Genetic diseases

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4- Single gene mutations not follow mendelian rules of inheritance:

Three groups of diseases resulting from mutation affecting single genes do not follow the mendelian rules of inheritance:

1. Diseases caused by triplet repeat mutations
2. Diseases caused by mutations in mitochondrial genes
3. Diseases associated with alteration of imprinted regions of the genome

1. Diseases caused by triplet repeat mutation:(Fragile X syndrome):

- The mutation is characterized by long repeating sequence of three nucleotide (CGG), so disrupt the function of that gene (FMR-1).
- It is one of the most common causes of familial mental retardation in males.
- In **normal** individuals, the average number of repeats is **29 (range of 6 to 55),** whereas affected individuals have 200 to 4000 repeats (full mutation); individuals have 55 to 200 CGG repeats are carriers with (premutations).
- This disease is X-linked but unlike other X-linked disorders;
- **1. Carrier males: (20%)** of males carry a fragile X mutation do not manifest the typical neurological or physical characteristics of fragile X. these carrier males (also known as **"transmitting males")**.
  2. Carrier females are also affected: (30% to 50%) of carrier women with the fragile X mutation on one chromosome show features of mild cognitive impairment or other behavioral disturbances and some develop premature ovarian failure.
- **Affected males; have** moderate to severe mental retardation
- Some children with autism-like symptoms
- The typical physical phenotype includes; a long face with a large mandible, large everted ears, and large testicles *(macroorchidism)*.

2. Diseases caused by mutation in mitochondrial genes:

- Mitochondria contain several genes encodes for enzymes of oxidative phosphorylation, usually the **ovum** contain the large part of mitochondria, so the inheritance of mitochondrial gene is maternal.
- Disease caused by mitochondrial genes are **rare:**
- ***Leber"s optic neuropathy***---progressive bilateral loss of central vision.

3. Diseases associated with genomic imprinting: Prader Willi &Angleman syndromes

- All humans **inherit two copies of each gene (maternal & paternal).** In many genes there is no difference between the two. However, functional differences exist in some genes
- **Genomic imprinting;** is an epigenetic process resulting in differential inactivation of either maternal or paternal alleles of certain genes.
- Maternal imprinting implies that the maternal allele is inactivated, whereas the paternal imprinting refers to inactivation of the paternal allele.
- Prader-Willi syndrome and Angelman syndrome; both disorders arise from

deletion of band of long arm of **chromosome 15,** but have different clinical features.

- ***Prader Willi syndrome***:
- Occurs when the paternal 15q12 is deleted, leaving behind only the "**silenced" maternal gene** product.

*Mental retardation
*__Hyperphagia/Obesity__
*Short stature
*Hypotonia
*Hypogonadism
*Small hands & feet.

- ***Angleman syndrome:***
- occurs when the **maternal** 15q12 is deleted, leaving behind only the **"silenced" paternal gene** product.

*Mental retardation.
*__Inappropriate laughter called happy puppet syndrome.__
* Ataxic gait.
* Seizures.

❖ Diagnosis of genetic diseases:

- Diagnosis of genetic diseases requires examination of genetic material (chromosomes and genes)

1. Cytogenetic analysis (Chromosomal abnormalities)
2. Molecular analysis (Gene abnormalities)

- **These done by the following techniques:**

- Karyotyping
- FISH
- PCR techniques.
- A combination of these techniques.

❖ In general, genetic analysis can be divided into prenatal and postnatal

- **Prenatal analysis**
- Should be offered to all patients who are at risk of genetically abnormal progeny.

It can be performed on cells obtained by **maternal blood, amniocentesis, chorionic villus biopsy, fetal blood (umbilical cord blood)**.

- **Some important indications are:**

1- **Advanced maternal age** (more than 34 years), because of greater risk of trisomies.
2- A parent who is a **carrier of structurally abnormal chromosome** (in such cases, the gametes may be unbalanced, so the progeny would be at risk for chromosomal disorders)
3- **Fetal abnormalities** observed on ultrasound.
4- A parent with a **previous child with a chromosomal abnormality.**
5- A parent who is a **carrier of an X-linked** disorder (to determine the fetal sex).

- **Postnatal analysis**
- Is usually performed on peripheral blood lymphocytes
- **Indications:**

1. Multiple congenital anomalies.

2. Unexplained mental or physical retardation.
3. Suspected aneuploidy (Down syndrome).
4. Suspected sex chromosome abnormality (turner syndrome).
5. Suspected fragile X-syndrome.
6. Infertility, to rule out sex chromosome abnormality.
7. Multiple spontaneous abortions.

- **Karyotype analysis of human chromosomes**
- **Karyotype preparation &analysis:**
- Cells (from blood, amniotic fluid, etc) are grown *in vitro* (in a cell culture dish) to increase their number
- Cell division is then arrested in **metaphase** with **colchicine** (prevents mitotic spindle from forming)
- Cells are centrifuged and lysed to release chromosomes; Chromosomes are stained with Geimsa stain, photographed, and grouped by size and banding patterns.
- **Limitations of karyotype analysis:**
- Resolution of this technique is fairly low
- It is applicable only to cells that are dividing or can be induced to divide in vitro.

- **FISH (Flourescence insitu hybridization)**

- FISH utilizes DNA probes that recognize sequences **specific to chromosomal regions.**
- The probe binds to its complementary sequence on the chromosome and thus labels the specific chromosomal region that can be visualized under a fluorescent microscope.
- **Limitations of FISH analysis:**
- Resolution of many genetic diseases are caused by alterations at the nucleotide level (i.e., mutations) that cannot be detected by FISH

- **Polymerase chain reaction (PCR)**
- Many genetic diseases are caused by alterations at the nucleotide level (i.e., mutations) that cannot be detected by FISH
- ***Advantages over other techniques:***
- It is remarkably sensitive.
- The use of polymerase chain reaction (PCR) allows several million-fold amplification of DNA or RNA, making it possible to utilize as few as 1 or 100 cells for analysis. A few drops of blood or a piece of biopsy tissue can supply sufficient DNA for PCR amplification.