

# Medical Genetics and Genetic Counseling

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# What is medical genetics?

- Any application of genetics to medical practice
- Study of inheritance of diseases in families
- Mapping of disease genes to specific locations on chromosomes
- Analysis of molecular mechanisms through which genes cause disease
- Diagnosis and treatment of disease
- Genetic counseling

# Why is medical genetics important to you?

- Genetic diseases make up a large percentage of the total disease burden in pediatric populations
- Increasing number of pediatric deaths are due to genetic disease in developing countries
- Better understanding of disease process
- Prevention
- Treatment

Genetic condition	Approximate prevalence
Down syndrome	1/700 to 1/1000
Cystic Fibrosis	1/2000 to 1/4000 (Caucasian)
Fragile X syndrome	1/4000 males; 1/8000 females
Neurofibromatosis type 1	1/3000 to 1/5000

# Types of genetic diseases

- Chromosome disorders
- Single-gene disorders
- Multifactorial disorders
- Mitochondrial disorders

# Why is making an accurate diagnosis important?

- Allows for discussion of natural history, prognosis, management, treatment, earlier/more frequent disease screening, recurrence risk and prenatal diagnostic options, and referral to advocacy groups or clinical trials
- Involves recognition of phenotypic signs, dysmorphology exam, family history and testing

# Common indications for genetics referral

- Evaluation of individual with developmental delay or intellectual disability
- Individual with single or multiple malformations
- Individual with chromosome disorder
- Individual at risk for genetic condition
- Individual with questions about genetic aspect of disease
- Couples with history of recurrent miscarriage
- Consanguinity
- Teratogen counseling
- Preconception counseling

# Principles of Dysmorphology

- **Malformation/Anomaly** (primary defect)
- Basic alteration in structure of a body part usually occurring by 8 – 10 fetal weeks
  - Example: Cleft lip, polydactyly

# Major Anomaly

- Basic alteration in embryological development severe enough to require intervention and which potentially has a long-term impact medically and/or psychologically
  - Ex: spina bifida, omphalocele, cleft lip/palate

# Minor Anomaly

- Basic alteration in embryological and/or fetal development which requires no treatment or can be, more or less, corrected
  - Ex: postaxial polydactyly, low-set ears, preauricular tag

# Common multiple congenital anomaly syndromes

- Down syndrome
  - Minor anomalies: sandal gap, small ears, single palmar crease
  - Major anomalies: Congenital heart defects, duodenal atresia, pyloric stenosis
- Trisomy 18
  - Minor anomalies: small ears with unraveled helices, small mouth, short sternum, short halluces (first toes)
  - Major anomalies: congenital heart defects, omphalocele, missing radius bone, diaphragmatic hernia, spina bifida
- Van der Woude syndrome
  - Major anomalies: cleft lip with or without cleft palate
  - Minor anomalies: pits or fistulas of the lower lip

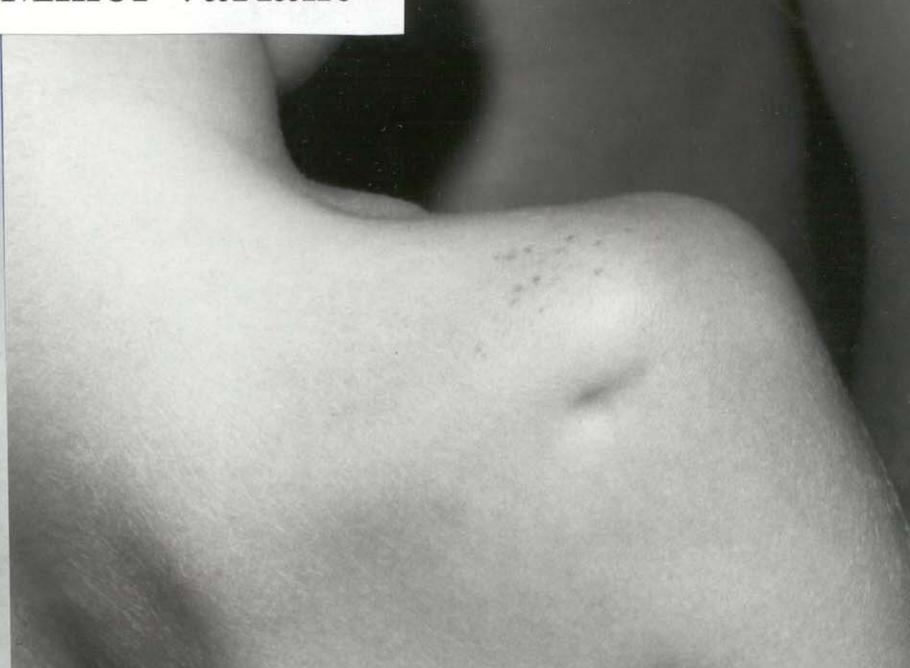
# Minor/Normal variant feature

- Low frequency (1% - 5%) congenital feature found in the normal population or as an integral part of a multiple congenital anomaly syndrome

Ex: simian line, 5<sup>th</sup> finger clinodactyly, 2-3 toe syndactyly, epicanthal fold, accessory nipple



**Minor variant**



# Comment on Anomalies

- Most malformation syndromes have more minor / normal variant type of anomalies than major anomalies

Ex. Down syndrome

# Down syndrome

- Low nasal root
- Uplanting palpebral fissures
- Overfolded, small ears
- Flattened maxillary and malar region



# Comment on Anomalies

- An anomaly is an anomaly whether it is major or minor; which means they each carry equal diagnostic importance. In fact, because minor anomalies are more numerous and often overlooked, they, as a group, may be potentially powerful diagnostically.

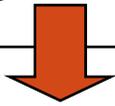
# Syndrome

- Recurring pattern of structural defects and/or secondary effects/defects that allow for secure recognition
- Combination of features most likely represents a specific etiology
  - Example: Roberts syndrome

# Sequence

- A situation where a single event (usually undefined) leads to a single anomaly (or situation) which has a cascading effect of local and/or distant deformations and/or disruptions
  - Ex: Potter, Pierre Robin, amniotic bands
- Sequences usually infrequently genetic, but can be incorporated as part of the features of a syndrome

# Sequence Scenario

<b>Potter/Oligo seq</b>	<b>Pierre Robin</b>	<b>Amn. Bands</b>
<b>Oligohydramnios</b>	<b>Micrognathia</b>	<b>Bands</b>
		
<b>Pul. hypoplasia</b>	<b>Glossoptosis</b>	<b>Constrictions</b>
<b>Jt contractures</b>	<b>Cleft palate</b>	<b>Fusions</b>
<b>Abn. ear cartilage</b>	<b>Low-set ears</b>	<b>Amputations</b>
<b>Lower inner eye folds</b>		<b>Cleft lip/palate</b>
<b>Prom. Nasal tip</b>		<b>Omphaloceles</b>

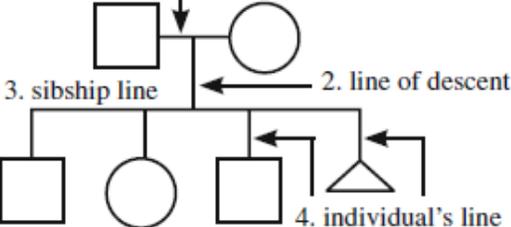
# Pedigree

- One of the most commonly used tools in medical genetics

# Patterns of inheritance

	Male	Female	Gender not specified	Comments
1. Individual	 b. 1925	 30y	 4 mo	Assign gender by phenotype (see text for disorders of sex development, etc.). Do not write age in symbol.
2. Affected individual				Key/legend used to define shading or other fill (e.g., hatches, dots, etc.). Use only when individual is clinically affected.  With $\geq 2$ conditions, the individual's symbol can be partitioned accordingly, each segment shaded with a different fill and defined in legend.
				
