Genetic Work-Up of Autism Spectrum Disorder in a Clinical Setting

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  • National Institute of Mental Health
    • Training Program in Childhood Neuropsychiatric Disorders
    • National Institute of Mental Health Research Education for Future Physician-Scientists in Child Psychiatry)
  • The Overlook Foundation.
Lecture Objectives

• The attendee will review the relevance of genetic variation to autism spectrum disorder and recent advances in autism genetic studies.

• The attendee will be aware of the current recommendations for genetic testing in autism spectrum disorder and particular patient subpopulations.

• The attendee will review case studies of genetic testing in patients with autism spectrum disorder to improve management of individuals with autism spectrum disorder.
Autism Spectrum Disorder
*a behaviorally defined disorder of development*

- Impaired Social Communication
- Restricted Interests, Repetitive Behaviors and/or Sensory Sensitivity
Autism Spectrum Disorder (ASD)
*a disorder manifesting in early childhood*

**Environmental**
- *In utero* exposures
  - Valproic acid
  - Alcohol
  - Thalidomide
- *In utero* infections
  - Rubella
  - Cytomegalovirus

**Genetic**
- Change in genetic material
- Inherited from parent
- May be spontaneous (new to patient)
The evidence that genetic risk factors may lead to ASD (1)

- In studies comparing concordance of ASD in twins, 40-90% of monozygotic twins (identical DNA) are concordant for diagnosis of ASD (compared to 0-30% of dizygotic twins)

- Siblings of individuals with ASD have a higher likelihood of having ASD (up to 26% recurrence risk for siblings)

There is a **preponderance of males** diagnosed with ASD (4 males : 1 female)

Increased rates of ASD in individuals with **known genetic syndromes** (ex. fragile X syndrome, Rett syndrome, Down’s syndrome…)

Traits consistent with autism (the **broader autism phenotype**) can be found in family members of those with ASD

What kind of genetic changes are associated with ASD risk?

- Large-scale rearrangements, deletions, and/or duplications of chromosomes (2-5 million base pairs)
- Submicroscopic deletions or duplications of genetic regions (10K-500K bases)
- Changes in the DNA base code (1-10s of bases)

Illustration by D. Leja, courtesy of the National Human Genome Research Institute, [http://www.genome.gov](http://www.genome.gov)
What kind of genetic changes are associated with ASD risk?

- Large-scale rearrangements, deletions, and/or duplications of chromosomes (2-5 million base pairs)
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- Changes in the DNA base code (1-10s of bases)
Examples of known genetic changes associated with ASD risk

| Large-scale rearrangements, deletions, and/or duplications of chromosomes (2-5 million base pairs) | Down’s syndrome (trisomy 21) |
| Submicroscopic deletions or duplications of genetic regions (10K-500K bases) | DiGeorge syndrome (deletion of a region of chromosome 22) |
| Changes in the DNA base code (1-10s of bases) | Tuberous sclerosis (disruptive mutations in the gene TSC2) |
Examples of known genetic changes associated with ASD risk

<table>
<thead>
<tr>
<th>Genetic Changes</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-scale rearrangements, deletions, and/or duplications</td>
<td>Down’s syndrome (trisomy 21)</td>
</tr>
<tr>
<td>Changes in the DNA base code (1-10s of bases)</td>
<td>Tuberous sclerosis (disruptive mutations in the gene TSC2)</td>
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</tbody>
</table>

No one risk factor accounts for a majority of ASD cases (not even a substantial minority)
The complex genetic architecture of ASD: Defining our terms (1)

- **Genome**— the entirety of an individual’s genetic code (3 billion base pairs)
- **Exome**— the part of the genome that codes for proteins
- **Allele**— one copy of the genetic material (i.e., one copy of a gene)
- **Large effect vs small effect alleles**— genetic changes in the allele that contribute to the risk of a disorder (the larger the effect the greater the chance of the disorder)
Models of ASD risk

