lethargy	7	6.3	6.18	0	17	0.99	-0.13
ABCs – Stereotypy	7	1.6	2.37	0	5	1.14	-0.95
ABCs – Hyperactivity	7	22.9	14.43	4	36	-0.39	-2.49
ABCs – Inappropriate Speech	7	4.6	2.99	0	9	0.01	-0.32
ADI Social	8	12.8	7.40	4	25	0.76	-0.62
ADI Com	7	7.4	5.56	2	18	1.16	1.49
ADI Comvv	1	12	-	12	12	-	-
ADI RRB	8	4.3	3.11	0	8	0.07	-1.60
ADI Dev	8	4.3	0.89	3	5	0.89	-1.48
ADOS Total	7	8.0	3.87	1	12	-0.87	0.71

CBCL Total	8	56.3	20.96	19	80	-0.93	-0.10
CBCL Affective Problems Score	7	5.0	2.77	0	8	-0.99	0.59
CBCL Externalizing Problems Score	8	12.1	8.08	0	23	-0.16	-0.93
CBCL Internalizing Problems Score	8	11.4	8.63	3	27	1.14	0.08
PQ-B Negative Symptoms	1	1	-	1	1	-	-
PQ-B Disorganized Symptoms	1	1	-	1	1	-	-

Table 13: Psychological Assessment Descriptive Statistics for CD4 Count with MRN and Adjusted Calcium Value.

Assessment	**N**	**Mean**	**SD**	**Min**	**Max**	**Skewness**	**Kurtosis**
ABAS Communication Score	3	41.0	29.10	8	63	-1.46	-
ABAS Social Score	3	40.7	22.68	15	58	-1.43	-
ABCs – Irritability	8	14.4	9.35	3	30	0.25	-0.60
ABCs – Lethargy	8	6.0	5.78	0	17	1.17	0.55
ABCs – Stereotypy	8	1.6	2.20	0	5	1.07	-0.69
ABCs – Hyperactivity	8	21.9	13.64	4	36	-0.13	-2.33
ABCs – Inappropriate Speech	8	4.6	2.77	0	9	-0.07	0.16
ADI Social	9	12.8	6.92	4	25	0.76	-0.22
ADI Com	8	8.0	5.40	2	18	0.73	0.27
ADI Comvv	1	12	-	12	12	-	-
ADI RRB	9	4.3	2.92	0	8	-0.03	-1.25
ADI Dev	9	4.1	0.93	3	5	-0.26	-2.02
ADOS Total	8	8.3	3.65	1	12	-1.09	1.26

CBCL Total	9	56.6	19.63	19	80	-1.02	0.40
CBCL Affective Problems Score	8	4.8	2.66	0	8	-0.62	-0.16
CBCL Externalizing Problems Score	9	12.2	7.56	0	23	-0.22	-0.52
CBCL Internalizing Problems Score	9	11.3	8.08	3	27	1.20	0.55
PQ-B Negative Symptoms	1	1	-	1	1	-	-
PQ-B Disorganized Symptoms	1	1	-	1	1	-	-

Table 14: Psychological Assessment Descriptive Statistics for CD8 Count with MRN and Adjusted Calcium Value.

Assessment	N	Mean	SD	Min	Max	Skewness	Kurtosis
ABAS Communication Score	3	41.0	29.10	8	63	-1.46	-
ABAS Social Score	3	40.7	22.68	15	58	-1.43	-
ABCs – Irritability	8	14.4	9.35	3	30	0.25	-0.60
ABCs – Lethargy	8	6.0	5.78	0	17	1.17	0.55
ABCs – Stereotypy	8	1.6	2.20	0	5	1.07	-0.69
ABCs – Hyperactivity	8	21.9	13.64	4	36	-0.13	-2.33
ABCs – Inappropriate Speech	8	4.6	2.77	0	9	-0.07	0.16
ADI Social	9	12.8	6.92	4	25	0.76	-0.22
ADI Com	8	8.0	5.40	2	18	0.73	0.27
ADI Comvv	1	12	-	12	12	-	-
ADI RRB	9	4.3	2.92	0	8	-0.03	-1.25
ADI Dev	9	4.1	0.93	3	5	-0.26	-2.02
ADOS Total	8	8.3	3.65	1	12	-1.09	1.26

CBCL Total	9	56.6	19.63	19	80	-1.02	0.40
CBCL Affective Problems Score	8	4.8	2.66	0	8	-0.62	-0.16
CBCL Externalizing Problems Score	9	12.2	7.56	0	23	-0.22	-0.52
CBCL Internalizing Problems Score	9	11.3	8.08	3	27	1.20	0.55
PQ-B Negative Symptoms	1	1	-	1	1	-	-
PQ-B Disorganized Symptoms	1	1	-	1	1	-	-

Table 15: Correlation Analysis between Outcomes and Potential Confounders (age at blood draw).

