

Different modes of inheritance

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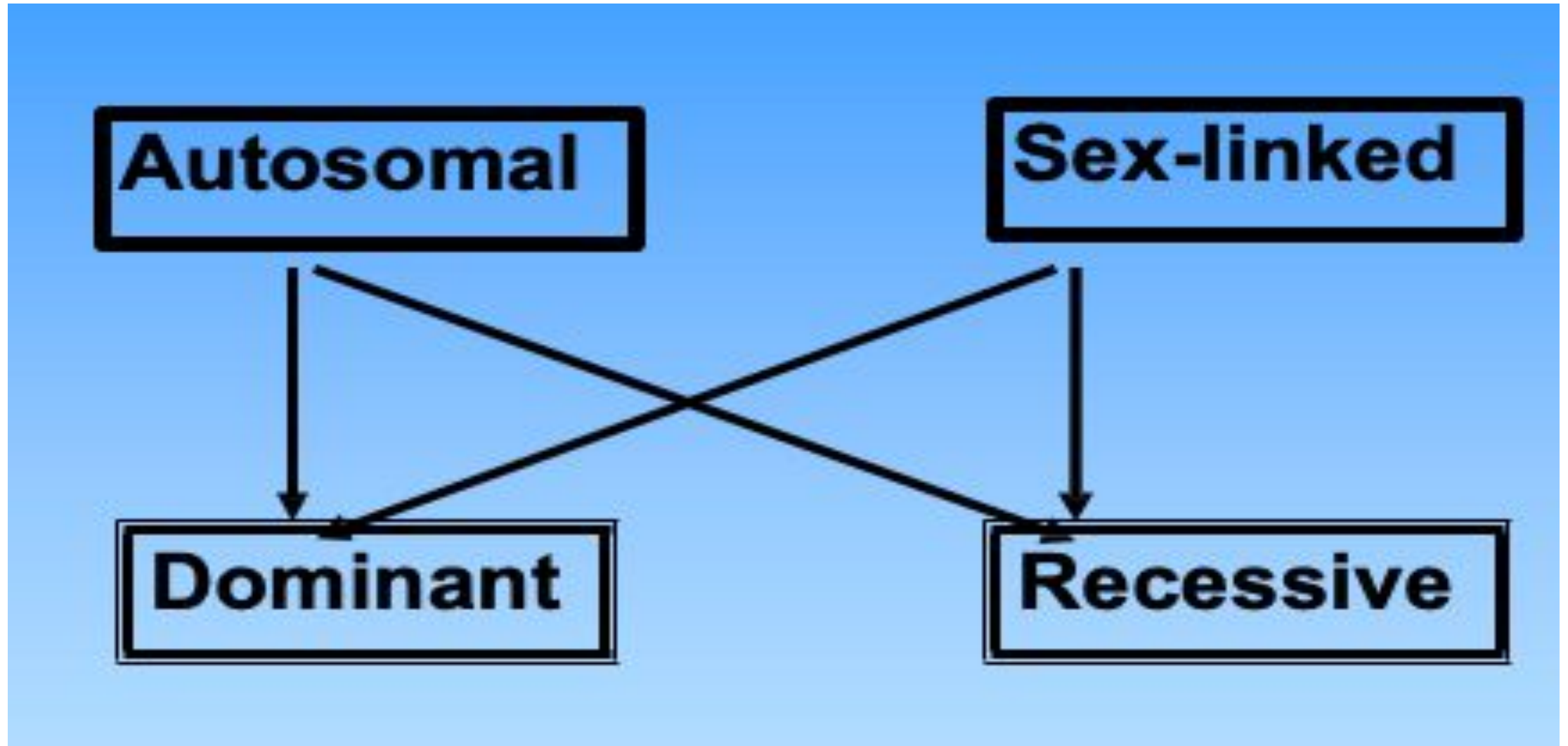
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Objectives

- Understand Mendelian autosomal and sex linked dominant and recessive inheritance
- Understand non conventional inheritance

Mendelian inheritance /Monogenic /monofactorial



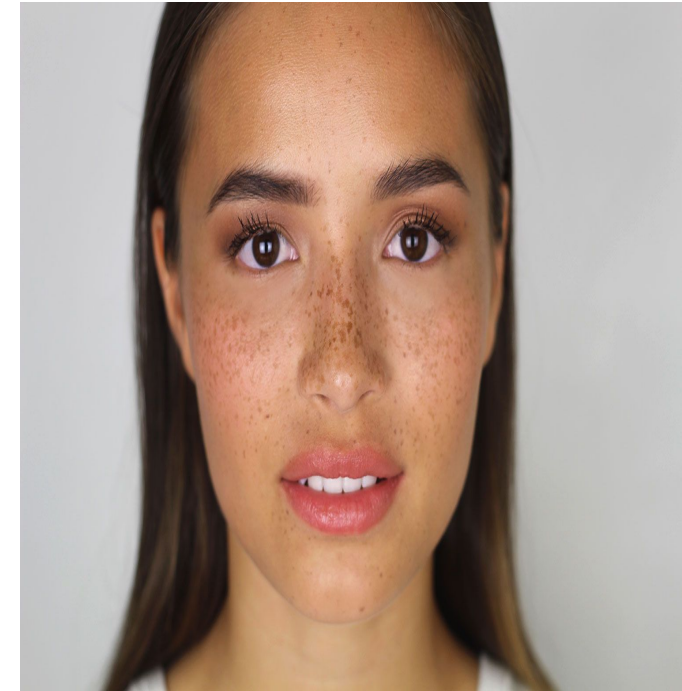
Autosomal dominant inheritance

□ Phenotypic trait determined by a dominant allele:

