GENE FUNCTION, BRAIN DEVELOPMENT AND BEHAVIOR IN X AND Y CHROMOSOME VARIATIONS

Armin Raznahan MD PhD
Chief, Developmental Neurogenomics Unit
Child Psychiatry Branch, NIMH
National Institutes of Health, Bethesda, MD, USA
FIRST STUDIES OF X/Y VARIATIONS IN OUR DIVISION BEGAN ~ 20 YEARS AGO
~300 families seen with a range of X/Y variations: XXX, XXXX, XXY, XYY, XXXY, XXXXY
Research emphasis on brain structure and gene function
FIRST STUDIES OF X/Y VARIATIONS IN OUR DIVISION BEGAN ~ 20 YEARS AGO
~300 families seen with a range of X/Y variations: XXX, XXXX, XXY, XYY, XXYY, XXXXY
Research emphasis on brain structure and gene function

WE BEGAN A NEW PHASE OF RESEARCH IN X/Y VARIATIONS 2 YEARS AGO
FIRST STUDIES OF X/Y VARIATIONS IN OUR DIVISION BEGAN ~ 20 YEARS AGO
~300 families seen with a range of X/Y variations: XXX, XXXX, XXY, XYY, XXYY, XXXXY
Research emphasis on brain structure and gene function

WE BEGAN A NEW PHASE OF RESEARCH IN X/Y VARIATIONS 2 YEARS AGO
Newer cellular and molecular technologies: e.g. “neurons in a dish”
Richer measures of the brain - structure, function + connectivity
Deeper and wider behavioral assessments for clinical feedback and science
FIRST STUDIES OF X/Y VARIATIONS IN OUR DIVISION BEGAN ~ 20 YEARS AGO
~300 families seen with a range of X/Y variations: XXX, XXXX, XXY, XYY, XXXY, XXXXY
Research emphasis on brain structure and gene function

WE BEGAN A NEW PHASE OF RESEARCH IN X/Y VARIATIONS 2 YEARS AGO
STARTED WITH XYY SYNDROME
NOW RECRUITING INDIVIDUALS WITH XXX AND XXY VARIATIONS
COLLABORATIVE PARTNERS

- Neurospin, Paris, France
- MIce, Toronto
- McGill, Montreal
- Yale, CT
- Penn, Drexel, Thomas Jefferson, PA
- UCLA, CA
- Baylor, TX
- NIH
- Baylor, TX
- UCSD, CA
1. PROVIDING A DETAILED PICTURE OF THE BEHAVIORAL ISSUES THAT CAN SOMETIMES ACCOMPANY DIFFERENT X AND Y CHROMOSOME VARIATIONS
OUR RESEARCH PROGRAM

1. PROVIDING A DETAILED PICTURE OF THE BEHAVIORAL ISSUES THAT CAN SOMETIMES ACCOMPANY DIFFERENT X AND Y CHROMOSOME VARIATIONS

2. SPECIFYING BRAIN SYSTEMS THAT ARE SENSITIVE TO X AND Y CHROMOSOME VARIATIONS – FIRST STEP TO TESTING IF MEASUREMENT OF THESE SYSTEMS CAN PREDICT FUTURE OUTCOMES
OUR RESEARCH PROGRAM

1. PROVIDING A DETAILED PICTURE OF THE BEHAVIORAL ISSUES THAT CAN SOMETIMES ACCOMPANY DIFFERENT X AND Y CHROMOSOME VARIATIONS

2. SPECIFYING BRAIN SYSTEMS THAT ARE SENSITIVE TO X AND Y CHROMOSOME VARIATIONS – FIRST STEP TO TESTING IF MEASUREMENT OF THESE SYSTEMS CAN PREDICT FUTURE OUTCOMES

3. CLARIFYING THE MOLECULAR CONSEQUENCES OF X- AND Y-CHROMOSOME VARIATION TO GUIDE RESEARCH INTO POTENTIALLY USEFUL TESTS AND TREATMENTS
1. THE IMPORTANCE OF STUDYING DIFFERENT X/Y VARIATIONS AT THE SAME TIME

“PROTO SEX CHROMOSOMES”

