AWARD NUMBER:     W81XWH-15-1-0354

TITLE:   "Neural Correlates of the Y Chromosome in Autism: XYY Syndrome as a Genetic Model"

PRINCIPAL INVESTIGATOR:    Timothy Roberts

CONTRACTING ORGANIZATION:  Children’s Hospital of Philadelphia
                           Philadelphia, PA 19104

REPORT DATE:   September 2016

TYPE OF REPORT:  Annual

PREPARED FOR:   U.S. Army Medical Research and Materiel Command
                           Fort Detrick, Maryland  21702-5012

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                           Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
A multimodal MRI, MRS and MEG (magnetoencephalography) design is employed in cohorts of boys with XYY, who are symptomatic for ASD and control cohorts of idiopathic ASD (ASD-I) and typical development (TD). Targeted recruitment for year 1 totaled 30 enrolled. At the point of this report, 25 subjects have been enrolled, 5 were eliminated for not meeting inclusion criteria upon clinical assessment, 19 have completed data acquisition, and 1 is pending imaging completion. Three of the 19 are pending confirmation of ASD diagnosis. Several more are in various stages of recruitment, scheduling, neuropsychological evaluation or imaging. MRI, MRS and MEG examinations have been conducted in the 17 subjects above with confirmed diagnoses (8TD, 8XYY+ASD, 1 ASD-I). QA suggests in general that complete studies have been tolerated and that data quality is good in the majority of cases. Additional steps to remove MEG trials corrupted by excessive head motion are underway to improve further the evaluable data yield. Data analysis is ongoing, priority having been given to standard approaches for MEG (source localization in BESA followed by consensus “peak” picking), MRS (alignment of “on” and “off” spectra, then subtraction and Gaussian modeling of the GABA and Cr resonances in GANNET) and DTI/HARDI. As mentioned above, about 50% of the data tolerated this strategy robustly. The remaining data are undergoing “scrubbing” to eliminate motion-related artifacts and reduce noise, to accommodate comparable analysis – these data are likely evaluable, but are not reported herein. Dependent variable extraction is underway and preliminary data are shown for illustration of feasibility. It is premature to conduct formal statistical analyses. Recruitment, acquisition and analysis is on track and completion is anticipated in the remaining 12 months of this award.
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1. INTRODUCTION

(Technical abstract from application): This proposal addresses two topics of great importance to the ASD community: mechanisms of heterogeneous clinical expression of ASD and mechanisms underlying conditions co-occurring with ASD, including seizures, attention, and anxiety disorders. Autism affects ~1% of the population (4:1 male predominance) and is heterogeneous with regard to etiological/risk factors, pathogenesis, and clinical presentations. Heritability studies have shown that genetic factors are important in ASD, but dissecting out the relationships among genes, imaging biomarkers, and behavioral phenotypes of ASD is confounded by both genetic heterogeneity and the paucity of neurobiological models. These problems can be circumvented by studying genetically defined ASD subgroups such as 47,XYY syndrome (XYY). XYY occurs in ~0.1% of the male population but has been reported in up to 1% of males with ASD. Approximately 33% of males with XYY satisfy diagnostic criteria for ASD (XYY+ASD). The behavioral and neuroimaging biomarkers of XYY+ASD identified in our preliminary studies overlap with those described in ASD-I and, similarly, comorbidities (seizures, attention, and anxiety disorders) exhibited in XYY+ASD are representative of those described in ASD-I. In this proposed study, we will examine the behavioral, neurophysiological and neuroimaging markers of ASD, and specifically compare the variance (heterogeneity) of these measures in XYY+ASD versus ASD-I. Having established the level at which XYY+ASD confers imaging/phenotypic heterogeneity reduction, the mechanism underlying these measures will be probed via neurochemical magnetic resonance spectroscopy of key neurotransmitters and myelin mapping. Clinically meaningful associations between such measures and behavioral ASD phenotypes will be identified.