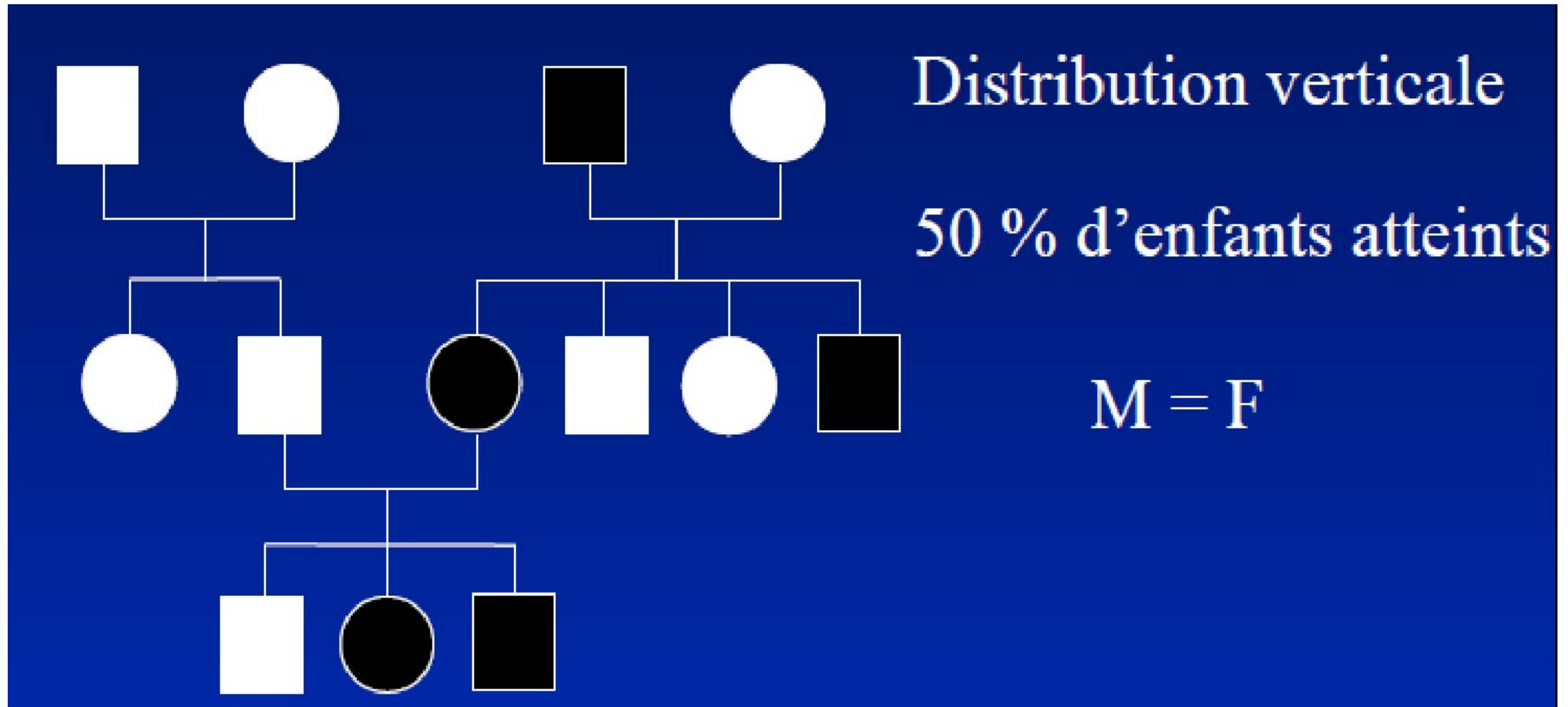
1- Freckles

2- Cheek dimples

3- The ability to roll the tongue into a U-shape.



Characteristics of dominant autosomal inheritance



- Male & female transmission and expression
- 50% risk for offspring of inheriting the mutation

Some rule breakers in dominant inheritance

Non penetrance: a person carrying the gene mutation but no sign of the disorder



Ectrodactyly

Variable expression: the manifestation of the disorder varies

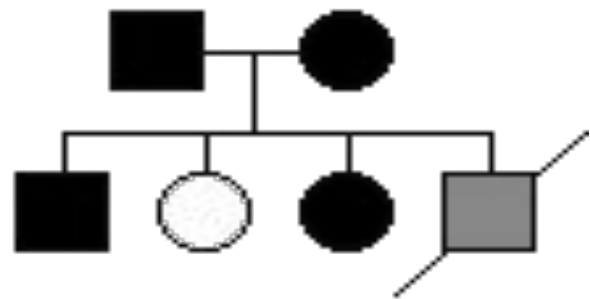


**Tibial aplasia /
ectrodactyly**



Are 2 dominant mutations worse than 1?

Usually yes...



Huntington Disease

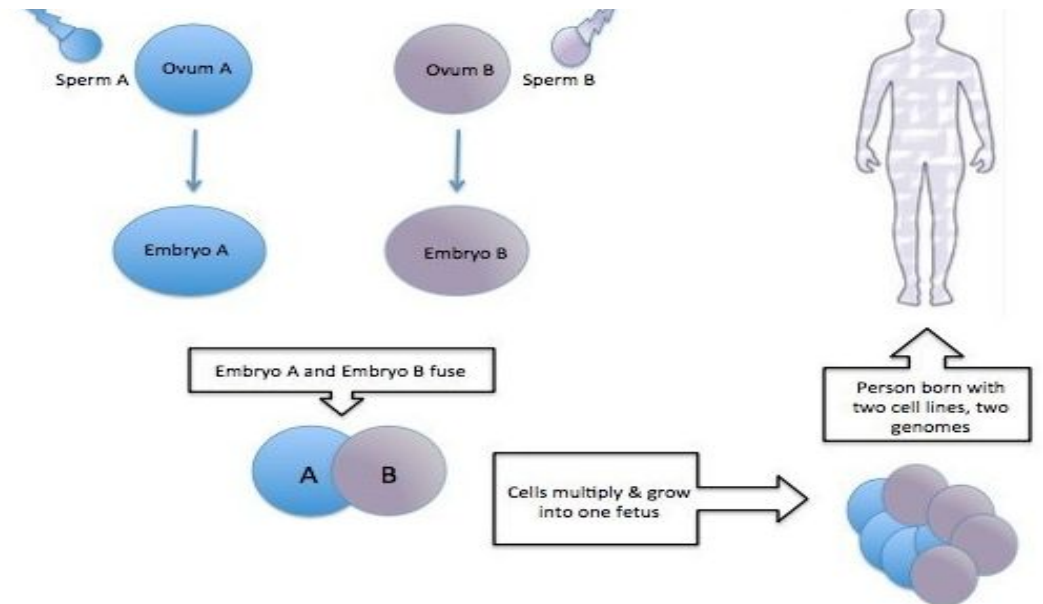
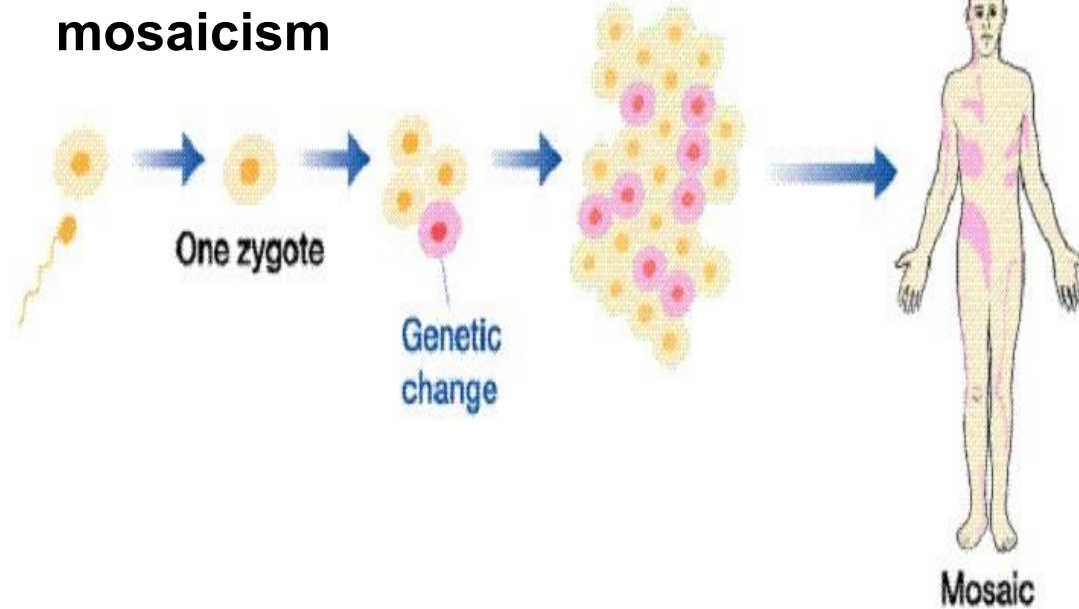


Achondroplasia

Are 2 dominant mutations worse than 1?

