Learning Objectives

1-What is mitochondrial disease?

2-What is genomic imprinting?

3-What is uniparental disomy?

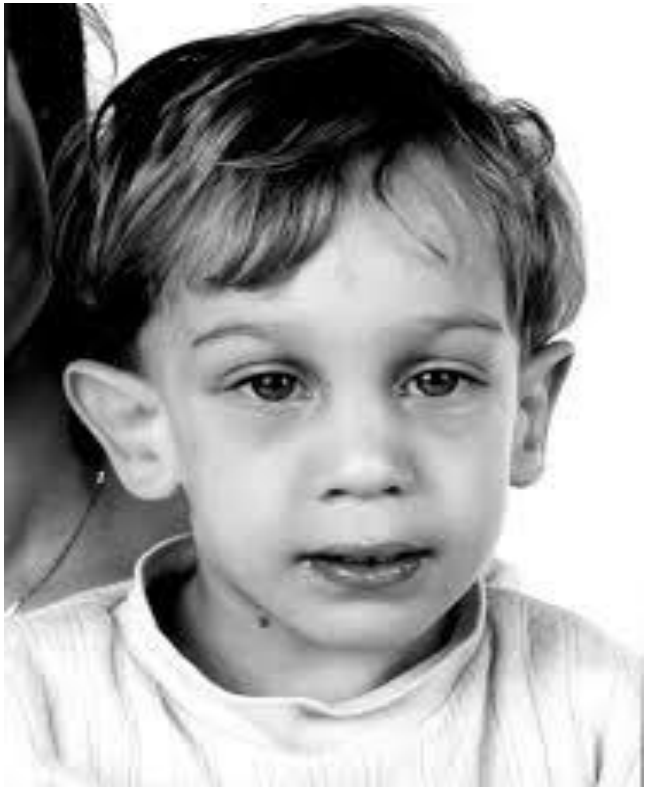
Single gene disorder with non classic inheritance:

- **Fragile X syndrome:**

Fragile X syndrome is a genetic condition that causes a range of developmental problems including learning disabilities and cognitive impairment. Usually, males are more severely affected by this disorder than females.

Affected individuals usually have delayed development of speech and language by age 2. Most males with fragile X syndrome have mild to moderate intellectual disability, while about one-third of affected females are intellectually disabled. Seizures occur in about 15 percent of males and about 5 percent of females with fragile X syndrome.

Most males and about half of females with fragile X syndrome have characteristic physical features that become more apparent with age. These features include a long and narrow face, large ears, a prominent jaw and forehead, unusually flexible fingers, flat feet, and in males, enlarged testicles (macroorchidism) after puberty.