A multimodal MRI, MRS and MEG (magnetoencephalography) design is employed in cohorts of boys with XYY, who are symptomatic for ASD and control cohorts of idiopathic ASD (ASD-I) and typical development (TD).

2. KEYWORDS

Autism spectrum disorder, ASD
47,XYY syndrome (XYY)
neuroimaging
MRI
MEG
Comorbid behaviors
3. ACCOMPLISHMENTS

What were the major goals of the project?

(from SOW): **Major Task 1:** Regulatory review and approval processes for studies involving human subjects at 2 sites (CHOP and TJU).

**Major Task 2:** Recruitment

**Major Task 3:** Data Acquisition

**Major Task 4:** Data Analysis

What was accomplished under these goals?

**Major Task 1:** Regulatory review and approval processes for studies involving human subjects at 2 sites (CHOP and Nemours/DuPont Hospital for Children).

All study protocols have been submitted reviewed and approved by both local IRB’s (CHOP / Nemours/DuPont Hospital for Children) as well as central DoD ethics review. Furthermore, since the co-PI Dr. Judith Ross moved to Nemours/DuPont Hospital for Children prior to commencement of this grant funding, approval was obtained by Nemours/DuPont Hospital for Children and all materials were reviewed by DoD. Where appropriate continuing renewal submissions have been submitted and approved in a timely fashion.

**Major Task 2:** Recruitment

Targeted recruitment for year 1 totaled 30 enrolled. At the point of this report, 25 subjects have been enrolled, 5 were eliminated for not meeting inclusion criteria upon clinical assessment, 19 have completed data acquisition, and 1 is pending imaging completion. Three of the 19 are pending confirmation of ASD diagnosis. Several more are in various stages of recruitment, scheduling, neuropsychological evaluation or imaging.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>8</td>
</tr>
<tr>
<td>XYY+ASD</td>
<td>8</td>
</tr>
<tr>
<td>ASD-I</td>
<td>1</td>
</tr>
<tr>
<td>XYY-unknown</td>
<td>3 (waiting on status)</td>
</tr>
<tr>
<td>XYY not meeting inclusion criteria</td>
<td>5</td>
</tr>
<tr>
<td>(Enrolled but not evaluable)</td>
<td></td>
</tr>
</tbody>
</table>
Major Task 3: Data Acquisition

MRI, MRS and MEG examinations have been conducted in the 17 subjects above with confirmed diagnoses (8TD, 8XYY+ASD, 1 ASD-I). QA suggests in general that complete studies have been tolerated and that data quality is good in the majority of cases. Additional steps to remove MEG trials corrupted by excessive head motion are underway to improve further the evaluable data yield.

Major Task 4: Data Analysis

Data analysis is ongoing, priority having been given to standard approaches for MEG (source localization in BESA followed by consensus “peak” picking), MRS (alignment of “on” and “off” spectra, then subtraction and Gaussian modeling of the GABA and Cr resonances in GANNET) and DTI/HARDI. As mentioned above, about 50% of the data tolerated this strategy robustly. The remaining data are undergoing “scrubbing” to eliminate motion-related artifacts and reduce noise, to accommodate comparable analysis – these data are likely evaluable, but are not reported herein. Dependent variable extraction is underway and preliminary data are shown for illustration of feasibility. It is premature to conduct formal statistical analyses.

Preliminary / Feasibility Analysis and Trend Observation of Dependent Variables acquired under Major Task 3 and Analyzed in Major Task 4:

Fig. 1a MEG recorded auditory evoked field source waveforms from right hemisphere Heschl’s gyrus in a representative 17-year old with typical development (blue) vs. an XYY participant on the autism spectrum (XYY+ASD), who exhibits a profound delay in the M100 peak (arrows).