*an interaction of effect size and number*

Risk factors with large effects

Risk factors with small effects

modeled after Berg & Geschwind, *Gen Biol* ‘12
Models of ASD risk
an interaction of effect size, number and type

Risk factors with large effects

Risk factors with small effects

modeled after Berg & Geschwind, Gen Biol ‘12

ASD risk factor threshold v1

ASD risk factor threshold v3
Models of ASD risk

*large effect/rare versus small effect/common*

- **Rare ASD risk factors** have larger effect sizes but are not causative: *Necessary but not sufficient*
- **Common ASD risk factors** have small effect sizes: *Not sufficient, ?necessary*

![Diagram showing the relationship between increasing allele frequency and increasing effect size.](Diagram)

modeled after State & Levitt, Nat. Neurosci 2011
The complex genetic architecture of ASD: no single risk factor is causative

Genetic risk factors for ASD exhibit:

- **Variable penetrance**– one genetic change may result in a phenotype in one individual but not in another
- **Pleiotropy**– one genetic change influences multiple phenotypes (ex. mutations in the gene \textit{CHD7} are associated with CHARGE syndrome, mutations in \textit{POGZ} have been found in ASD and schizophrenia)
- **Locus heterogeneity**– many genetic changes contribute to one phenotype (ASD)

Multiple genetic risk factors contribute to ASD, but the same genetic risk factor in different individuals may result in different manifestations.
The complex genetic architecture of ASD: *how do we identify genetic ASD risk factors?*

**Recurrence within family:**
- Multiplex
- Risk factor is inherited
- More common variants

**No recurrence within family:**
- Simplex
- Risk factor in patient only
- More rare variants
The complex genetic architecture of ASD: Defining our terms (2)

- **Copy number variants (CNVs)**—10K to 500K base pair regions duplicated or deleted from the genome
- **Single nucleotide variants (SNVs)**—Rare changes to the base pair code (1 base pair)
- **Insertion/deletions (indels)**—Changes to the genome that delete or insert 1-10s of base pairs
- **De novo (dn) variants**—arise by mutation in the child’s DNA, not present in the parents’ DNA
- **Inherited variants**—transmitted from the parents
  - If the parent has a detectable phenotype (learning disability, cognitive deficits, other psychiatric conditions), the variant may contribute to risk but the threshold for having ASD is not met
The complex genetic architecture of ASD: 
*Defining our terms* (3)

- **Karyotype**— technique to look for microscopically visible rearrangements, duplications, and/or deletions of chromosomes (2,000K-5,000K bases)
- **Chromosomal microarray (CMA)**— technique to look for CNVs in an individual’s genome
- **Whole exome sequencing (WES)**— detects the sequence of the individual’s genome that codes for proteins (approximately 19K genes, 30,000K bases)
- **Whole genome sequencing (WGS)**— detects the entire sequence of the individual’s genome (3 billion bases)
- **Polymerase chain reaction (PCR)**— detects the sequence of one region (1K bases)
Examples of known genetic changes associated with ASD risk

<table>
<thead>
<tr>
<th>Large-scale rearrangements, deletions, and/or duplications of chromosomes (2-5 million base pairs)</th>
<th>Variant</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneuploidy</td>
<td>Karyotype</td>
<td></td>
</tr>
<tr>
<td>CNVs</td>
<td>CMA</td>
<td></td>
</tr>
<tr>
<td>WGS</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Submicroscopic deletions or duplications of genetic regions (10K-500K bases)</th>
<th>Variant</th>
<th>Test</th>
</tr>
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<tbody>
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<td>CNVs</td>
<td>CMA</td>
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<tr>
<td>WGS</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Changes in the DNA base code (1-10s of bases)</th>
<th>Variant</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>WES</td>
<td></td>
</tr>
<tr>
<td>Indels</td>
<td>WGS</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
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</tbody>
</table>
Simplex Family Studies of ASD
de novo rare variants increase risk for ASD