3. Multiple individuals, number known				Number of siblings written inside symbol. (Affected individuals should not be grouped).
4. Multiple individuals, number unknown or unstated				"n" used in place of "?".
5. Deceased individual	 d. 35	 d. 4 mo	 d. 60's	Indicate cause of death if known. Do not use a cross (†) to indicate death to avoid confusion with evaluation positive (+).
6. Consultand				Individual(s) seeking genetic counseling/testing.
7. Proband	 P	 P		An affected family member coming to medical attention independent of other family members.
8. Stillbirth (SB)	 SB 28 wk	 SB 30 wk	 SB 34 wk	Include gestational age and karyotype, if known.
9. Pregnancy (P)	 LMP: 7/1/2007 47,XY,+21	 20 wk 46,XX		Gestational age and karyotype below symbol. Light shading can be used for affected; define in key/legend.

# Patterns of inheritance

1. Definitions	Comments
<p data-bbox="310 760 514 784">1. relationship line</p>  <p data-bbox="310 873 472 898">3. sibship line</p> <p data-bbox="632 873 821 898">2. line of descent</p> <p data-bbox="604 1003 821 1027">4. individual's line</p>	<p data-bbox="850 764 1871 846">If possible, male partner should be to left of female partner on relationship line.</p> <p data-bbox="850 902 1850 984">Siblings should be listed from left to right in birth order (oldest to youngest).</p>

# Patterns of Inheritance

- Mendelian inheritance
  - Autosomal dominant
  - Autosomal recessive
  - X-linked recessive
  - X-linked dominant
  - Mitochondrial
  - Multifactorial
- Non-Mendelian patterns
  - Mitochondrial
  - Imprinting
  - Multifactorial
  - Sporadic
- Complexities in presentation
  - Reduced penetrance
  - Age-dependent penetrance
  - Variable expressivity
  - Anticipation
  - Sex-limited
  - New mutation
  - Germline mosaicism
  - Consanguinity
  - Skewed x-inactivation
  - Small families

# Evaluating a pedigree

- Transmission
  - Vertical – phenotype seen in generation after generation
  - Horizontal – phenotype seen in siblings but not previous generations
- Sex ratio
  - Number of males and females displaying phenotype – equal or unequal?
- Segregation - which parent passes on the trait and to whom?
  - Do fathers appear to pass the trait or disease onto sons and daughters?
  - Do mothers appear to pass the trait on to sons and daughters?
  - % of children affected - Compare to expected recurrence risk

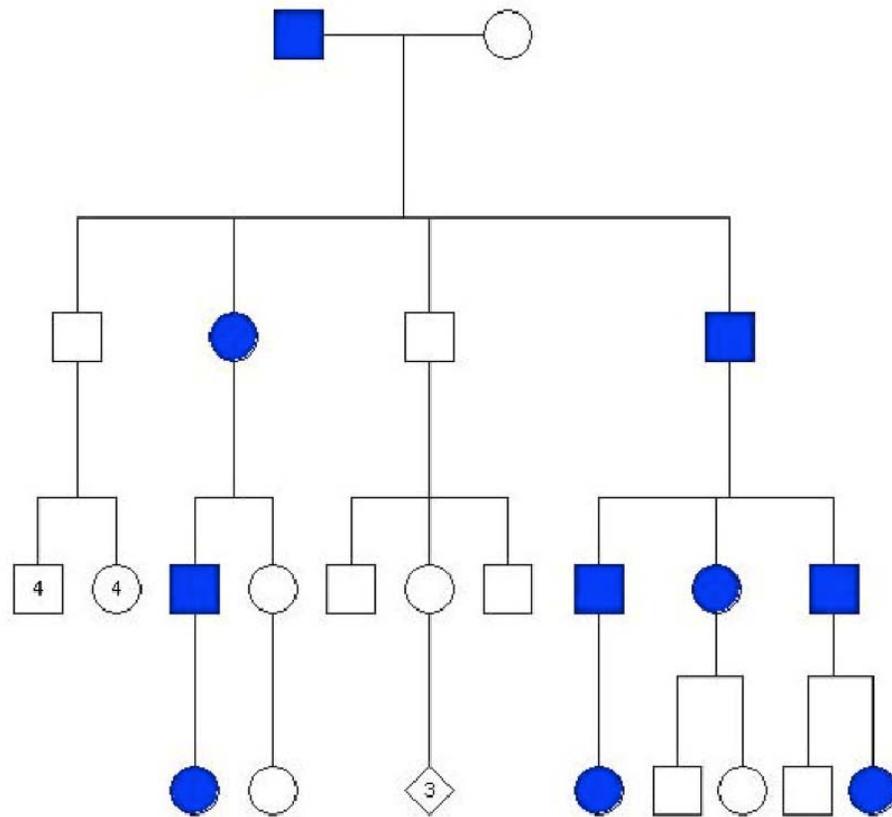
# Mendelian Inheritance

- The rules... not the exceptions.