Assessment		T4 Age	PTH Age	TSH Age	IgG Age	IgM Age	Calcium Age
ABAS Communication	Correlation	-0.86621	-0.79544	0.59879	-	-	-0.46118
	P- value	*0.1338*	*0.4145*	*0.5913*	-	-	*0.5388*
ABAS Social	Correlation	-0.98600	-0.81872	0.24945	-	-	-0.64284
	P- value	*0.0140*	*0.3894*	*0.8395*	-	-	*0.9572*
ABCs – Irritability	Correlation	-0.55800	-0.46490	0.69465	-0.28354	-0.31670	-0.45135
	P- value	*0.2499*	*0.4301*	*0.0833*	*0.7165*	*0.6833*	*0.1904*
ABCs – Lethargy	Correlation	0.74482	0.85962	-0.40563	0.96415	0.94970	0.61116
	P- value	*0.0894*	*0.0618*	*0.3666*	*0.0358*	*0.0503*	0.0605
ABCs – Stereotypy	Correlation	-0.27530	-0.08217	0.77802	0.53248	0.51130	-0.13538
	P- value	*0.5975*	*0.8955*	*0.0394*	*0.4675*	*0.4887*	*0.7092*
ABCs – Hyperactivity	Correlation	-0.37011	-0.27402	0.46020	0.455650	0.48131	-0.49512
	P- value	*0.4702*	*0.6555*	*0.2988*	*0.5535*	*0.5187*	*0.1457*
ABCs – Inappropriate Speech	Correlation	-0.36109	-0.38990	0.53794	-0.87399	-0.89696	-0.63708
	P- value	*0.4819*	*0.5164*	*0.2129*	*0.1260*	*0.1030*	*0.0476*
ADI Social	Correlation	0.48691	0.63899	0.18842	-0.05907	-0.06361	0.12785
	P- value	*0.2211*	*0.1720*	*0.6550*	*0.9248*	*0.9191*	*0.6248*
ADI Com	Correlation	0.52136	0.57893	-0.10582	0.33463	0.34645	0.09182
	P- value	*0.2301*	*0.3064*	*0.8214*	*0.5820*	*0.5679*	*0.7352*
ADI Comvv	Correlation	-	-	-	-	-	-0.13127
	P- value	-	-	-	-	-	*0.8333*
ADI RRB	Correlation	0.55196	0.48550	0.32943	-0.44039	-0.46609	-0.05048
	P- value	*0.1561*	*0.3290*	*0.4256*	*0.4580*	*0.4288*	*0.8474*
ADI Dev	Correlation	-0.59089	-0.40850	0.51519	-0.67704	-0.66631	-0.35739
	P- value	*0.1230*	*0.4247*	*0.1913*	*0.2093*	*0.2194*	*0.1590*
ADOS Total	Correlation	-0.57352	-0.65248	0.29040	-0.30936	-0.36181	-0.39905
	P- value	*0.2340*	*0.2327*	*0.5275*	*0.6906*	*0.6382*	*0.2533*
CBCL Total	Correlation	-0.24950	-0.22181	0.37339	0.51282	0.50450	-0.13121
	P- value	*0.5512*	*0.6727*	0.3622	*0.3769*	*0.3861*	*0.6548*
CBCL Affective Problems Score	Correlation	0.25019	0.33557	0.23489	-0.05600	-0.06348	-0.07362
	P- value	*0.6325*	*0.5809*	*0.6121*	*0.9440*	*0.9365*	*0.8398*
CBCL Externalizing Problems Score	Correlation	-0.49541	-0.51953	0.62562	0.76348	0.76248	-0.04628
	P- value	*0.2119*	*0.2908*	*0.0971*	*0.1331*	*0.1336*	*0.8752*
	Correlation	0.42238	0.45012	-0.20394	0.73919	0.73141	0.29250

CBCL Internalizing Problems Score	*P- value*	*0.2972*	*0.3704*	*0.6281*	*0.1535*	*0.1602*	*0.3102*
PQ- B Negative Symptoms	Correlation	-1.00000	-	-	-	-	-0.49143
	P- value	-	-	-	-	-	*0.3222*
PQ-B Disorganized symptoms	Correlation	-1.00000	-	-	-	-	-0.36653
	P- value	-	-	-	-	-	*0.4748*

Table 16: Correlation Analysis between Outcomes and Potential Confounders (continued)

Assessment		Phosphorous	CD4 Count	CD8 Count	Race	Sex
ABAS Communication	Correlation	1.00000	0.60462	0.95038	-0.50532	-0.74185
	P- value	-	*0.5867*	*0.2014*	*0.4947*	*0.2582*
ABAS Social	Correlation	1.00000	0.86198	0.99730	-0.78004	-0.55717
	P- value	-	*0.3385*	*0.0468*	*0.2200*	*0.4428*
ABCs – Irritability	Correlation	-.02139	0.58598	0.12017	-0.14554	0.48487
	P- value	*0.9728*	*0.1269*	*0.7768*	*0.6883*	*0.1555*
ABCs – Lethargy	Correlation	-0.94757	0.23031	0.31803	-0.13258	-0.16615
	P- value	*0.0143*	*0.5832*	*0.4427*	*0.7150*	*0.6464*
ABCs – Stereotypy	Correlation	-0.62609	0.86679	0.49674	-0.38311	0.11699
	P- value	*0.2585*	*0.0053*	*0.2105*	*0.2745*	*0.7476*
ABCs – Hyperactivity	Correlation	-0.22882	0.59835	0.31081	-0.30236	0.33327
	P- value	*0.7112*	*0.1171*	*0.4537*	*0.3958*	*0.3467*
ABCs – Inappropriate Speech	Correlation	0.26074	0.25581	-0.12822	-0.25610	0.30851
	P- value	*0.6718*	*0.5409*	*0.7622*	*0.4751*	*0.3858*
ADI Social	Correlation	-0.83207	0.35019	0.36718	-0.38676	0.33866
	P- value	*0.0399*	*0.3555*	*0.3310*	*0.1251*	*0.1836*
ADI Com	Correlation	-0.66709	0.57848	0.85696	-0.02458	0.46840
	P- value	*0.1478*	*0.1330*	*0.0066*	*0.9280*	*0.0673*
ADI Comvv	Correlation	-	-	-	-0.52705	0.79057
	P- value	-	-	-	*0.3615*	*0.1114*
ADI RRB	Correlation	-0.10842	0.05151	-0.09797	-0.08788	0.44146
	P- value	*0.8380*	*0.8953*	*0.8020*	*0.7373*	*0.0761*
ADI Dev	Correlation	0.43351	-0.20613	-0.39642	-0.19719	0.44189
	P- value	*0.3905*	*0.5947*	*0.2908*	*0.4481*	*0.0757*
ADOS Total	Correlation	0.01589	0.29431	-0.07999	0.75810	-0.12514
	P- value	*0.9798*	*0.4792*	*0.8507*	*0.0111*	*0.7305*
CBCL Total	Correlation	0.03523	0.51406	0.24245	-0.09053	-0.26551
	P- value	*0.9472*	*0.1568*	*0.5296*	*0.7582*	*0.3589*
CBCL Affective Problems Score	Correlation	-0.15066	0.18165	0.01715	-0.71474	-0.16638
	P- value	*0.8089*	*0.6668*	*0.9679*	*0.0202*	*0.6460*
CBCL Externalizing Problems Score	Correlation	0.08420	0.78636	0.43984	0.09330	-0.05875
	P- value	*0.8740*	*0.0120*	*0.2361*	*0.7511*	*0.8419*
	Correlation	0.06650	-0.09699	-0.07369	-0.09330	-0.05875

CBCL Internalizing Problems Score	*P- value*	*0.9004*	*0.8040*	*0.8506*	*0.7525*	*0.0563*
PQ- B Negative Symptoms	Correlation	-	-	-	0.91766	0.0000
	P- value	-	-	-	*0.0099*	*1.0000*
PQ-B Disorganized symptoms	Correlation	-	-	-	0.70165	0.37210
	P- value	-	-	-	*0.1202*	*0.4676*