ASD risk is linked to de novo rare structural variants (or CNVs):
• Pathogenic de novo CNVs were found in 5-10% of probands (irrespective of IQ or ADOS score severity)
• Girls or those with low IQ were more likely to have de novo, large, gene-rich CNVs
• By modeling, several hundred genetic regions are predicted to contribute to ASD risk

Simplex Family Studies of ASD

de novo rare variants increase risk for ASD

ASD risk is linked to de novo rare sequence variants (SNVs):

- De novo SNVs (and indels) that cause disruptions to protein coding regions (Likely Gene Disrupting (LGD) variants) occur more often in probands than unaffected siblings
- Individuals with LGD variants are more likely to have low IQ
- Several hundred to 1000 individual genes contribute to risk

Family Studies Point to Autism Risk Genes

Synapse Formation

Gene Regulation

<table>
<thead>
<tr>
<th>Genes</th>
<th>Genes</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN2A</td>
<td>GRIN2B</td>
<td>SETD5</td>
</tr>
<tr>
<td>NRXN1</td>
<td>DSCAM</td>
<td>INTS6</td>
</tr>
<tr>
<td>SYNGAP1</td>
<td>SHANK3</td>
<td>CUL3</td>
</tr>
<tr>
<td>ANK2</td>
<td>ILF2</td>
<td>KATNAL2</td>
</tr>
<tr>
<td>ADNP</td>
<td>GIGYF1</td>
<td>WAC</td>
</tr>
<tr>
<td>SHANK2</td>
<td>MYT1L</td>
<td>RANBP17</td>
</tr>
<tr>
<td>SCN2A</td>
<td>GABRB3</td>
<td>DNMT3A</td>
</tr>
<tr>
<td>NRXN1</td>
<td>TRIO</td>
<td>WDFY3</td>
</tr>
<tr>
<td>SYNGAP1</td>
<td>ETFB</td>
<td>SLC6A1</td>
</tr>
<tr>
<td>ANK2</td>
<td>CTNNBP2</td>
<td>PHF2</td>
</tr>
<tr>
<td>ADNP</td>
<td>AKAP9</td>
<td>ZNF559</td>
</tr>
<tr>
<td>SHANK2</td>
<td>NLGN3</td>
<td>MFRP</td>
</tr>
<tr>
<td>TBR1</td>
<td></td>
<td>MIB1</td>
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</table>
The complex genetic architecture of ASD: 
*take home messages*

- **Individually**, rare large effect risk factors are found in small percentages of the total ASD population.
  - Fragile X trinucleotide repeat expansion (the most common genetic risk factor associated with ASD) is only found in 2-3% of total ASD cases.
  - 16p11.2 deletions and duplications are each found in < 1% of ASD cases (versus < 0.1% in the population).

- **Collectively**, rare variants can be found in a substantial minority of patients.
  - 10-30% of ascertained ASD cases have some kind of de novo rare variant (structural or sequence).
  - Adding inherited variants increases the yield to > 30%.

- **Common, small effect risk factors** contribute more to overall risk, but we don’t yet know what these might be.
Variant Specific Studies

*grouping rare variants to look for group effects*

- rarechromo.org
- simonsvipconnect.org
- depts.washington.edu/uwautism/research/research-projects/tiger-study

<table>
<thead>
<tr>
<th>Copy Number Variants</th>
<th>16p11.2 Deletions</th>
<th>16p11.2 Duplications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q21.1 Deletions</td>
<td>1q21.1 Duplications</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genes Associated with Features of Autism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTL6B</td>
</tr>
<tr>
<td>ADNP</td>
</tr>
<tr>
<td>ANK2</td>
</tr>
<tr>
<td>ANKRD11</td>
</tr>
<tr>
<td>ARID1B</td>
</tr>
<tr>
<td>ASH1L</td>
</tr>
<tr>
<td>ASXL3</td>
</tr>
<tr>
<td>BAF190</td>
</tr>
<tr>
<td>BCL11A</td>
</tr>
<tr>
<td>CHD2</td>
</tr>
</tbody>
</table>
Autism Spectrum Disorder

