GENETICS
GENETICS

• Genetics is the study of heredity or inheritance. The study of genetics helps to explain how traits are passed from parents to their young.

• Gregor John Mendel - Father of Genetics.
Body made of organs

Organs made of tissues

Tissue made of cells

Cells contain nucleus

Nucleus contain chromosomes

Chromosome made of DNA
COMPARED TO BOOK....

- **Book of life**
  - Two volumes

- **Each volume**
  - 23 chapters

- **Each chapter**
  - Has many sentences

- **Each sentence**
  - Conveys meaning

- **Sentence**
  - Has many words

- **Words made of alphabets**

- **Two chromosomal sets (Mum & Dad)**

- **Each set**
  - Has 23 chromosomes

- **Each chromosome**
  - Has many genes

- **Each gene**
  - Has specific function

- **Gene**
  - Has many codons

- **Codons**
  - Are three letter word made of A,T,G,C
ETIOLOGY OF GENETIC DISORDERS

• Chromosomal
• Single gene
• Mitochondrial
• Multifactorial
CHROMOSOMAL DISORDERS

• Damage to chromosomes due to physical or chemical disturbances or errors during meiosis.

• Two Types:
  1. Chromosome Structure
  2. Chromosome Number
CHROMOSOME STRUCTURE

1. Deletion – during cell division, especially meiosis, a piece of the chromosome breaks off, may be an end piece or a middle piece

2. Inversion – a segment of the chromosome is turned 180°, same genes but opposite position

3. Duplication – a doubling of a chromosome segment because of attaching a broken piece form a homologous chromosome, or by unequal crossing over.

4. Translocation – movement of a chromosome segment from one chromosome to a non-homologous chromosome

* Translocation is of more clinical importance
SIMPLE TRANSLOCATION

- Centromere
- p
- q

RECIPROCAL TRANSLOCATION

Robertsonian Translocation

Chromosomal rearrangement that is formed by fusion of the whole long arms of two acrocentric chromosomes (chromosomes with the centromere near the very end).
1. Monosomy – only one of a particular type of chromosome (2n -1)

2. Trisomy – having three of a particular type of chromosome (2n + 1)

3. Polyploidy – having more than two sets of chromosomes; triploids (3n = 3 of each type of chromosome), tetraploids (4n = 4 of each type of chromosome).

   \[ n=23 \ ; \ 2n=46 \]
CLINICAL SCENARIO 1

• 10 day old baby, presenting with poor suck
• On examination, hypotonic, dysmorphic facies, single palmer crease both hands.
• Diagnosis
• Counseling
• Confirmation
FURTHER STEPS

• Diagnosis: Clinical features consistent with Down syndrome
• Counseling: Important aspect, discuss with the parents the likely condition and the need for confirmatory testing
• Confirmation: FISH (Fluorescent in situ hybridization) for chromosome 21 (Reported in 48-72 hours) and karyotyping (reported in 2-3 weeks)
• Need for cytogenetic testing: Down syndrome occurs due to non-dysjunction of chromosome leading to trisomy 21 or due to unbalanced Robertsonian translocation or mosaic pattern with cells with normal chromosome and trisomy
NON-DYSJUNCTION OF CHROMOSOME

Failure to move apart during Meiosis I or Meiosis II
KARYOTYPING REPORT - DOWN SYNDROME

1 2 3 4 5
6 7 8 9 10
11 12 13 14 15
16 17 18 19 20
21 22 X Y
CLINICAL SCENARIO 2

• 1.8 kg male baby born at term had a fisted hand rocker bottom feet, hypospadias, loud systolic murmur & developed respiratory distress in a few hrs of life
EDWARD SYNDROME

- small mouth, small jaw, short neck
- occiput, or back part of the skull, is prominent
- shield chest, or short and prominent sternum; and wide-set nipples
- dysplastic, or malformed ears
- clenched hands with overlapping fingers
- flexed big toe; prominent heels

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KARYOTYPING REPORT CONFIRMS TRISOMY 18
CLINICAL SCENARIO 3

• 12 year old girl was brought by mother for primary amenorrhea. She was short statured. CVS examination showed systolic murmur in the left upper sternal border. She had hyperconvex nails with café-au-lait spots.