# Mendelian inheritance

- AUTOSOMAL DOMINANT
  - Affected offspring usually have one affected parent (heterozygote) and one unaffected parent
  - Transmission
    - Vertical
  - Sex ratio
    - Equal number of males and females affected
  - Segregation
    - Either parent passes on the trait to sons and daughters
    - Expected recurrence risk 50%

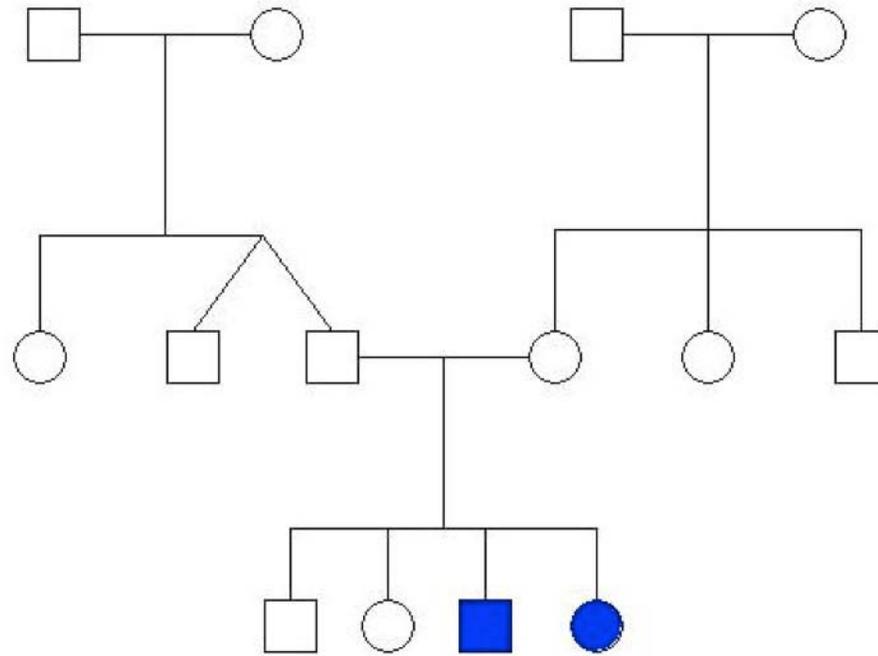
# Autosomal Dominant



# Mendelian inheritance

- AUTOSOMAL RECESSIVE
  - The parents of affected individuals are both heterozygotes (carriers)
  - Transmission
    - Horizontal
  - Sex ratio
    - Equal number of males and females affected
  - Segregation
    - Either parent passes on the trait to sons and daughters
    - Expected recurrence risk 25%

# Autosomal recessive



# Mendelian inheritance

- X-LINKED
  - Transmission
    - Vertical with “skipped generations”
  - Sex ratio
    - Much more frequent in males than females

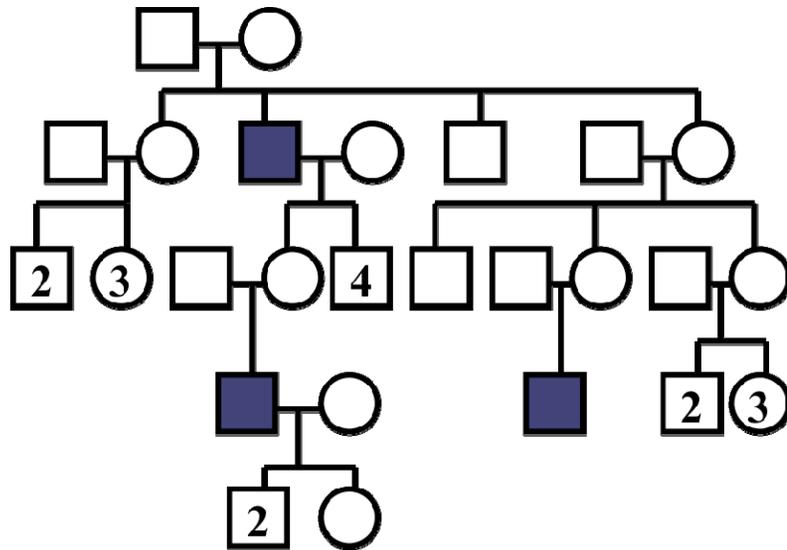
# Mendelian inheritance

- X-LINKED
  - Segregation
    - Carrier mother
      - Half of her sons (affected)
      - Half of her sons (unaffected noncarriers)
      - Half of her daughters (unaffected carriers)
      - Half of her daughters (unaffected noncarriers)
    - Affected father
      - All sons (unaffected noncarriers)
      - All daughters (unaffected carriers)
    - Expected recurrence risk depends on the mating type





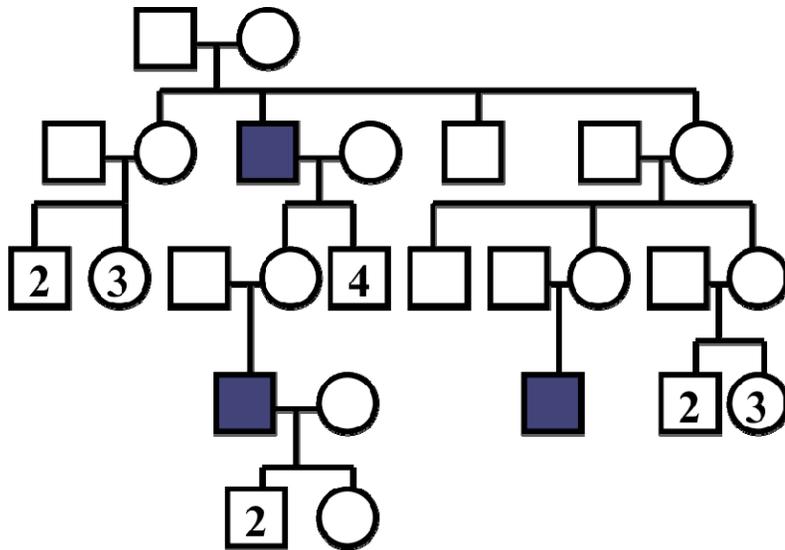
# What is the mode of inheritance?



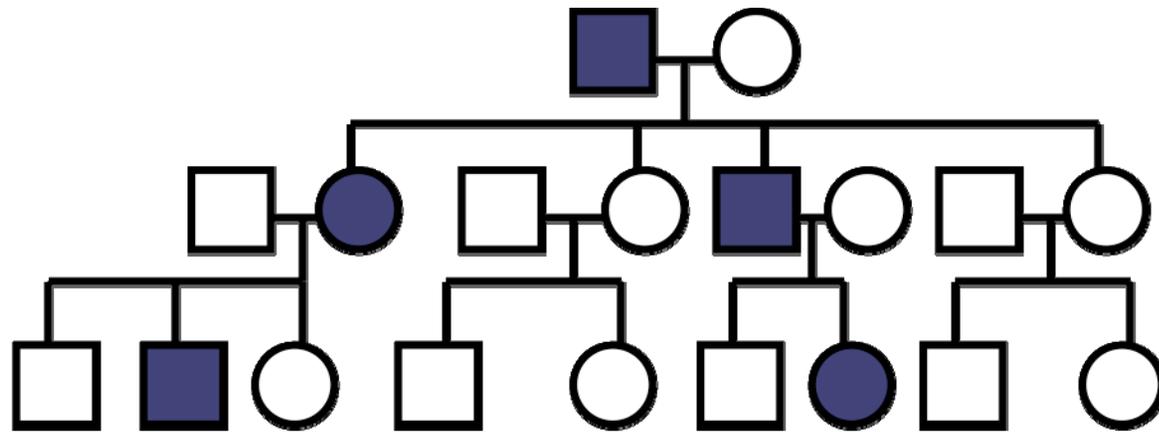
- “Skipped generations”
- Only males affected
- Affected males related through carrier females
- No male to male transmission

# What is the mode of inheritance?

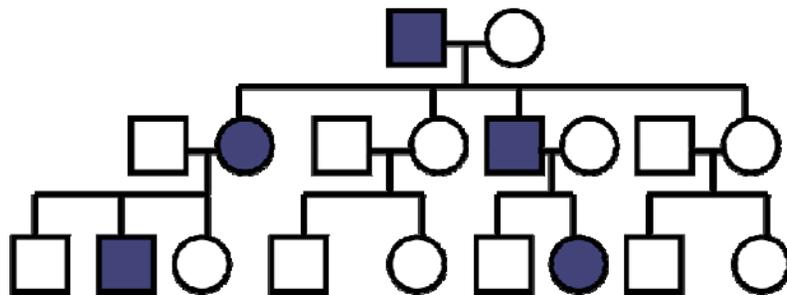
- **X- linked**



What is the mode of inheritance?



