Non-Traditional Types of Gene Disorders:

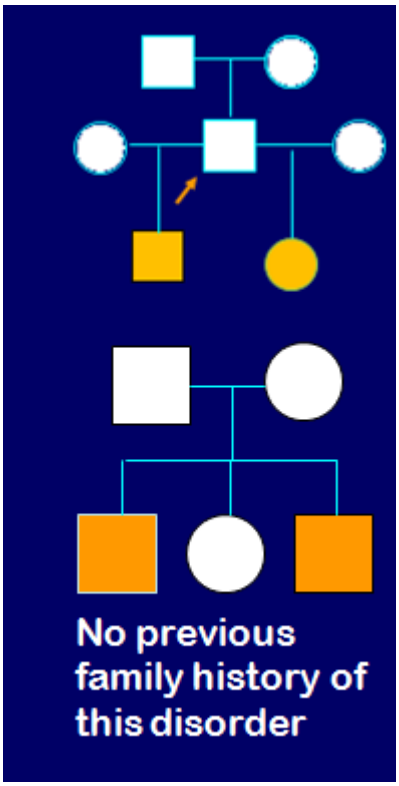
These disorders do NOT follow the Mendelian Inheritance rules.

A. Mosaicism:

Either: Somatic or Gonadal

1. **Gonadal:** Occurs in the Ovum or Sperm (X and Y), resulting in many types of diseases including: Hemophilia A, Osteogenesis imperfecta, Duchenne muscular dystrophy, Achondroplasia,
2. **Germ line**: The individual presents with an autosomal dominant disease for the first time in the family.
3. **Somatic**: Occurs post-zygotic formation. Effects a certain percentage of cells in certain organs.
    a. For example: Down's Syndrome. Two normal cell lines emerge, but during the 2nd meiosis, non-disjunctional segregation occurs.

During development, the parental cells divide normally with mutated cell, so there are two cell lines, one is normal and the other is mutated.



In this pedigree, we can see that the parents are completely normal.

Yet the children have acquired the mutation.

Mosaicism is most apparent when you see a mutation suddenly appearing after many generations of NORMAL individuals.

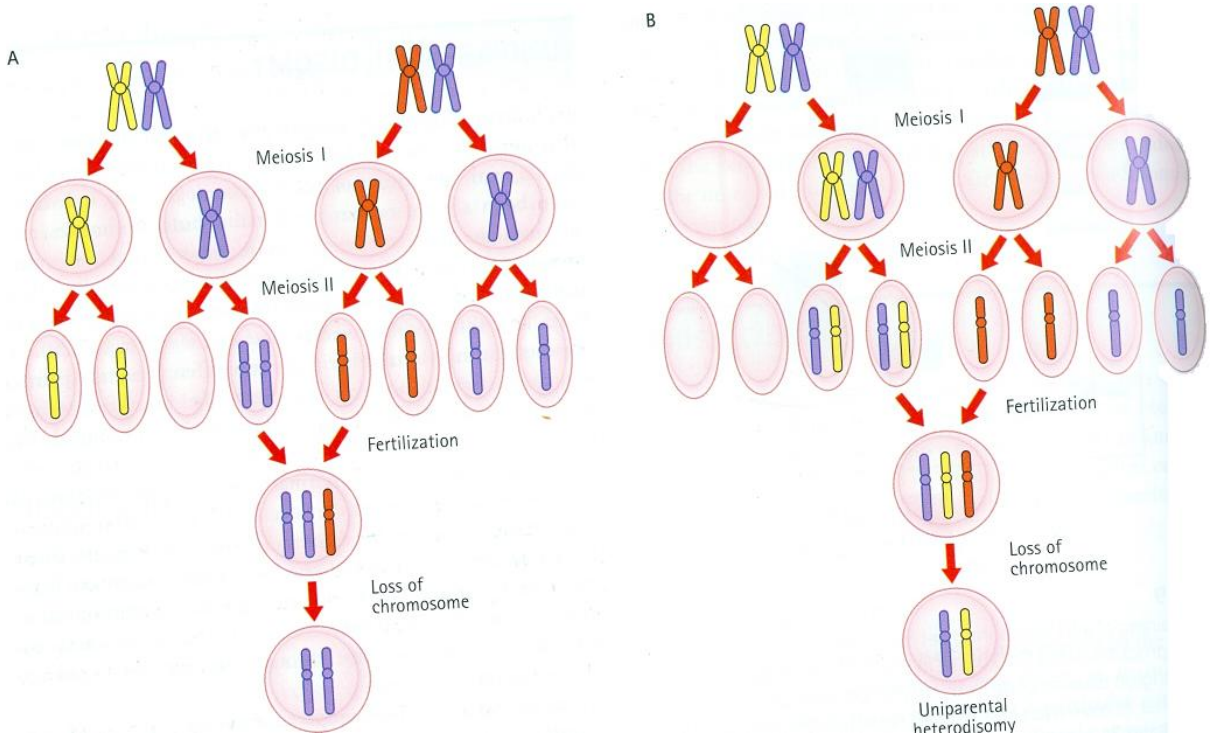
In this pedigree, we can also assume that the FATHER is a carrier, because both of his children have the disorder, and his children are from different wives.