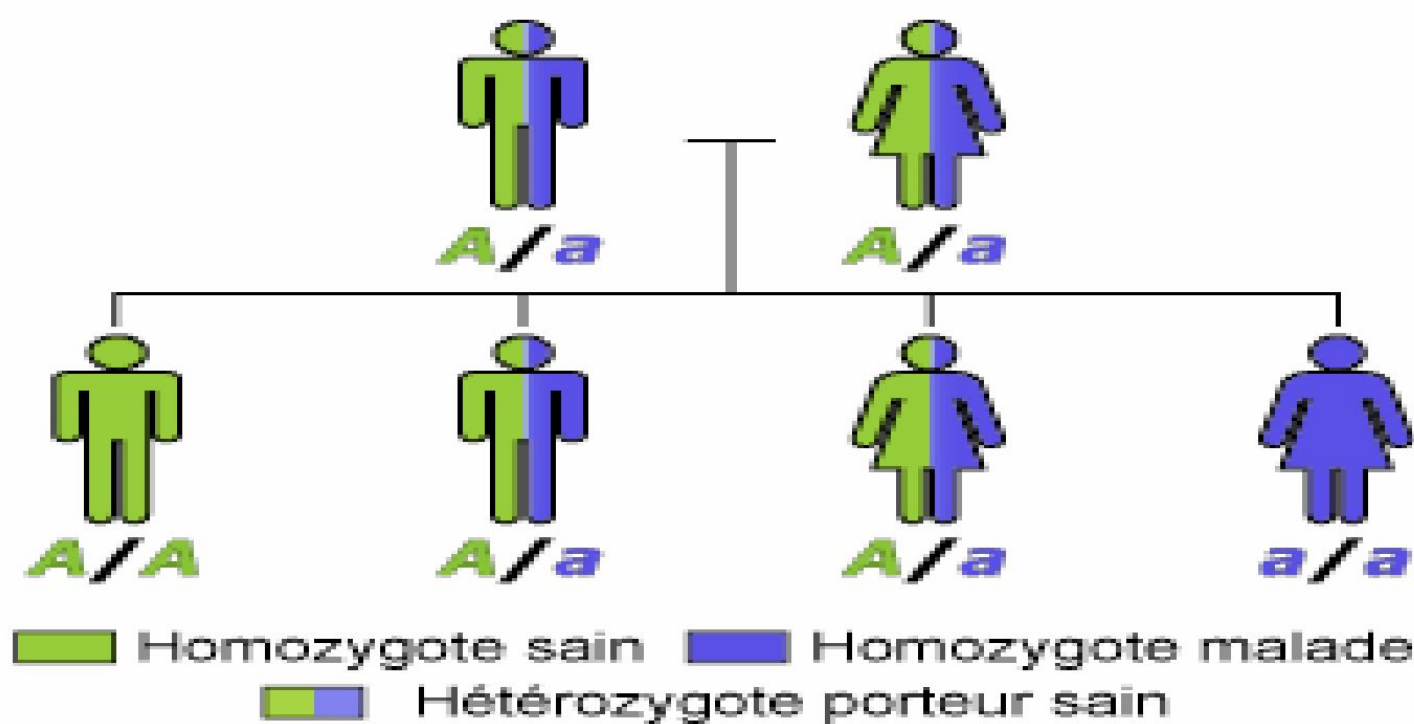
□ But sometimes no...

- New dominant mutations (parents not affected)



chimera

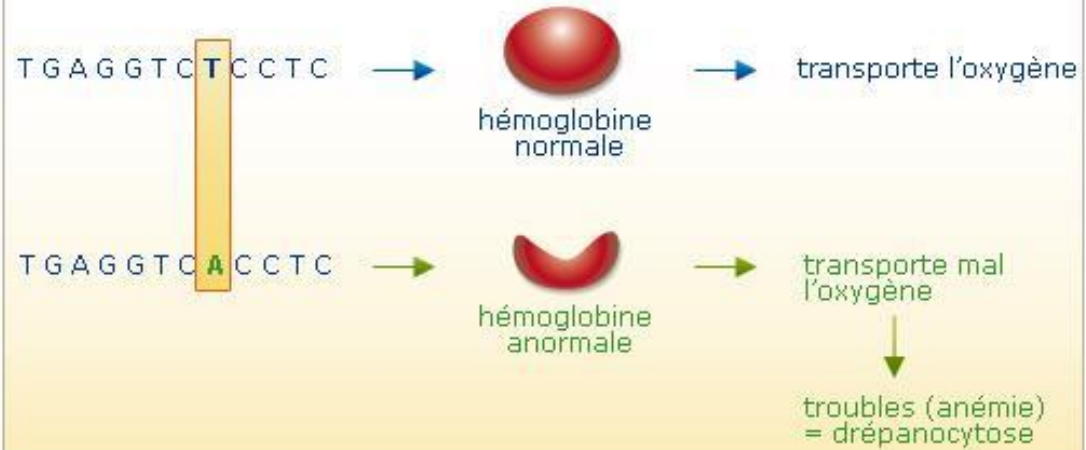
Autosomal recessive inheritance



- Parents unaffected carrier 25% risk for child to be a/a
50% probability to be A/a ; 25% probability to be A/A