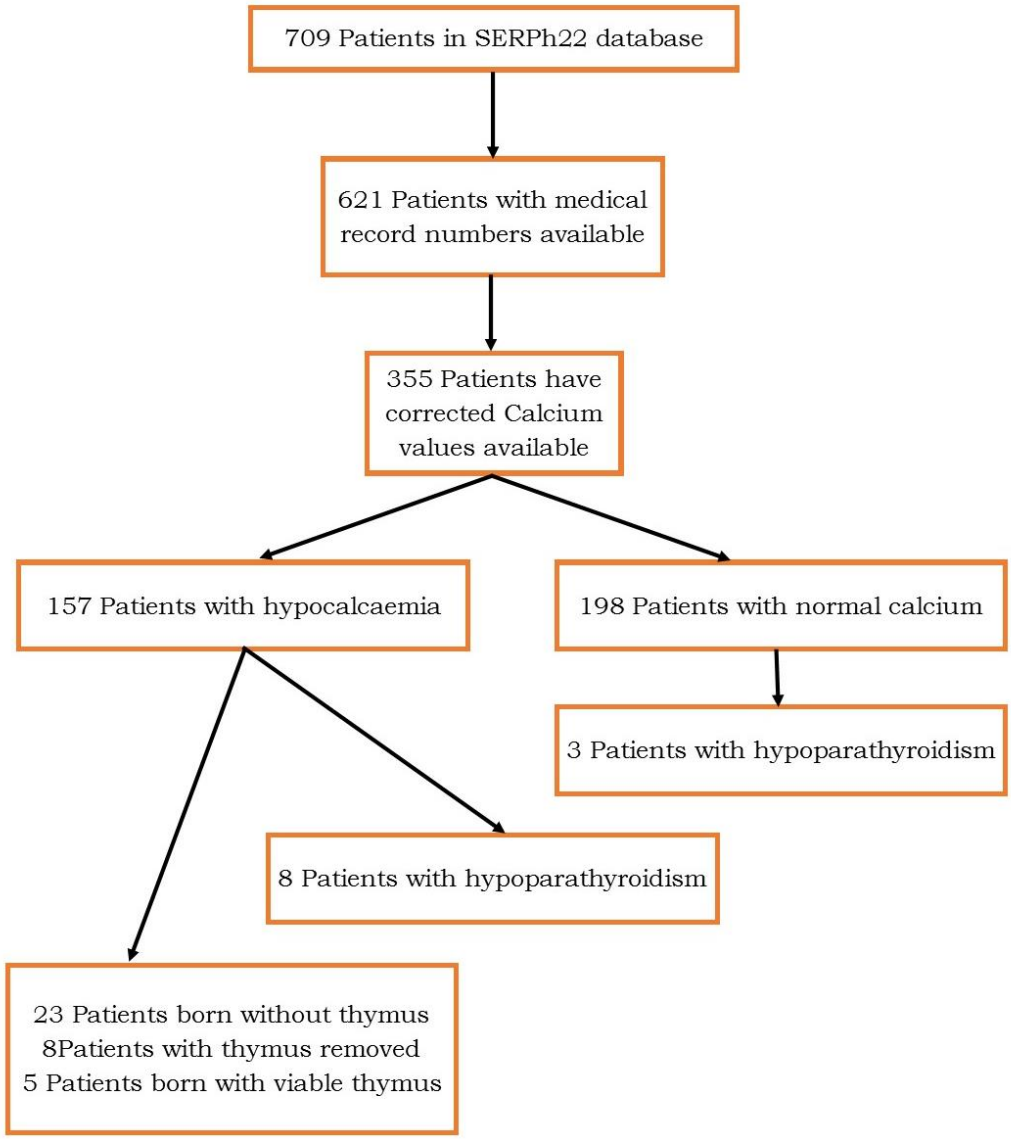
Table 17: Crude Correlation Analysis between Outcome and Predictors.

Assessment		T4	PTH	TSH	IgG	IgA	IgM	Calcium
ABAS Communication	Correlation	-0.98094	0.66155	0.5988	-0.52086	-0.34871	-0.76077	-0.92751
	P- value	*0.0191*	*0.5398*	*0.5913*	*0.6512*	*0.7732*	*0.4496*	*0.0725*
ABAS Social	Correlation	-0.93263	0.59062	-	-	-	-	-0.89317
	P- value	*-0.93596*	*0.69062*	*0.2495*	*-0.80621*	*0.03367*	*-0.95036*	*-0.89317*
ABCs – Irritability	Correlation	0.16950	-0.95324	0.6947	-0.59331	-0.11553	-0.51847	-0.74293
	P- value	*0.7482*	*0.0121*	*0.0833*	*0.1210*	*0.7853*	*0.1880*	*0.0138*
ABCs – Lethargy	Correlation	-0.49000	-0.16552	0.4056	0.88173	0.66151	0.94344	0.03573
	P- value	*0.3238*	*0.7902*	*0.3666*	*0.0038*	*0.0740*	*0.0004*	*0.9219*
ABCs – Stereotypy	Correlation	-0.13249	-0.90967	0.7780	-0.22386	0.35588	-0.30820	-0.71175
	P- value	*0.8024*	*0.0321*	*0.0394*	*0.5941*	*0.3869*	*0.4577*	*0.0210*
ABCs – Hyperactivity	Correlation	0.38511	-0.95409	0.4602	-0.74590	0.04287	-0.65131	-0.67639
	P- value	*0.4509*	*0.0117*	*0.2988*	*0.0336*	*0.9197*	*0.0802*	*0.0317*
ABCs – Inappropriate Speech	Correlation	0.18153	-0.63078	0.5379	-0.85625	-0.72298	-0.80438	-0.38128
	P- value	*0.7307*	*0.2539*	*0.2129*	*0.0066*	*0.0427*	*0.0161*	*0.2770*
ADI Social	Correlation	0.22428	-0.84170	0.1884	0.11641	0.03700	0.67405	-0.04252
	P- value	*0.5934*	*0.0356*	*0.6550*	*0.7488*	*0.9192*	*0.0326*	*0.8713*
ADI Com	Correlation	-0.00935	-0.12612	0.1058	0.06943	0.40339	0.09879	-0.03182
	P- value	*0.9841*	*0.8399*	*0.8214*	*0.8591*	*0.2817*	*0.8004*	*0.9069*
ADI Comvv	Correlation	-	-	-	-	-	-	0.74900
	P- value	-	-	-	-	-	-	*0.1451*
ADI RRB	Correlation	-0.18425	-0.39440	0.3294	0.06516	-0.30293	0.44354	0.14290
	P- value	*0.6623*	*0.4391*	*0.4256*	*0.8581*	*0.3949*	*0.1992*	*0.5843*
ADI Dev	Correlation	0.53309	-0.42655	0.5152	-0.28693	-0.14017	0.01959	-0.29409
	P- value	*0.1737*	*0.3990*	*0.1913*	*0.4215*	*0.6993*	*0.9572*	*0.2519*

