STAR Training – 2/22/2018

Genetics and Genetic Testing for Autism:

Demystifying the Journey to Find a Cause

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Conflicts of Interest

- None.

Objectives

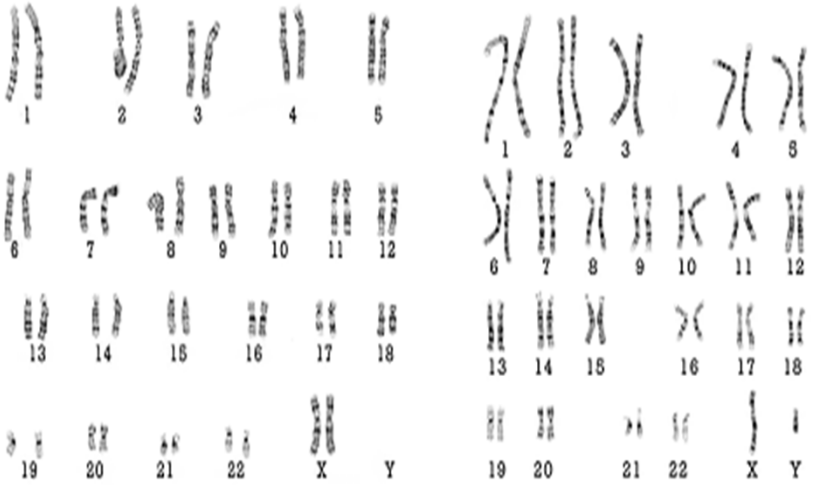
- To provide general background information about our current understanding of the genetics of autism spectrum disorder
- To summarize types of genetic tests and general approach to genetic evaluation of autism spectrum disorder
- To highlight considerations for genetic testing and the utility of genetic counseling for individuals/families thinking about genetic testing
- To provide information about genetic counseling services at the Center for Autism and Related Disorders (CARD) and the Kennedy Krieger Institute

Overview

- Genetics 101
- Genetics of Autism
- Clinical Genetic Testing
  - Types of tests
  - Possible results
  - Inheritance patterns
  - Considerations
- Genetic Counseling
- Questions