Fig. 1b Age dependence of M100 latency in TD (red) and XYY+ASD (green) shows maturational trajectory towards shortening (as has been previously reported in both TD and ASD-I). Note that at any given age the offset between TD latency and XYY+ASD latency is approx. 20ms, consistent with the individual depicted in Fig 1a. Note previous reports in ASD-I have discussed ~10ms analogous M100 latency delays.
Fig. 2a High Angular Resolution Diffusion Imaging (HARDI) allows depiction of the thalamocortical projections of the white matter auditory pathway – the acoustic radiations (red) without the confounds of fiber crossing and complex white matter architecture that limit typical DTI. These masked regions can then be interrogated to reveal parameters (e.g. fractional anisotropy, FA, and mean diffusivity, MD, associated with local white matter microstructure.

Fig. 2b Interrogating a HARDI-defined mask in the left acoustic radiation shows an anticipated maturational trend towards decreasing values ($R^2=58\%$) – it is premature to assess Group differences in the slope of this trajectory. Analogous data (not shown) show maturational trajectories for the right hemisphere acoustic radiations and for fractional anisotropy (rather than MD).

Fig. 3a Edited magnetic resonance spectra are acquired using the modified (macromolecular-suppressed) MEGAPRESS sequence from a voxel in left superior temporal gyrus and aligned to improve editing subtraction using the GANNET software package. A GABA resonance can be identified in the subtracted spectrum at 3.01 ppm (arrow).
Table 2. Co-morbidities associated with XYY+ASD

<table>
<thead>
<tr>
<th>Medical and Psychiatric diagnoses or clinically significant findings</th>
<th>XYY+ASD (n=8)</th>
<th>TD (n=8)</th>
<th>Childhood Prevalence</th>
<th>Prevalence in ASD-I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEATURES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotonia</td>
<td>7 (88%)</td>
<td>0</td>
<td>0.1 – 22%</td>
<td>51%</td>
</tr>
<tr>
<td>Tremor</td>
<td>2 (25%)</td>
<td>0</td>
<td>1%</td>
<td>34%</td>
</tr>
<tr>
<td><strong>MEDICAL DIAGNOSES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor Delay/Dyspraxia</td>
<td>6 (75%)</td>
<td>0</td>
<td>&lt;5%</td>
<td>34%</td>
</tr>
<tr>
<td>Seizures</td>
<td>0</td>
<td>0</td>
<td>1%</td>
<td>14-35%</td>
</tr>
<tr>
<td><strong>PSYCHIATRIC DIAGNOSES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADD or ADHD</td>
<td>5 (63%)</td>
<td>0</td>
<td>2 – 16%</td>
<td>28%</td>
</tr>
<tr>
<td>Verbal or Motor Tic</td>
<td>2 (25%)</td>
<td>0</td>
<td>5 – 10%</td>
<td>9%</td>
</tr>
<tr>
<td>Oppositional Defiant</td>
<td>4 (50%)</td>
<td>0</td>
<td>1 – 16%</td>
<td>30%</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (33%)</td>
<td>0</td>
<td>&lt;1%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 (75%)</td>
<td>0</td>
<td>15 – 20%</td>
<td>42%</td>
</tr>
<tr>
<td>Bipolar/mood disorder</td>
<td>1 (13%)</td>
<td>0</td>
<td>0.4 – 6.3%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Table 2. XYY is associated with significant occurrence of co-morbid behaviors/diagnoses. Although stratified analyses is premature, a later goal of this study is to identify neural features relating to such behaviors.

**What opportunities for training and professional development has the project provided?**

Nothing to report
How were the results disseminated to communities of interest?

Nothing to report, although scientific meeting abstracts are planned for fall 2016 submission

What do you plan to do during the next reporting period to accomplish the goals?

Continue / complete recruitment, acquisition and analysis. Perform statistical analyses and prepare manuscripts.
4. IMPACT

What was the impact on the development of the principal discipline(s) of the project? - Nothing to report yet

What was the impact on other disciplines? - Nothing to report yet

What was the impact on technology transfer? - Nothing to report yet

What was the impact on society beyond science and technology? - Nothing to report yet

5. CHANGES/PROBLEMS

Changes in approach and reasons for change - none

Actual or anticipated problems or delays and actions or plans to resolve them

Although there have been no significant problems encountered and no study design changes made, at present we have enrolled 25 out of a targeted 30 (per year) participants. Given a slight commencement delay, we feel this is on track. However, we have augmented our recruitment strategies to include use of the CHOP Recruitment Enhancement Core (REC) – which allows us to reach out to a larger target audience of potential participants, both typically developing and, especially, those with ASD of no known genetic etiology. We anticipate this will accelerate our recruitment, especially in the control ASD-I group.