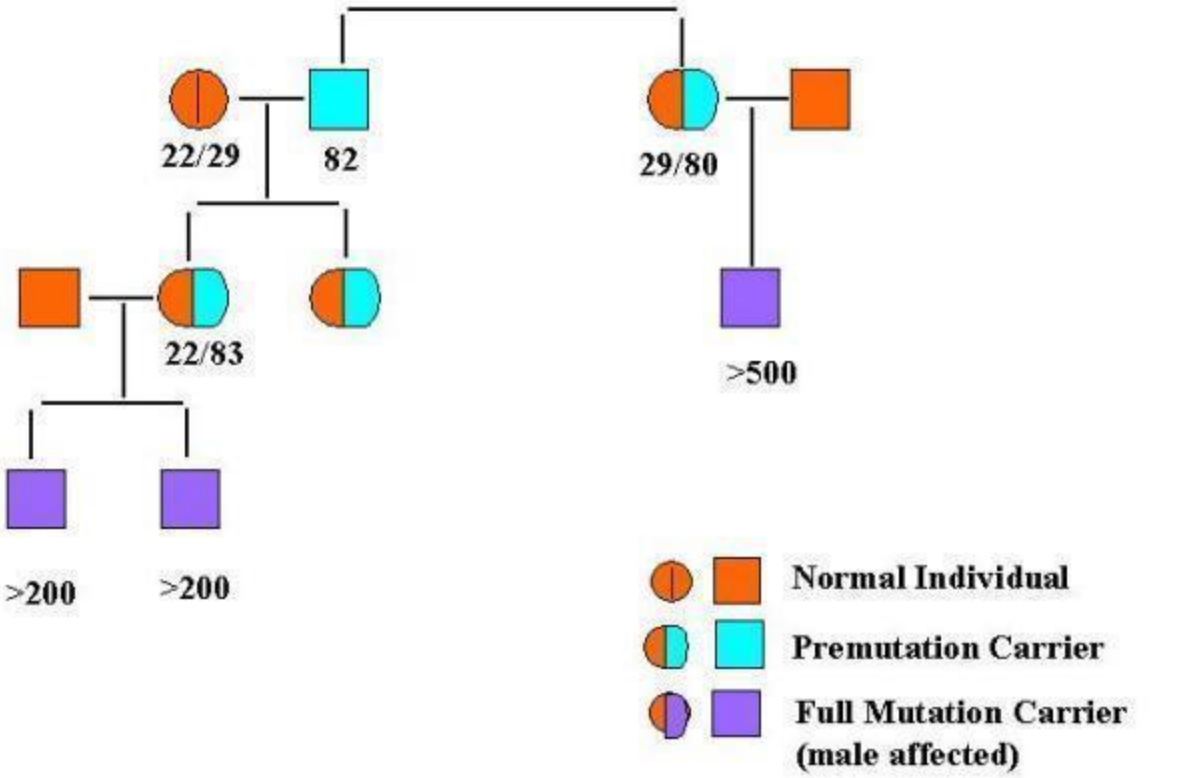


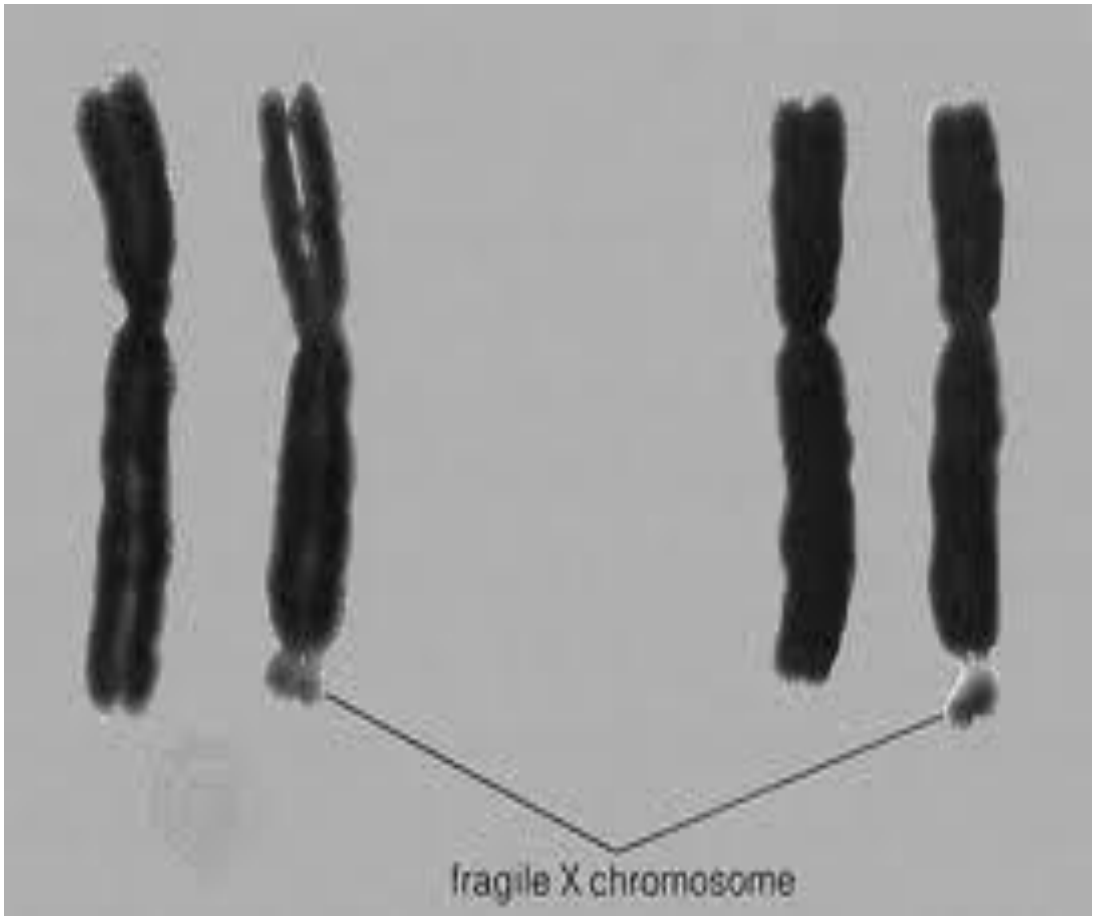
Mutations in the FMR1 gene cause fragile X syndrome. The FMR1 gene provides instructions for making a protein called fragile X mental retardation 1 protein, or FMRP. This protein helps regulate neural functions.