**co-occurring conditions**

<table>
<thead>
<tr>
<th>Medical/Genetic</th>
<th>Developmental/Psychiatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Epilepsy (8-30%)</td>
<td>• Intellectual Disability (~45%)</td>
</tr>
<tr>
<td>• Gastrointestinal distress (9-70%)</td>
<td>• Attention Deficit Hyperactivity Disorder (28-44%)</td>
</tr>
<tr>
<td>• Immune dysfunction (~38%)</td>
<td>• Tic Disorder (14-38%)</td>
</tr>
<tr>
<td>• Known genetic syndromes (~5%)</td>
<td>• Motor Abnormality (~79%)</td>
</tr>
<tr>
<td>• Anxiety (42-56%)</td>
<td>• Depression (12-70%)</td>
</tr>
<tr>
<td>• Depression (12-70%)</td>
<td>• Obsessive Compulsive Disorder (7-24%)</td>
</tr>
<tr>
<td>• Obsessive Compulsive Disorder (7-24%)</td>
<td>• Psychosis (12-17%)</td>
</tr>
</tbody>
</table>

*rates per Lai et al. Lancet 2014 (percentage of individuals with ASD showing noted conditions)
Autism Spectrum Disorder
co-occurring conditions by variant class

<table>
<thead>
<tr>
<th>16p11.2 Deletion CNV</th>
<th>16p11.2 Duplication CNV</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 16% of carriers have ASD</td>
<td>• 20% of carriers have ASD</td>
</tr>
<tr>
<td>• Intellectual disability (higher than in duplication)</td>
<td>• Intellectual disability (lower than in deletion)</td>
</tr>
<tr>
<td>• Seizures in 22%</td>
<td>• Seizures in 19%</td>
</tr>
<tr>
<td>• Family history of learning disabilities</td>
<td>• Family history of reduced IQ</td>
</tr>
<tr>
<td>• Macrocephaly</td>
<td>• Microcephaly</td>
</tr>
<tr>
<td>• Increased BMI</td>
<td>• Decreased BMI</td>
</tr>
<tr>
<td>• Brain abnormalities (cerebellar hypoplasia, enlarged ventricles)</td>
<td>• Brain abnormalities (posterior fossa, Chiari Type I malformations)</td>
</tr>
</tbody>
</table>

D’Angelo et al. *JAMA Psych* ’16
### Autism Spectrum Disorder
**co-occurring conditions by variant class**

<table>
<thead>
<tr>
<th>Rett Syndrome</th>
<th>PTEN hamartoma tumor syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caused by mutation of gene <em>MeCP2</em></td>
<td>Caused by mutations in the gene <em>PTEN</em></td>
</tr>
<tr>
<td>Almost exclusively girls</td>
<td>Associated with macrocephaly &gt; 2 SD</td>
</tr>
<tr>
<td>Regression starting 6 - 18 months with loss of speech, use of hands</td>
<td><em>PTEN</em> disruption also associated with benign and malignant tumor development</td>
</tr>
<tr>
<td>Severe seizures</td>
<td></td>
</tr>
<tr>
<td>Microcephaly</td>
<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td></td>
</tr>
</tbody>
</table>

*MeCP2* and *PTEN* are genes associated with these conditions.
Identifying a specific genetic diagnosis...