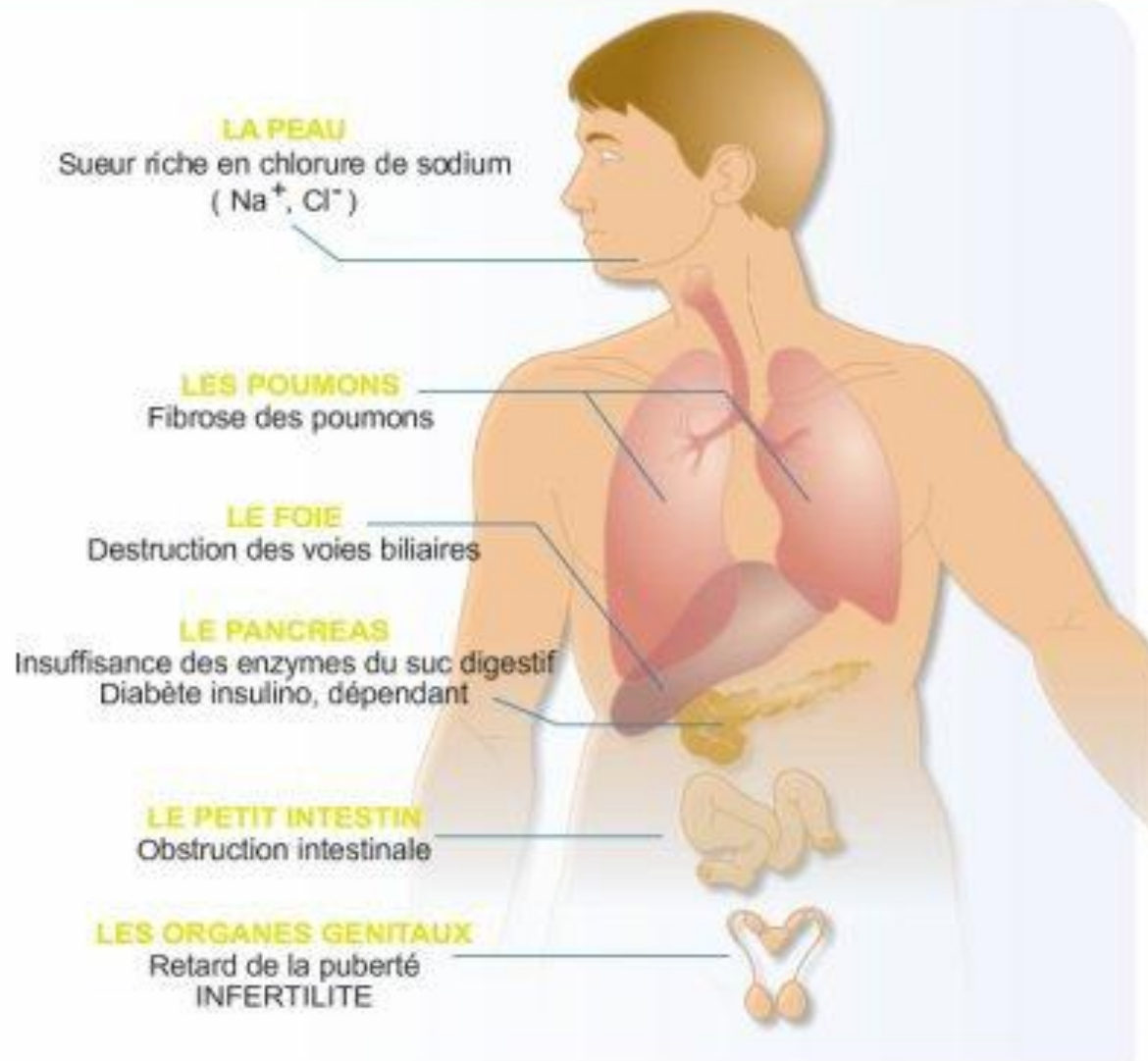
Sickle cell disease

Deux portions du gène de l'hémoglobine



mucoviscidose

Les organes atteints par la mucoviscidose



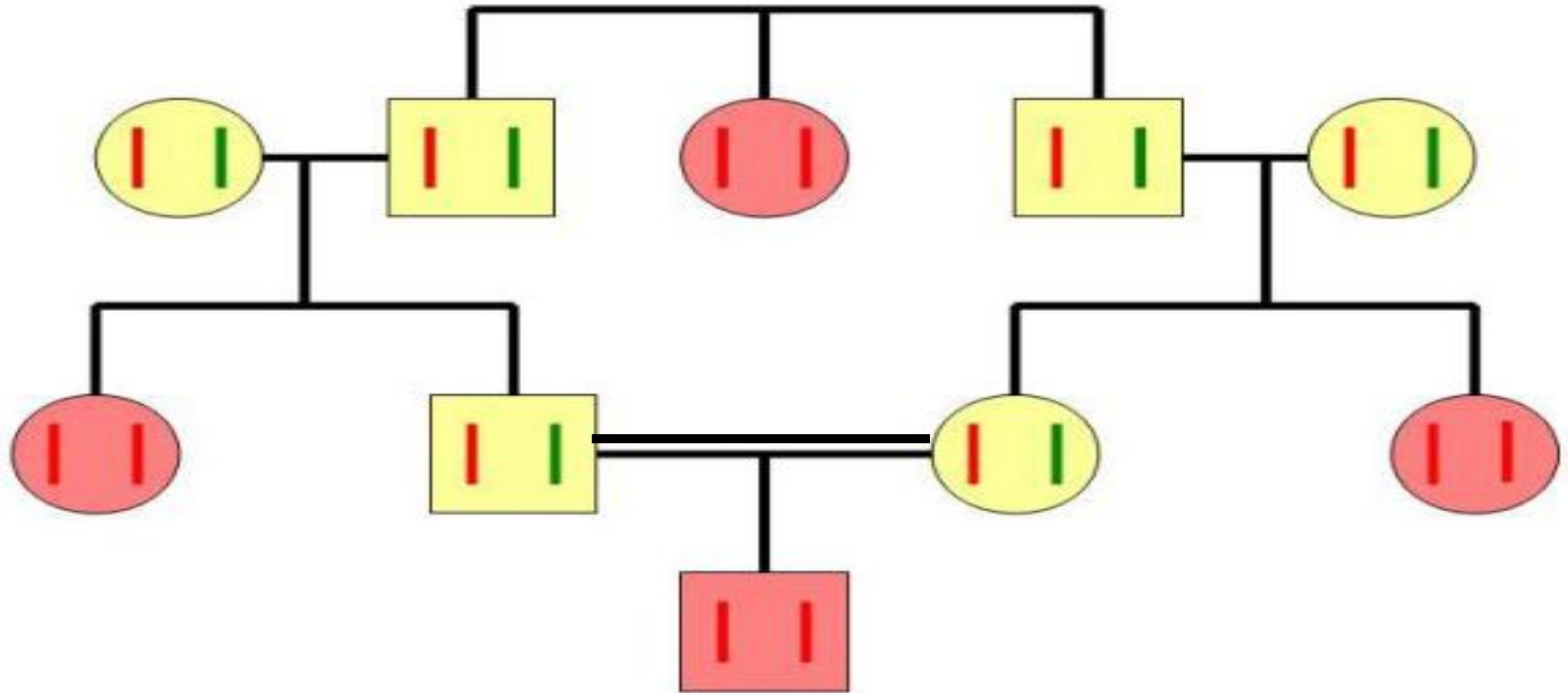
Une espérance
de vie désormais
**supérieure
à 40 ans**
et qui devrait
encore progresser

Specificities of Autosomic recessive Inheritance

1) Consanguinity

- is the kinship of two individuals characterized by the sharing of common ancestor(s)
- The proportion of inbred unions is higher in the ancestry of people with AR diseases.
- In this case, the man and the woman have a greater risk of having received an identical allele at a given locus from their common ancestor and of having children who are homozygous for this allele.

- More common in consanguineous unions (more genetic material shared!)



2) Genetic heterogeneity

Allelic or intralocus heterogeneity is the fact that a disease may be due to different (allelic) mutations in the same gene (one disease / several disease alleles).

A sick individual carrying two different mutations at the same locus is called a composite heterozygote