What we think the X and Y chromosome looked like ~300 million years ago
1. THE IMPORTANCE OF STUDYING DIFFERENT X/Y VARIATIONS AT THE SAME TIME
1. THE IMPORTANCE OF STUDYING DIFFERENT X/Y VARIATIONS AT THE SAME TIME
1. THE IMPORTANCE OF STUDYING DIFFERENT X/Y VARIATIONS AT THE SAME TIME

“PSEUDOAUTOSOMAL REGION” (PAR)

NON-PAR X-Y HOMOLOGS
1. THE IMPORTANCE OF STUDYING DIFFERENT X/Y VARIATIONS AT THE SAME TIME

SHARED BETWEEN X AND Y CHROMOSOMES

- “PSEUDOAUTOSOMAL REGION” (PAR)
- NON-PAR X-Y HOMOLOGS
1. THE IMPORTANCE OF STUDYING DIFFERENT X/Y VARIATIONS AT THE SAME TIME

SHARED BETWEEN X AND Y CHROMOSOMES

- "PSEUDOAUTOSOMAL REGION" (PAR)
- NON-PAR X-Y HOMOLOGS
- X-SPECIFIC GENES ("X-LINKED")
1. THE IMPORTANCE OF STUDYING DIFFERENT X/Y VARIATIONS AT THE SAME TIME

**Shared between X and Y chromosomes**

- "PSEUDOAUTOSOMAL REGION" (PAR)
- Non-Par X-Y homologs
- X-specific genes ("X-linked")
- Y-specific genes ("Y-linked")
1. THE IMPORTANCE OF STUDYING DIFFERENT X/Y VARIATIONS AT THE SAME TIME

MALE HORMONAL BACKGROUND
1. THE IMPORTANCE OF STUDYING DIFFERENT X/Y VARIATIONS AT THE SAME TIME

XX + [FEMALE HORMONAL BACKGROUND] -> XXX
1. THE IMPORTANCE OF STUDYING DIFFERENT X/Y VARIATIONS AT THE SAME TIME

MALE HORMONAL BACKGROUND

FEMALE HORMONAL BACKGROUND
2. TALKING ABOUT DIFFERENCES
2. TALKING ABOUT DIFFERENCES
2. TALKING ABOUT DIFFERENCES

TASK 1

POULATION AVERAGE
2. TALKING ABOUT DIFFERENCES
2. TALKING ABOUT DIFFERENCES

POPULATION AVERAGE

TIME 1  TIME 2  TIME 3  TIME 4  TIME 5
1. PROVIDING A DETAILED PICTURE OF THE BEHAVIORAL ISSUES THAT CAN SOMETIMES ACCOMPANY DIFFERENT X AND Y CHROMOSOME VARIATIONS

2. SPECIFYING BRAIN SYSTEMS THAT ARE SENSITIVE TO X AND Y CHROMOSOME VARIATIONS – FIRST STEP TO TESTING IF MEASUREMENT OF THESE SYSTEMS CAN PREDICT FUTURE OUTCOMES

3. CLARIFYING THE MOLECULAR CONSEQUENCES OF X- AND Y- CHROMOSOME VARIATION TO GUIDE RESEARCH INTO POTENTIALLY USEFUL TESTS AND TREATMENTS
MENTAL HEALTH DIAGNOSES IN DIFFERENT X/Y VARIATIONS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% of 35 XXX&lt;sup&gt;1&lt;/sup&gt;</th>
<th>% of 51 XXY&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism Spectrum Disorder</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Tic Disorder</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td>17</td>
<td>63</td>
</tr>
<tr>
<td>Oppositional Defiant Disorder</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>40</td>
<td>16</td>
</tr>
<tr>
<td>Obsessive Compulsive Spectrum Disorder</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% of 35 XXX&lt;sup&gt;1&lt;/sup&gt;</th>
<th>% of 51 XXY&lt;sup&gt;2&lt;/sup&gt;</th>
<th>% of 65 XYY&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism Spectrum Disorder</td>
<td>0</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Tic Disorder</td>
<td>3</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td>17</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>Oppositional Defiant Disorder</td>
<td>-</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>12</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>40</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Obsessive Compulsive Spectrum Disorder</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

