Genetic Diseases
LEC. 4

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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):

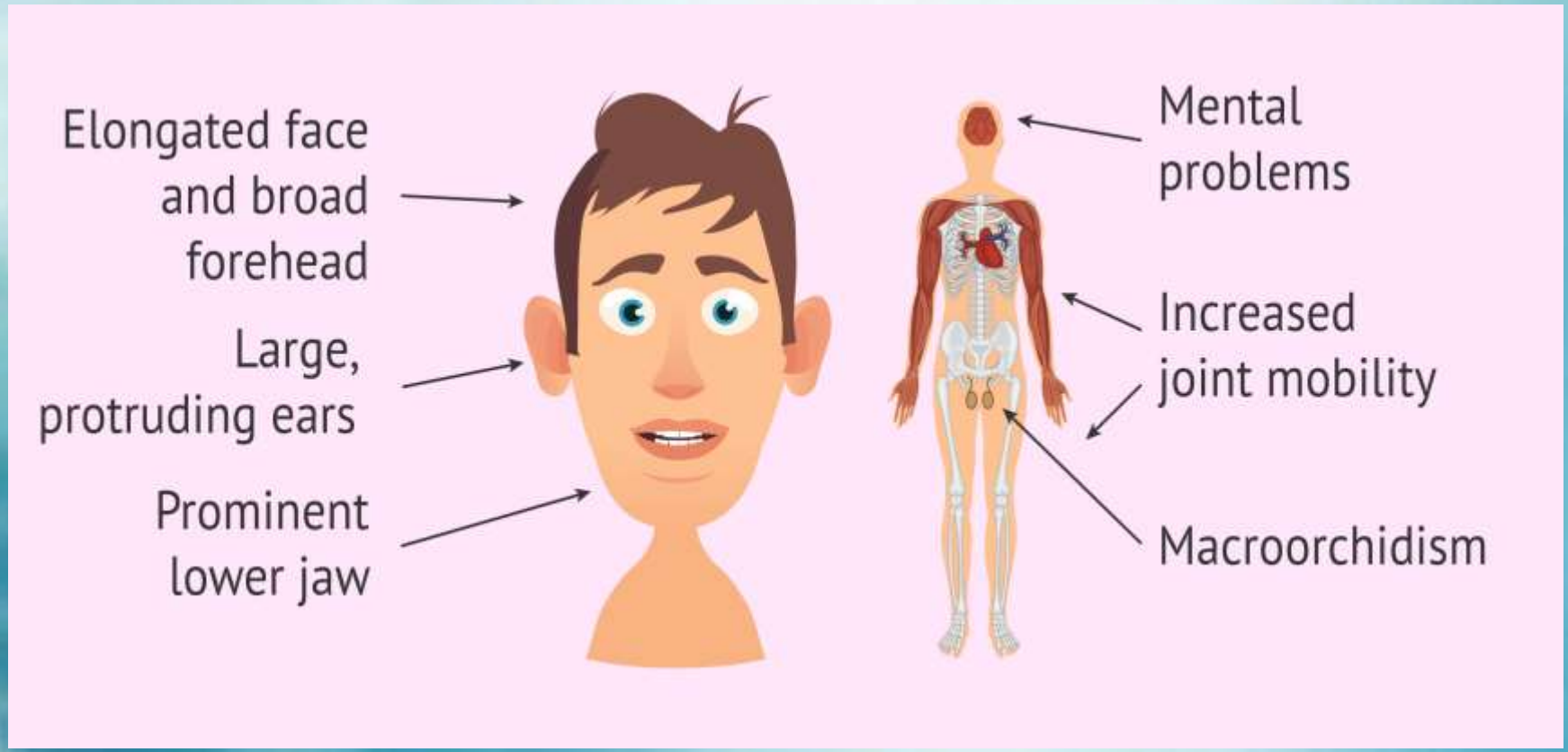
- The mutation is characterized by long repeating sequence of three nucleotide (CGG), so disrupt the function of that gene (FMR-1).
- It is one of the most common causes of familial mental retardation in males.
- In **normal** individuals, the average number of repeats is **29 (range of 6 to 55),** whereas 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