- Provides **diagnostic resolution** for the family (and ends the diagnostic odyssey)
- Important for understanding **recurrence risk** for family
- Gives the clinician a **potential roadmap** for prognosis and potential medical or psychiatric complications
- Opens the door to **family organizations and clinical trials** based on a specific genetic diagnosis (fragile X syndrome, *PTEN* syndrome)

“There is a big difference between us and the rest of the autism community….we have an honest-to-God genetic diagnosis.” – *NYT article in 2013*, a quote by a father referring to the *PTEN* variant found in genome of his child
Genetic Testing is Standard of Care!
a complete evaluation includes genetic testing

Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies


The American Journal of Human Genetics 86, 749–764, May 14, 2010

ACMG PRACTICE GUIDELINES

Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions

G. Bradley Schaefer, MD1 and Nancy J. Mendelsohn, MD2; for the Professional Practice and Guidelines Committee
Genetic Testing is Standard of Care! a complete evaluation includes genetic testing

Psychiatric Interview
- Current Functioning
- Patient History
- Family History

Psychological Evaluation
- Social Communication
- Cognitive
- Adaptive

Medical Evaluation
- Physical Exam
- Neurological
- Laboratory Workup

Incorporate genetic testing here!
Genetic Testing in Autism Spectrum Disorder

*what do we order?*

- First, confirm the diagnosis of ASD (or intellectual disability)

- For cases of idiopathic autism (no identifiable cause):
  - **Chromosomal microarray** to detect CNVs
    - In all cases of idiopathic autism
    - Irrespective of sex, IQ, or other associated conditions
  
  - **Fragile X testing** to detect trinucleotide repeat expansion
    - In all males
    - In females with low IQ/family history
Physical Exam in Autism Spectrum Disorder can give clues to genetic diagnosis

- Constitutional— height, weight, BMI, head circumference (HC)
- Craniofacial morphology— eye spacing, palate defects, nasal bridge
- Neurological— focal or asymmetric findings
- Skin— café au lait spots, neurofibromas, Ash Leaf spots
- Musculoskeletal— digit abnormalities, palmar creases
- Cardiac— congenital heart defects
- Urogenital— congenital urogenital defects

More physical exam abnormalities increase the likelihood of an underlying genetic etiology for ASD.
Genetic Testing in Autism Spectrum Disorder
what do we order?

• Based on physical exam, may include specific tests for:
  
  • **PTEN testing**
    If head circumference is > 2 SD above the mean and other body measurements not similarly elevated
  
  • **MeCP2 testing**
    In females with microcephaly, regression, seizures
  
  • **DiGeorge (chr22q11.2 deletion) testing**
    If presence of cardiac anomalies, palatal defects, cognitive deficiencies
Genetic Testing in Autism Spectrum Disorder

flowchart guided by results

Chromosomal microarray to detect CNVs

Variant Found

Variant Not Found
Genetic Testing in Autism Spectrum Disorder

*flowchart guided by results*

**Chromosomal microarray** to detect CNVs

- Variant Found
  - Pathogenic
    - VOUS
  - Benign
- Variant Not Found
The complex genetic architecture of ASD: 
*Defining our terms (3)*

- **Pathogenic**— associated with disease/disorder
- **Benign**— not associated with disease/disorder
- **Variant of unknown significance (VOUS)**— unclear if variant is associated with disease/disorder
- **Inherited**— allele passed on from parent
- **De novo**— variant arose in the child, not inherited
Genetic Testing in Autism Spectrum Disorder

flowchart guided by results

Chromosomal microarray to detect CNVs

Variant Found

Pathogenic

VOUS

Test Parents

De Novo Variant

Inherited, Parent +Dx

Benign

Inherited, Parent -Dx

Variant Not Found

Consider additional genetic testing

Test Parents

De Novo Variant

Inherited, Parent +Dx
Genetic Testing in Autism Spectrum Disorder case 1

• 15 year old young man diagnosed with ASD and Intellectual Disability
  • Referred for irritability, aggression, oppositionality
  • Family history notable for Schizoaffective Disorder in mother, but otherwise unknown (adopted in early childhood, father unknown)
  • Medical history significant for prematurity, oral aversion necessitating g-tube, asthma, central apnea after sedation for tonsillectomy, decreased tone
  • Physical exam showed HC elevated compared with height/weight but not > 2 SD
  • Dysmorphic facies (depressed nasal bridge, mild frontal bossing)

