

1-1-2013

# Genomics and Autism Spectrum Disorder (ASD)

Norah L. Johnson PhD, RN, CPNP  
*Marquette University, norah.johnson@marquette.edu*

Ellen Giarelli EdD, RN, CRNP  
*Drexel University*

Catherine E. Rice PhD  
*Centers for Disease Control and Prevention*

---

Published version. *Genomics and Autism Spectrum Disorder (ASD)*. National Human Genome Research Institute. International Society of Nurses in Genetics and Genomics, Philadelphia, PA. October 26, 2013. Power Point Presentation. [Permalink](#). © 2013 National Human Genome Research Institute. Used with permission.

# Genomics and Autism Spectrum Disorder (ASD)

- Norah L. Johnson PhD, RN, CPNP, Marquette University, Milwaukee, WI, USA.
- Ellen Giarelli EdD, RN, CRNP, Drexel University, Philadelphia, PA, USA.
- Catherine E. Rice, PhD, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA.



**Acknowledgement: Celine Lewis PhD, Research manager, Genetics Alliance, UK.**

# Purpose

To understand the current state of the evidence regarding translation of genetics and genomics into nursing care of children with (ASD)



# Defining ASD

- Autism first introduced as a developmental disability or “pervasive developmental disorders” (PDD) (Diagnostic and Statistical Manual of Mental Disorders [DSM-III] American Psychiatric Association [APA], 1980)
- PDD-Not Otherwise Specified (PDD-NOS) added in the revised DSM III-R (APA, 1987)
- Asperger’s disorder added as a PDD in the DSM-IV and the DSM-IV TR (APA, 1994; 2000) and the International Classification of Diseases, tenth edition International Statistical Classification of Diseases and Related Health Problems (ICD-10), (World Health Organization [WHO], 1992)

# Rising Prevalence of ASD

- 1940's until the 1980's 1/2000 (0.05%)
- Now
  - 6-7/ 1,000 children (0.6%–0.7%).
  - >1%
  - 2.6% among children in areas of Asia, Europe, and North America.
  - 4-5 boys are affected for every girl.

(Centers for Disease Control and Prevention (CDC), 2012; Fombonne, 2009; Kim et al., 2011)

# ASD Phenotype

- Numerous phenotypic dimensions suggests causal heterogeneity
- Core domains associated with ASDs (social, communication, restricted, repetitive behaviors) distributed in a more continuous way in the population

(Walsh, Elsabbagh, Bolton, & Singh, 2011; Constantino, 2011)

# Heritability

- Identical twins shared 60% to 90% of autistic traits compared to fraternal twins who only shared 0% to 10% (Rosenberg et al., 2009)
- Sibling recurrence as high as 19% (Ozonoff et al., 2011)
- Co-occurrence of ASD and single gene disorders (e.g. tuberous sclerosis) (Freitag, Staal, Klauck, Duketis, & Waltes, 2010)
- No single risk factor explains the changes identified in ASD prevalence over time (Rice, 2011)

# Environment

- Environmental factors (influences other than genetic mutations) (Hallmeyer et al., 2011)
- Gestational exposure to high levels of environmental pollutants, for eg. pesticides (Shelton, Hertz-Picciotto, & Pessah, 2012)
- Complications during pregnancy, for eg. viral infections, maternal stress (Altadottir et al., 2010; Kinney, Munir, Crowley, & Miller, 2008)
- Artificial insemination and ovulation-inducing drugs in mothers  $\geq 35$  years old (Lyall, Pauls, Spiegelman, Santangelo, & Ascherio, 2012)



# Environmental Epigenetics

- Study of changes in gene expression that occur without changes in DNA sequence
- Histone methylation is different in persons with ASD compared to controls on genes regulating neuronal connectivity, social behaviors, and cognition (Shulha et al., 2012)
- Early Autism Risk Longitudinal Investigation (EARLI) ([www.earlistudy.org](http://www.earlistudy.org))
  - Hypothesis: epigenetic changes from methylation related to environmental exposure during pregnancy might increase the risk of ASD

# The Promise of Genetics



- An understanding of molecular and cellular mechanisms promises to:
  - Improve the opportunities to intervene in a rational way and
  - Lead to the path to treatment or cure.
- **Why so hard to find the genetic answer?**
  - Individuals are ~99% identical, genetically
  - Highly heterogeneous disorder
  - Until very recently, limited ability to search through the genome
  - Often not due to single gene ....not a 1 to 1 relationship between genetic risk and outcome
  - Variations are the basis for genetic risk
- ASD research is interested in the ~1% difference