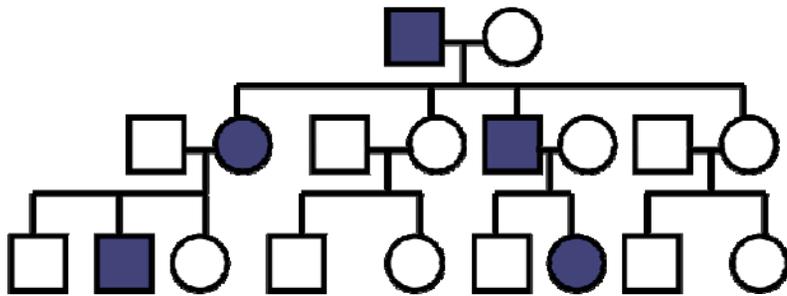
# What is the mode of inheritance?



- **Vertical pattern**
- **# of males = # of females**
- **See male to male transmission**
- **Every affected child has an affected parent**

# What is the mode of inheritance?

- **Autosomal dominant**

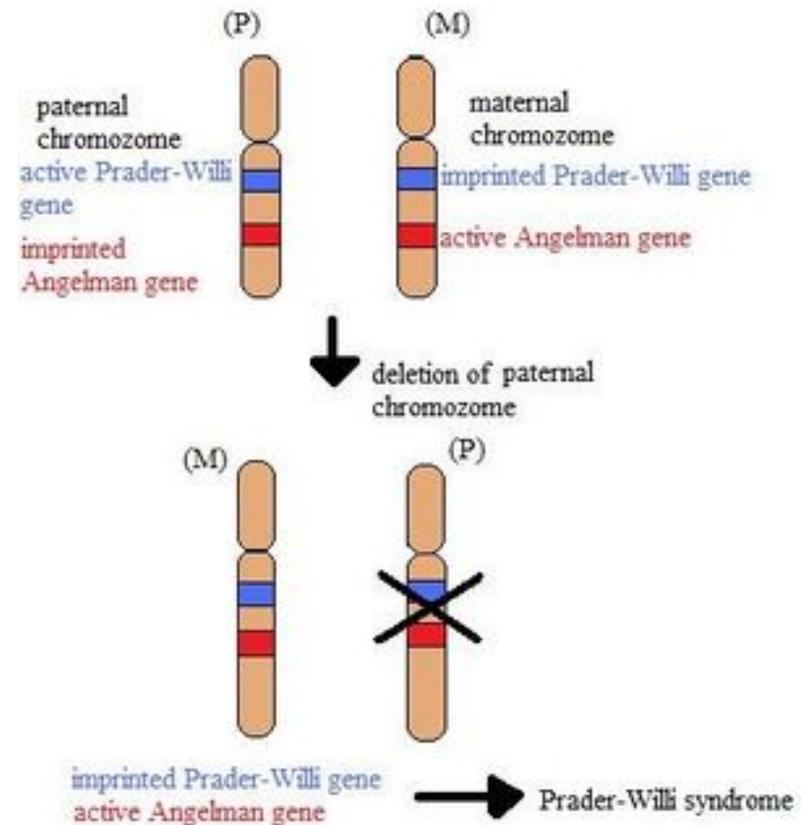


# Non-Mendelian inheritance

- Mitochondrial
  - A relatively small number of diseases are caused by mutations in the mitochondrial DNA (ATP/energy producing cytoplasmic organelles)
  - Mitochondria have their own DNA
  - Inherited exclusively through the maternal line (located in cytoplasm).
  - Heteroplasmy (within a single cell, there is a mixture of mitochondria, some containing mutant DNA and some containing normal DNA)
    - Larger the % of mutant DNA, the more severe the expression disease
    - % of mutant DNA can change over time, leading to variable expression

# Non-Mendelian inheritance

- Imprinting
  - Phenotype depends upon which parent passed on the gene.
  - 3-4 Mb deletion on chromosome 15 inherited from the mother results in Angelman syndrome; if inherited from the father it results in Prader-Willi syndrome.



# Non-Mendelian inheritance

- Multifactorial
  - A trait or disorder caused by a combination of genetic and environmental factors.
  - No characteristic pattern of inheritance.
  - Empiric risk
    - Based on direct observation of data
    - Average – may not apply to all families

# Non-Mendelian inheritance

- Multifactorial
  - Recurrence risk is higher if:
    - Closer relationship of relative
    - More than one family member affected
    - If phenotype is common in one sex and the opposite sex is affected in family

# Factors that affect expression of disease-causing genes

- Reduced penetrance
  - Individual with a disease-causing mutation may not have the disease phenotype.
  - Offspring are at risk.
  - Example
    - Retinoblastoma

# Factors that affect expression of disease-causing genes

- Age-dependent penetrance
  - Delay of onset of symptoms of a genetic disease.
  - Individuals may have children before they know that they are affected.
  - Carriers of the disease-causing gene may pass away before the onset of symptoms.
  - Examples
    - Huntington disease
    - Hereditary breast and ovarian cancer

# Factors that affect expression of disease-causing genes

- Variable expression / expressivity
  - Different than penetrance
  - Severity of the phenotype varies widely, even within a family.
  - An individual's presentation may be so mild that they are not aware that they are affected and can pass on the condition to their children.