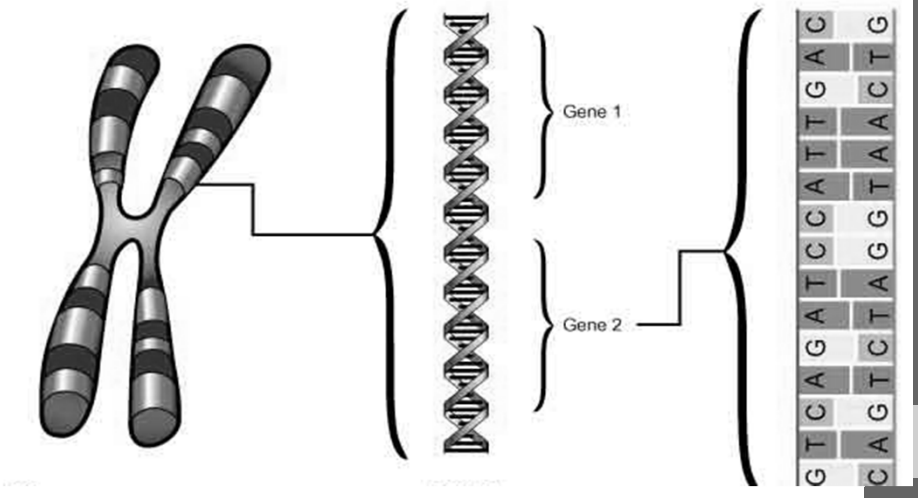
Genetics 101

Chromosomes



http://health.hawaii.gov/genetics/files/2013/05/xy.gif

Chromosomes → Genes → DNA



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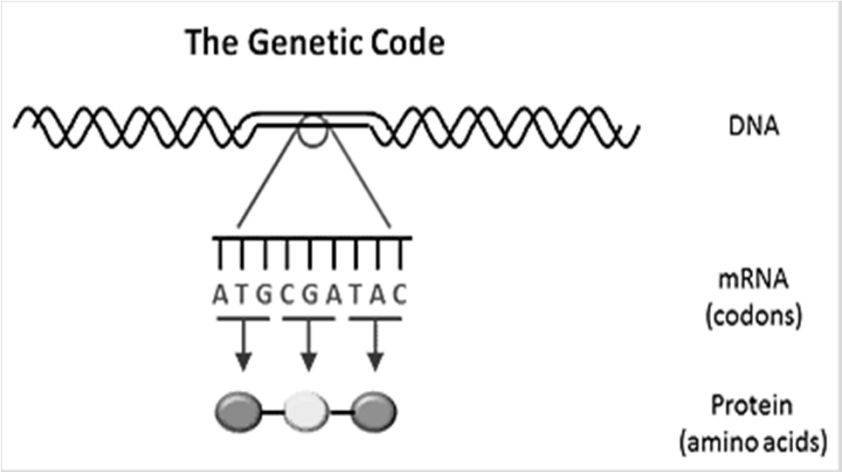
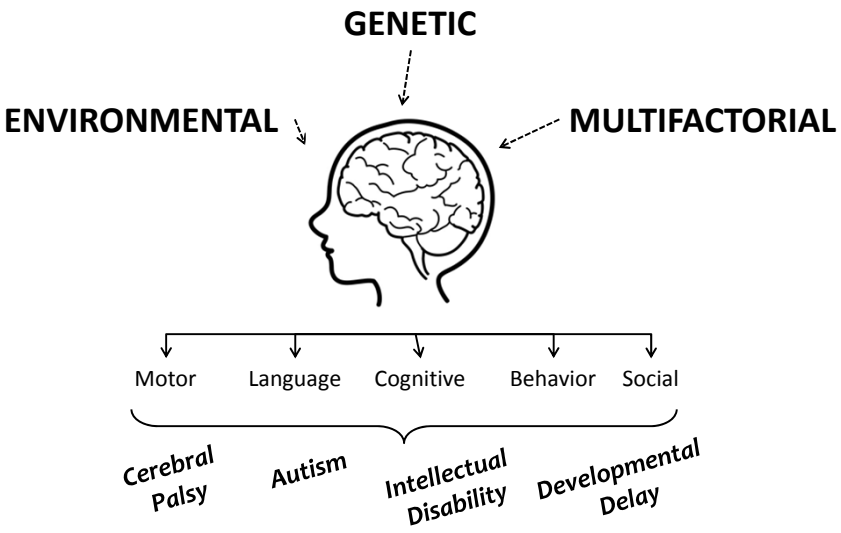
DNA → Proteins



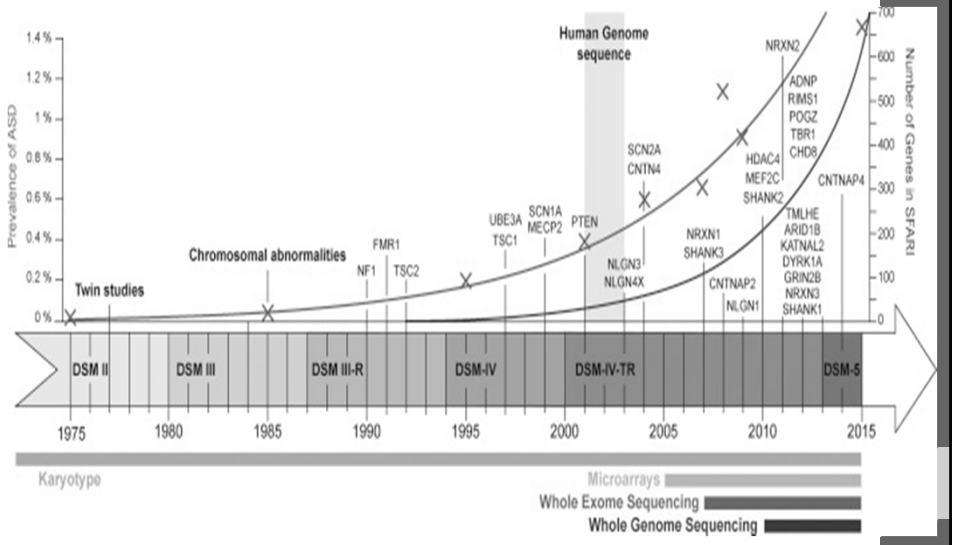
Genetics & Autism



Genetics of Autism

- Multifactorial: there is no singular known cause for autism
  - Genetics
  - Environment
  - Other factors
- There is a strong, complex genetic component
  - Various types of genetic changes in multiple genes
- Our knowledge of the genetics of autism is not perfect:
  - We're still discovering associations with specific genetic changes to autism
  - There is a lot we still do not know
  - Many times, we cannot find the underlying genetic cause