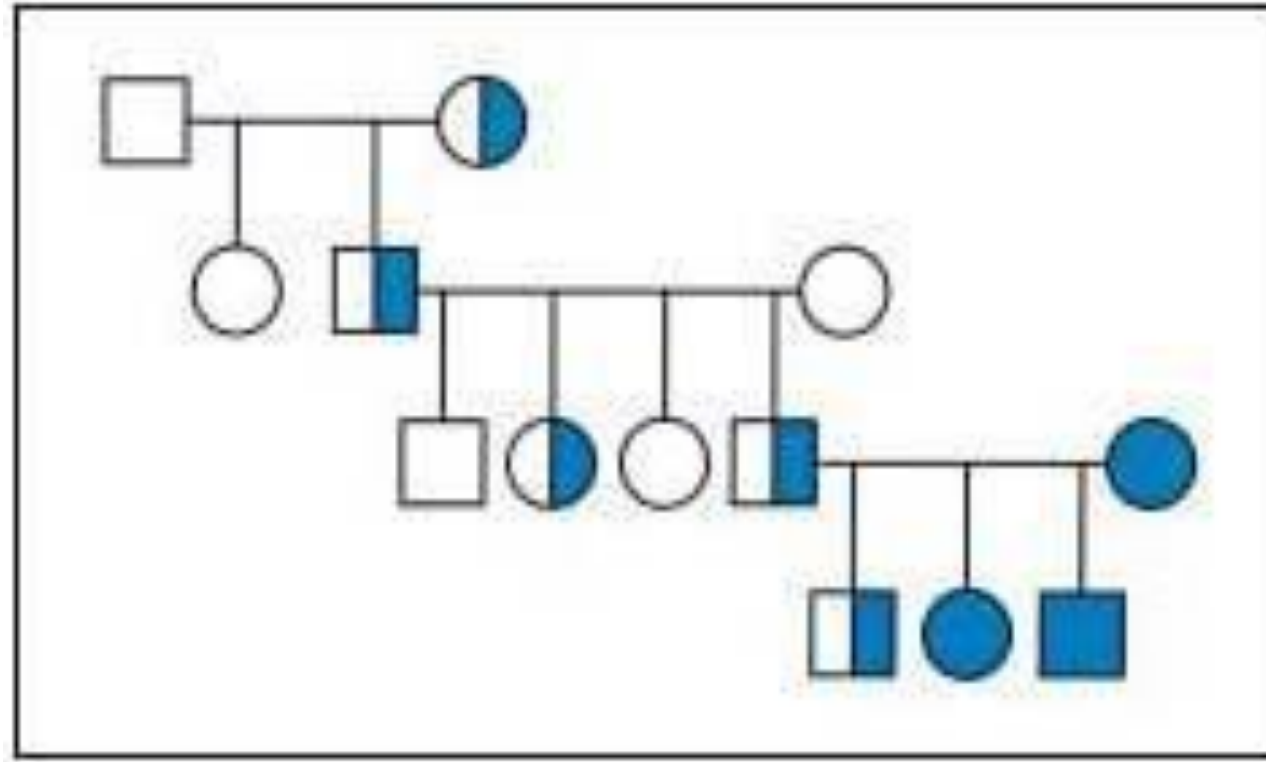
2) Genetic heterogeneity

Interlocus heterogeneity means that an apparently identical phenotype can be produced by mutations in different genes (one disease / several genes).

E.g. more than 150 genes have been identified as being involved in retinitis pigmentosa (AD, AR and RLX), which are degenerative diseases of the retina.

3) Frequency of heterozygotes, healthy carriers

An example of an autosomal recessive “rule breaker”



**Pseudodominance:
recessive condition**

Sex-linked heredity

□ X-linked heredity

- Both sexes can be affected by the disease
- Generally, heterozygous girls are less severely affected than boys.
- Affected women can transmit the disease to children of both sexes with a risk of $1/2$.
- In the offspring of an affected male
 - all daughters receive the mutated gene; however,
 - there is never a boy affected (no father-son transmission)

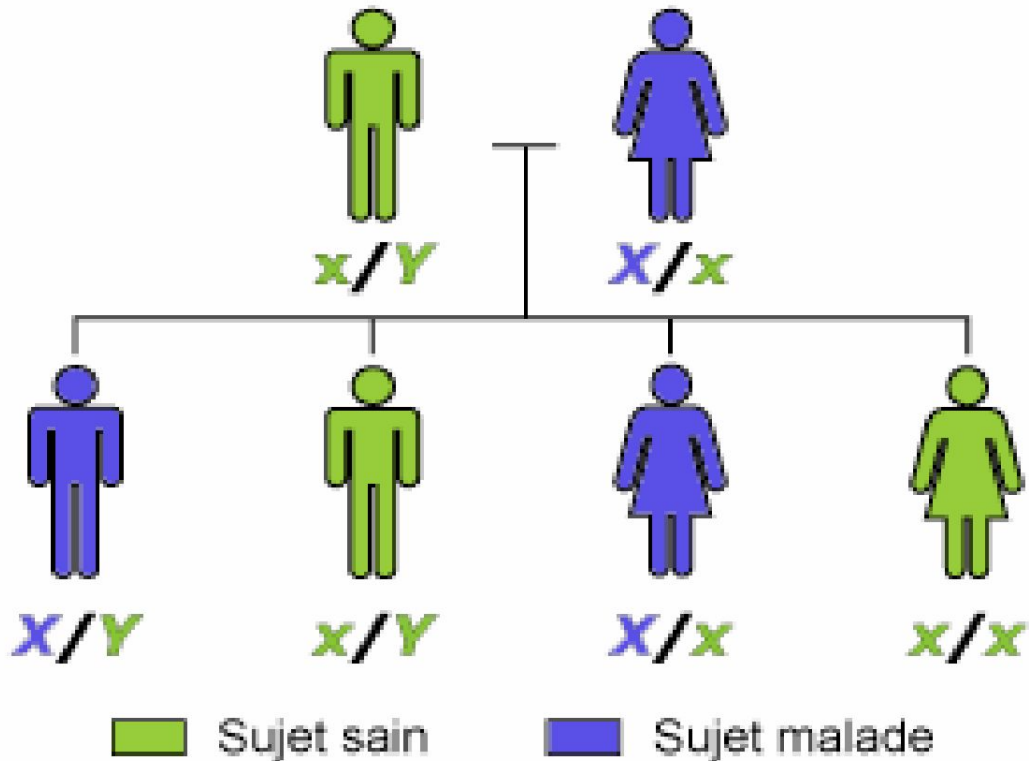
Sex-linked heredity

□ X-linked heredity

- dominance or recessivity does not arise in males:
 - Either the gene is mutated: they are affected,
 - Or the gene is normal: they are healthy.
- The question of dominance or recessivity only arises in female individuals:
 - If the disease occurs when only one gene is mutated, it is **dominant**,
 - If the disease occurs only when both copies are mutated, it is **recessive**.