- Very little is known about diversity in systems-level brain architecture
- Not sure what is normal and what is atypical
- Genetic influences emerge from rare variants may have *small, cumulative* effects
- Research is in infancy
  - Needs ways to connect genetic variation to specific behaviors
  - Then apply to ASD and subgroups
- Following significant leads
  - “*Father’s age linked to risk for autism and schizophrenia*”, 2012
  - “*Grandfather’s age linked to risk of autism*”, 2013



# Research of ASD: Gene and Variation Discovery

## **SINGLE GENES MUTATIONS**

- Rate mutations in “syndromic” and “idiopathic” ASD point to complex mechanisms
- Some syndrome and medical conditions are attributable to single genes
- Unlikely there is only one path to the disorder

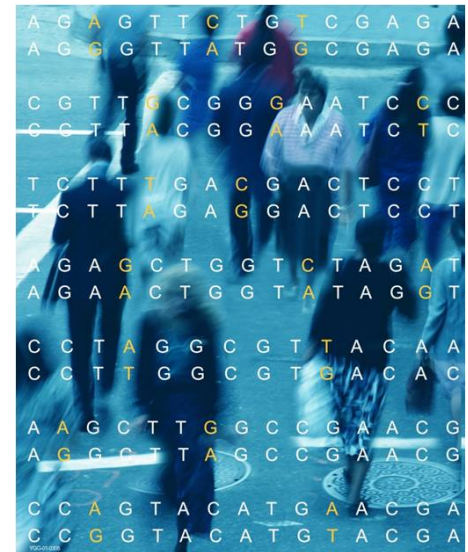
## **VARIATIONS**

- Single nucleotide polymorphisms
- Structural gains and losses of genetic materials at submicroscopic resolution (CNV)
- Common and rare variations mutations contribute to ASD risk
  - Nature of contributions is open to debate

# Single genes: Associated syndromes and medical conditions

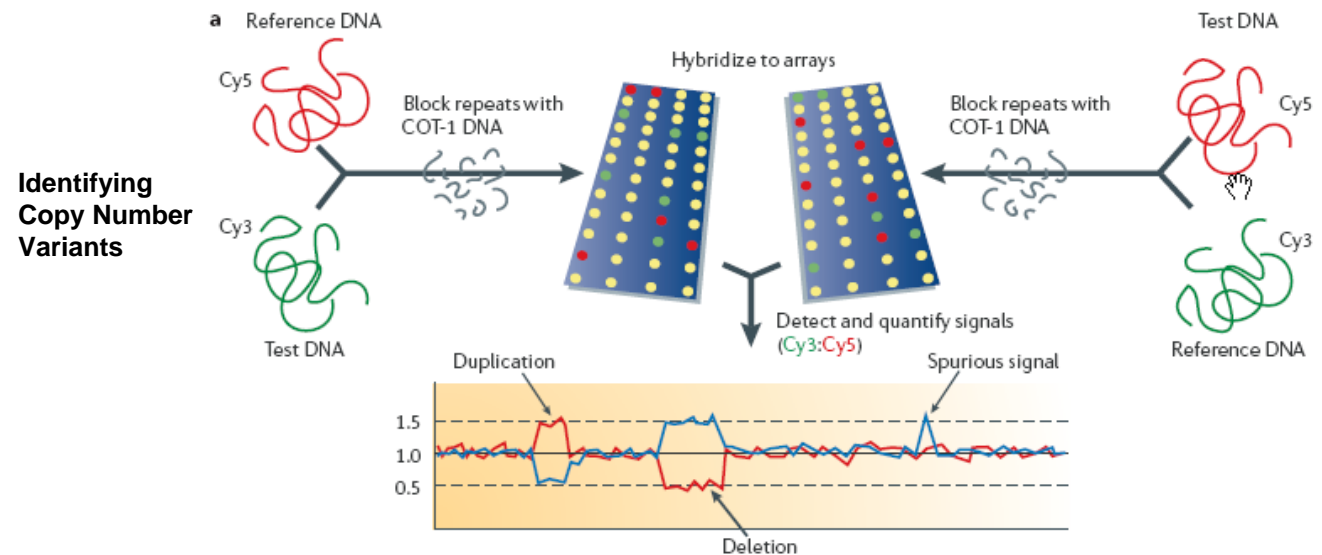
Individuals with the following conditions account for ~ 5-10 % of cases of ASD