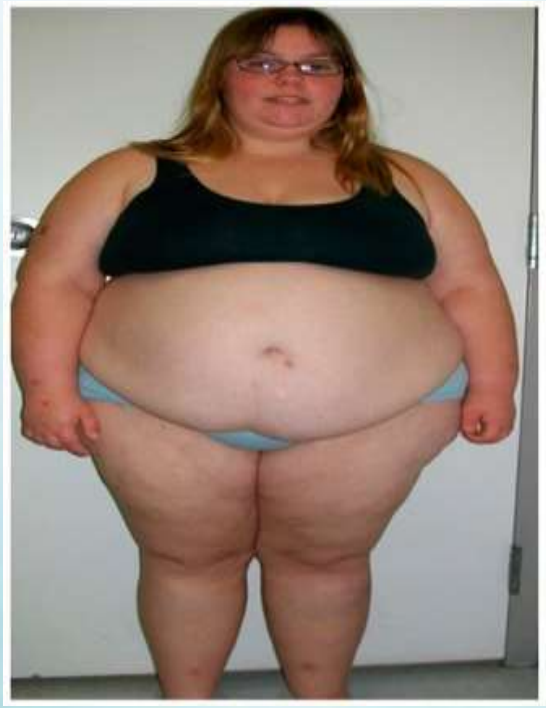
*Hyperphagia/Obesity

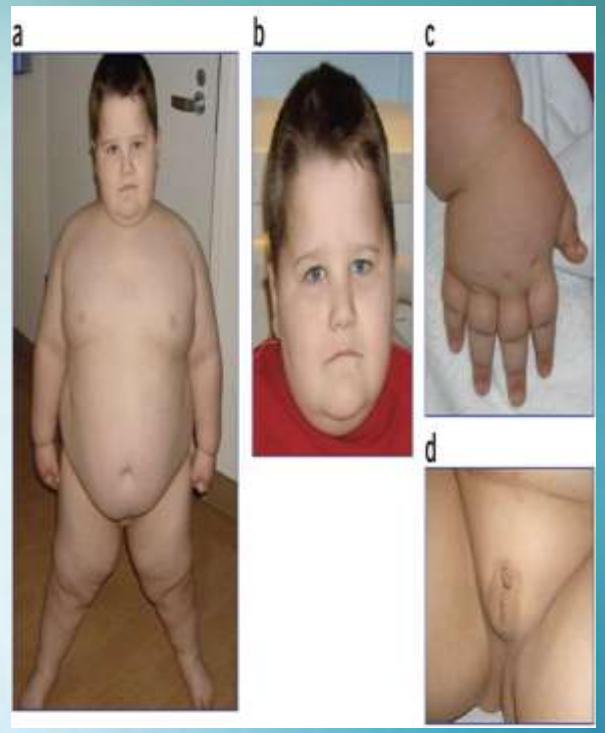
*Short stature

*Hypotonia

*Hypogonadism

*Small hands & feet.





➢ *Angleman syndrome:*

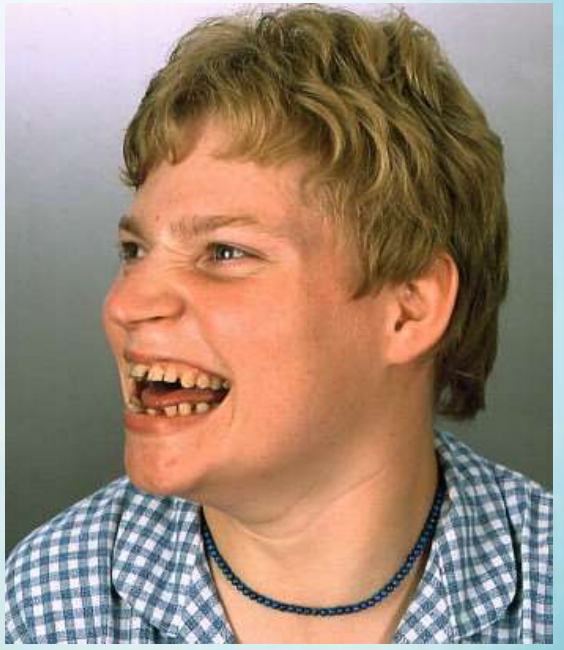
- occurs when the **maternal** 15q12 is deleted, leaving behind only the **“silenced” paternal gene** product.

