The NIMH Intramural Research Program Study of X- and Y-Chromosome Variations

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The Developmental Neurogenomics Unit

The Developmental Neurogenomics Unit (DNU) is a multi-disciplinary laboratory dedicated to better understanding how X- and Y-chromosome variations influence development.

We harness the knowledge gained from cellular, brain scan, cognitive and behavioral measures to determine how variation in X- and Y-chromosome dosage can impact different aspects of biology and development.

We believe this information will help to better inform care-providers and provide a necessary starting point for invention of better tests and treatments.

Key Findings So Far

We have published several studies on profiles of **behavior and learning** in groups with different X- and Y-chromosome variations (including XXY[1], XYY[2], trisomy X[3], XXYY[4], and XXXXY[5] groups). These studies (i) help healthcare professionals to better target their assessment when meeting new patients, (ii) show the great variability in outcome within any one variation group, and (iii) provide new behavioral measures which we can use for linking back to the brain and genome.

By comparing brain scans across different groups we found how X- and Y-chromosomes influence **brain organization**[6,7,8,9,10,11,12]**.** We see greatest anatomical changes in sets of brain regions important for language, decision making, mood regulation and social cognition.

We have also begun detailing how X- and Y-chromosome variations impact **genome structure and function**[13,14]. These studies reveal those changes in gene expression which may ultimately be the starting point for changes in brain, behavior and development.

More about our Study

A long history: Our lab is based at the world's largest research dedicated hospital - the National Institutes of Health Clinical Center in Bethesda, Maryland, near Washington, D.C. The NIMH Intramural Research program Study of X- and Y-chromosome variations began in 1995, and the current phase of this study began in 2015. Partnering closely with the AXYS community, we have seen over 350 families with X- and Y-chromosome variations since the study began, and published nearly 20 studies detailing our findings.

A core mission: We believe it is important to study X- and Y-chromosome variations as poorly understood but not rare diagnoses. We recognize the need to better understand the range of possible outcomes for individuals with X- and Y-chromosome variations. We think that gathering and analyzing detailed ("deep-phenotypic") information across different X- and Y-chromosome variations is critical for better-understanding biological factors that can help us personalize care for affected individuals and families.

Day 1	Admissions Consent Orientation	Cognitive tests for young person & parents	Questionnaires	MRI Scans of Brain
Day 2	Physical Exam and Blood Draw	Detailed Assessment: Language and social development	Detailed mental health assessment	Debrief & next steps

What we measure and why

Genome

Brain structure/function

Cognition Behavior Functioning

REPORTS FOR FAMILY ⟷ **SCIENTIFIC ANALYSIS AND PUBLICATIONS**

Who to contact for more information:

If you are interested in participating in our research study, please email our research coordinator, Jonathan Blumenthal, at jb364e@nih.gov

Four Key Strategies

To achieve the best understanding of X- and Y-chromosome variations, we believe it is important to:

1) Take time for ultra-detailed assessments that consider all aspects of life for the young person and their family
2) Compare findings and experiences across different X- and Y-chromosome variations to see shared and unique features
3) Combine measures across levels of analysis, studying the relationship between genes, the brain, and behavior
4) Use a longitudinal approach to measure changes across development

Next Steps

Enrollment: Our goal is to enroll ~100 families for each X- and Y-chromosome variation. We will begin seeing trisomy X individuals in December 2019.

Science: Our ongoing and future analyses are targeting 2 key goals in X- and Y-variation disorders:

1. Using biological data to **personalize care**
2. Making **brain cells from skin** to inform development of new treatments

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