# Factors that affect expression of disease-causing genes

- Variable expression / expressivity
  - Factors that may influence variable expression within a family:
    - Environmental exposures
    - Modifier genes
  - Example
    - Neurofibromatosis type I

# Factors that affect expression of disease-causing genes

- Anticipation
  - More severe expression and/or earlier age of onset in more recent generations.
  - Sometimes caused by expansion of DNA repeats

# Factors that affect expression of disease-causing genes

- Anticipation
  - Expansion may be more likely to occur when inherited through mother or father, depending on the condition
  - Examples
    - Huntington disease
    - Myotonic dystrophy

# Factors that affect expression of disease-causing genes

- New mutation
  - Affected proband with no history of the disease in the family
    - Especially in an autosomal dominant condition
      - Example NF1
    - Recurrence risks:
      - Low (possible germline mosaicism)
      - The risk to offspring depends on the inheritance pattern of the condition

# Factors that affect expression of disease-causing genes

- Germline mosaicism
  - Relatively rare phenomenon
  - Two or more offspring affected with no family history
    - Especially dominant conditions
  - More than one genetically distinct germ cell line
  - Increased risk to siblings of an affected proband

# Factors that affect expression of disease-causing genes

- Germline mosaicism
  - Examples:
    - Duchenne muscular dystrophy
    - Hemophilia A
    - Achondroplasia
    - Neurofibromatosis type I
    - Osteogenesis imperfecta type II

# Factors that affect expression of disease-causing genes

- Skewed X-inactivation (in X-linked conditions)
  - The majority of the active X-chromosomes carry the mutation
  - Manifesting heterozygotes – females with the disease phenotype, usually mildly affected
  - Example
    - Duchenne muscular dystrophy

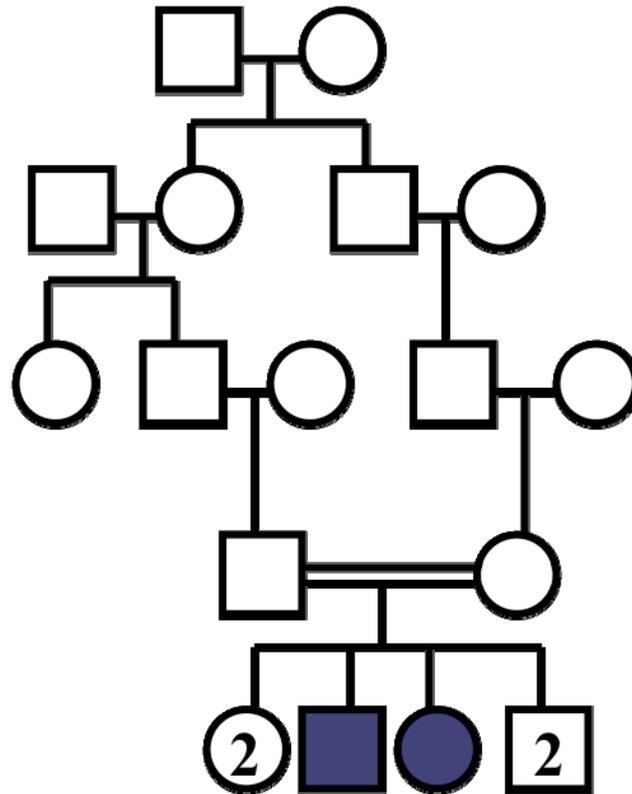
# Other factors

- Consanguinity
  - Relatives share genes, including disease-causing genes, inherited from a common ancestor
  - With consanguinity, offspring are more likely to be affected with a recessive disorder
  - More rare recessive disorder, more likely consanguinity

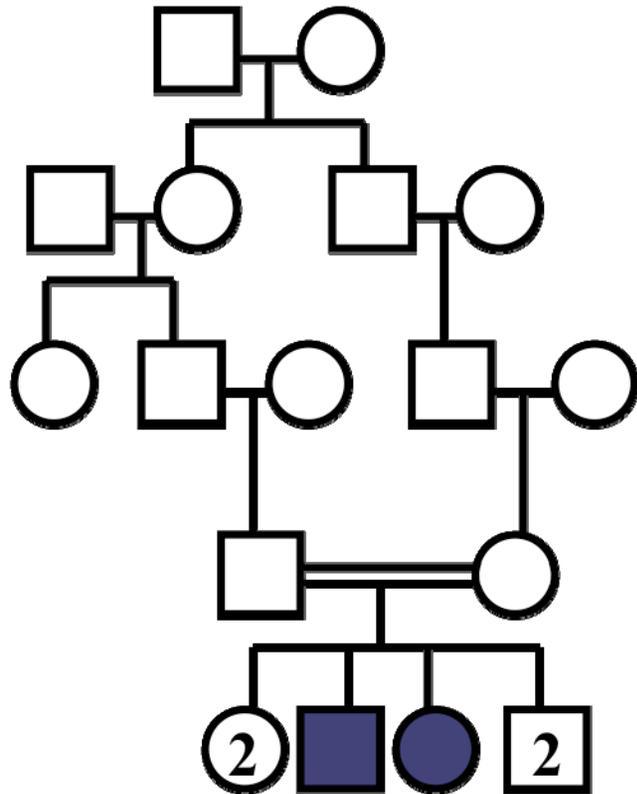
# Other factors

- Small families
  - Pattern of inheritance may not be evident in small families.

What is the mode of inheritance?



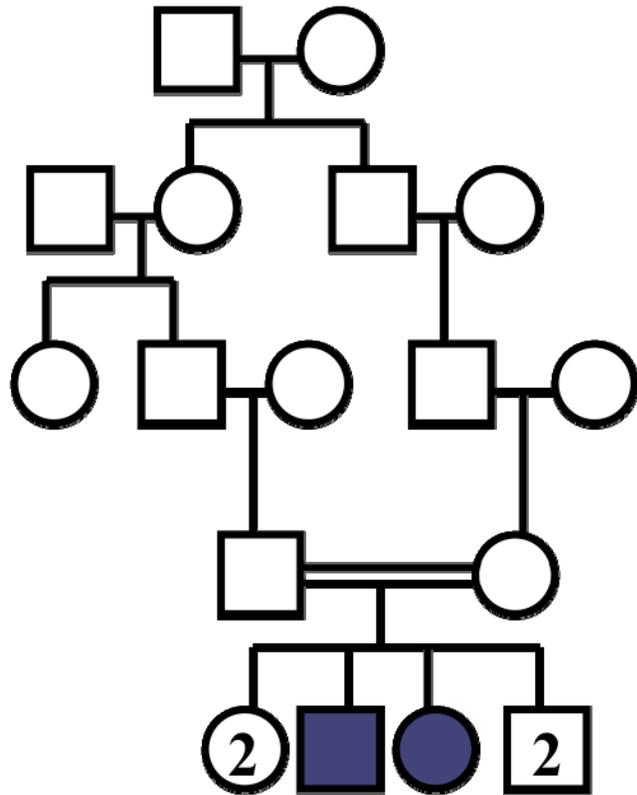
# What is the mode of inheritance?