Nearly all cases of fragile X syndrome are caused 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. Loss or a shortage (deficiency) of this protein disrupts nervous system functions and leads to the signs and symptoms of fragile X syndrome.

Males and females with 55 to 200 repeats of the CGG segment are said to have an FMR1 gene premutation. Most people with a premutation are intellectually normal.

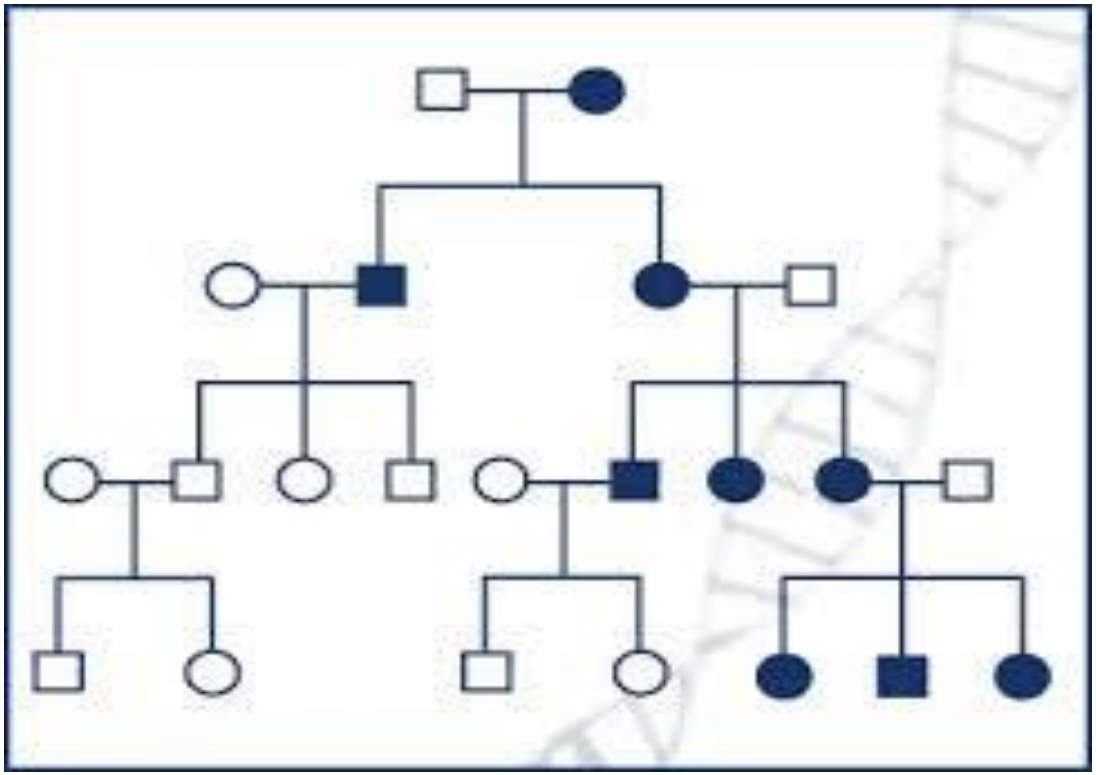
Fragile X Syndrome Pedigree




fragile X chromosome

Mitochondrial Inheritance

- Is also known as maternal inheritance. This inheritance pattern applies to genes contained in mitochondrial DNA. Because egg cells, but not sperm cells, contribute mitochondria to the developing embryo, only females pass mitochondrial conditions to their children. Mitochondrial disorders can appear in every generation of a family and can affect both males and females, but fathers do not pass mitochondrial traits to their children.
- Example: Leber Hereditary Optic Neuropathy.