ADOS Total	Correlation	-0.19630	-0.72804	0.2904	-0.12018	-0.20090	-0.05985	-0.21034
	P- value	*0.7093*	*0.1631*	*0.5275*	*0.7768*	*0.6333*	*0.8881*	*0.5597*
CBCL Total	Correlation	-0.14678	-0.18749	0.3734	0.02990	0.32033	-0.60052	-0.26664
	P- value	*0.7287*	*0.7221*	*0.3622*	*0.9346*	*0.3669*	*0.0664*	*0.3568*
CBCL Affective Problems Score	Correlation	0.07219	-0.31997	0.2349	0.21645	0.12681	0.32380	-0.12543
	P- value	*0.8919*	*0.5997*	*0.6121*	*0.6067*	*0.7648*	*0.4340*	*0.7299*
CBCL Externalizing Problems Score	Correlation	-0.18747	-0.29043	0.6256	0.06311	0.54071	-0.66282	-0.43542
	P- value	*0.6566*	*0.5766*	*0.0971*	*0.8625*	*0.1066*	*0.0367*	*0.1197*
CBCL Internalizing Problems Score	Correlation	-0.16382	0.21621	0.2039	0.58587	0.25923	0.26264	0.25957
	P- value	*0.6983*	*0.6807*	*0.6281*	*0.0751*	*0.4695*	*0.4635*	*0.3702*
PQ- B Negative Symptoms	Correlation	-1.00000	-	-	1.00000	1.00000	-1.00000	-0.12636
	P- value	-	-	-	-	-	-	*0.8115*
PQ-B Disorganized symptoms	Correlation	-1.00000	-	-	1.00000	1.00000	-1.00000	-0.06441
	P- value	-	-	-	-	-	-	*0.9035*

FIGURES

FIGURE 1. Study Patient Selection - Calcium



APPENDIX

EMORY UNIVERSITY | Institutional Review Board

TO: Bradley Pearce, PhD
Principal Investigator
SPH: Epidemiology

DATE: December 12, 2014

RE: **Continuing Review Expedited Approval**
CR4_IRB00045086

IRB00045086
Pathophysiological mechanisms of autism risk in patients with 22q11 deletion syndrome

Thank you for submitting a renewal application for this protocol. The Emory IRB reviewed it by the expedited process on **11/11/2014**, per 45 CFR 46.110, the Federal Register expeditable categories F[5] and [7], and/or 21 CFR 56.110. This reapproval is effective from **12/11/2014** through **12/10/2015**. Thereafter, continuation of human subjects research activities requires the submission of another renewal application, which must be reviewed and approved by the IRB prior to the expiration date noted above. Please note carefully the following items with respect to this reapproval:

- The following documents were reviewed in this renewal:
  - IRB00045086CleanUpdate2012, version date: 10/27/2011
  - CHILD PHONE Scriptbpjan2012, modified date: 1/19/2012
  - Consent_22q11, modified date: 11/17/2011
  - Cover letter for consent, modified date: 1/19/2011
  - Phone script22q11, version date: 1/17/2011

Please note that the reviewer has requested that the following items be corrected via the submission of an amendment:

- Please revise the assent document (CHILD PHONE Scriptbpjan2012) to include all of the necessary elements. The template found on the IRB website may provide guidance on the elements to be included (http://irb.emory.edu/documents/assent-template.doc).
- Please clarify what the purpose of the phone script included in the consent section (Phone script22q11). If this is a consent document to be used in parallel or in replacement for the main consent, please include it in the main consent document, with a stamping header included.
- Please revise the main consent document to include a version date in the footer, as well as remove the 17 year-old assent signature line from the from the document, as the policy for assent for 17 year olds has changed.
- Please clarify whether you will only be obtaining oral/verbal consent. If only receiving oral/verbal consent, then please remove the signature line from teh consent document. You will also need to request a waiver of documentation of consent.
- If you are collecting any optional samples, please include the consent and HIPAA language from our template about optional studies (http://irb.emory.edu/documents/Emory_BioMed_ICFHIPAA_Template.doc).

Any reportable events (e.g., unanticipated problems involving risk to subjects or others, noncompliance, breaches of confidentiality, HIPAA violations, protocol deviations) must be reported to the IRB according to our Policies & Procedures at www.irb.emory.edu, immediately, promptly, or periodically. Be sure to check the reporting guidance and contact us if you have questions. Terms and conditions of sponsors, if any, also apply to reporting.

Before implementing any change to this protocol (including but not limited to sample size, informed consent, and study design), you must submit an amendment request and secure IRB approval.

In future correspondence about this matter, please refer to the IRB file ID, name of the Principal Investigator, and study title. Thank you.

Sincerely,

Heather Smith, MS
IRB Analyst Assistant
This letter has been digitally signed

CC:			
	Coleman	Karlene	Nursing - Main
	Cubells	Joseph	H.Genetics
	Fernandez-Carriba	Samuel	Marcus Center
	Hannah	Haylea	Public Health
	Kobrynski	Lisa	Allergy
	Last	Rohini	Medical School
	Muldoon	Meghan	Public Health
	Oster	Matthew	RTP
	Ousley	Opal	Psychiatry - Main
	Sarrett	Jennifer	ECAS: Center for the Study of Human Health
	Weng	Lei	Public Health

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - E-mail: irb@emory.edu - Web: http://www.irb.emory.edu/
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EMORY UNIVERSITY | Institutional Review Board

TO: Bradley Pearce, PhD
Principal Investigator
SPH: Epidemiology

DATE: December 14, 2015

RE: **Continuing Review Expedited Approval**
CR5_IRB00045086

IRB00045086
Pathophysiological mechanisms of autism risk in patients with 22q11 deletion syndrome

Thank you for submitting a renewal application for this protocol. The Emory IRB reviewed it by the expedited process on 12/10/2015, per 45 CFR 46.110, the Federal Register expeditable category(ies) [insert category(ies)], and/or 21 CFR 56.110. This reapproval is effective from **12/11/2015** through **12/10/2016**. Thereafter, continuation of human subjects research activities requires the submission of another renewal application, which must be reviewed and approved by the IRB prior to the expiration date noted above. Please note carefully the following items with respect to this reapproval:

- The following documents were reviewed in this submission:
  - IRB00045086CleanUpdate2012, modified date: 10/10/2012
  - CHILD PHONE Scriptbpjan2012, modified date: 1/19/2012
  - Consent_22q11, modified date: 11/17/2011
  - Phone script22q11, modified date: 11/17/2011

Any reportable events (e.g., unanticipated problems involving risk to subjects or others, noncompliance, breaches of confidentiality, HIPAA violations, protocol deviations) must be reported to the IRB according to our Policies & Procedures at www.irb.emory.edu, immediately, promptly, or periodically. Be sure to check the reporting guidance and contact us if you have questions. Terms and conditions of sponsors, if any, also apply to reporting.