Changes that had a significant impact on expenditures – none

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents – none

6. PRODUCTS

Publications, conference papers, and presentations – none yet

Website(s) or other Internet site(s) – none

Technologies or techniques – none

Inventions, patent applications, and/or licenses – none

Other Products – none
7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

No change: Roberts, Miller, Bloy, Ross

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

See appended current “Other Support” documentation from Drs. Roberts and Ross.

Dr. Roberts (additions):

2U54HD084964-25 (Yudkoff, Core Director: Roberts)
08/01/1997 – 10/31/2020 0.60 calendar NIH/NICHD $102,065
Intellectual and Development Disabilities Research Center: Neuroimaging/circuitry Core
The overall goal of this project is to support research at the Children’s Hospital of Philadelphia/University of Pennsylvania that is relevant to intellectual disabilities. Dr. Roberts serves as Director of the Neuroimaging/Neurocircuitry core and provides expertise with multi modal imaging and quantitative analyses of pre-clinical (micro) and clinical level images.

2U54HD084964-25 (Yudkoff, Project PI: Roberts)
11/01/2015 – 10/31/2020 1.08 calendar NIH/NICHD $151,647
Intellectual and Development Disabilities Research Center: MEG Studies in Minimally/ Non-verbal Children with ASD. This study examines brain activity in low functional children with ASD and low IQ controls to explore the extension of biomarkers associated with autism per se and language impairment in particular in lower functioning populations, not typically served by research studies.

R21-MH109158 (Roberts, PI; Ross co-PI)
7/1/2016-6/30/2018 1.2 calendar month NIH/NIMH $150,000
Structural and functional characteristics of XYY – Relationship to ASD. Goal: to compare the imaging phenotype of boys with 47,XYY syndrome +/- ASD diagnosis. Although there is considerable scientific synergy with the present R21 proposal, and indeed the inclusion of an XYY cohort negative for ASD was a final recommendation (post-funding) of the DoD peer-review, there is no budgetary overlap. The R21 specifically addresses the question that within XYY carriers, is there an imaging phenotype difference between those with symptoms of ASD vs. those without (a vital question about which imaging phenotypes are common to XYY and which vary based on ASD diagnosis). This question could not be addressed within the scope of the DoD proposal, although we were indeed recommended to pursue other funding to address this specific question, which will augment the scientific goals of the present proposal. Cohorts compared will consist only of XYY+ASD and XYY-ASD. Thus the two studies will both recruit some XYY+ASD subjects (33% of the DoD recruitment, 50% of the R21 recruitment). This will serve to increase the N in this heterogeneous group and improve our statistical power, as well as providing exactly contemporaneous recruitment within each study itself (to control for seasonal and/or systematic time-varying changes).
Dr. Ross:

**R21 MH109158-01A1** (MPI: Roberts, Ross)
04/01/16-3/31/18 1.2 calendar NIH/NIMH $150,000
Structural and Functional Characteristics of XYY - Relationship to ASD (See above)

**1P30GM114736-01** (PI: Shaffer, co-I: Ross)
08/01/2015 – 07/31/2020 1.2 calendar NIH/NIGMS $750,000
Center for Pediatric Research (CPR)
This COBRE Phase III grant builds on the success of COBRE Phase I and II and will sustain
the infrastructure cores, mentorship program and pilot project programs to provide the Center
for Pediatric Research with the resources to drive translational research programs focused on
pediatric diseases at Nemours.