B. <u>Uniparental Disomy</u>

In which two homologous chromosomes are inherited from ONE parent.

Isodisomy: same origin, same chromosome is duplicated (due to non-disjunction in meiosis II)

Heterodisomy: the parent passes one copy of each homolog (due to non-disjunction in meiosis I)



C. **<u>Genetic Imprinting</u>**: Has been mentioned before, but briefly put:
It is the way genes are expressed depending on which parent they were inherited from.

D. **<u>Mitochondrial Diseases</u>**:

The Mitochondria is an Organelle found in all nucleated cells. It is believed to be a symbiotic organelle originating from bacteria.

Many important reactions occur within the mitochondria including: Oxidative phosphorylation, ATP generation, the formation of ROS's and many others.

The mitochondria has its own DNA which is Circular!! There are NO introns indicting that the ENTIRE DNA is utilized and gives rise to proteins. There are 37 genes in this DNA. There are NO histones either.

The mitochondria is of Maternal inheritance!!

Some mitochondrial genes interact with nuclear genes

Of the 37genes, these are what they code for:

2 ribosomal RNA

22 Transfer RNA

13 polypeptide coding for oxidative phosphorylation

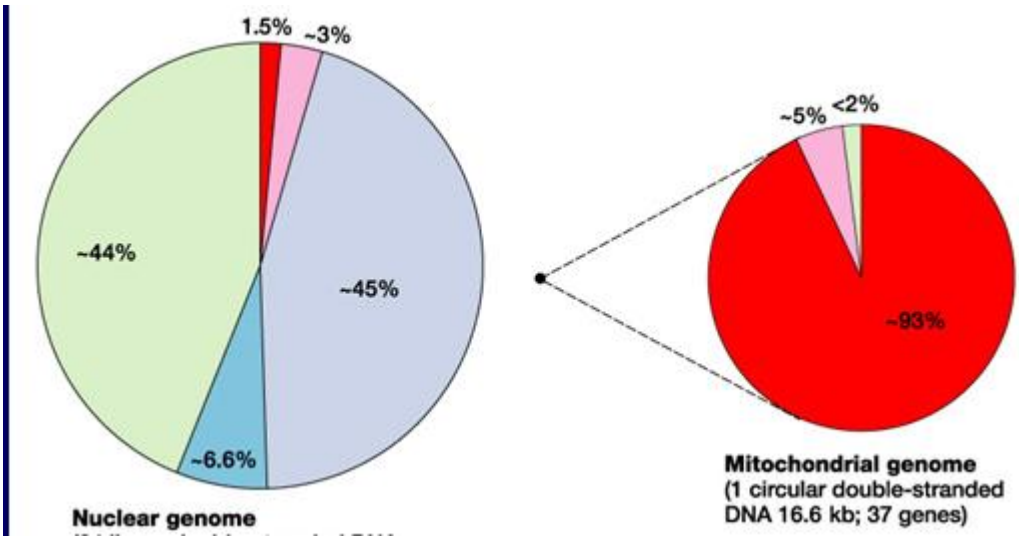
90 nuclear genes coding peptide transported to mitochondria to participate in oxidative phosphorylation.