### MENTAL HEALTH DIAGNOSES IN DIFFERENT X/Y VARIATIONS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% of 35 XXX</th>
<th>% of 51 XXY</th>
<th>% of 65 XYY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism Spectrum Disorder</td>
<td>0</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Tic Disorder</td>
<td>3</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td>17</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>Oppositional Defiant Disorder</td>
<td>-</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>12</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>40</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Obsessive Compulsive Spectrum Disorder</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

## XYY: PRE- AND POSTNATAL XYY DIAGNOSIS GROUPS

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>PRE vs. POSTNATAL DETECTION GROUPS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Prenatal Diagnosis [n (% of 24]</strong></td>
<td><strong>Postnatal Diagnosis [n (% of 41]</strong></td>
</tr>
<tr>
<td>Autism Spectrum Disorder</td>
<td>1 (4%)</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>Tic Disorder</td>
<td>1 (4%)</td>
<td>9 (22%)</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td>17 (71%)</td>
<td>26 (63%)</td>
</tr>
<tr>
<td>Oppositional Defiant Disorder</td>
<td>-</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>5 (21%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>1 (4%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Obsessive Compulsive Spectrum Disorder</td>
<td>-</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

*Torres et al, In Preparation*
### XYY: COMMUNITY vs. RESEARCH DIAGNOSES

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>COMMUNITY vs. RESEARCH DIAGNOSES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-NIH [N (% of 65)]</td>
</tr>
<tr>
<td>Autism Spectrum Disorder</td>
<td>20 (31%)</td>
</tr>
<tr>
<td>Tic Disorder</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td>35 (54%)</td>
</tr>
<tr>
<td>Oppositional Defiant Disorder</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>Obsessive Compulsive Spectrum Disorder</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

 Torres et al, *In Preparation*
<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>EFFECT OF DIAGNOSTIC THRESHOLD</th>
<th>FULL ONLY [n (% of 65)]</th>
<th>FULL or PARTIAL [n (% of 65)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tic Disorder</td>
<td></td>
<td>10 (15%)</td>
<td>14 (22%)</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td></td>
<td>43 (66%)</td>
<td>50 (77%)</td>
</tr>
<tr>
<td>Oppositional Defiant Disorder</td>
<td></td>
<td>4 (6%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td></td>
<td>11 (17%)</td>
<td>20 (31%)</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td></td>
<td>6 (9%)</td>
<td>19 (30%)</td>
</tr>
<tr>
<td>Obsessive Compulsive Spectrum Disorder</td>
<td></td>
<td>2 (3%)</td>
<td>4 (6%)</td>
</tr>
</tbody>
</table>

Torres et al, *In Preparation*
PROFILES OF COGNITION AND BEHAVIOR IN DIFFERENT X/Y VARIATIONS

REFERRED: Tartaglia and Ross, multiple reports e.g. Pediatrics, 2012 | Lee et al, JCPP, 2012 | Farmer et al, In Preparation
X/Y VARIATIONS AND BEHAVIOR

Summary and next steps ...

• There is evidence that presence of extra X and Y chromosomes can increase risk for mental health difficulties, but ...
  – We lack data from population-based samples
  – A person can fall below diagnostic thresholds, but still experience difficulties

• There is a pressing need for larger and more detailed studies of mental health across different X/Y variation groups, and dissemination of these findings to community practitioners

• Although much more needs to be done, available studies suggest that language, social functioning, and control of mood/attention may be particularly sensitive to increases in both X and Y chromosome count
1. PROVIDING A DETAILED PICTURE OF THE BEHAVIORAL ISSUES THAT CAN SOMETIMES ACCOMPANY DIFFERENT X AND Y CHROMOSOME VARIATIONS

2. SPECIFYING BRAIN SYSTEMS THAT ARE SENSITIVE TO X AND Y CHROMOSOME VARIATIONS – FIRST STEP TO TESTING IF MEASUREMENT OF THESE SYSTEMS CAN PREDICT FUTURE OUTCOMES