- Sex chromosome trisomies, XYY and Klinefelter syndrome (XXY)
- Fragile X, Rett
- Tuberous Sclerosis
- Smith-Magenis
- Angelman, Pader-Willi
- Velocardiofacial (deletion 22q11.q)



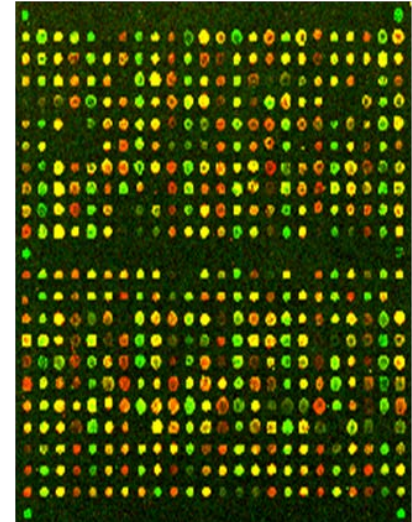
# Structural gains and losses of genetic materials called copy number variants (CNV)

- Large *de novo* CNV (~500 kbp) account for about 6-10% of ASD
  - Carry large, clearly identifiable, risks
  - Inheritance assessment suggests that 1/3 rd are *de novo*
- New hotspots emerging eg. 15q25 highlighting
  - specific genes *IMMP2L*, *ATXBP1*, *CTNNA3* (1-2% of patients)



# Copy number variants

- 16p11.2 deletions and duplications
  - 1% of cases of “idiopathic” ASD
- 7q11.23 duplications strongly associated with ASD
  - This is the Williams syndrome region
  - Ch 7- speech and language disorders
- 4 regions have recurrent *de novo* and rare transmitted CNVs (found only in cases of ASD)
  - 1q21.1
  - 15q13.3 [**\*\***anxiety and epilepsy]
  - 16p13.2
  - 16q23.3



# Contributions of Common Variants

- Rare and common mutations may contribute to ASD risk
  - **Cerebellum development**
    - ( *EN2* -Engrailed 2 gene, Chr 7)
  - **Brain cell migration, differentiation, and synapse formation**
    - (gamma aminobutyric acid receptor genes, Chr 4, 5, 15)
  - **Stress response social skills**
    - ( *OXTR* -oxytocin receptor genes, Chr 3)
  - **Neuronal migration in developing brain**
    - ( *RELN* -Reelin gene, Chr 7)
  - **Serotonin transport**
    - ( *SLC6A4* - a serotonin transporter gene, Chr 17) (Sakuri, Cai, Grice, & Buxbaum, 2011)



## Associated Features among 8-year olds, n=3924

Abnormalities in eating, drinking, sleeping	57%
<b>Abnormalities in mood or affect</b>	<b>68%</b>
Abnormalities in cognitive skills	48%
Aggression	48%
<b>Argumentative, destructive, oppositional</b>	<b>60%</b>
Delayed motor milestones	65%
<b>Hyperactivity, attention deficits</b>	<b>85%</b>
Lack of fear or excessive fearfulness	40%
<b>Odd responses to sensory stimuli</b>	<b>62%</b>
Self-injurious behavior	28%
Staring spells, seizure-like activity	30%
Temper tantrums	52%

Gene Function Outcome	Brain Segment	Gene	Chr
Developmental Disabilities	Not Known	Several Copy number variants (deletions and duplications)	16 16p11.2
Intellectual Disabilities			
Obsessions Compulsions Depression	Synapses	<i>SLC64A</i>	17q11.2
Cognitive deficits Language Disorder Speech disorder	Synapses	Duplication <i>SHANK3</i>	22q11.2

# Chromosomal microarray analysis

## Comparative genomic hybridization (CGH)

- ❑ **Method for the analysis of copy number variants (gains/losses) in the entire genome**
- ❑ **Considered medically necessary for diagnosing a genetic abnormality in children with apparent non-syndromic ASD when:**
  - Biochemical test for metabolic disease is non-diagnostic, **AND**
  - *FMR1* gene analysis (for Fragile X syndrome), when clinically appropriate, is negative, **AND**
- ❑ **The child has one or more of the following** (Miller, 2010)
  - *Major malformations (dysmorphology)*
  - *A single major malformation or multiple minor malformations,*
  - *A single major malformation and multiple minor malformations,*
  - *The results for the genetic testing have the potential to impact the clinical management of the patient,*
  - *Testing is requested after the parent(s) have face-face genetic counseling.*