Timeline



Purpose of Genetic Testing

- Genetic testing is a **tool** to identify the underlying genetic cause for an individual's diagnosis of autism spectrum disorder
  - Genetic testing does **not** diagnose an individual with autism
  - Testing analyzes genetic material for a particular types of genetic changes (chromosomes, DNA variants)
- There is no single genetic test to look for every type of genetic change at one time.
- Our testing is limited to our knowledge of genetics and our technology at the time testing is performed.
- Genetic testing has been recommended by multiple medical/healthcare organizations (American Academy of Pediatrics).

Reasons for Genetic Testing

- Prognosis
- Medical management
  - In rare cases, a specific treatment may be known
  - Most likely there will not be a definitive “cure” at this time
- Establish inheritance pattern to determine risks to family members and future children
  - Genetic changes are not always inherited
  - Allows for reproductive options for future pregnancies
- Psychosocial benefits
  - Closure
  - Opportunity to connect with other families
  - Alleviation of guilt/blame

Clinical Genetic Testing

Types of Genetic Changes

~~MUTATION~~ ⇨ VARIANT

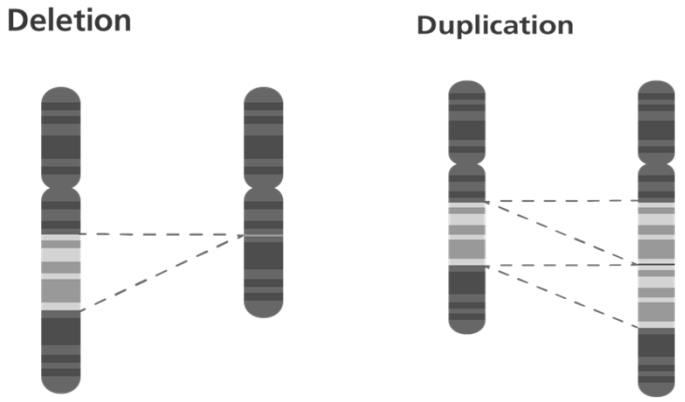
- ***Variant*** is neutral term that means a change in DNA/chromosome.
- Everyone has variants
  - Unique, normal changes
  - **Causative (pathogenic)**
- Changes in the chromosomes (that may affect many genes)
  - Numerical chromosome abnormality
  - **Copy number variant: deletion or duplication of a region of a chromosome**
  - Structural chromosomal abnormality/rearrangement
- Changes in a single gene
  - **DNA sequence alteration**
  - Deletion or duplication

Testing Strategy

- **<u>FIRST TIER</u>**
  - Chromosome microarray
  - Fragile X syndrome testing
  - Specific single gene DNA tests, depending on indication
- **<u>SECOND TIER</u>**
  - Molecular DNA tests: specific genes vs. whole exome sequencing

Chromosome Microarray

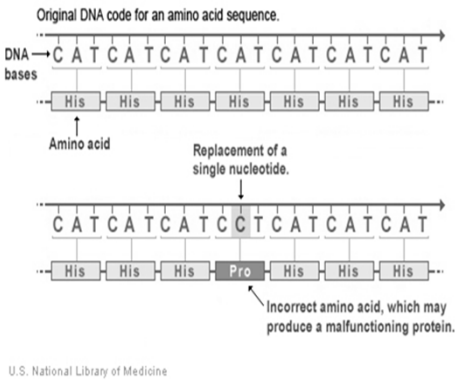
- Detect copy number variation: deletions/duplications across all the chromosomes



