

# Etiology of ASD:

## Do you offer a genetic evaluation to every patient with ASD?

---



Paul Carbone, MD  
Associate Professor of Pediatrics  
University of Utah

# Review

- The signs of ASD emerge in the first 2 years of life
- Providers identify children at risk for autism by observing for early signs (orienting to name, joint attention) and screening (M-CHAT-R)
- ASD is ideally diagnosed by an interdisciplinary team with the used of standardized tools (e.g. ADOS-2)
- ASD is a behaviorally defined condition that has many different etiologies
  - Multifactorial etiology with genetic and environmental factors

# Genetics of ASD

- Clinically and etiologically heterogeneous, yet highly heritable (64%)
- **Polygenic model**- many inherited common variants, epigenetic and environmental interactions
- **Major gene model** - genetic risk factors of a disease as due to often single and more rare genetic variants, each of which contributes a large risk for developing a disease
  - Syndromes, copy number variants, and single nucleotide variants

# Genetics of ASD

- Now estimated that there are between 400 – 1000 ASD risk genes, many of which converge on common molecular pathways
- Testing for copy number variations (CNVs) with chromosomal microarray has aided the identification of specific ASD etiologies
- Next generation sequencing identifies additional ASD etiologies
  - Common but no single variant accounts for more than 1%
- Diagnostic yield of genetic evaluation of ASD estimated to be 30 – 40%

**Table 19.1. Genetic Etiologies: Examples of Clinical Syndromes, CNVs, and SNVs Associated With ASD**<sup>40,42,44,54,56–59,63</sup>

<b>Genetic syndromes</b> often suspected clinically and confirmed by genetic testing (implicated genes in parentheses)	<b>Recurrent CNVs</b> commonly identified by whole genome chromosomal microarray analysis	<b>Single gene mutations,</b> including SNVs and small insertions or deletions identified by whole exome sequencing <sup>a</sup>
Angelman syndrome ( <i>UBE3A</i> ) CHARGE syndrome ( <i>CHD7</i> ) Cohen syndrome ( <i>VPS13B</i> ) Cornelia de Lange syndrome ( <i>NIPBL</i> , <i>RAD21</i> , <i>SMC3</i> , <i>HDAC8</i> , <i>SMC1A</i> ) Down syndrome/Trisomy 21 Fragile X syndrome ( <i>FMR1</i> ) Neurofibromatosis Type 1 ( <i>NF1</i> ) <i>PTEN</i> hamartoma tumor syndrome ( <i>PTEN</i> ) Rett syndrome ( <i>MECP2</i> ) Smith-Lemli-Opitz ( <i>DHCR7</i> ) Timothy syndrome ( <i>CACNA1C</i> ) Tuberous sclerosis ( <i>TSC1</i> , <i>TSC2</i> )	1q21.1 deletion 1q21.1 duplication 3q29 deletion 7q11.23 duplication 15q11.2-q13.1 (BP2-BP3) duplication 15q13.2-q13.3 (BP4-BP5) deletion 16p11.2 deletion 16p11.2 duplication 16p13.11 deletion 17q12 deletion 22q11.2 deletion 22q11.2 duplication	<i>ADNP</i> <i>ANK2</i> <i>ARID1B</i> <i>ASH1L</i> <i>CHD2</i> <i>CHD8</i> <i>DYRK1A</i> <i>GRIN2B</i> <i>KATNAL2</i> <i>NRXN1a</i> <i>POGZ</i> <i>SCN2A</i> <i>SHANK3</i> <i>SUV420H1</i> <i>SYNGAP1</i> <i>TBR1</i>

# Genetic Etiologic Investigations in Patients with ASD

1. Consider genetics referral
2. Comprehensive history, physical exam,
  - If syndrome or metabolic disorder suspected back to step 1 and/or order appropriate targeted tests
3. Laboratory studies
  - Discuss and offer chromosomal microarray analysis
  - Consider metabolic testing
  - Discuss and offer Fragile X analysis
  - If female consider evaluation for Rett Syndrome, MECP2 testing
4. Consider referral to genetics, additional workup might include whole exome sequencing



- No copy number variants
- Variant related to autism
- Variant of unknown significance
- Variant related to some other condition

# Potential Benefits of Establishing a Genetic Etiologic Diagnosis

- Improving accuracy of counseling provided to patients and families:
  - Prognosis or expected clinical course
  - Recurrence risk for the family
- Providing condition-specific family support, such as:
  - Improving psychosocial outcomes for patients and their families
- Identifying and treating medical conditions associated with the genotype
- Refining treatment options, including:
  - Avoiding therapeutic interventions that may be based on unfounded etiologic theories
  - Avoiding ineffective or potentially harmful treatments
  - Providing access to emerging etiology-specific treatments
- Avoiding additional diagnostic tests, which may be unnecessary, expensive, and/or uncomfortable.
- Facilitating acquisition of needed services and access to research treatment protocols.

# Other Etiologic Workup

- Electroencephalography

- Not recommended unless clinical concern for seizures, atypical regression

- Neuroimaging

- Evaluation of atypical regression, microcephaly, macrocephaly, seizures, evaluation for intracranial manifestations of genetic disorders, abnormal neurologic examination or other clinical indications

Schaefer, G. B., et al. (2013). "Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions." *Genet Med* **15**(5): 399-407.

# Environmental Risk Factors

- Exposure to drugs/chemicals:
  - Thalidomide
  - Valproic acid
  - High exposure to air pollution/pesticides
  - organophosphates
- Prenatal infections:
  - Rubella
- Perinatal factors:
  - Prematurity
  - Low birth weight
  - SGA
  - Neonatal jaundice
  - Intrapartum hypoxia
- Prenatal factors:
  - Advanced maternal/paternal age
  - Gestational diabetes
  - Breech position
  - Interpregnancy interval
  - Conception during winter months
  - Maternal weight gain during pregnancy
  - Folate supplementation (lower risk)
  - Maternal influenza infection
  - Maternal asthma

# Genes not vaccines....

## Shifting hypotheses about autism and vaccines

1. The combination measles-mumps-rubella vaccine causes autism by damaging the intestinal lining, allowing entrance of encephalopathic proteins
2. Thimerosal is toxic to the nervous system
3. The simultaneous administration of multiple vaccines overwhelms or weakens the immune system

# SPARK

Simons Powering Autism Research



- National autism research project designed to facilitate research that accelerates our understanding of the causes of autism
- Individuals with a diagnosis of autism and their biological family members share information about their medical and family history, as well as provide a DNA sample
- University of Utah Child Development Program— one of the newest SPARK clinical sites

[www.SPARKforAutism.org/Utah](http://www.SPARKforAutism.org/Utah)

