Overview of Genetics of Behavioral Disorders in Children: Autism Spectrum Disorders as a Case Study

Abha R. Gupta, MD, PhD
Developmental-Behavioral Pediatrics
Department of Pediatrics and Child Study Center
DSM-5 criteria for Autism Spectrum Disorder

A. Persistent deficits in social communication and social interaction across multiple contexts

B. Restricted, repetitive patterns of behavior, interests, or activities

C. Symptoms must be present in the early developmental period.

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. Not better explained by intellectual disability or global developmental delay
Autism Spectrum Disorder (ASD)

- Prevalence:
  - 0.6/100 (Fombonne 2005)
  - 1.47/100 (CDC 2014)

- No known cure, limited treatment

- Pathophysiology largely unknown

- Strong evidence for genetics
Evidence for genetic basis of ASD

Sibling recurrence risk: 18.7% (Ozonoff et al 2011)

Twin studies (Bailey et al 1995, Hallmayer et al 2011)
• Identical twins share an ASD diagnosis more frequently than fraternal twins
• Identical twins do not always share an ASD diagnosis

10% of cases also have a genetic syndrome
• Fragile X
• Tuberous sclerosis
ASDs are complex disorders with:

- Wide clinical variability
- Multiple causal factors
- A great deal of genetic heterogeneity

There is no one gene for autism, not even a few. There are likely hundreds.
Chromosomal regions implicated in ASD

Abrahams and Geschwind 2008
ASD and schizophrenia

Red: ASD
Blue: schizophrenia
Black: both

Merikangas et al 2009
Whole-exome sequencing

Sample preparation DNA (5 µg)

Template dNTPs and polymerase

Cluster growth

Bridge amplification

100–200 million molecular clusters

Metzker 2010
Whole-genome sequencing

Ion Proton
Cost per human genome
Genetic architecture of ASD

G-banding/FISH

15q mat dup
22q11 del
22q tel del
2q tel del

Single gene, Mendelian
Cytogenetic

Common autism (multiple genes, environment)

Genome-wide Arrays
~8% diagnostic yield in ASD at EGL

Emory Genetics Laboratory
Gene co-expression analysis

Autism-associated genes from de novo mutations

Map of gene expression in the developing human brain

Coexpression network analysis

Gene expression correlation

Negative

Positive

Convergence of autism-associated genes

Midfetal development

Layer 5/6 glutamatergic projection neurons

Prefrontal and primary motor-somatosensory cortex

Willsey et al 2013
Commercial autism gene panel

Genes Included on the Panel

This panel sequences 62 individual autosomal and X-linked genes. These genes were selected to represent the most common single gene etiologies associated with a syndrome that includes autism as a significant clinical feature.

<table>
<thead>
<tr>
<th>Genes Included on the Panel</th>
<th>Greenwood Genetic Center</th>
<th>Next Generation Sequencing</th>
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<tbody>
<tr>
<td>APLS2</td>
<td>FOXP2</td>
<td>Syndromic Autism 62-gene Panel</td>
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<tr>
<td>ARX</td>
<td>GABRB3</td>
<td>CONTACT INFORMATION</td>
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<tr>
<td>ATRX</td>
<td>HOXA1</td>
<td>JoAnne Babb, Molecular Diagnostic Sample Coordinator</td>
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<tr>
<td>AVPR1A</td>
<td>HPRT1</td>
<td><a href="mailto:jhbabb@ggc.org">jhbabb@ggc.org</a></td>
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<td>BDNF</td>
<td>KDM5C</td>
<td>1-800-473-9411 (toll free) or 864-941-8147</td>
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<tr>
<td>BRAF</td>
<td>L1CAM</td>
<td>Kellie King, MS, Laboratory Representative</td>
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<tr>
<td>CACNA1C</td>
<td>MBDS</td>
<td><a href="mailto:kkling@ggc.org">kkling@ggc.org</a></td>
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<tr>
<td>CASK</td>
<td>MECP2</td>
<td>1-800-473-9411 (toll free) or 864-388-1055</td>
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<tr>
<td>CDKL5</td>
<td>MED12</td>
<td>Julie Jones, Ph.D., Director of Molecular Diagnostic Laboratory</td>
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<tr>
<td>CHD7</td>
<td>MEF2C</td>
<td><a href="mailto:juliejones@ggc.org">juliejones@ggc.org</a></td>
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<tr>
<td>CNTNAP2</td>
<td>MET</td>
<td>1-800-473-9411 (toll free) or 864-388-1049</td>
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<td>VPS13B</td>
<td>MID1</td>
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<td>CREBBP</td>
<td>NHS</td>
<td>This brochure is published by Greenwood Genetic Center, a nonprofit institute organized to provide clinical genetic services and laboratory testing, to develop educational programs and materials, and to conduct research in the field of medical genetics.</td>
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<td>Information for Healthcare Providers</td>
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Yale SCHOOL OF MEDICINE
Rett syndrome and \textit{MECP2}

- Mutations in \textit{MECP2} cause most cases of Rett syndrome.
- \textit{MECP2} controls the expression of other genes.
- Patients show abnormal neurons but not neuronal death: Can viable but defective neurons be repaired?
- Mutant mice lacking \textit{MECP2} develop neurological symptoms.
- Reactivation of \textit{MECP2} in adult mutant mice reversed symptoms (Guy et al 2007).
- Absence of \textit{MECP2} doesn’t irreversibly damage neurons.
Fragile X syndrome (FXS) and \textit{FMR1}

- Loss of \textit{FMR1} causes FXS.
- \textit{FMR1} controls the expression of other genes.
- Pathophysiology involves hyperactivity of a glutamate receptor.
- Mutant mice lacking \textit{FMR1} develop neurological symptoms.
- Reducing activity of the glutamate receptor rescued symptoms (Dolen \textit{et al} 2007).
- R-baclofen corrects deficits (Henderson \textit{et al} 2012).
Tuberous sclerosis (TS) and TSC

- Mutations in TSC1 and TSC2 cause TS.
- Pathophysiology involves a signaling pathway in the hippocampus (mammalian target of rapamycin).
- Mutant mice lacking 1 copy of TSC2 show cognitive deficits. Treatment of adult mutant mice with rapamycin improved behavioral deficits (Ehninger et al 2008).
- Mutant mice lacking 1 or 2 copies of TSC1 in cerebellum show decreased neuronal activity, abnormal social interaction, and repetitive behavior. Treatment with rapamycin prevented deficits (Tsai et al 2012).
Future directions

• Increase study populations by ten-fold
• Whole-genome sequencing: regulatory elements
• Pathway analysis
• Epigenetics
• Biomarkers: neuroimaging, eye tracking
• Genetic overlap between neuropsychiatric disorders
• Functional analysis of variants: bridging genetics and neuroscience
  • *In vitro* and *in vivo* studies
  • Postmortem brain tissue, induced pluripotent stem cells, animal systems
Thank you for your attention!