Genomic Imprinting and Uniparental Disomy

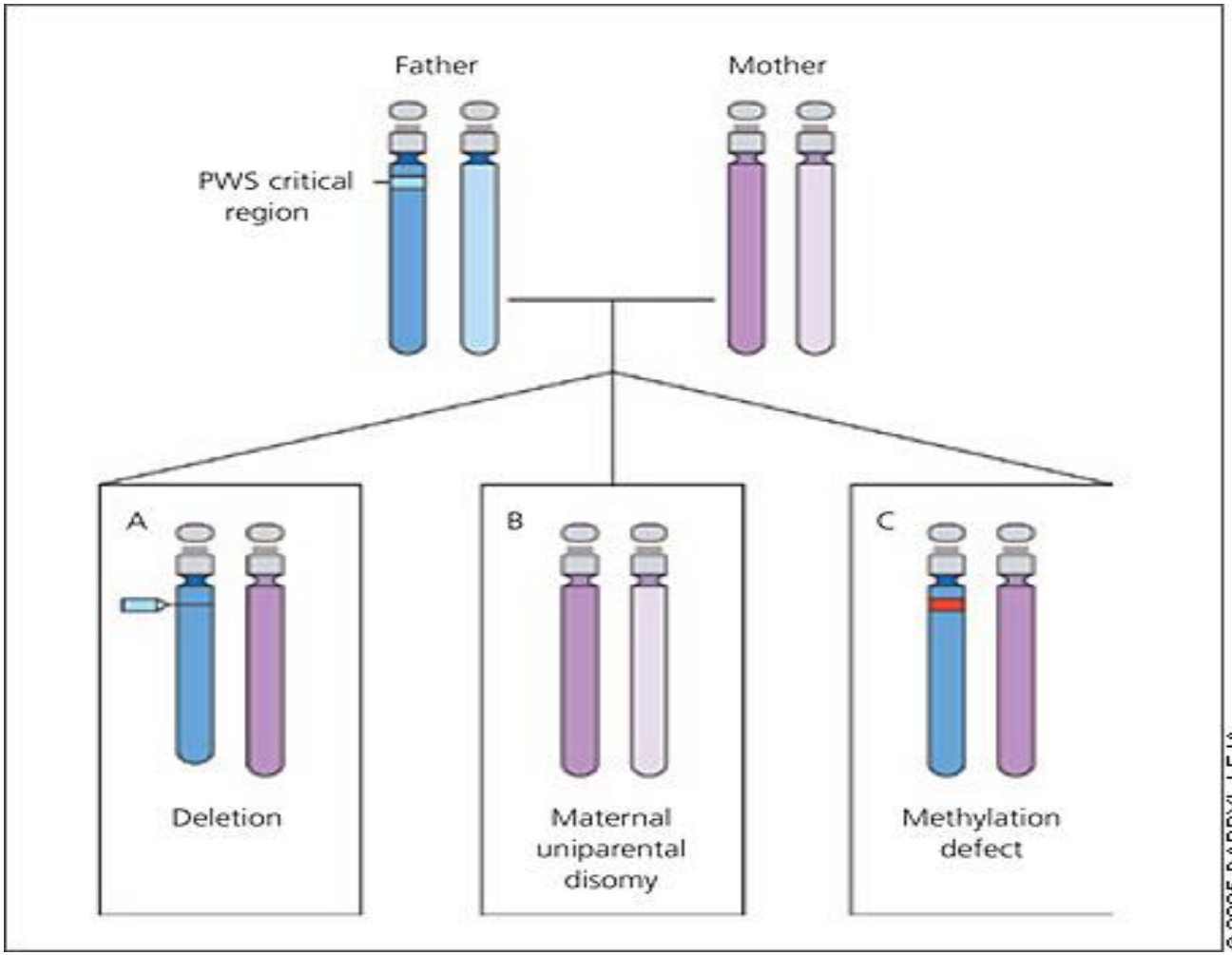
- Genomic Imprinting:

People inherit two copies of their genes, one from their mother and one from their father. Usually both copies of each gene are active in cells. In some cases only one of the two copies is normally active, some genes are normally active only when they are inherited from a person's father; others are active only when inherited from a person's mother. This phenomenon is known as genomic imprinting.

- Uniparental Disomy(UPD): occurs when a person receives two copies of a chromosome from one parent.

- Prader-Willi Syndrome:

People with Prader-Willi syndrome typically have mild to moderate mental retardation. Short stature, and small hands and feet. Both affected males and affected females have underdeveloped genitals. Puberty is delayed or incomplete, and most affected individuals are unable to have children (infertile).