Order Chromosomal Microarray and Fragile X testing
Genetic Testing in Autism Spectrum Disorder

case 1

- **CMA** (SNP-based array) and **Fragile X** testing ordered
  - Fragile X testing showed normal number of repeats
  - CMA showed a 1Mb deletion of chromosome 1:
    
    notation: 46, XY, del(1) (p31.1p31.3)
    means: #chr, sex, change(chr #) (region affected)

- Look up region/gene on:
  - UCSC browser: [http://genome.ucsc.edu](http://genome.ucsc.edu)
  - ExAC database: [http://exac.broadinstitute.org](http://exac.broadinstitute.org)
  - **Unique site:** [http://www.rarechromo.org](http://www.rarechromo.org)
  - OMIM site: [http://www.omim.org](http://www.omim.org)
Genetic Testing in Autism Spectrum Disorder

flowchart guided by results

Chromosomal microarray to detect CNVs

Variant Found

Pathogenic

Benign

VOUS

Variant Not Found
Genetic Testing in Autism Spectrum Disorder

*flowchart guided by results: case 1*

**Chromosomal microarray** to detect CNVs

Variant Found

Pathogenic
Genetic Testing in Autism Spectrum Disorder

Case 1

1p interstitial deletions

Index
You will find information on:
- Deletions from 1p13 to 1p22 on pages 5 to 6 - red page bar
- Deletions from 1p21 to 1p22 on page 6 - green page bar
- Deletions from 1p21/2 to 1p31/2 on pages 7 to 9 - orange page bar
- Deletions from 1p31 to 1p32 on pages 10 to 11 - blue page bar
- Deletions from 1p32 to 1p34 on page 11 - brown page bar
- Deletions from within 1p34 on page 12 - purple page bar
- Deletions from 1p34/5/6 to 1p36 on page 12 to 13 - grey page bar

Images from www.rarechromo.org pamphlet on chr 1 deletions
Autism is a disorder of development notation: 46, XY, del(1) (p31.1p31.3) 
means: #chr, sex, change(chr #) (affected region)

- Individuals with chr 1p31 to 1p32 deletions may present with:
  - Hypoplastic corpus callosum
  - Ventriculomegaly, congenital hydrocephalus
  - Tethered spinal cord
  - Renal complications (stones, hydronephrosis)
  - Heart and genital malformations
  - Seizures

Image from www.rarechromo.org pamphlet on chr 1 deletions
Genetic Testing in Autism Spectrum Disorder

**case 1**

**notation:** 46, XY, del(1) (p31.1p31.3)

**means:** #chr, sex, change(chr #) (affected region)

- Recommendations for our patient:
  - MRI with monitoring for seizure development
  - Monitor for renal complications
  - Consider cardiac exam
  - Carefully consider potential adverse effects of medications by organ system and avoid those that may adversely affect renal system, prescreen for cardiac conditions

Image from [www.rarechromo.org](http://www.rarechromo.org) pamphlet on chr 1 deletions

Genetic Testing in Autism Spectrum Disorder case 2

• 5 year old boy diagnosed with ASD
  • Referred for aggression, obsessive traits
  • Family history notable for paternal ASD diagnosis, maternal history of learning disability and maternal family members with ASD and Down’s syndrome
  • Medical history significant for developmental delay, astigmatism, mild asthma, sleep apnea
  • Physical exam showed average body measurements, no dysmorphia, cognitive faculties largely intact