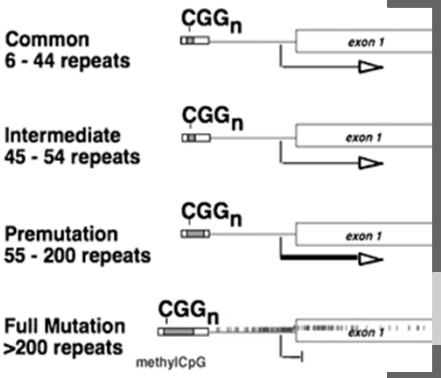
https://www.yourgenome.org/facts/

Molecular (DNA) tests

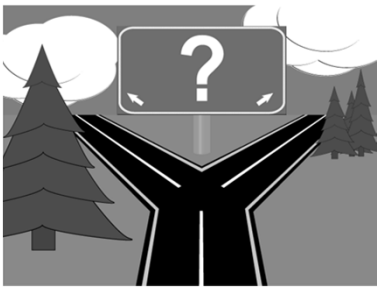
- Single genes:
  - Fragile X syndrome
- Panel: looking at a set number of genes associated with a particular feature/condition
- Whole exome sequencing: analyzing the protein coding segments of all 20,000 genes



U.S. National Library of Medicine



Possible Results from Genetic Testing



Positive (Abnormal)

- Identified a known genetic change related to autism
- Resources are available for information about other individuals with the same/similar genetic cause
  - UNIQUE: Rare Chromosome Disorder Support Group
  - Simons VIP connect
  - Facebook groups
  - Clinicaltrials.gov

Understanding chromosome disorders Unique

SIMONS VIP CONNECT

Negative (Normal)

- Did not identify any of the genetic changes analyzed on that particular test
- **Does not** rule out an underlying genetic cause because our knowledge and technology is not perfect
- Consider further workup/testing

Variant of Uncertain Significance

- Genetic change identified without clear evidence that it is related to autism or a benign change
- Testing other family members may be recommended
- This interpretation may change over time as new information is learned

Incidental/Unexpected Finding

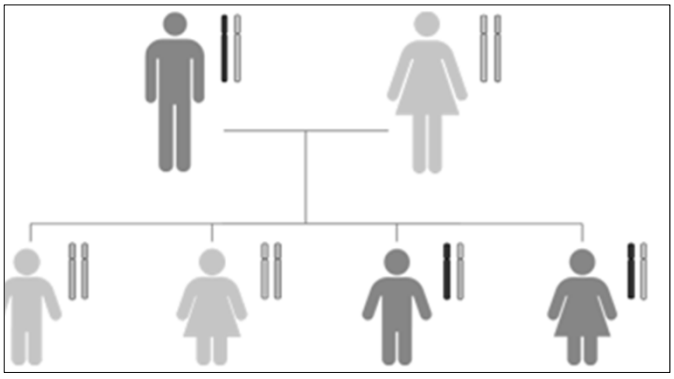
- Genetic change identified that is unrelated to autism
- Examples:
  - Parental relationships: consanguinity, non-paternity, non-maternity
  - Carrier status
  - Risks for other health conditions

Inheritance

Inheritance

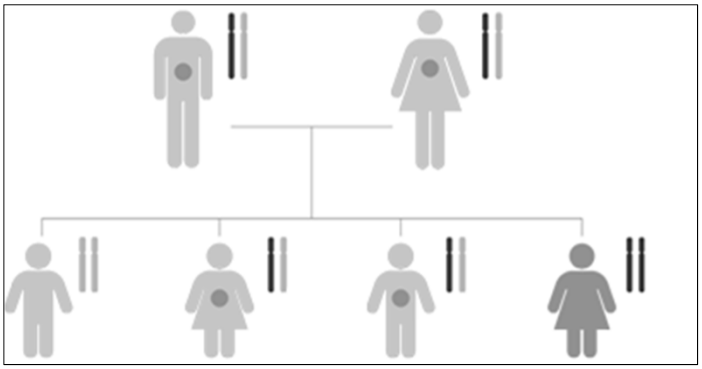
- We inherit one copy of each chromosome (and therefore one copy of each gene) from each of our parents
- Patterns of inheritance:
  - Autosomal Dominant
  - Autosomal Recessive
  - X-linked
- Genetic disorders are not always inherited
  - Sporadic or “de novo”