Before implementing any change to this protocol (including but not limited to sample size, informed consent, and study design), you must submit an amendment request and secure IRB approval.

In future correspondence about this matter, please refer to the IRB file ID, name of the Principal Investigator, and study title. Thank you.

Sincerely,

Heather Smith, MS
Research Protocol Analyst
This letter has been digitally signed

CC:			
	Coleman	Karlene	*SON: Nursing Research
	Cubells	Joseph	*SOM: Hum Gen: Admin
	Fernandez Carriba	Samuel	SOM: Peds: Marcus Center
	Hannah	Haylea	SPH: Career Services
	Kobrynski	Lisa	SOM: Peds: Allergy
	Muldoon	Meghan	SPH: Career Services
	Oster	Matthew	SOM: Peds: Children's Hrt Ctr
	Ousley	Opal	*SOM: Psych: Admin
	Sarrett	Jennifer	*ECAS: Ctr Study Human Health
	Weng	Lei	SPH: Career Services

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu/

Appendix 1: Variables Examined for CHOA Data Pull.

General Variables

- Birth History
    - Emergency C-section
    - Gestational Age
    - Birthweight and percentile
    - Apgar score at 1, 5, 10 min
- Calcium and Albumin– value and date
- Phosphorus – value and date
- PTH – value, interpretation and date
- Thyroid- date, values (TSH, Free T4, Free T3, Total T3, Thyroid Antibodies, Calcitonin, Thyroglobulin), interpretation
- Vitamin D – Levels if available and notes of medication used to treat (may be in discharge summary or progress notes) – examples: Tums, Calcium Carbonate, Calcitriol, Vitamin D, ergocalciferol, cholecalciferol
- 22Q diagnosis (FISH or Microarray result)- deletion size if applicable
- Thymus (yes/no)- radiology or cardiovascular surgery report
    - If there is a radiology or cardiovascular surgery report, need to know if any of following phrases present:
        - Thymus present
        - Thymus absent
        - No thymus seen
        - Small thymus
        - Partial thymus
        - Large thymus
        - Missing thymus
        - Abnormal thymus (specify details if listed)
- Mitogens- PHA, Con A, PWM
- CD3, CD4, CD8, CD19, CD56 – count, percentage and date
- WBC count, Lymphocyte percentage and date
- Absolute lymphocyte total count and date
- IgA, IgG, IgM, IgE levels and date
- Vaccines: tetanus, pneumococcus, measles, diphtheria, rubella, varicelle zoster virus (protective titer values), reactions to vaccines
- If available, treatment and outcomes of above abnormalities.

Cardiac Related

ICD-9 CODE	ICD-9 CODE DESCRIPTION
745.2	TETRALOGY OF FALLOT
745.4	VENTRICULAR SEPTAL DEFECT
745.0	COMMON TRUNCUS (Includes arteriosus)
746.1	TRICUSPID ATRESIA AND STENOSIS CONGENITAL
746.7	HYPOPLASTIC LEFT HEART SYNDROME
746.01	ATRESIA OF PULMONARY VALVE CONGENITAL
747.31	PULMONARY ARTERY COARCTATION AND ATRESIA
745.10	COMPLETE TRANSPOSITION OF GREAT VESSELS

745.12 CORRECTED TRANSPOSITION OF GREAT VESSELS
745.19 OTHER TRANSPOSITION OF GREAT VESSELS
747.41 TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION
747.42 PARTIAL ANOMALOUS PULMONARY VENOUS CONNECTION
747.10 COARCTATION OF AORTA (PREDUCTAL) (POSTDUCTAL)
745.11 DOUBLE OUTLET RIGHT VENTRICLE
746.2 EBSTEIN'S ANOMALY
747.11 INTERRUPTION OF AORTIC ARCH
747.21 CONGENITAL ANOMALIES OF AORTIC ARCH
746.9 UNSPECIFIED CONGENITAL ANOMALY OF HEART (Including CHD)
747.31 PULMONARY ARTERY COARCTATION AND ATRESIA
745.5 OSTIUM SECUNDUM TYPE ATRIAL SEPTAL DEFECT
Additional sum ICD-9 codes: 745.0- 746.85, 746.87-746.9, 747.1-747.4, 747.9

Palate Related

ICD-9 CODE ICD-9 CODE DESCRIPTION
749.00 CLEFT PALATE UNSPECIFIED
749.01 CLEFT PALATE UNILATERAL COMPLETE
749.02 CLEFT PALATE UNILATERAL INCOMPLETE
749.03 CLEFT PALATE BILATERAL COMPLETE
749.04 CLEFT PALATE BILATERAL INCOMPLETE
749.20 CLEFT PALATE WITH CLEFT LIP UNSPECIFIED
749.21 CLEFT PALATE WITH CLEFT LIP UNILATERAL COMPLETE
749.22 CLEFT PALATE WITH CLEFT LIP UNILATERAL INCOMPLETE
749.23 CLEFT PALATE WITH CLEFT LIP BILATERAL COMPLETE
749.24 CLEFT PALATE WITH CLEFT LIP BILATERAL INCOMPLETE
749.25 OTHER COMBINATIONS OF CLEFT PALATE WITH CLEFT LIP

G-tube Related

ICD-9 CODE ICD-9 CODE DESCRIPTION
536.40 GASTROSTOMY COMPLICATION UNSPECIFIED
536.41 INFECTION OF GASTROSTOMY
536.42 MECHANICAL COMPLICATION OF GASTROSTOMY
536.49 OTHER GASTROSTOMY COMPLICATIONS
V44.1 GASTROSTOMY STATUS
V55.1 ATTENTION TO GASTROSTOMY

Nasogastric Tube Related – no good option here

ICD-9 CODE ICD-9 CODE DESCRIPTION
V53.59 FITTING AND ADJUSTMENT OF OTHER GASTROINTESTINAL APPLIANCE AND DEVICE
783.3 FEEDING DIFFICULTIES AND MISMANAGEMENT

Constipation Related

ICD-9 CODE ICD-9 CODE DESCRIPTION
564.00 UNSPECIFIED CONSTIPATION
564.01 SLOW TRANSIT CONSTIPATION
564.02 OUTLET DYSFUNCTION CONSTIPATION
564.09 OTHER CONSTIPATION