*What other organizations were involved as partners?*

Nemours / Dupont Hospital for Children

8. **SPECIAL REPORTING REQUIREMENTS:** None

9. **APPENDICES:** None
### ACTIVE

<table>
<thead>
<tr>
<th>Grant Number</th>
<th>Title</th>
<th>Principal Investigator</th>
<th>Start Date – End Date</th>
<th>Calendar Time</th>
<th>Agency</th>
<th>Total Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>2U54HD086984-25</td>
<td>Intellectual and Development Disabilities Research Center</td>
<td>Roberts</td>
<td>08/01/1997 – 10/31/2020</td>
<td>0.6 calendar</td>
<td>NIH/NICHD</td>
<td>$102,065</td>
</tr>
<tr>
<td></td>
<td>The overall goal of this project is to support research at the Children's Hospital of Philadelphia/University of Pennsylvania that is relevant to intellectual disabilities. Dr. Roberts serves as Director of the Neuroimaging/Neurocircuitry core and provides expertise with multi modal imaging and quantitative analyses of pre-clinical (micro) and clinical level images.</td>
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<tr>
<td>2U54HD086984-25</td>
<td>Intellectual and Development Disabilities Research Center: MEG Studies in Minimally/Non-verbal Children with ASD</td>
<td>Roberts</td>
<td>11/01/2015 – 10/31/2020</td>
<td>1.08 calendar</td>
<td>NIH/NICHD</td>
<td>$151,647</td>
</tr>
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<td></td>
<td>This study examines brain activity in low functional children with ASD and low IQ controls to explore the extension of biomarkers associated with autism per se and language impairment in particular in lower functioning populations, not typically served by research studies.</td>
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<tr>
<td>R01DC008871-07A1</td>
<td>Electrophysiological signatures of language impairment in autism spectrum disorder</td>
<td>Roberts</td>
<td>09/18/2014-08/31/2019</td>
<td>1.8 calendar</td>
<td>NIH/NIDCD</td>
<td>$212,500</td>
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<tr>
<td></td>
<td>The major goal of this study is to explore candidate biological bases for stratification of the heterogeneous ASD population according to a “dominant deficit” classification in which both thalamocortical white matter maturation and excitation/inhibition imbalance are considered components of a delayed electrophysiological response, M100.</td>
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<tr>
<td>R01HD073258-04</td>
<td>Magnetoencephalographic studies of lexical processing and abstraction in autism</td>
<td>Embick</td>
<td>09/01/2012 – 05/31/2017</td>
<td>1.2 calendar</td>
<td>NIH/NICHD</td>
<td>$123,877</td>
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<tr>
<td></td>
<td>The goal of this study is to identify features in the acoustic properties of words that diminish capability for abstraction in ASD, using MEG as a surrogate for characteristic brain activity, and to remediate them with signal processing.</td>
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<tr>
<td>AR140197</td>
<td>Neural correlates of the Y chromosome in autism: XYY Syndrome as Genetic Model</td>
<td>Roberts</td>
<td>08/15/2015-08/14/2017</td>
<td>1.2 calendar</td>
<td>US Department of Defense CDMRP</td>
<td>$109,314</td>
</tr>
<tr>
<td></td>
<td>Project goals are to evaluate the structural and functional determinants of autism in boys with 47,XYY on the autism spectrum compared to matched idiopathic ASD and typically-developing control groups.</td>
<td></td>
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</tr>
<tr>
<td>R21-MH109158</td>
<td>Structural and functional characteristics of XYY – Relationship to ASD</td>
<td>Roberts, PI</td>
<td>07/01/2016-06/30/2018</td>
<td>1.2 calendar</td>
<td>NIH/NIMH</td>
<td>$150,000</td>
</tr>
<tr>
<td></td>
<td>Goal: to compare the imaging phenotype of boys with 47,XYY syndrome +/- ASD diagnosis</td>
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<tr>
<td>1R21-NS090192-01A1</td>
<td>Thalamic activity and structure and surface neural oscillations in autism</td>
<td>Edgar</td>
<td>08/01/2015 – 07/31/2017</td>
<td>0.36 calendar</td>
<td>NIH/NINDS</td>
<td>$150,000</td>
</tr>
</tbody>
</table>
The major goal is to develop methods to examine thalamic structure and function and thalamic contributions to resting-state abnormalities in autism spectrum disorders