1. CLARIFYING THE MOLECULAR CONSEQUENCES OF X- AND Y-CHROMOSOME VARIATION TO GUIDE RESEARCH INTO POTENTIALLY USEFUL TESTS AND TREATMENTS
STRUCTURAL MAGNETIC RESONANCE BRAIN IMAGING
STRUCTURAL MAGNETIC RESONANCE BRAIN IMAGING
Globally Divergent but Locally Convergent X- and Y-Chromosome Influences on Cortical Development

Armin Raznahan¹, Nancy Raitano Lee¹, Deanna Greenstein¹, Gregory I. Wallace¹,², Jonathan D Blumenthal¹, Liv S Clasen¹ and Jay N Giedd¹

¹Section on Brain Imaging, Child Psychiatry Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892 USA and ²Department of Speech and Hearing Sciences, George Washington University, Washington, DC 20052 USA

Address correspondence to Armin Raznahan. Email: raznahana@mail.nih.gov

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Core sample</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XX</td>
<td>XY</td>
<td>XXX</td>
<td>XXY</td>
<td>XY</td>
<td>YY</td>
<td>XXXY</td>
</tr>
<tr>
<td>Sample size</td>
<td>80</td>
<td>89</td>
<td>28</td>
<td>58</td>
<td>26</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>12.8</td>
<td>12.8</td>
<td>12.3</td>
<td>12.8</td>
<td>12.4</td>
<td>14.1</td>
<td>12.9</td>
</tr>
<tr>
<td>SD</td>
<td>5.07</td>
<td>4.61</td>
<td>5.68</td>
<td>4.93</td>
<td>4.91</td>
<td>5.45</td>
<td>4.82</td>
</tr>
<tr>
<td>Mean IQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full scale*</td>
<td>115</td>
<td>116</td>
<td>92</td>
<td>96</td>
<td>91</td>
<td>87</td>
<td>56</td>
</tr>
<tr>
<td>Verbal*</td>
<td>115</td>
<td>113</td>
<td>93</td>
<td>94</td>
<td>89</td>
<td>81</td>
<td>61</td>
</tr>
<tr>
<td>Performance*</td>
<td>111</td>
<td>114</td>
<td>94</td>
<td>99</td>
<td>95</td>
<td>95</td>
<td>56</td>
</tr>
</tbody>
</table>
X AND Y EFFECTS ON CORTICAL ANATOMY: REGIONAL MEASURES

CONVERGENT EFFECTS OF X- AND Y-CHROMOSOME DOSAGE ON LOCAL BRAIN ANATOMY

Raznahan et al, Cerebral Cortex, 2014
X AND Y EFFECTS ON CORTICAL ANATOMY: REGIONAL MEASURES

CONVERGENT EFFECTS OF X- AND Y-CHROMOSOME DOSAGE ON LOCAL BRAIN ANATOMY

Raznahan et al, Cerebral Cortex, 2014 + Independent replications by Reiss Lab [Hong, J Neurosc, 2014 | Lepage, GBB, 2014]
WHAT ABOUT OTHER BRAIN STRUCTURES?

Deeper parts of the brain show a similar pattern of X and Y chromosome effects on their anatomy to what we found in our initial studies of the brain's outer cortical sheet.
WHAT ABOUT OTHER BRAIN STRUCTURES?

Deeper parts of the brain show a similar pattern of X and Y chromosome effects on their anatomy to what we found in our initial studies of the brain's outer cortical sheet:

1. Just like in the cortex, there are specific anatomical hotspots within each of these structures that seem to be particularly sensitive to changes in X and Y chromosome dosage.

2. Cortical, subcortical and cerebellar sub-regions which show the biggest structural change in X/Y variations lie within brain networks that we use for language, attentional control, future planning, complex decision making, processing our own emotions and those of others.

Reardon et al, J Neurosc, 2016 | Mankiw et al, J Neurosc, 2017
X/Y VARIATIONS AND THE BRAIN

Summary and next steps ...

• Analysis of regional brain anatomy suggests that specific brain systems may be particularly sensitive to the effects of X/Y variations.

• We need to understand how these anatomical changes relate to brain connectivity and functioning, as well as the wide variability in behavioral/cognitive effects we see in each X/Y variation group.

• We do not know how stable or dynamic these brain changes are over development.