Reflux Related

ICD-9 CODE	ICD-9 CODE DESCRIPTION
530.81	ESOPHAGEAL REFLUX

GERD Related

ICD-9 CODE	ICD-9 CODE DESCRIPTION
530.81	ESOPHAGEAL REFLUX

Vomiting Related

ICD-9 CODE	ICD-9 CODE DESCRIPTION
536.2	PERSISTENT VOMITING
779.33	OTHER VOMITING IN NEWBORN
787.01	NAUSEA WITH VOMITING
787.03	VOMITING ALONE

Diarrhea Related

ICD-9 CODE	ICD-9 CODE DESCRIPTION
564.5	FUNCTIONAL DIARRHEA
787.91	DIARRHEA

Abdominal Pain Related

ICD-9 CODE	ICD-9 CODE DESCRIPTION
789.00	ABDOMINAL PAIN UNSPECIFIED SITE
789.01	ABDOMINAL PAIN RIGHT UPPER QUADRANT
789.02	ABDOMINAL PAIN LEFT UPPER QUADRANT
789.03	ABDOMINAL PAIN RIGHT LOWER QUADRANT
789.04	ABDOMINAL PAIN LEFT LOWER QUADRANT
789.05	ABDOMINAL PAIN PERIUMBILIC
789.06	ABDOMINAL PAIN EPIGASTRIC
789.07	ABDOMINAL PAIN GENERALIZED
789.09	ABDOMINAL PAIN OTHER SPECIFIED SITE

Craniofacial Related

ICD-9 CODE	ICD-9 CODE DESCRIPTION
756.0	CONGENITAL ANOMALIES OF SKULL AND FACE BONES

Hearing Related

ICD-9 CODE	ICD-9 CODE DESCRIPTION
315.34	SPEECH AND LANGUAGE DEVELOPMENTAL DELAY DUE TO HEARING LOSS
388.12	NOISE-INDUCED HEARING LOSS
388.2	SUDDEN HEARING LOSS UNSPECIFIED
389.00	CONDUCTIVE HEARING LOSS UNSPECIFIED
389.01	CONDUCTIVE HEARING LOSS EXTERNAL EAR
389.02	CONDUCTIVE HEARING LOSS TYMPANIC MEMBRANE
389.03	CONDUCTIVE HEARING LOSS MIDDLE EAR
389.04	CONDUCTIVE HEARING LOSS INNER EAR
389.05	CONDUCTIVE HEARING LOSS, UNILATERAL
389.06	CONDUCTIVE HEARING LOSS, BILATERAL
389.08	CONDUCTIVE HEARING LOSS OF COMBINED TYPES
389.10	SENSORINEURAL HEARING LOSS UNSPECIFIED
389.11	SENSORY HEARING LOSS, BILATERAL
389.12	NEURAL HEARING LOSS, BILATERAL

389.13 NEURAL HEARING LOSS, UNILATERAL
389.14 CENTRAL HEARING LOSS
389.15 SENSORINEURAL HEARING LOSS, UNILATERAL
389.16 SENSORINEURAL HEARING LOSS, ASYMMETRICAL
389.17 SENSORY HEARING LOSS, UNILATERAL
389.18 SENSORINEURAL HEARING LOSS, BILATERAL
389.20 MIXED HEARING LOSS, UNSPECIFIED
389.21 MIXED HEARING LOSS, UNILATERAL
389.22 MIXED HEARING LOSS, BILATERAL
389.8 OTHER SPECIFIED FORMS OF HEARING LOSS
389.9 UNSPECIFIED HEARING LOSS
V41.2 PROBLEMS WITH HEARING

Endocrine Related

ICD-9 Code	ICD-9 Code Description
275.41	HYPOCALCEMIA
243	CONGENITAL HYPOTHYROIDISM
244.0	POSTSURGICAL HYPOTHYROIDISM
252.1	HYPOPARATHYROIDISM
245.2	HASHIMOTO'S THYROIDITIS (AUTOIMMUNE HYPOTHYROIDISM)
268	HYPOVITAMINOSIS D (RICKETS & OTHERWISE UNSPECIFIED DEFICIENCY)
275.49	PSUEDOHYPOPARATHYROIDISM
790.6	OTHER ABNORMAL BLOOD CHEMISTRY
794.5	NONSPECIFIC ABNORMAL RESULTS OF FUNCTION STUDY OF THYROID
794.6	NONSPECIFIC ABNORMAL RESULTS OF OTHER ENDOCRINE FUNCTION STUDY

SAS Output

ABC SCORES WITH CALCIUM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Number of Observations Read	10
Number of Observations Used	10

ABC SCORES WITH CALCIUM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Dependent Variable: abcs1r abcs1r

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	466.3561943	233.1780971	4.86	0.0474
Error	7	335.7438057	47.9634008		
Corrected Total	9	802.1000000			

R-Square	Coeff Var	Root MSE	abcs1r Mean
0.581419	56.30538	6.925561	12.30000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
CALCIUM_RESULT	1	442.7176455	442.7176455	9.23	0.0189
sex	1	23.6385487	23.6385487	0.49	0.5053

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CALCIUM_RESULT	1	277.7800038	277.7800038	5.79	0.0470
sex	1	23.6385487	23.6385487	0.49	0.5053

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	42.78766105	15.93478101	2.69	0.0313
CALCIUM_RESULT	-4.25049554	1.76621700	-2.41	0.0470
sex	3.74814172	5.33900815	0.70	0.5053

ABC SCORES WITH CALCIUM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Number of Observations Read	10
Number of Observations Used	10

ABC SCORES WITH CALCIUM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Dependent Variable: abcs3r abcs3r

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	23.43588330	11.71794165	4.39	0.0580
Error	7	18.66411670	2.66630239		
Corrected Total	9	42.10000000			

R-Square	Coeff Var	Root MSE	abcs3r Mean
0.556672	96.05186	1.632882	1.700000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
CALCIUM_RESULT	1	21.32747407	21.32747407	8.00	0.0255
sex	1	2.10840923	2.10840923	0.79	0.4034

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CALCIUM_RESULT	1	22.85969282	22.85969282	8.57	0.0221
sex	1	2.10840923	2.10840923	0.79	0.4034

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	11.98222250	3.75703997	3.19	0.0153
CALCIUM_RESULT	-1.21933845	0.41643169	-2.93	0.0221
sex	-1.11939420	1.25881033	-0.89	0.4034

ABC SCORES WITH CALCIUM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Number of Observations Read	10
Number of Observations Used	10

ABC SCORES WITH CALCIUM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Dependent Variable: abcs4r abcs4r

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	740.250149	370.125074	2.97	0.1166
Error	7	873.349851	124.764264		
Corrected Total	9	1613.600000			