Role: co-investigator

**#276932/#412802 (Roberts)**  
Clinical Research Associates  
*MEG / MRS Study of STX209*  
11/01/2015-10/31/2016  
0.6 calendar  
Clinical Research Associates  
*MEG / MRS Study of STX209*  
$248,061

The goal of this study is to test MEG and MRS candidate biomarker responses to acute administration of a GABA-B agonist in a dose escalation trial

**UM1CA097452-11 (Adamson)**  
NIH/NCCF  
*MEG / MRS Study of STX209*  
08/01/2012 – 07/31/2017  
0.6 calendar  
NIH/NCCF  
*MEG / MRS Study of STX209*  
$22,067

Role: co-investigator

**#345621(Sherr)**  
Simons Foundation  
*Brain Imaging and Cell Signaling: Insights into the Biology of Autism*  
09/01/2015-08/31/2018  
0.6 calendar  
Simons Foundation  
*Brain Imaging and Cell Signaling: Insights into the Biology of Autism*  
$21,672

Role: co-investigator

**R01MH107506-01A1 (Edgar)**  
NIH/NIMH  
*A longitudinal study of brain development in children with autism*  
03/01/2016 – 02/28/2021  
1.2 calendar  
NIH/NIMH  
*A longitudinal study of brain development in children with autism*  
$499,851

**OVERLAP**

There is no overlap
ROSS, JUDITH, M.D. (MPI, Nemours/DuPont Hospital for Children site)

OTHER SUPPORT

ACTIVE

1. Patient-Centered Outcomes Research Institute (Ross: co-I, PI: Wysocki) 1/1/13-12/31/16 0.6 calendar Contract # 805 $303,151
   Shared Medical Decision Making in Pediatric Diabetes
   The goal of this grant is to evaluate shared medical decision making impact on patient centered outcomes in children with Type I diabetes mellitus.

2. AR140197 (MPI: Roberts, Ross) 08/15/2015-08/14/2017 1.2 calendar
   US Department of Defense CDMRP $153,479
   Neural correlates of the Y chromosome in autism: XYY Syndrome as Genetic Model
   Project goals are to evaluate the structural and functional determinants of autism in boys with 47,XYY compared to matched idiopathic ASD and typically-developing control groups. Although there is considerable scientific synergy with the R21 (#4 below), the recruited cohorts differ. There is no budgetary overlap.

3. R21 MH109158-01A1 (MPI: Roberts, Ross) 04/01/16-3/31/18 1.2 calendar
   NIH/NIMH $192,758
   Structural and Functional Characteristics of XYY - Relationship to ASD
   The goal of this project is to compare structural and functional neuroimaging findings in boys with XYY who meet diagnostic criteria for autism versus those who do not (please see above #3).

4. 1P30GM114736-01 (PI: Shaffer, co-I: Ross) 08/01/2015 – 07/31/2020 1.2 calendar
   NIH/NIGMS $750,000 Center for Pediatric Research (CPR)
   This COBRE Phase III grant builds on the success of COBRE Phase I and II and will sustain the infrastructure cores, mentorship program and pilot project programs to provide the Center for Pediatric Research with the resources to drive translational research programs focused on pediatric diseases at Nemours.

5. R01 HD04965305 (Ross: co-I, PI: Reiss) 07/01/2012-06/30/2017 0.3 calendar
   NIH $64,555
   Genes, Brain and Behavior in Turner Syndrome
   The goal of this project will use advanced, multi-modal magnetic resonance imaging (MRI) techniques, to elucidate the effects of X monosomy and X-linked imprinting on neurodevelopment and neural function in young girls with TS.

PENDING: None

OVERLAP: None