Perform CMA and Fragile X testing based on ASD diagnosis
Genetic Testing in Autism Spectrum Disorder

flowchart guided by results

Chromosomal microarray to detect CNVs

Variant Found

Pathogenic

Benign

VOUS

Variant Not Found
Genetic Testing in Autism Spectrum Disorder

Case 2

- **CMA** (SNP-based array) and **Fragile X** testing ordered
  - Fragile X testing showed normal number of repeats
  - CMA showed a 0.383Mb duplication of chromosome 1:
    
    notation: 46, XY, dup(1) (q21.1)
    
    means: #chr, sex, change(chr #) (affected region)

- Look up region/gene on:
  
  - UCSC browser: http://genome.ucsc.edu
  - ExAC database: http://exac.broadinstitute.org
  - **Unique site:** http://www.rarechromo.org
  - OMIM site: http://www.omim.org
Autism is a disorder of development. The notation 46, XY, dup(1) (q21.1) means the following:

- **#chr, sex, change(chr #) (affected region)**

Images from [www.rarechromo.org](http://www.rarechromo.org)
pamphlet on chr 1q microduplications
Genetic Testing in Autism Spectrum Disorder

**flowchart guided by results**

Chromosomal microarray to detect CNVs

Variant Found

- Pathogenic
- Benign

**VOUS**

Test Parents

- De Novo Variant
- Inherited, Parent +Dx
- Inherited, Parent -Dx

Consider additional genetic testing
Genetic Testing in Autism Spectrum Disorder  
*what do we order?*

If CMA and Fragile X testing show no abnormalities, consider whole exome sequencing (WES):

*Findings of abnormal development as detected on physical exam increases the likelihood of a positive genetic result* *

<table>
<thead>
<tr>
<th>Categories by physical exam</th>
<th>CMA</th>
<th>WES</th>
<th>CMA or WES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential (0-3 anomalies)</td>
<td>4</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Equivocal (4-5)</td>
<td>11</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Complex (≥ 6)</td>
<td>24</td>
<td>17</td>
<td>37</td>
</tr>
</tbody>
</table>

* as reported in Tammimies et al. JAMA 2015
Whole exome sequencing to detect SNVs

Variant Found

- Pathogenic
- Benign

VOUS

Test Parents

- De Novo Variant
- Inherited, Parent +Dx
- Inherited, Parent -Dx

An inherited SNV in a neuronal voltage gated sodium channel associated with epilepsy and atypical response to sodium channel blockers
Whole exome sequencing to detect SNVs

Variant Not Found

Consider karyotype or testing for abnormal methylation, imprinting, whole genome sequencing
Genetic Testing in Autism Spectrum Disorder

*take home messages*

• If there is a diagnosis of idiopathic ASD (or intellectual disability) start with:
  • Chromosomal microarray (CMA) to detect CNVs
  • **Fragile X** testing to detect trinucleotide repeat expansion (all males, females with low IQ or family Hx)
  • **Gene specific** testing based on individual presentation/exam

• If CMA is positive, consider relevance of result to ASD risk:
  • **If likely** to contribute to ASD risk, no further testing
  • **If unlikely** to contribute to ASD risk, consider further testing

• If CMA is negative, consider further testing
  • More physical anomalies predict higher likelihood of finding on whole exome sequencing (**WES**) especially if compared to parent samples
  • Consider **karyotype** if WES is negative
Final thoughts…

• The community practitioners are ideally positioned to **begin a dialogue** with the family regarding genetic testing in individuals with ASD.

• A diagnosis of idiopathic ASD **necessitates** a genetic evaluation, and should be part of our overall evaluation process.

• **Clinicians** can better monitor for symptoms and co-morbid conditions that are known to be associated with specific risk variants.

• **Families** that receive a genetic diagnosis can be better informed regarding family recurrence risks, and may be eligible for variant specific studies and family groups.

• Refer families with positive genetic findings for **genetic counseling**. Ethical implications of genetic testing in adolescents (ex. right to know) and the parents (ex. reporting of secondary findings) deserves thoughtful consideration.
Bibliography