R-Square	Coeff Var	Root MSE	abcs4r Mean
0.458757	53.70093	11.16979	20.80000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
CALCIUM_RESULT	1	738.2229611	738.2229611	5.92	0.0453
sex	1	2.0271876	2.0271876	0.02	0.9022

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CALCIUM_RESULT	1	561.0311010	561.0311010	4.50	0.0717
sex	1	2.0271876	2.0271876	0.02	0.9022

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	67.08820614	25.70018326	2.61	0.0349
CALCIUM_RESULT	-6.04063429	2.84861778	-2.12	0.0717
sex	1.09762141	8.61094280	0.13	0.9022

ADI SOCIAL SCORE WITH IGM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Number of Observations Read	23
Number of Observations Used	23

ADI SOCIAL SCORE WITH IGM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Dependent Variable: adisoc adisoc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	31.6695227	15.8347614	0.37	0.6934
Error	20	849.2869990	42.4643500		
Corrected Total	22	880.9565217			

R-Square	Coeff Var	Root MSE	adisoc Mean
0.035949	65.44924	6.516468	9.956522

Source	DF	Type I SS	Mean Square	F Value	Pr > F
IGM_RESULT	1	0.47732029	0.47732029	0.01	0.9166
sex	1	31.19220244	31.19220244	0.73	0.4016

Source	DF	Type III SS	Mean Square	F Value	Pr > F
IGM_RESULT	1	2.64950893	2.64950893	0.06	0.8053
sex	1	31.19220244	31.19220244	0.73	0.4016

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	8.079065096	2.89087171	2.79	0.0112
IGM_RESULT	0.003107546	0.01244077	0.25	0.8053
sex	2.421220442	2.82503317	0.86	0.4016

CBCL SCORES WITH IGM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Number of Observations Read	17
Number of Observations Used	17

CBCL SCORES WITH IGM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Dependent Variable: cbcltotpr cbcltotpr

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	985.111136	492.555568	1.01	0.3887
Error	14	6815.830041	486.845003		
Corrected Total	16	7800.941176			

R-Square	Coeff Var	Root MSE	cbcltotpr Mean
0.126281	42.47991	22.06456	51.94118

Source	DF	Type I SS	Mean Square	F Value	Pr > F
IGM_RESULT	1	684.7261227	684.7261227	1.41	0.2554
sex	1	300.3850128	300.3850128	0.62	0.4453

Source	DF	Type III SS	Mean Square	F Value	Pr > F
IGM_RESULT	1	350.2305651	350.2305651	0.72	0.4106
sex	1	300.3850128	300.3850128	0.62	0.4453

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	51.23137914	12.67625401	4.04	0.0012
IGM_RESULT	-0.05054374	0.05959169	-0.85	0.4106
sex	9.35350851	11.90777922	0.79	0.4453

CBCL SCORES WITH IGM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Number of Observations Read	17
Number of Observations Used	17

CBCL SCORES WITH IGM RESULT, CONTROLLING FOR SEX

The GLM Procedure

Dependent Variable: cbclepr cbclepr

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	374.079084	187.039542	2.38	0.1286
Error	14	1098.979739	78.498553		
Corrected Total	16	1473.058824			

R-Square	Coeff Var	Root MSE	cbclepr Mean
0.253947	78.85811	8.859941	11.23529

Source	DF	Type I SS	Mean Square	F Value	Pr > F
IGM_RESULT	1	312.2275927	312.2275927	3.98	0.0660
sex	1	61.8514918	61.8514918	0.79	0.3897

Source	DF	Type III SS	Mean Square	F Value	Pr > F
IGM_RESULT	1	194.3990488	194.3990488	2.48	0.1379
sex	1	61.8514918	61.8514918	0.79	0.3897

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	12.46922285	5.09010100	2.45	0.0281
IGM_RESULT	-0.03765628	0.02392881	-1.57	0.1379
sex	4.24434331	4.78152291	0.89	0.3897

CBCL INTERNALIZING PROBLEMS SCORE WITH IGG RESULT, CONTROLLING FOR SEX

The GLM Procedure

Number of Observations Read	17
Number of Observations Used	17

CBCL INTERNALIZING PROBLEMS SCORE WITH IGG RESULT, CONTROLLING FOR SEX

The GLM Procedure

Dependent Variable: cbclipr cbclipr

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	66.3857505	33.1928753	0.76	0.4848
Error	14	609.1436612	43.5102615		
Corrected Total	16	675.5294118			

R-Square	Coeff Var	Root MSE	cbclipr Mean
0.098272	53.65355	6.596231	12.29412

Source	DF	Type I SS	Mean Square	F Value	Pr > F
IGG_RESULT	1	48.58182427	48.58182427	1.12	0.3086
sex	1	17.80392626	17.80392626	0.41	0.5327

Source	DF	Type III SS	Mean Square	F Value	Pr > F
IGG_RESULT	1	14.18967210	14.18967210	0.33	0.5770
sex	1	17.80392626	17.80392626	0.41	0.5327

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	11.75275513	5.76953881	2.04	0.0610
IGG_RESULT	0.00218325	0.00382308	0.57	0.5770
sex	-2.50550825	3.91682159	-0.64	0.5327

ANALYSIS OF CALCIUM AND THYMUS

The GLM Procedure

Class Level Information		
Class	Levels	Values
THYMUS	3	1 2 3

Number of Observations Read	339
Number of Observations Used	48

ANALYSIS OF CALCIUM AND THYMUS

The GLM Procedure

Dependent Variable: CALCIUM_RESULT CALCIUM_RESULT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	5	2.55310384	0.51062077	0.35	0.8819
Error	42	61.97502116	1.47559574		
Corrected Total	47	64.52812500			