<u>Some nucleotide participates in more than one gene Replication</u>

Mitochondrial DNA replicate by lengthening of the loops in opposite directions to each other.

The genes are mostly involved for the production of proteins in oxidative phosphorylation, the citric acid cycle, the electron transport chain and for enzymes that metabolize Fatty Acids.

Comparing Nuclear Genome with Mitochondrial



The Mitochondrial genome is HIGHLY conservative, which means that 95% of its DNA is of a CODING sequence. Very stable, very little change occurs to DNA, meaning it is VERY susceptible to mutations. (10X more than the Nuclear genome.)

As with the Nuclear genome, only 1.5% of the DNA gives rise to functional producing protein

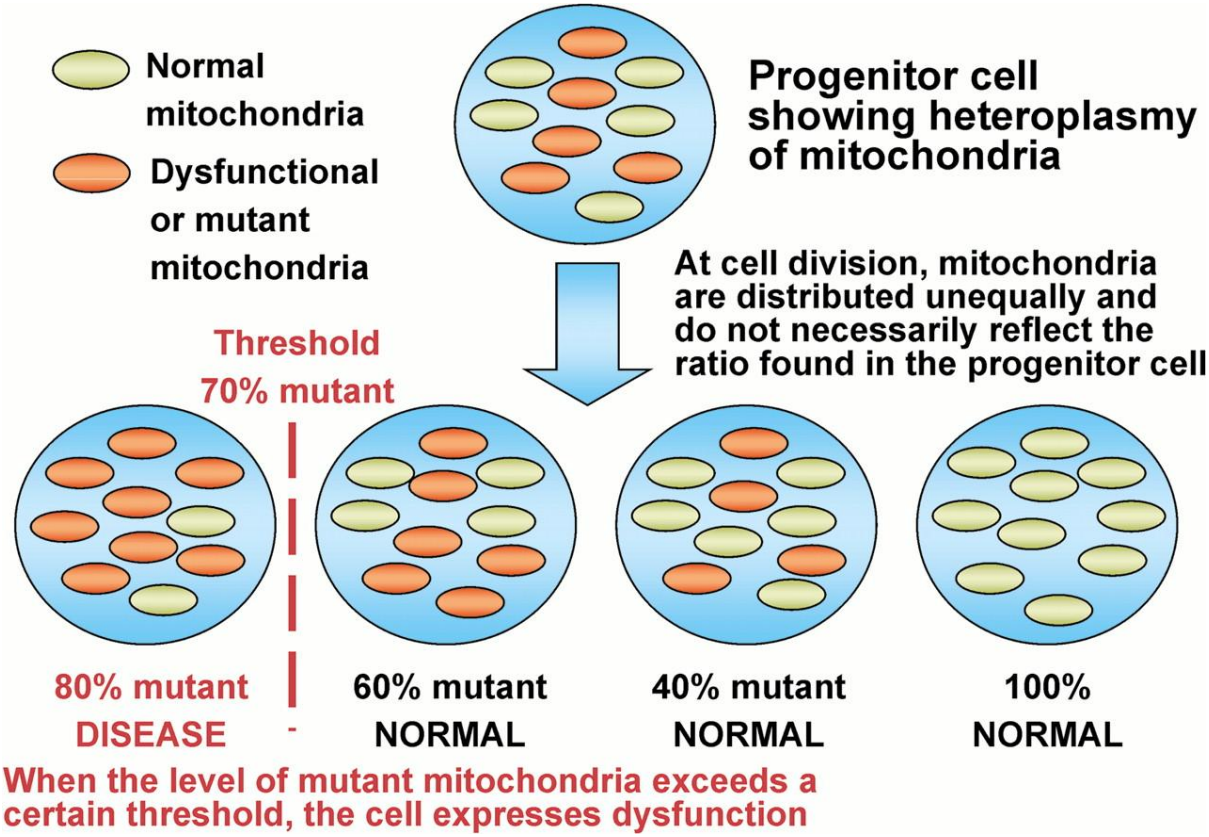
During fertilization, the ovum has all mitochondria, thus the phenotype come from the mother's side

Spermatic mitochondria will be degraded as it is Not stable for long time

Mutations in mitochondria # and structure lead to energy depletion disorders.