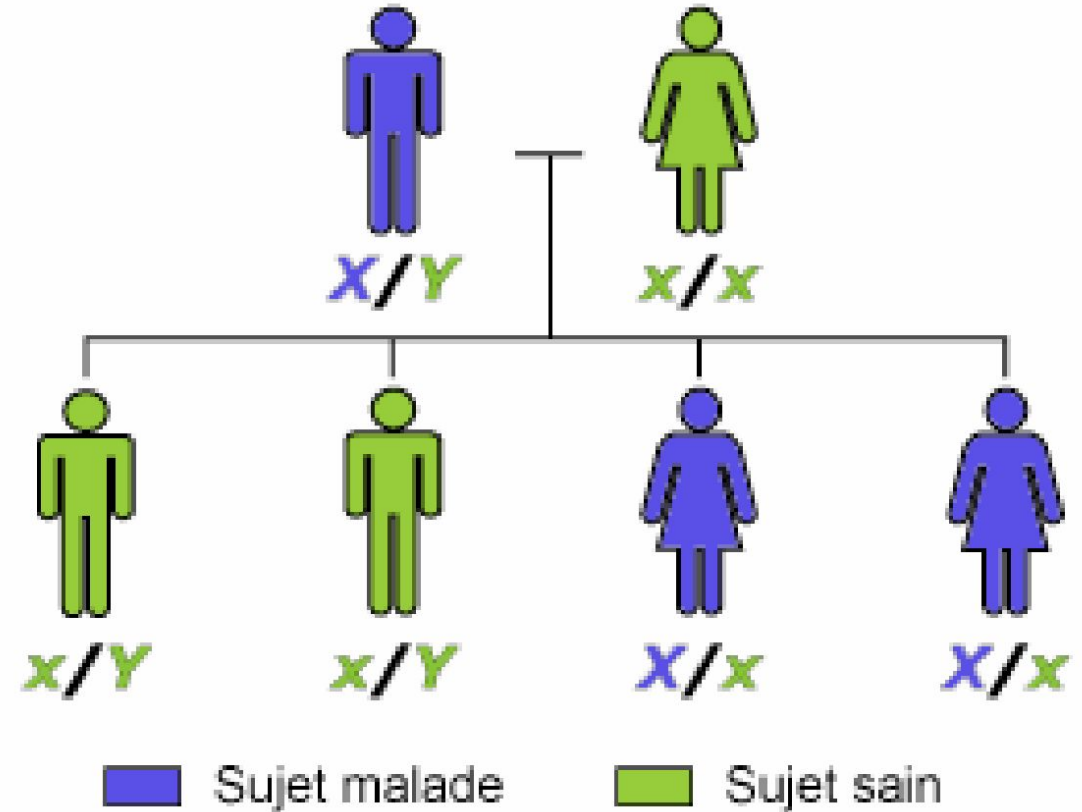
X linked - Dominant

Case of a sick mother and a healthy father



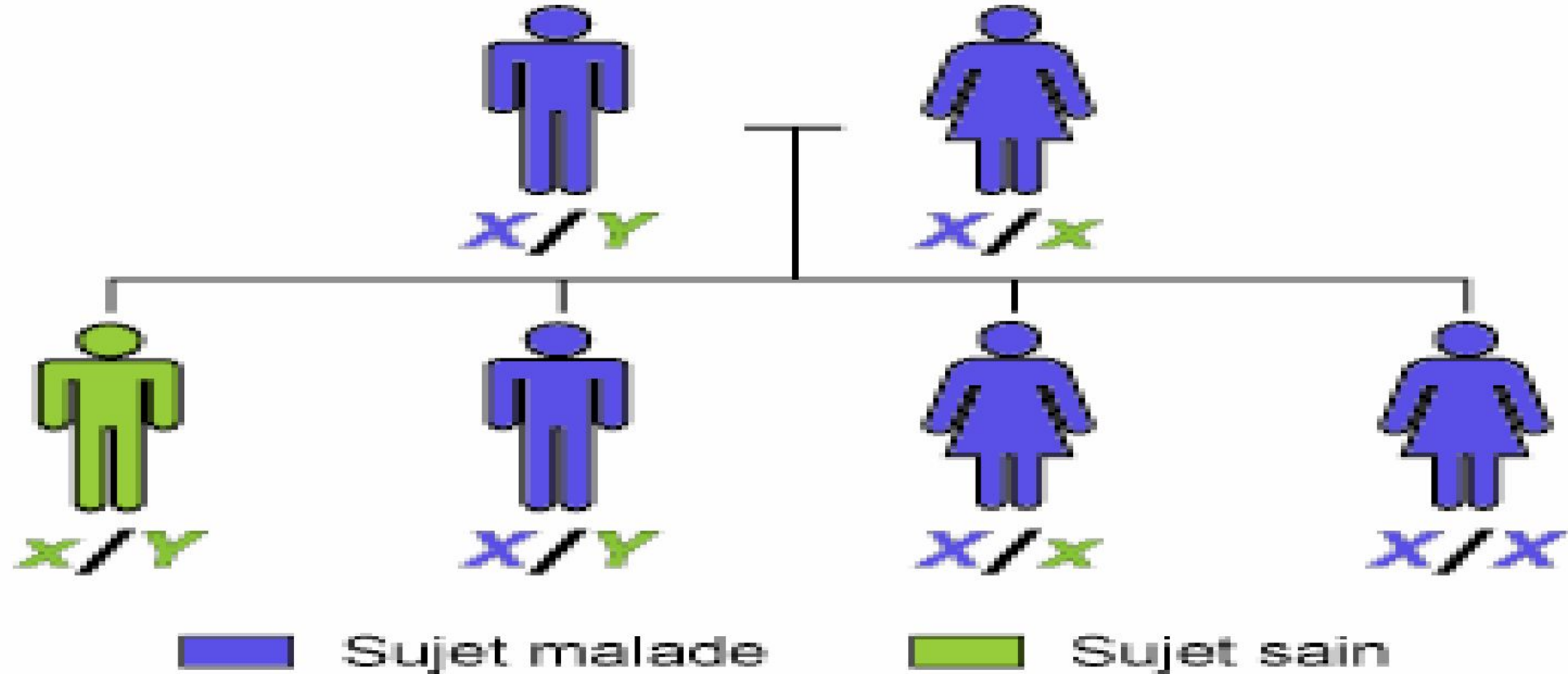
- Risk for offspring :
- that a boy will be ill is 50%.
 - that a girl will be ill is 50%.

Case of a sick father and a healthy mother



- With each pregnancy, the risk :
- that a boy will be ill is 0%.
 - that a girl will be ill is 100%.

Case of a sick father and a sick mother



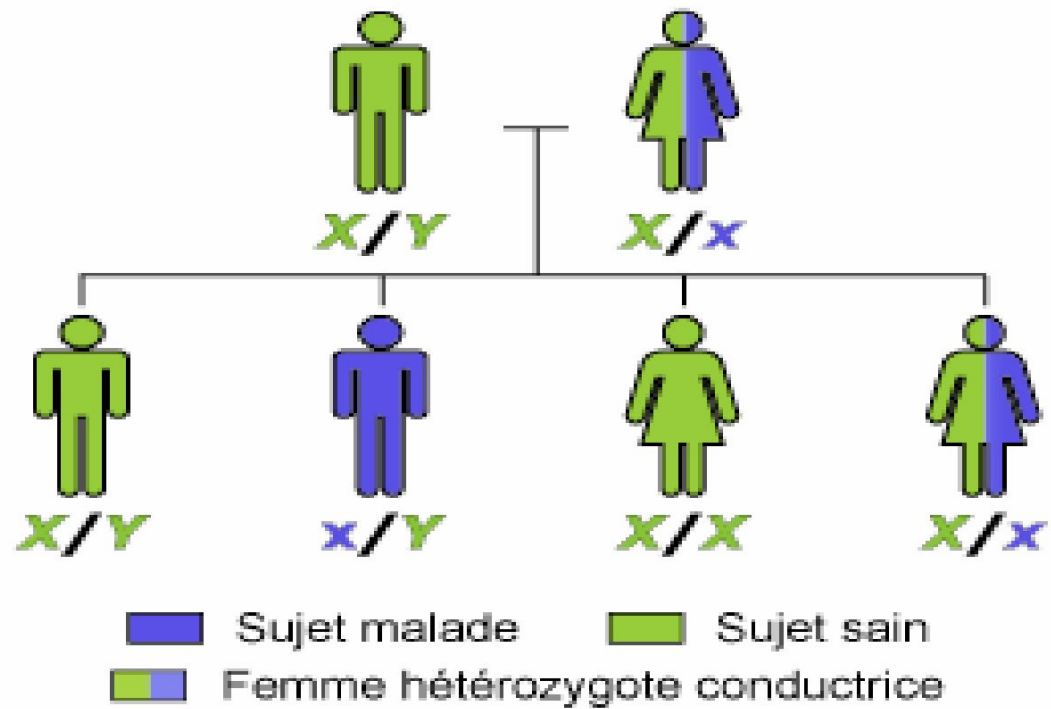
With each pregnancy, the risk :

- that a boy will be ill is 50%.
- that a girl will be ill is 100%.