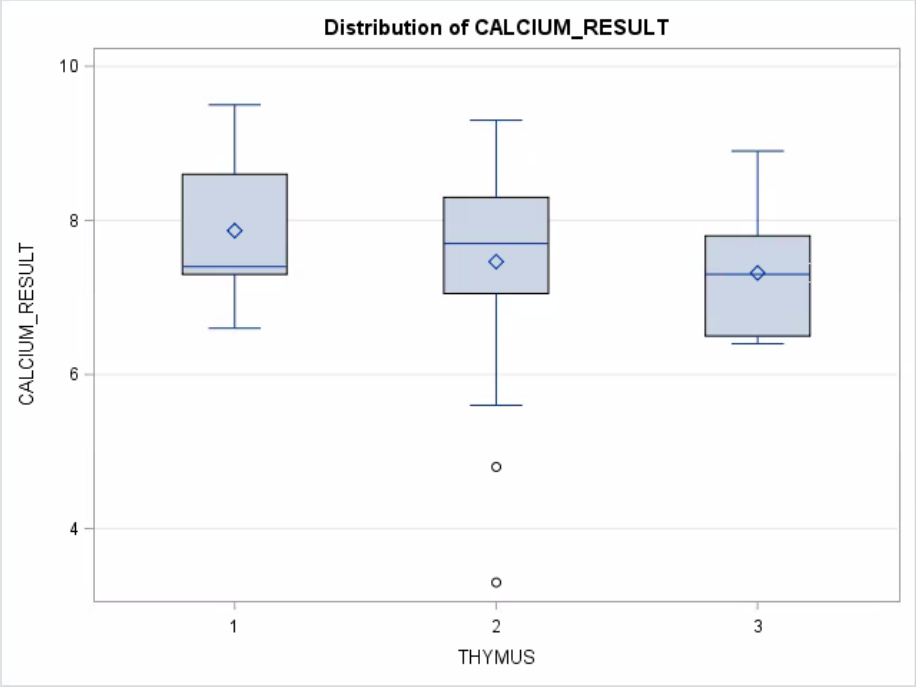
R-Square	Coeff Var	Root MSE	CALCIUM_RESULT Mean
0.039566	16.18306	1.214741	7.506250

Source	DF	Type I SS	Mean Square	F Value	Pr > F
THYMUS	2	1.60747565	0.80373782	0.54	0.5841
race	1	0.79287832	0.79287832	0.54	0.4676
sex	1	0.01257979	0.01257979	0.01	0.9269
CA_AGE	1	0.14017008	0.14017008	0.09	0.7594

Source	DF	Type III SS	Mean Square	F Value	Pr > F
THYMUS	2	2.24979612	1.12489806	0.76	0.4729
race	1	0.84339775	0.84339775	0.57	0.4539
sex	1	0.02303360	0.02303360	0.02	0.9012
CA_AGE	1	0.14017008	0.14017008	0.09	0.7594

ANALYSIS OF CALCIUM AND THYMUS

The GLM Procedure



Level of THYMUS	N	CALCIUM_RESULT		race		sex		CA_AGE	
		Mean	Std Dev	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
1	9	7.86666667	0.99121138	6.00000000	1.22474487	0.66666667	0.50000000	1.40934270	3.26143517
2	28	7.46428571	1.32475415	5.25000000	1.14260910	0.39285714	0.49734746	0.35794893	0.77199359
3	11	7.31818182	0.87614860	4.36363636	1.36181697	0.63636364	0.50452498	1.36008096	3.16743283

ANALYSIS OF CALCIUM AND THYMUS

The GLM Procedure

Class Level Information		
Class	Levels	Values
THYMUS	3	1 2 3

Number of Observations Read	100
Number of Observations Used	16

ANALYSIS OF CALCIUM AND THYMUS

The GLM Procedure

Dependent Variable: PTH_RESULT PTH_RESULT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	5	324.271264	64.854253	0.39	0.8431
Error	10	1652.233111	165.223311		
Corrected Total	15	1976.504375			

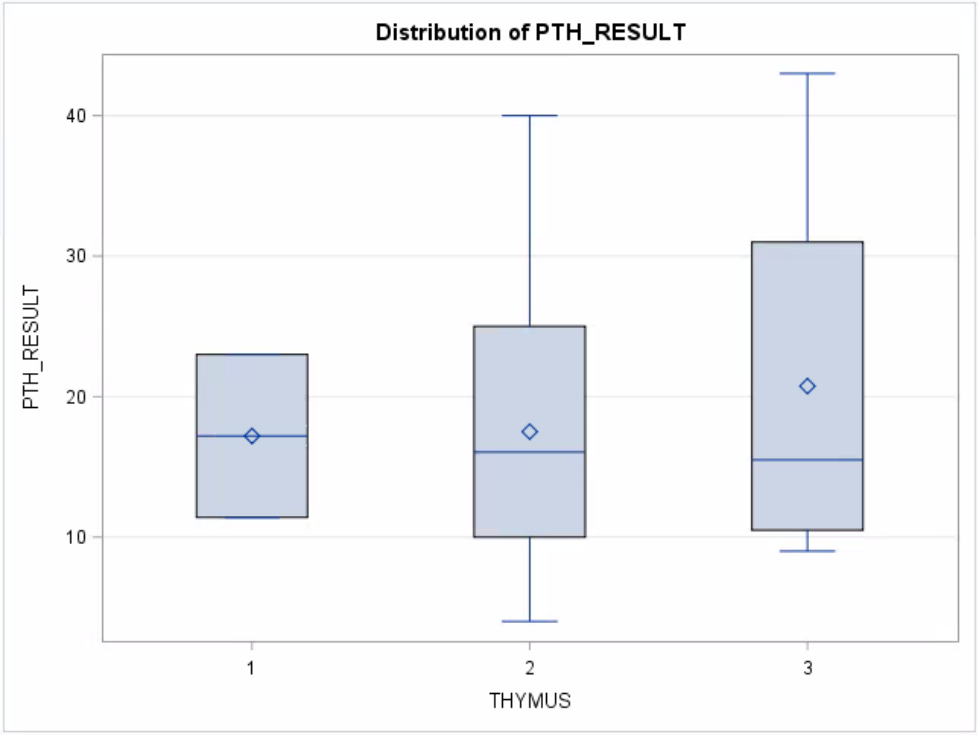
R-Square	Coeff Var	Root MSE	PTH_RESULT Mean
0.164063	70.31205	12.85392	18.28125

Source	DF	Type I SS	Mean Square	F Value	Pr > F
THYMUS	2	32.6653750	16.3326875	0.10	0.9068
PTH_AGE	1	16.9217834	16.9217834	0.10	0.7555
sex	1	274.2813502	274.2813502	1.66	0.2266
race	1	0.4027552	0.4027552	0.00	0.9616

Source	DF	Type III SS	Mean Square	F Value	Pr > F
THYMUS	2	119.0804807	59.5402403	0.36	0.7061
PTH_AGE	1	9.9491024	9.9491024	0.06	0.8111
sex	1	239.8589785	239.8589785	1.45	0.2560
race	1	0.4027552	0.4027552	0.00	0.9616

ANALYSIS OF CALCIUM AND THYMUS

The GLM Procedure



Level of THYMUS	N	PTH_RESULT		PTH_AGE		sex		race	
		Mean	Std Dev	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
1	2	17.2000000	8.2024387	-59.2640771	1.00913156	1.00000000	0.00000000	6.00000000	1.41421356
2	10	17.5100000	11.3715483	-58.0623829	3.26024108	0.40000000	0.51639778	5.20000000	1.13529242
3	4	20.7500000	15.4137385	-55.7853929	5.47497573	0.75000000	0.50000000	4.75000000	0.95742711