• The similarity between X and Y chromosome effects on regional brain anatomy is a key observation that needs to be better understood.
OUR RESEARCH PROGRAM

1. PROVIDING A DETAILED PICTURE OF THE BEHAVIORAL ISSUES THAT CAN SOMETIMES ACCOMPANY DIFFERENT X AND Y CHROMOSOME VARIATIONS

2. SPECIFYING BRAIN SYSTEMS THAT ARE SENSITIVE TO X AND Y CHROMOSOME VARIATIONS – FIRST STEP TO TESTING IF MEASUREMENT OF THESE SYSTEMS CAN PREDICT FUTURE OUTCOMES

1. CLARIFYING THE MOLECULAR CONSEQUENCES OF X- AND Y-CHROMOSOME VARIATION TO GUIDE RESEARCH INTO POTENTIALLY USEFUL TESTS AND TREATMENTS
X AND Y CHROMOSOME DOSAGE EFFECTS ON GENE EXPRESSION

1.5 MILLION BEADS IN COLLABORATION WITH DR. JUDITH ROSS, NEMOURS
WE FIRST SEARCHED ALL 20,000 MEASURED GENES AND ASKED...

"Are there any genes that are always showing different expression between groups that differ in X or Y chromosome count?"
ONLY 10 GENES BEHAVE THIS WAY, AND 8 OF THESE 10 ARE FROM THE SMALL GROUP OF NON-PAR X/Y HOMOLOG GENES.

Raznahan et al, Under Submission
ONLY 10 GENES BEHAVE THIS WAY, AND 8 OF THESE 10 ARE FROM THE SMALL GROUP OF NON-PAR X/Y HOMOLOG GENES.

AS A GROUP, THE FULL SET OF 18 NON-PAR X/Y HOMOLOG GENES APPEAR TO BE VERY SENSITIVE TO CHANGES IN X AND Y CHROMOSOME COUNT.

Raznahan et al, Under Submission
ONLY 10 GENES BEHAVE THIS WAY, AND 8 OF THESE 10 ARE FROM THE SMALL GROUP OF NON-PAR X/Y HOMOLOG GENES.

As a group, the full set of 18 non-par X/Y homolog genes appear to be very sensitive to changes in X and Y chromosome count...

...and one of these (ZFX) seems to cause X variation effects on non-sex chromosome genes.

Raznahan et al, Under Submission
X/Y VARIATIONS AND GENE FUNCTION

Summary and next steps ...

• X/Y variations cause changes in the expression of key sex chromosome genes, which can play a role in shaping wider expression changes in other chromosomes.

• We are now building on this finding in 4 directions:
  – Measuring gene expression with more powerful methods in a greater range of cell types from a greater range of X/Y variation groups, with larger sample sizes in each group.
X/Y VARIATIONS AND GENE FUNCTION

Summary and next steps ...

• X/Y variations cause changes in the expression of key sex chromosome genes, which can play a role in shaping wider expression changes in other chromosomes

• We are now building on this finding in 4 directions:
  – Measuring gene expression with more powerful methods in a greater range of cell types from a greater range of X/Y variation groups, with larger sample sizes in each group
  – Measuring chemical tags that cells use to switch genes “on” and “off”
X/Y VARIATIONS AND GENE FUNCTION

Summary and next steps ...

• X/Y variations cause changes in the expression of key sex chromosome genes, which can play a role in shaping wider expression changes in other chromosomes

• We are now building on this finding in 4 directions:
  – Measuring gene expression with more powerful methods in a greater range of cell types from a greater range of X/Y variation groups, with larger sample sizes in each group

  – Measuring chemical tags that cells use to switch genes “on” and “off”

  – Taking pictures of single cells to understand how extra X and Y chromosomes fit into the nucleus and change nuclear organization

• Using stem cell technologies to “reprogram” skin cells from individuals with X/Y variations into different types of brain tissue, so we can start building cellular models to link in with neuroimaging and behavioral data
X/Y VARIATIONS AND GENE FUNCTION

Summary and next steps ...