X linked - recessive

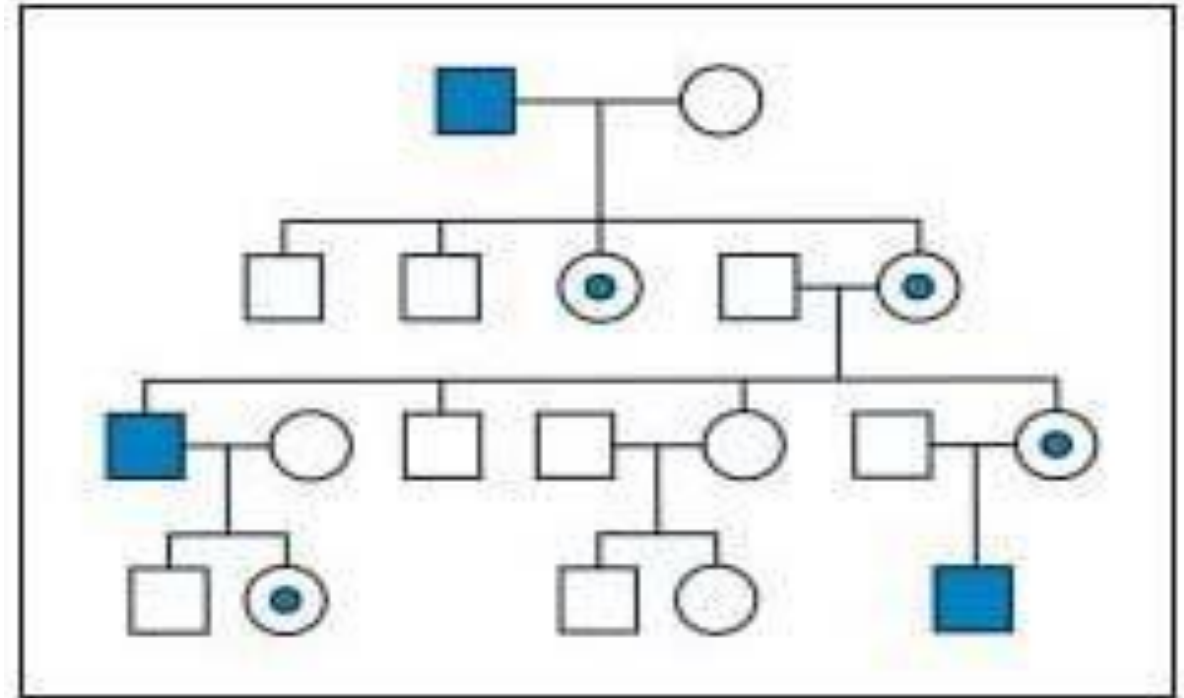
- Only boys are affected.
- There are no affected individuals in the paternal line and father-son transmission is never observed.

Maternal transmission



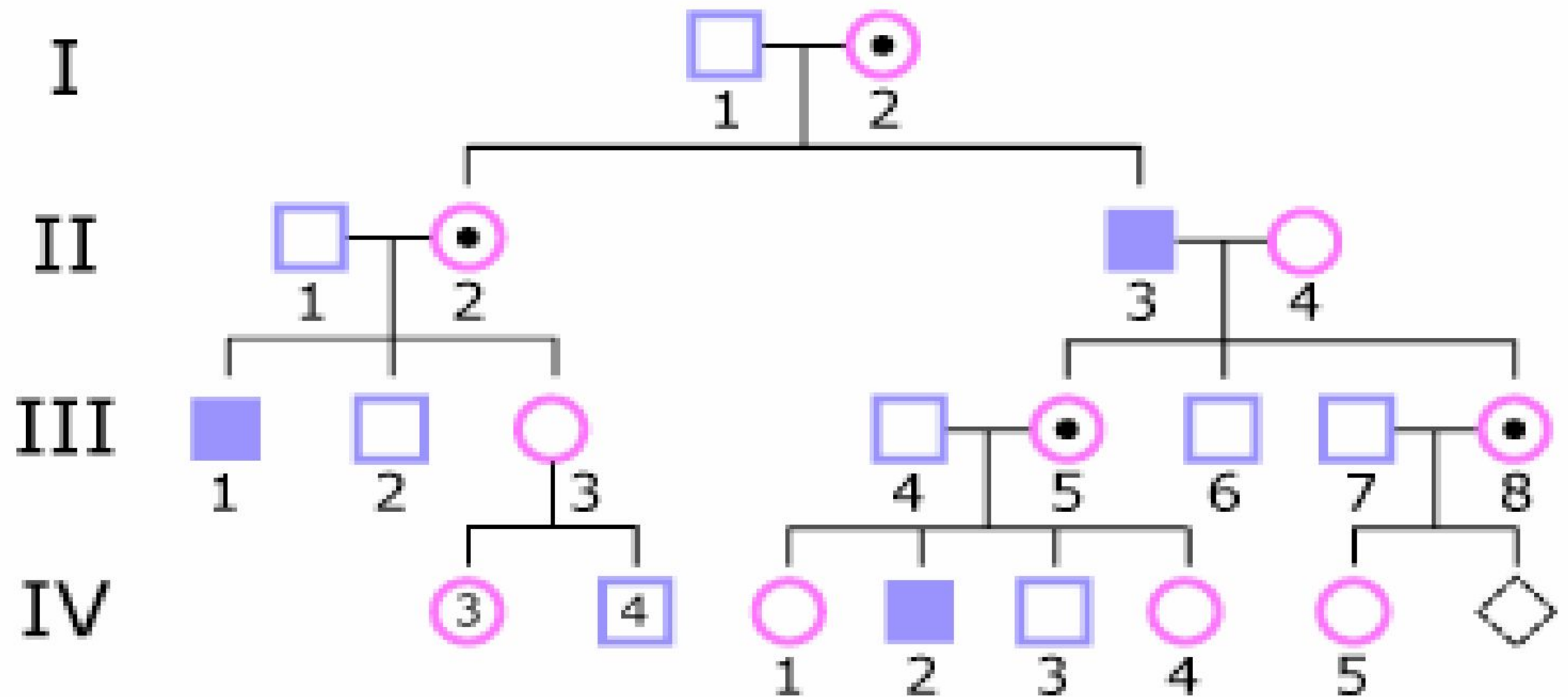
The risk for a boy to be sick is 50%.
 - For a girl to be a carrier is 50%.

Paternal transmission

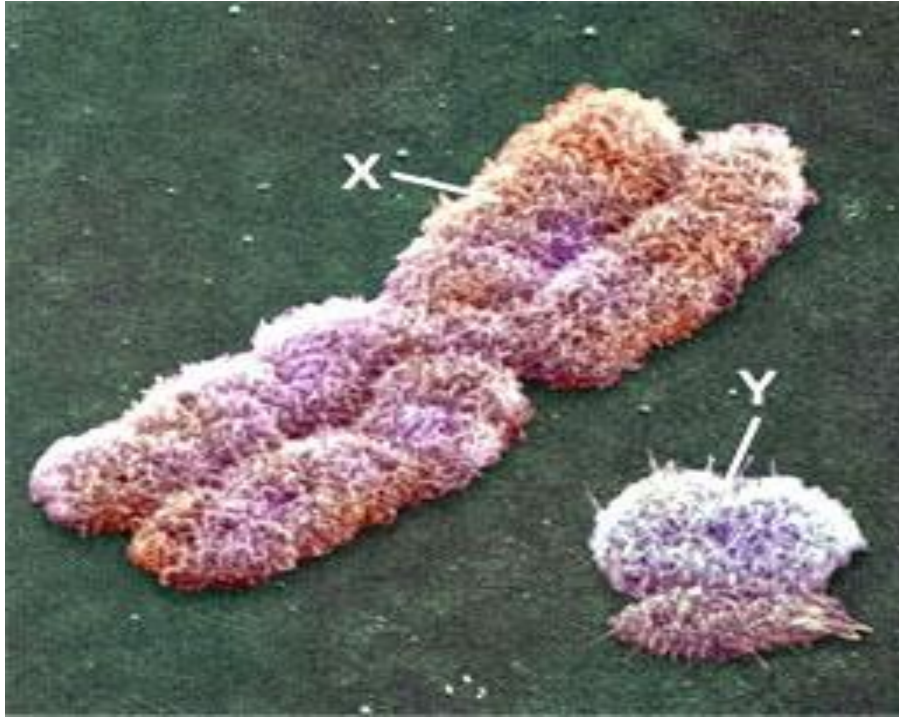


All daughters carriers
All sons normal

Haemophilia



Y – linked transmission?