• Her bone age is normal

• Next best investigation to do
KARYOTYPING - TURNERS SYNDROME

45, X
CLINICAL SCENARIO 4

• 2 year old boy, presented with developmental delay. He had episodes of colic during infancy. Child is very friendly and sociable. He had dental abnormality.
FACIAL FEATURES

Possum picture

- Puffy eyes
- Small bulbous nose
- Long philtrum
- Small widely spaced teeth
- Overhanging lower lip
- Small chin
DIAGNOSIS

• Diagnosis of Williams syndrome suspected
• Confirmation of diagnosis by FISH (Fluorescent in situ hybridization) testing
• Microdeletion where segment of chromosome gets deleted which cannot be picked up by routine karyotyping
• Investigation of choice- FISH for Microdeletion analysis for locus 7q 11.23
FISH ASSAY

Note: the “control probe” helps identify the #7 chromosomes.

Control probe only

Elastin gene

Positive Williams Syndrome FISH assay
(Chromosome 7)
The elastin gene is found on only one chromosome. The other copy carries an elastin gene deletion.

Control probe

Elastin gene

Negative Williams Syndrome FISH assay
(Chromosome 7)
The elastin gene is found on both chromosomes. This individual does not have Williams Syndrome.
SINGLE GENE DISORDERS

- Occurs due to genetic mutation – either Point mutation (change in single nucleotide) or Frame shift mutations
- Single gene disorders
  - Autosomal dominant
  - Autosomal recessive
  - X-Linked dominant
  - X-Linked recessive
  - Y-Linked
AUTOSOMAL DOMINANT

50% risk of offspring of affected father/mother being affected

Independent of sex
AUTOSOMAL DOMINANT

E.g.: Huntington’s Disease, Achondroplasia, Neurofibromatosis
AUTOSOMAL RECESSIVE

Carrier parents have 25% risk of having affected offspring
50% - carrier offspring
25% - normal
AUTOSOMAL RECESSIVE

e.g. Majority of inborn errors of metabolism Gauchers disease, Morquio syndrome
X-LINKED DOMINANT

- Female with one mutant allele will be affected.
- Affected male – all daughters affected, no sons affected.
- 50% of sons and 50% of daughters of affected mother will be affected.
- Hence, resembles autosomal dominant.
X-LINKED DOMINANT

E.g.: Fragile X, Incontinentia pigmenti
X-LINKED RECESSIVE

- 50% of sons of carrier female to be affected.
- 50% of daughters of carrier females to be carriers.
- Affected males do not transmit to sons.
- All daughters of affected male to be carriers.
X-LINKED RECESSIVE

E.g.: Hemophilia, Duchenne muscular dystrophy
Y-LINKED

Only male to male transmission
E.g. Male infertility
POLYMORPHISM

• Polymorphism is a genetic variant that appears in at least 1% of a population.
• Example: ABO blood groups
DIAGNOSIS OF SINGLE GENE DISORDER

- Molecular analysis for the gene
- PCR analysis (Polymerase Chain Reaction)/ Sanger sequencing
- Newer technique where multiple genes are responsible for same phenotype - Next gen sequencing
- If unknown mutation – Whole exome sequencing
- Importance of molecular diagnosis: Prognostication and for prenatal diagnosis during next pregnancy
MITOCHONDRIAL INHERITENCE

- Only females can transmit the trait to offspring; Affected female will transmit disease to male and female children alike.
- Mother with a small no. of mtDNA mutated unaffected. If mitochondria with mutated mtDNA replicate more in the zygote, the baby can become affected.
- Hence disease status depends on mutated mtDNA load; Presents as energy failure.

E.g.: Electron transport defects, Pyruvate dehydrogenase deficiency.
In multifactorial conditions a genetic mutation may predispose an individual to a disease.

Other genetic and environmental factors contribute to whether or not the disease develops.

Example:

- Skin color - many genes and UV exposure
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TAKE HOME MESSAGE

• Genetic disorders include
  ➢ Chromosomal disorders (e.g. Down syndrome),
  ➢ Microdeletion disorders (e.g. William syndrome),
  ➢ Single gene disorders- Autosomal dominant, Autosomal recessive, X- linked dominant, X- linked recessive
  ➢ Mitochondrial and multifactorial inheritance

• Definitive diagnosis by cytogenetics or molecular testing are essential for prognosticating and for prenatal diagnosis during subsequent pregnancies.
THANK YOU