Father
Mother
PWS critical region
A
Deletion
B
Maternal uniparental disomy
C
Methylation defect
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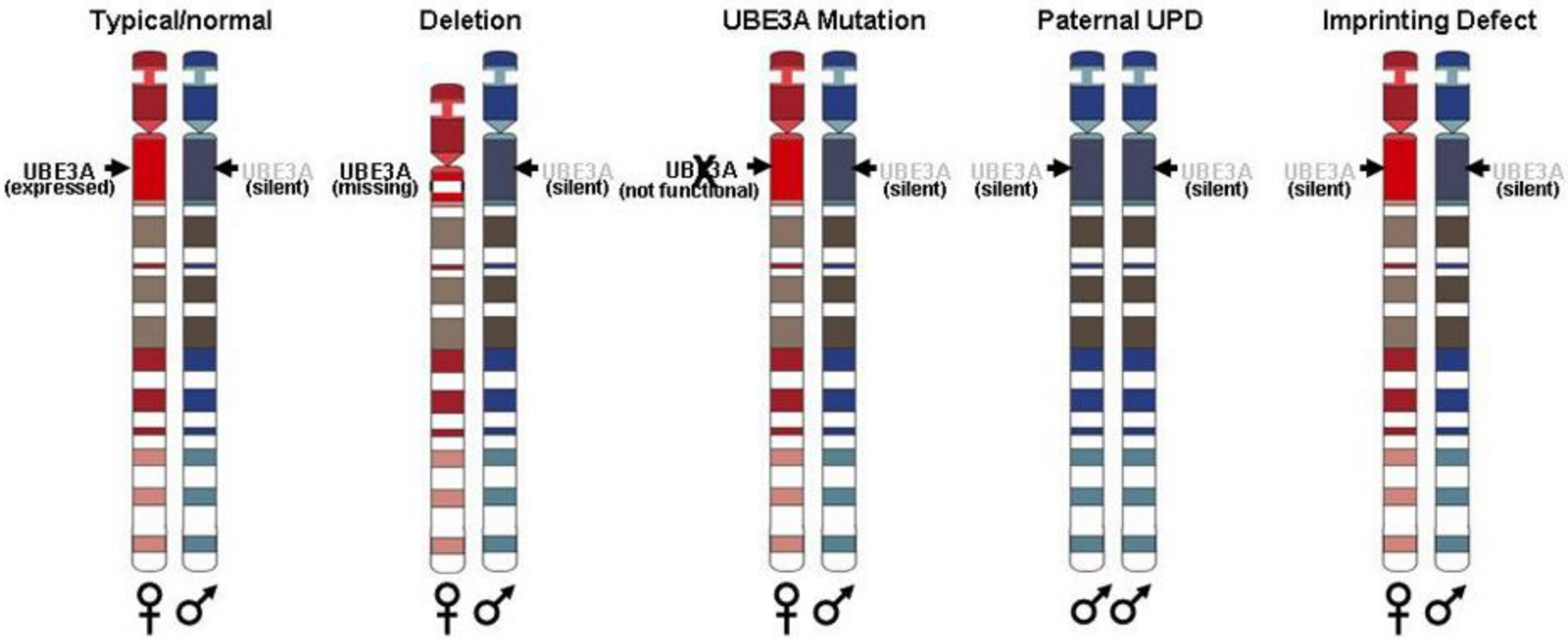
- Most cases of Prader-Willi syndrome (about 70 percent) occur when a segment of the paternal chromosome 15 is deleted in each cell. In another 25 percent of cases, a person with Prader-Willi syndrome has two copies of chromosome 15 inherited from his or her mother (maternal copies) instead of one copy from each parent. This phenomenon is called maternal uniparental disomy.

- Angelman Syndrome:

Characteristic features of this condition include delayed development, mental retardation, and problems with movement and balance (ataxia). Most affected children also have recurrent seizures (epilepsy) and a small head size (microcephaly). Frequent smiling, laughter, and Hyperactivity


Typical/normal
UBE3A (expressed)
UBE3A (silent)
Deletion
UBE3A (missing)
UBE3A (silent)
UBE3A Mutation
UBE3A (not functional)
UBE3A (silent)
Paternal UPD
UBE3A (silent)
UBE3A (silent)
Imprinting Defect
UBE3A (silent)
UBE3A (silent)

- Many of the characteristic features of Angelman syndrome result from the loss of function of a gene called UBE3A.
- 70 percent occur when a segment of the maternal chromosome 15 containing this gene is deleted. 11 percent, Angelman syndrome is caused by a mutation in the maternal copy of the UBE3A gene.
- In a small percentage of cases, Angelman syndrome results when a person inherits two copies of chromosome 15 from his or her father (paternal copies). This phenomenon is called paternal uniparental disomy