- **Horizontal pattern**
- **# of Males = # of Females**
- **Consanguinity**

# What is the mode of inheritance?

- **Autosomal recessive**



# Genetic testing

- Covers an array of techniques including analysis of human DNA, RNA, or protein
- Diagnose a disease in an individual with symptoms
- Measure risk of developing a disease
- Preconception testing or prenatal testing
- Non-clinical uses such as paternity testing and forensics

# Karyotype

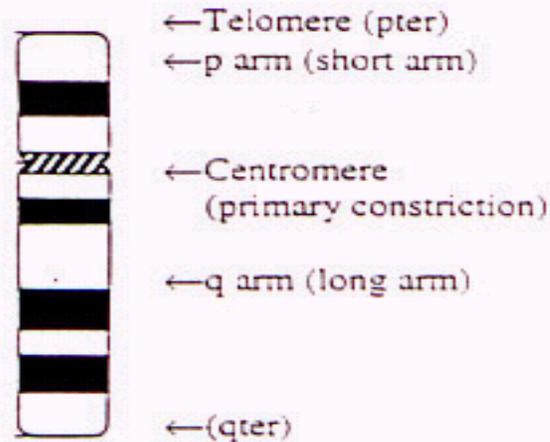
- A photographic representation of the chromosomes of a single cell, cut and arranged in pairs based on their banding pattern and size according to a standard classification
- The karyotype is used to look for abnormal numbers or structures of chromosomes

# Chromosome Functions

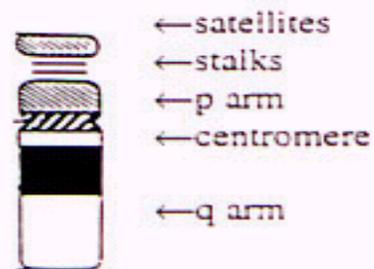
- To transmit genetic information from one generation of cells to the next (mitosis)
- To transmit genetic information from one generation of organisms to the next (meiosis)

# Chromosome Structure

## Metaphase Chromosome Structure

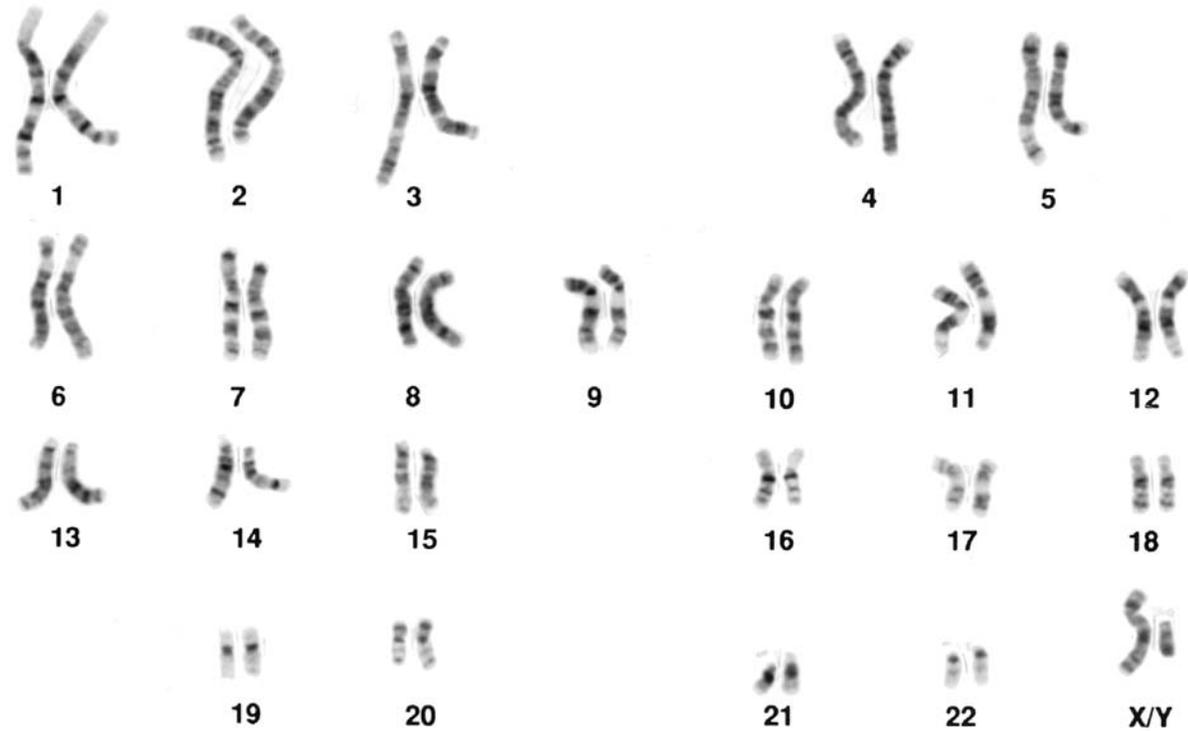


- The centromere is "divided" into two segments, the p10 faces the short arm and the q10 faces the long arm



Acrocentric chromosomes: 13-15, 21, 22

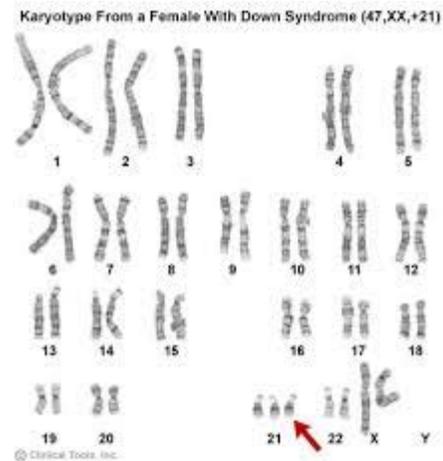
# Karyotype



**Normal Karyotype**

# Aneuploidy

**Aneuploidy** is the presence of an abnormal number of chromosomes in a cell, such as having 45 or 47 chromosomes when 46 is expected.



# Aneuploidy

- An estimated 10 - 30% of all fertilized eggs have a chromosome abnormality
- Aneuploidy is the leading known cause of pregnancy loss > 25% of all miscarriages
- Aneuploidy is the leading genetic cause of intellectual disability
- 0.3% of liveborns are aneuploid
- Among oocytes studied 20 - 25% are aneuploid
- Among sperm studied 1 - 2% are aneuploid