Organs that need energy, are the most effected including the: brain, muscle, pancreas, ophthalmic tissues. Leading to many neurological problems, muscle dystrophy…

The Severity of the disease is variable, it depends on how many mitochondria mutated are inherited.



The inheritance of mitochondria is by the phenomenon of **Heterosomy**: unequal distribution of maternal mitochondria

***Pedigree: Very similar to autosomal dominant inheritance.

-Both males and females are effected BUT there is the tendency to SKIP generations and the transmission of the disorder only occurs from MOTHER to offspring, not by the father.

-If father effected, all his children are normal.

-If mother effected, the son will ALWAYS be effected. The daughter: may acquire mutation, but not enough mitochondria to see clinical picture.

The Mitochondria is also important for the determination of the origin of man.

-Start in Africa, segregation, Middle East ,segregation, Europe, Far East…

Use of Y chromosome can also determine the origin of man by its short tandem repeats which are more stable.

E. **Trinucleotide expansion**:

Can either occur in the coding or the non coding regions(3'or 5' end)

Coding: Expansion of CAG Spinocerebellar ataxia type 1 (neurodegeneration)and Huntington's

Non coding: untranslated areas, different diseases,

5': Fragile X syndrome, Spinocerebellar ataxia type 2

3': Myotonic dystrophy

Introns: Friedrich Ataxia

Fragile X:

Second leading cause of mental retardation after Down's Syndrome

Occurs mostly in males (1 in 4,000 males) (1 in 8000 females)

1 in 259 females are carries.

X linked, q arm (Xq27.3)

Polymorphic repeat of CCG at the 5' of the nontranslated region in exon 1, Methylation occurs at the first c, starting upstream of the mutation, the gene (FGR1) cannot be expressed, no protein will be produced.

There are Many forms of Fragile X:

Fragile X Syndrome: Full Mutation→(200-2000 CCG repeats), Life-long disorders.

Fragile X tremor ataxia Syndrome: (55-200 repeats, less proteins produced) Seen in elderly males. Many disorders especially frontal lobe dementia can be seen.

Premutation-related disorders: females with emotional problems, will be AUTISTIC…

Males Phenotype: severe mental retardation, long faces, prominent ear, large testis**, 1/3 pts have Autism,** can't live independently

Females: less frequent, mild to moderate retardation, attention problems, anxious

*Expansion will be stable if the repeats of CCG less than 45

**Unstable 55-200

***More than 200 expansion will lead to a full mutation, gene inactivated

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How to Diagnose Fragile X:

-Clinical Presentation of the patient

-Family Pedigree map is drawn out

-Use of Cytogenics: identifying chromosomes

Use culture media with added **FOLATE**. Fragile X is sensitive to folate and can be easily seen when karyotyping

The Chromosome at the end of the q arm of the X chromosome looks as if there is a deletion but it is only the folate which might be stained

-Molecular studies: to look up for the gene itself

Fragile- 16-50% have autism, add the info in the slide

Premutation primary ovarian insufficiency : It is an Associated condition, premature ovarian failure

Will increase the acquirement of the disease by 13-fold.

***The last slide has a revision of ALL the inheritances of Single Gene Inheritance

Remember all the characteristics for each one!!

Focus on the pattern of the pedigree: whether the disease skips a generation or not

Remember the alleles: homozygote of Autosomal dominant disorders usually show the most severe cases, usually leads to abortion, intrauterine deaths

X linked disorders: Male have the more severe version of the disease and they can't transmit the mutation to their offspring.

-→If the Mother is dominant: 50% affected males, 50% carriers daughter, the rest are normal

Autosomal Recessive: females always s carrier

Y linked disorders: Males are always affected.

Good Luck Doctors ☺

Bilasan Hammo