Autosomal Dominant



- Genes on numbered chromosomes
- One gene copy not working → affected with condition
- **50%** chance in each pregnancy to have affected child
- Same for males and females

Autosomal Recessive

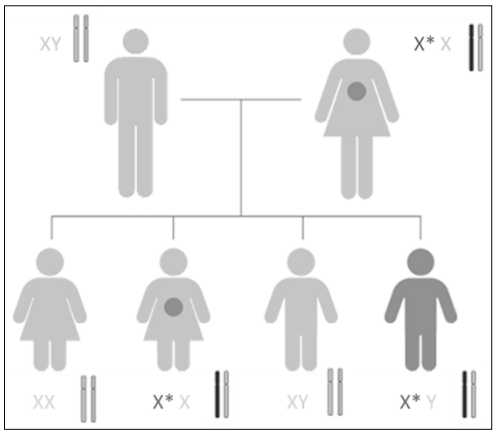


- Genes on numbered chromosomes
- One gene copy not working → unaffected carrier
- Both gene copies not working → affected with condition
- **25%** chance in each pregnancy to have affected child
- Same for males and females

X-Linked Disorders

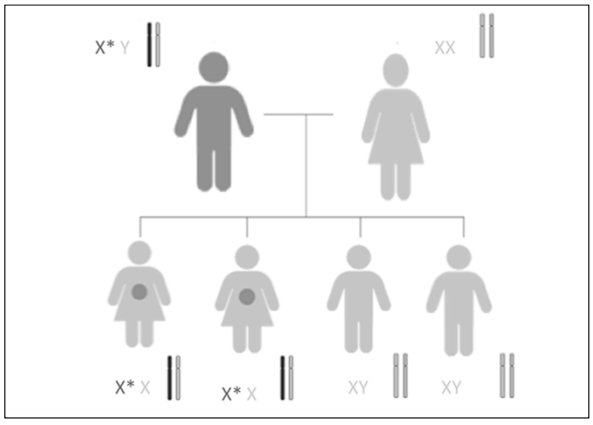
- Males have one X chromosome therefore only one copy of the gene
  - If only copy of gene not working, he will be affected
- Females have two X chromosomes therefore two gene copies
  - If one copy is not working, she is a carrier
  - Carriers usually unaffected or partially affected

X-Linked – mother carries mutation



- Sons: 50% chance affected
- Daughters: 50% chance carrier

X-Linked – father carries mutation



- All daughters are carriers
- All sons are unaffected

Other scenarios

- De novo variant – spontaneous genetic change in child, not inherited from parents
- Mosaicism – variant is present in egg/sperms cells of the parent, but not elsewhere. The parent is likely unaffected, but is at increased risk to have another child with the condition
- Variable expression - range of signs and symptoms that can occur in different people with the same genetic change, even within the same family

Family-Building Options

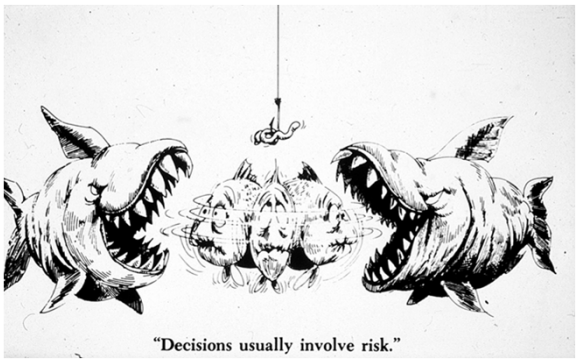
Preimplantation Genetic Diagnosis

Prenatal Diagnosis

Donor Eggs/Sperm

Adoption

Considerations:
Genetic Testing is a Choice



Logistics

- Typically performed on a blood sample
  - Alternative samples: buccal (cheek swab), saliva
- Start testing in the individual diagnosed with autism
  - May consider targeted testing in parents once results received
  - In affected siblings, start with the sibling who is more severely affected
- Insurance coverage
  - Most insurances have benefits for genetic testing, but pre-authorization may be the first step
  - Most genetic testing laboratories have patient friendly billing policies
- Results come back at varying times:
  - Chromosome microarray: 4-6 weeks
  - Fragile X syndrome testing: 3-4 weeks
  - Whole exome sequencing: 4-5 months