# Limitations of karyotype

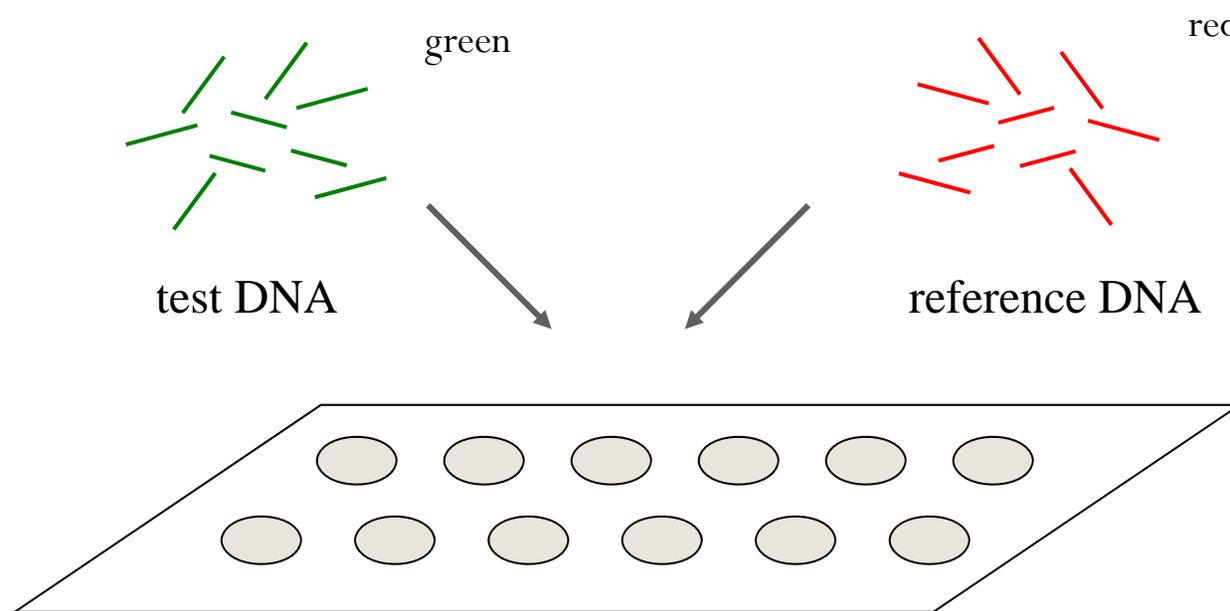
- Does not detect small rearrangements.
- Does not detect low level mosaicism

# Microarray-based Comparative Genomic Hybridization (aCGH)

- **Chromosomal microarray (CMA)**
- Genome wide screening for copy number variants
- For CMA to have higher resolution than a G-banded karyotype, CMA must detect CNVs smaller than 5 Mb and must have whole-genome coverage

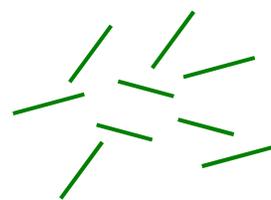
# What is array CGH, cont.

Patient (test) and control (reference) DNAs are labeled with different fluorescent molecules, then co-hybridized in equal amounts to the array of DNA probes



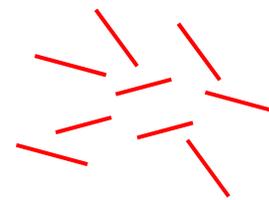
# What is array CGH, cont.

Given a normal karyotype, each probe on the array should hybridize equally to test (“green”) and reference (“red”) DNA. This will produce a “yellow” signal. The slide is scanned and images analyzed by computer.



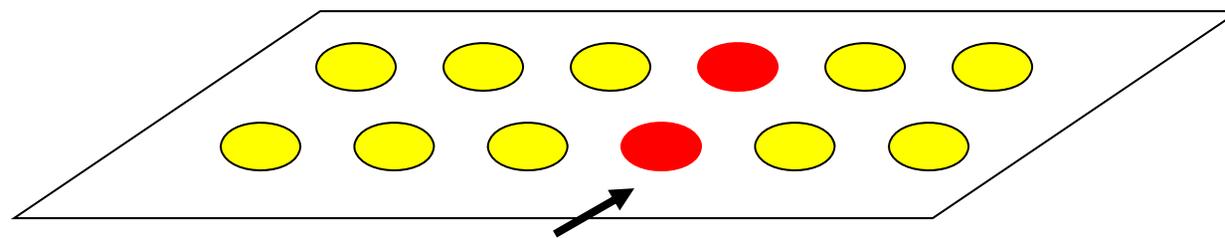
green

test DNA



red

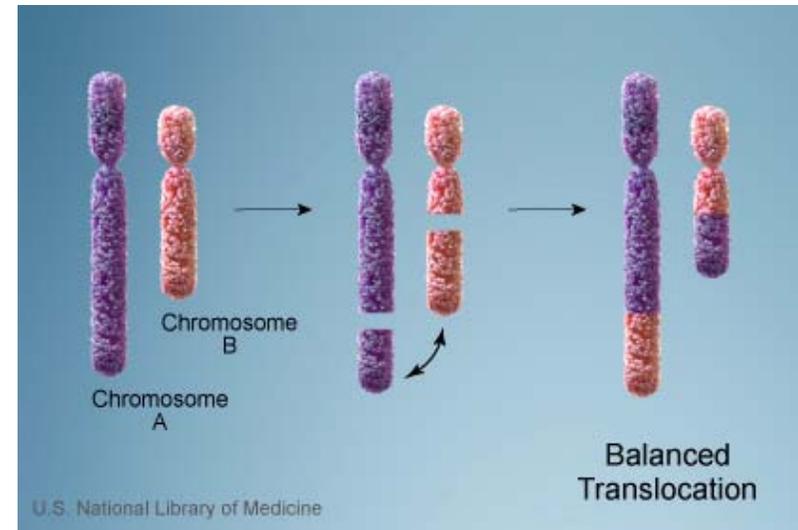
reference DNA



patient has a deletion of these two loci

# Limitations of array CGH

- Does not provide information on balanced rearrangements
- Ability to detect mosaicism is limited (down to 20% - possibly lower)
- Interpretation of array findings can be challenging
  - confounding factors include variable expressivity of some CNV's, penetrance, and lack of sufficient data to classify some rare CNV's as benign or disease-causing

