Single gene disorders

Dr. Tejashree Singh
(Specialist Gynecologist, Zulekha Hospital, Dubai)
• **Definition**: abnormal alleles present at a single locus of a chromosome

• Also called as “**Mendelian**” because like the garden peas, they occur in fixed proportions amongst the offspring's of specific mating

• Affect mainly the pediatric age group; 90% manifest before puberty, only 1% occur after the reproductive period
Homozygous & Heterozygous

- **Alleles** are genes on the same spot of the same chromosome (one from each parent) that code for the same thing (like eye color)
- When alleles are identical: **homozygous** for that trait
- When there are different alleles, the individual is **heterozygous**
- **Homozygous pairs**: dominant (AA, BB) or recessive (aa, bb)
- **Heterozygous individuals**: dominant allele gains expression; the recessive allele is present but hidden (Aa, Bb)
Defined at the level of phenotype

- **Dominant**: Any phenotype expressed in both homozygote & heterozygote states
- **Recessive**: A phenotype expressed only in a homozygote state
One pair of homologous chromosomes

Homozygous Alleles

Heterozygous Alleles

Homozygous

Bb
bb

Heterozygous

BB
Bb
bB
Patterns of inheritance

- Gene: autosomal or sex chromosome
- Phenotype: dominant or recessive

4 Basic patterns of inheritance

- Autosomal dominant (AD)
- Autosomal recessive (AR)
- X-linked dominant (XD)
- X-linked recessive (XR)
Incidence

Estimated total incidence of genetic disorders varies

• AD = 3 - 9/1000 (1/200)
• AR = 2 – 2.5/1000
• X-Linked = 0.5 – 2/1000
Autosomal dominant (AD)

• One mutated copy of the gene in each cell can cause the person to be affected

• Over half of the Mendelian phenotypes are AD traits

• Incidence; very high in a few AD traits
  1/500: hypercholesterolemia
  1/2500-1/3000: neurofibromatosis
  1/2500-1/3000: polycystic kidney disease
Man with a dominant disorder has two affected children and two unaffected children.
50% (1 in 2) chance of inheriting the changed gene and being affected and 50% chance normal child.
Characteristics of AD inheritance

- Inheritance = 1 : 2
- Every affected child has one affected parent
- Tends to occur in every generation of an affected family
- Equal numbers of affected males and females
- Transmission male - male possible
- New mutations frequent
- Examples: Achondroplasia, Huntington's chorea, Osteogenesis imperfecta
Autosomal recessive (AR)

- Disease can only occur when individual has 2 mutant alleles
- Each mutant allele is inherited from each parent
- Consanguinity plays an important role
- Genetic isolation: increased risk
  Ashkenazi: Tay-sachs, Gauchers disease
  Finnish: Congenital chloride losing diarrhea
25% chance (1 in 4) of inheriting a mutated gene from both the parents and having an affected child;
50% (2 in 4) children will be carriers;
25% (1 in 4) will be normal
Characteristics of AR inheritance

- Inheritance = 1 : 4
- An affected person usually has unaffected parents who carry a single copy of the mutated gene (carriers)
- They are not seen in every generation of an affected family
- Equal transmission in males and females
- New mutations rare
- Examples: Cystic fibrosis, Thalassemia, Sickle cell disease, Phenylketonuria, Albinism
Affected father can have two (all) affected daughters, No affected sons (transmits Y)

Affected mother can have an affected daughter and an affected son – 50% (1 in 2) chance of affected children
Characteristics of XD inheritance

- Inheritance:
  1 : 2 offspring of affected females
  Affected males: all daughters, no sons affected
- Females are more affected than males
- Severely manifests in males
- Examples: Rett disease, Incontinentia pigmenti, Vit D resistant rickets, Xg blood group
X-linked recessive (XR)

All daughters are carriers and sons are not affected.

Son has a 50% (1 in 2) chance of being affected.
Daughter has a 1 in 2 chance of being a carrier and 1 in 2 chance of being normal.
Characteristics of XR inheritance

- Inheritance = 1 : 2 sons of carrier females
- Daughters of all affected males are carriers
- Male - male transmission not possible
- Knight’s move pattern of transmission: any male grandchildren of affected male would be at risk
- Examples: Duchenne muscular dystrophy, G6PD deficiency, Red-green color blindness, Hemophilia
Exceptions to the Mendel’s rule

• Co-dominance: if expression of two alleles can be detected in the presence of each other
  Example: Roan Black & white feathered birds

• Co-dominance with multiple alleles
  Example: Blood groups
  Blood types A and B are co-dominant while O is recessive
Fragile X Syndrome

- A genetic syndrome: the most common single gene cause of autism
- X linked disorder
- There is mutation of the fragile X mental retardation (FMR 1) gene on the X chromosome resulting in an increase in the number of CGG trinucleotide repeats with methylation
- This does not allow the proper development of neural synapses in the brain
- This methylation causes constriction of the X chromosome which appears fragile hence the name.
Fragile X Syndrome

- In females, a mutation in one of the two copies of a gene in each cell causes the disorder.
- In males, a mutation in only one copy of a gene can cause the disorder.
- In females, FMR 1 gene pre-mutation (carrier status on the X chromosome) can expand to more than 200 CGG repeats when the cells develop into eggs therefore, these women have an increased risk of having a child with fragile X syndrome.
- In men, this pre-mutation does not expand. It is passed onto the next generation.
- Men pass the pre-mutation to their daughters and not to their sons who get the Y chromosome.
THANK YOU