Limitations/Risks of Genetic Testing: Not "just" a blood test

- Will not lead to definitive cure or treatment
- Results not always clear-cut
  - Positive/abnormal
  - Negative/normal
  - Variant of uncertain significance
  - Incidental/unexpected finding
- Genetic test results often have implications for family members
- Genetic discrimination and information privacy

The Genetic Information Nondiscrimination Act (GINA)

- GINA outlines protections and limitations of existing legislation to protect against potential discrimination based on genetic test results. At the federal level:
  - GINA prohibits group and individual health insurers from using genetic information (including genetic test results and family history) as eligibility or premium criteria and from requiring a patient to take a genetic test.
  - GINA prohibits employers with greater than 15 employees from using genetic information in decisions related to the hiring, firing, promotion, etc. of employees.
- GINA does not protect against discrimination based on genetic information as it may apply to:
  - life insurance
  - long-term care insurance
  - disability insurance
  - members of the federal government and/or military

Genetic Counseling

Genetic Counseling

- Genetic counseling is the process of helping individuals understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease.
- Genetic counselors have advanced training in medical genetics and counseling to interpret genetic test results, and to guide and support patients seeking more information about such things as:
  - How inherited diseases and conditions might affect them or their families.
  - How family and medical histories may impact the chance of disease occurrence or recurrence.
  - Which genetic tests may or may not be right for them, and what those tests may or may not tell.
  - How to make the most informed choices about healthcare conditions.

Genetic Counselors

- Genetic Counselors work in a variety of settings including:
  - Prenatal and Preconception – for women who are pregnant or thinking about becoming pregnant
  - Pediatric – for children and their family members
  - Cancer – for patients with cancer and their family members
  - Cardiovascular – for patients with diseases of the heart or circulatory system and their family members
  - Neurology – for patients with diseases of the brain and nervous system and their family members.
  - And more
- Find A Genetic Counselor Tool:
  - https://www.nsgc.org/findageneticcounselor

Informed Consent

✓ **Nature/Scope**	❑ simple explanation of test ❑ purpose = find genetic cause ❑ possible result outcomes
✓ **Benefits**	❑ May identify the genetic cause/diagnosis ❑ Medical & psychosocial benefits to diagnosis
✓ **Limitations**	❑ Does not rule-out all genetic conditions ❑ Will not lead to definitive cure or treatment ❑ May need to test parents
✓ **Risks**	❑ Ambiguous results ❑ Unexpected/unrelated information ❑ Familial implications
✓ **Costs**	❑ Check with insurance for authorization!

Genetic Counseling at CARD

- Either a healthcare provider makes a recommendation for first-tier genetic testing or family expresses interest in testing. Provider will place a referral for genetic counseling at CARD for pre-test counseling.
  - Informed consent
  - Family history
  - Coordinate sample collection
- Going to a genetic counseling appointment does not commit you to have genetic testing
- Result disclosure
  - In person meeting with a neurogeneticist and genetic counselor for interpretation of any abnormal genetic test results and further evaluation
  - Discuss options for further workup/testing if results are normal

Research Opportunities

SPARK

Igniting autism research
Improving lives

Summary

- We know there is a genetic component to autism spectrum disorder, but we do not have a complete knowledge of every genetic cause.
- Genetic testing is available as a tool to potentially identify a genetic cause, based on current knowledge and technology capabilities.
- Genetic testing is a choice.
  - Reasons to do genetic testing: informational for prognosis and medical management as well as family planning
  - Reasons some families choose not to do testing: risks for uncertain/unexpected results, no guarantee of positive result/management information, concerns for discrimination
- Genetic counseling is strongly recommended for individuals/families before, during, and after genetic testing.
- Genetic counseling is available at CARD and at the Kennedy Krieger Institute.

Resources

- National Society of Genetic Counselors: Find a Genetic Counselor Tool
  - www.nsgc.org
- Genetics Home Reference
  - www.ghr.nlm.nih.gov
- Genetics and Rare Diseases Information Center:
  - https://rarediseases.info.nih.gov/gard

QUESTIONS?

Thank you!

Specific Questions?
CONTACT ✉:
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