*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:**

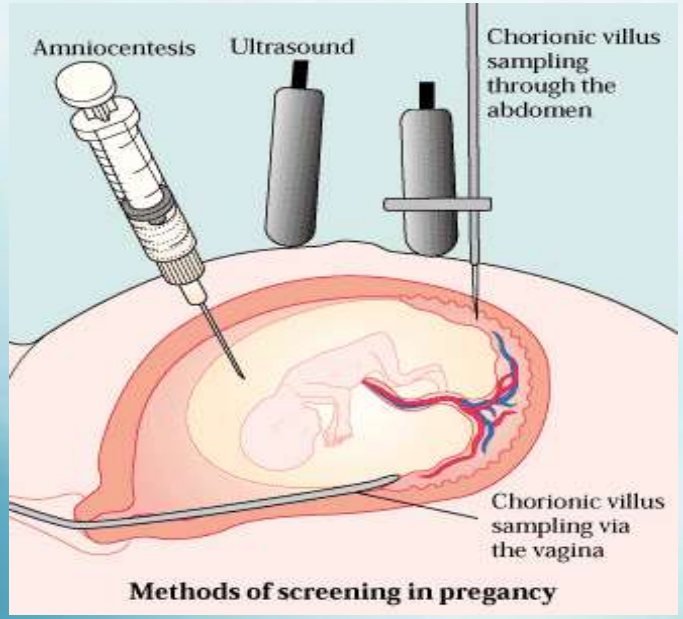
- Karyotyping
- FISH
- PCR techniques.
- A combination of these techniques.

❖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)**.



Methods of screening in pregancy

➢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.

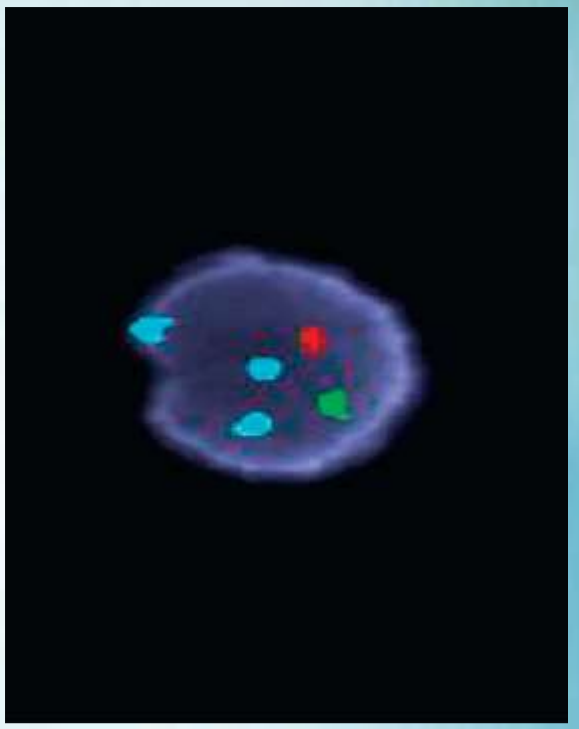
Karyotype analysis of human chromosomes

- **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.

photograph of the 46 human chromosomes in a somatic cell, arrested in metaphase.

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



FISH: nucleus from a male patient with suspected trisomy 18. Three different fluorescent probes have been used in a "FISH cocktail"; the green probe hybridizes to the X chromosome centromere *(one copy)*, the red probe to the Y chromosome centromere *(one copy)*, and the aqua probe to the chromosome 18 centromere *(three copies)*.

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.

Thanks