# Perceptions of Causes

- The perceived causes reported most commonly by parents of autistic children include
  - Genetic influences (73%)
    - Only 10% had seen a genetic professional related to an ASD
  - Pregnancy and/or delivery problems (23%)
  - Childhood illness (20%)
  - Vaccines to child or pregnant mother (27%)
  - Diet (9%)
  - Environmental exposure (11%)
  - Age at birth (mothers-8%, fathers 9%)

(Mercer et al, 2006; Selkirk, 2009)

# Nursing Implications for Research

- Nurses counsel and refer patients for participation in clinical trials
- The International Society for Autism Research (INSAR) interdisciplinary collaboration <http://www.autism-insar.org/>
- Collaborative consortiums
  - The Autism Genetic Resource Exchange <http://agre.autismspeaks.org>;
  - The Simons Foundation Autism Research Initiative <http://sfari.org/>
  - The Autism Genome Project [www.autismgenome.org](http://www.autismgenome.org)
  - The National Database for Autism Research <http://ndar.nih.gov>

# Research Communities

- Simmons Simplex Community Research ‘Simplex’ families (only one child with ASD) helps identify whether genetic changes are:
  - inherited from the parent (already present in the family) (Fishbach & Lord, 2010)
  - A result of a *de novo* mutation in the child resulting in the potential to connect environmental and genetic links to ASD (Sebat et al., 2007)
  - Autism Genetic Resource Exchange
  - Research families participate in research looking for ASD candidate genes (<http://agre.autismspeaks.org>)

# Implications for Patient Participation in Research

- Many research methodologies and implications for participation (for eg. some research is only aggregate findings that may offer no individual clinically useful individual information for symptoms and prognosis or therapeutic interventions, in the short term) (Miller, Hyeems, & Bytautas, 2010)
- Complex to align genes with the behavioral symptoms of ASD, which also limits the development of a clinically valid genetic test (McMahon et al., 2006)

# Nursing Implications- Education

- The National Genetics Education and Development Center (<http://www.tellingstories.nhs.uk/>)
- Know risk factors and how to identify possible signs of ASD
- When to refer for additional assessment and intervention
- Family history:
  - Broader autism phenotype in apparently unaffected family members, across generations.

# Nursing Implications-Practice

- **Assess for possible ASD in all child encounters** (Centers for Disease Control and Prevention, 2012)
  - How a child communicates, interacts, behaves, learns, and plays and is guided by diagnostic criteria.
  - Early recognition of autism and for screening all children algorithms in the USA (Johnson & Myers, 2007) and in the United Kingdom (National Collaborating Center for Women's and Children's Health, 2010)
  - Without a definitive cause for ASD, parents are left to come to their own interpretations for the cause and beliefs affect future decisions parents made about health care (Hebert & Koulouglioti, 2010)
  - Parents experience stress during diagnosis and need a plan for life-long behavioral interventions for the child (Giarelli, Souders, Pinto-Martin, Block & Levy, 2005)



# Clinical Relevance

- Without a definitive diagnostic test for ASD, diagnosis may be delayed.
- Centers for Disease Control and Prevention ([www.cdc.gov/autism](http://www.cdc.gov/autism), [www.cdc.gov/actearly](http://www.cdc.gov/actearly)).
- Public education system. The Individuals with Disabilities Education Act (IDEA; <http://idea.ed.gov/>) enables early intervention or special education assessment to begin at any time there is a developmental concern.



# Summary

- Many genes on different chromosomes may be involved in ASD
- Chromosomal disorders and syndromes are risk factors for ASD
- Nurses will continue to play an important in research, education, and practice for children with ASD and their families' health

# Clinical Resources

- Autism Society of America (<http://www.autism-society.org>)
- Autism Speaks (<http://www.autismspeaks.org>)
- National Autistic Society (<http://www.autism.org.uk>)
- National Institutes of Health  
<http://www.health.nih.gov/topic/Autism>
- National Health Service  
<http://www.nhs.uk/conditions/Autistic-spectrum-disorder>
- Vaccine information  
<http://www.cdc.gov/vaccines/hcp.htm>