• X/Y variations cause changes in the expression of key sex chromosome genes, which can play a role in shaping wider expression changes in other chromosomes

• We are now building on this finding in 4 directions:
  – Measuring gene expression with more powerful methods in a greater range of cell types from a greater range of X/Y variation groups, with larger sample sizes in each group
  – Measuring chemical tags that cells use to switch genes “on” and “off”
  – Taking pictures of single cells to understand how extra X and Y chromosomes fit into the nucleus and change nuclear organization
  – Using stem cell technologies to “reprogram” skin cells from individuals with X/Y variations into different types of brain tissue, so we can start building cellular models to link in with neuroimaging and behavioral data
“Turning Discovery into Health”

Raising awareness about X/Y variations and encouraging greater investment in clinical research

Providing gold-standard information about mental health issues that can arise, and getting this to community practitioners so families are better served
“Turning Discovery into Health”

**SHORT**

Raising awareness about X/Y variations and encouraging greater investment in clinical research

Providing gold-standard information about mental health issues that can arise, and getting this to community practitioners so families are better served

**MEDIUM**

Converting Terabytes of data gathered in the lab to try and explain the range of severity within any single X/Y variation group -> more accurate prognoses

Testing the potential for “wearables” to help make day-to-day predictions about well-being
Turning Discovery into Health

- Raising awareness about X/Y variations and encouraging greater investment in clinical research

- Providing gold-standard information about mental health issues that can arise, and getting this to community practitioners so families are better served

- Converting Terabytes of data gathered in the lab to try and explain the range of severity within any single X/Y variation group → more accurate prognoses

- Testing the potential for “wearables” to help make day-to-day predictions about well-being

- Moving from discovery of affected brain circuits to targeted interventions that modify circuit function

- Moving from discovery of key genetic players to interventions that support healthy brain development
THANKS

**NIMH, Bethesda, MD, USA**
DEVELOPMENTAL NEUROGENOMICS UNIT
Jonathan Blumenthal, Liv Clasen, Ari Fish, Francois Lalonde, Siyuan Liu, Catherine Mankiw, Kirk Reardon, Jill Russ, Jakob Seidlitz, Erin Torres, Anastasia Xenophontos

**CHILD PSYCHIATRY BRANCH**
Judy Rapoport, Jay Giedd, Kwangmi Ahn, Phillip Shaw, Nitin Gogtay
Nancy Lee, Dede Greenstein
Aaron Alexander-Bloch

**BRAIN AND COGNITION BRANCH**
Greg Wallace

**Philadelphia, PA, USA**
Judith Ross

**Paris, FRANCE**
*Institute Pasteur*
Roberto Toro

**IoP, KCL, London, UK**
Emily Simonoff
Patrick Bolton
Declan Murphy

**Baylor, TX, USA**
*Frank Probst*

**UCLA, CA, USA**
Daniel Geschwind
Ronald Swerdloff
YanHe Lue
THANKS

NIMH, Bethesda, MD, USA
DEVELOPMENTAL NEUROGENOMICS UNIT
Jonathan Blumenthal, Liv Clasen, Ari Fish, Francois Lalonde, Siyuan Liu, Catherine Mankiw, Kirk Reardon, Jill Russ, Jakob Seidlitz, Erin Torres, Anastasia Xenophontos

CHILD PSYCHIATRY BRANCH
Judy Rapoport, Jay Giedd, Kwangmi Ahn, Phillip Shaw, Nitin Gogtay
Nancy Lee, Dede Greenstein
Aaron Alexander-Bloch

BRAIN AND COGNITION BRANCH
Greg Wallace

Philadelphia, PA, USA
Judith Ross

Toronto, ON, CANADA
Jason Lerch

Paris, FRANCE
Institute Pasteur
Roberto Toro

IoP, KCL, London, UK
Emily Simonoff
Patrick Bolton
Declan Murphy

Baylor, TX, USA
Frank Probst

UCLA, CA, USA
Daniel Geschwind
Ronald Swerdloff
YanHe Lue
COME OVER AND SAY HELLO ...

Study of X and Y Chromosome Variations:

XXY  XXXY  XXXXY  XYY  XXYY  XXX  XXXX  XXXXX

Armin Raznahan, MD, PhD, Principal Investigator
Jonathan Blumenthal, MA, Associate Investigator