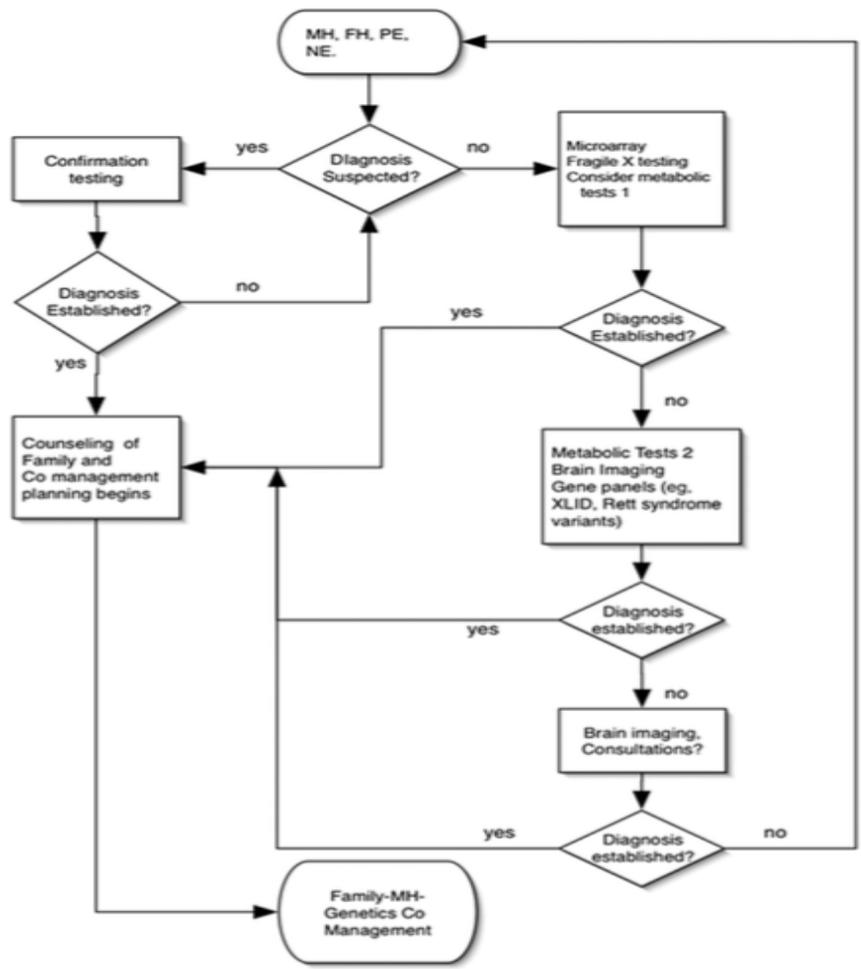


# Making a diagnosis in an a child with DD/ID

- The term “developmental delay” is usually reserved for younger children (typically younger than 5 years), and the term “intellectual disability” is usually applied to older children when IQ testing is valid and reliable
- Diagnostic yield with karyotyping with DD/ID is 3.7%
- Diagnostic yield of 12.2% in individuals with developmental delay, intellectual disability, autism spectrum disorders, or multiple congenital abnormalities

# Making a diagnosis in a child with DD/ID

1. CMA testing for CNV is recommended as a first-line test in the initial postnatal evaluation of individuals with the following:
  - A. Multiple anomalies not specific to a well-delineated genetic syndrome.
  - B. Apparently nonsyndromic DD/ID.
  - C. Autism spectrum disorders.



# Making a diagnosis in an a child with DD/ID

- CMA should not be ordered when a rapid turnaround time is needed (ex: STAT newborn analysis)
- Not always appropriate as a first-tier test. For example, karyotyping may be more appropriate when a common aneuploidy (Trisomy 21) is suspected or when individual has family history of chromosome abnormality
- Karyotyping will help clarify recurrence risk for family in case of aneuploidy

# Making a diagnosis in a child with Autism Spectrum Disorders

- Advances in clinical testing technology have increased the diagnostic yield from 6–10% a few years ago to 30–40%. Therefore, genetic testing should be discussed with all patients and families with ASDs.

## evaluation of autism spectrum disorder

### First tier

Three-generation family history with pedigree analysis

Initial evaluation to identify known syndromes or associated conditions

Examination with special attention to dysmorphic features

If specific syndromic diagnosis is suspected, proceed with targeted testing

If appropriate clinical indicators present, perform metabolic and/or mitochondrial testing (alternatively, consider a referral to a metabolic specialist)

Chromosomal microarray: oligonucleotide array-comparative genomic hybridization or single-nucleotide polymorphism array

DNA testing for fragile X (to be performed routinely for male patients only)<sup>a</sup>

### Second tier

*MECP2* sequencing to be performed for all females with ASDs

*MECP2* duplication testing in males, if phenotype is suggestive

*PTEN* testing only if the head circumference is >2.5 SD above the mean

Brain magnetic resonance imaging only in the presence of specific indicators (e.g., microcephaly, regression, seizures, and history of

# Diagnostic yield in ASDs

- CMA (10%)
- Fragile X (1–5%)
- *MECP2* (4% of females)
- *PTEN* (5% of those with head circumferences >2.5 SDs that are tested)
- Karyotype (3%)
- Other (10%). Currently, there are no published studies that collate the yield on the other identifiable etiologies of autism. As noted above, identifiable brain anomalies, genetic syndromes, metabolic disorders, and other diagnosable conditions will be identified in the genetic evaluation of persons with ASDs. Using empiric estimates and clinical experience, this has been estimated as 10%.<sup>74</sup>

# Making a diagnosis in a child with Autism Spectrum Disorders

**Table 5 Selected genetic syndromes that are known etiologies of autism spectrum disorders**

22q11.2 deletions including velocardiofacial (Shprintzen) syndrome

Angelman syndrome

CHARGE syndrome

de Lange syndrome

Fragile X syndrome

*MED12* disorders (including Lujan–Fryns syndrome)

Prader–Willi syndrome

PTEN-associated disorders (Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome)

Rett syndrome

Smith–Lemli–Opitz syndrome

Smith–Magenis syndrome

Sotos syndrome

Tuberous sclerosis

*PTEN*, phosphatase and tensin homolog.

# Single gene testing

- DNA sequencing is the process of reading nucleotide bases in a DNA molecule
- Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder

# Fragile X syndrome

- Developmental problems including learning disabilities and cognitive impairment
  - Usually, males are more severely affected by this disorder than females
- Most males and about half of females with fragile X syndrome have characteristic physical features that become more apparent with age
  - long and narrow face, large ears, a prominent jaw and forehead, unusually flexible fingers, flat feet, and in males, enlarged testicles (macroorchidism) after puberty

# Fragile X syndrome

- Mutations in the FMR1 gene located on the X-chromosome
  - Caused (most cases) by a mutation in which a DNA segment, known as the CGG triplet repeat, is expanded within the FMR1 gene
    - Normally, this DNA segment is repeated from 5 to about 40 times. In people with fragile X syndrome, however, the CGG segment is repeated more than 200 times.
- The abnormally expanded CGG segment turns off (silences) the FMR1 gene, which prevents the gene from producing FMRP (protein)
- Males and females with 55 to 200 repeats of the CGG segment are said to have an FMR1 gene premutation.
  - increased risk of disorders called fragile X-associated primary ovarian insufficiency (FXPOI) and fragile X-associated tremor/ataxia syndrome (FXTAS).

# Panels

- Sequencing for 2 or more genes related to genetic disease
- Panel related to phenotype
  - Example: Epilepsy panel
- Whole exome sequencing (WES)
  - Sequencing of all exons (coding regions) of thousands of genes (20,000+) simultaneously
- When should panels be considered?
  - When phenotype doesn't correspond to a single disorder
  - When disorder in question has high degree of genetic heterogeneity
  - Other specific tests for the phenotype have not been diagnostic

# Interpreting results of genetic tests

- **Pathogenic variant:** variant is a recognized cause of some or all of the patient's phenotype
- **Likely pathogenic variant:** previously unreported variant, but based on its gene location and the predicted effect on protein function, it is likely to be the cause of some or all of the patient's phenotype
- **Benign variant:** not responsible for the patient's phenotype
- **Likely benign variant:** previously unreported variant, but based on its gene location and predicted lack of effect on protein function, it is likely to be benign and not responsible for the patient's phenotype
- **Variant of unknown or uncertain significance (VUS)**

# Questions?

Feel free to contact me!

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