Gene poor

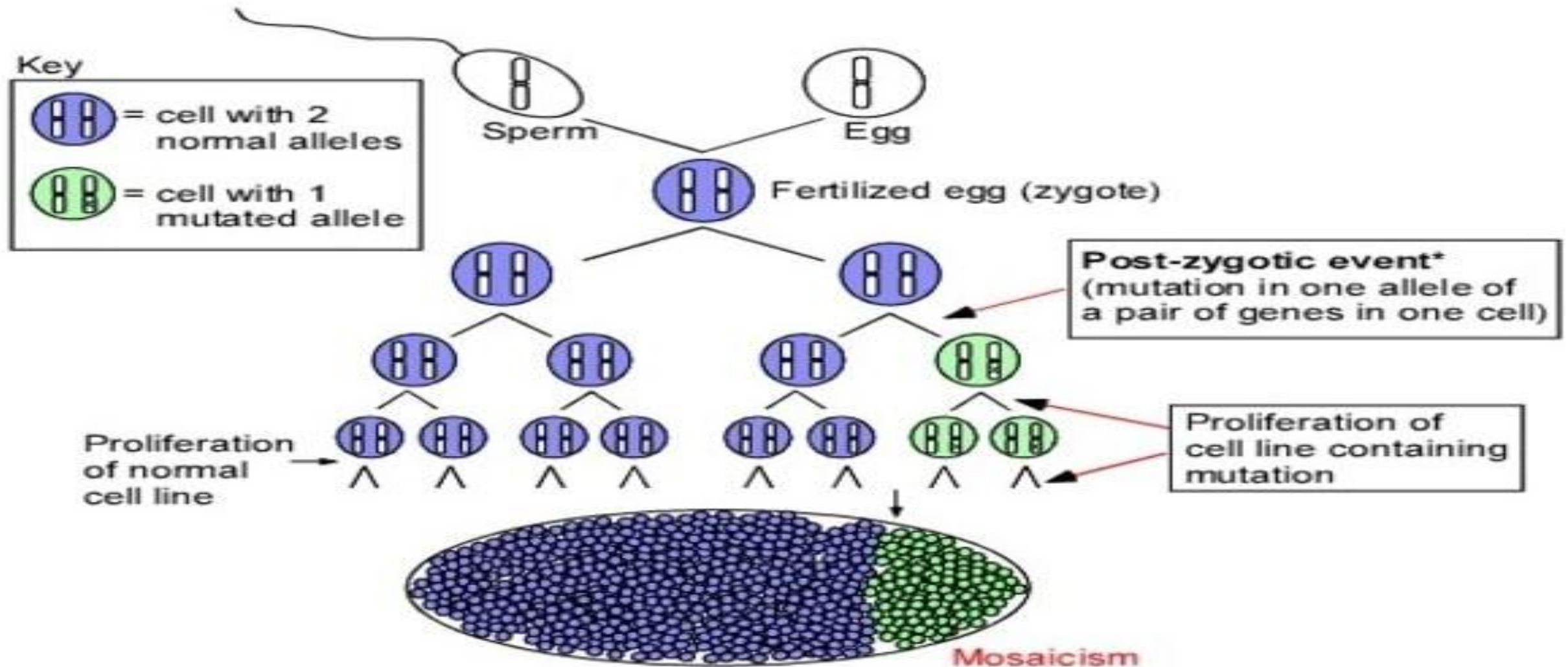
Infertility and ICSI...

Transmit to all sons but not to daughters

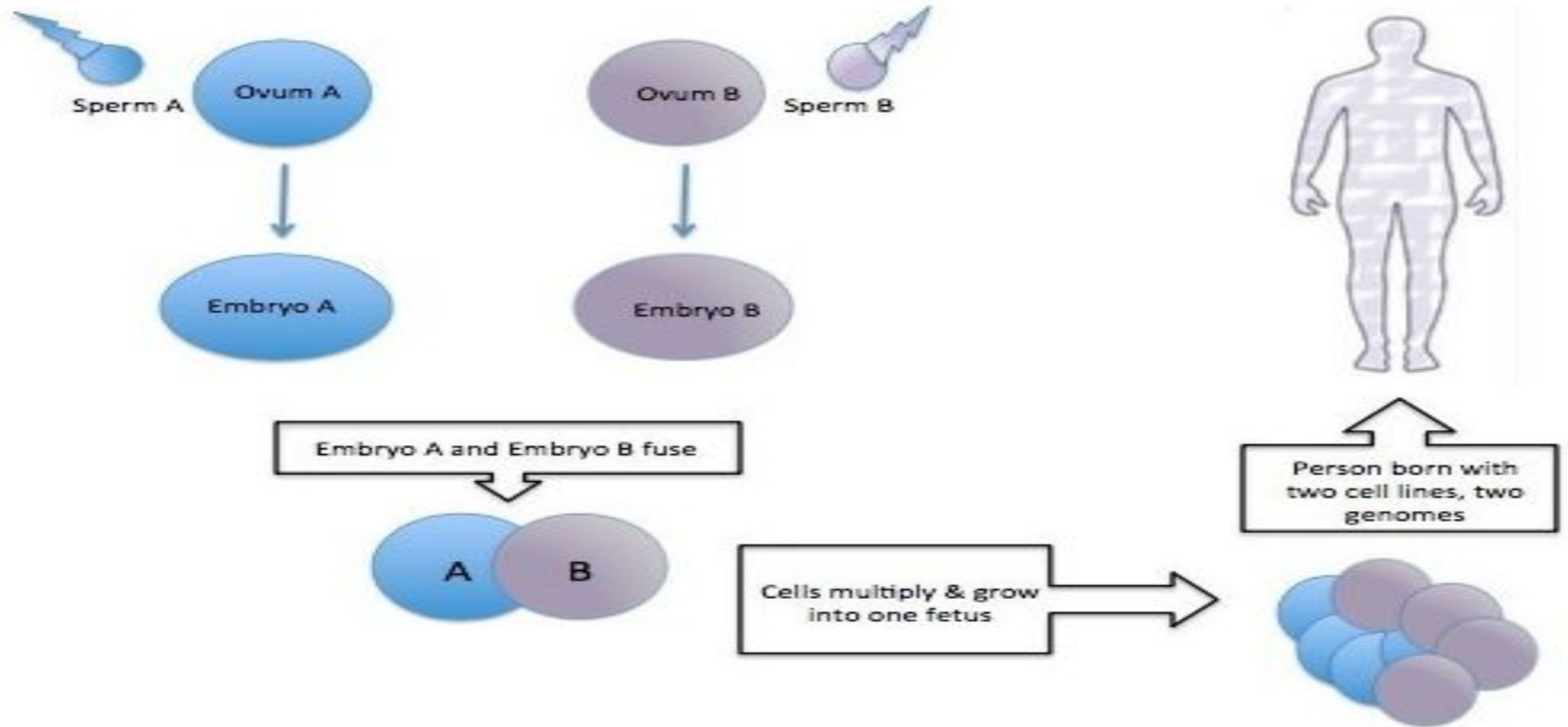
Non-conventional heredity

- Mosaicism / chimerism
- Mitochondrial inheritance
- Parental imprinting
- Uniparental disomy
- Dynamic mutation
- Multifactorial inheritance

Mosaicism: presence of at least 2 different populations of cells from the same zygote



Chimerism is the result of the fusion of two egg cells into a single embryo at an early stage

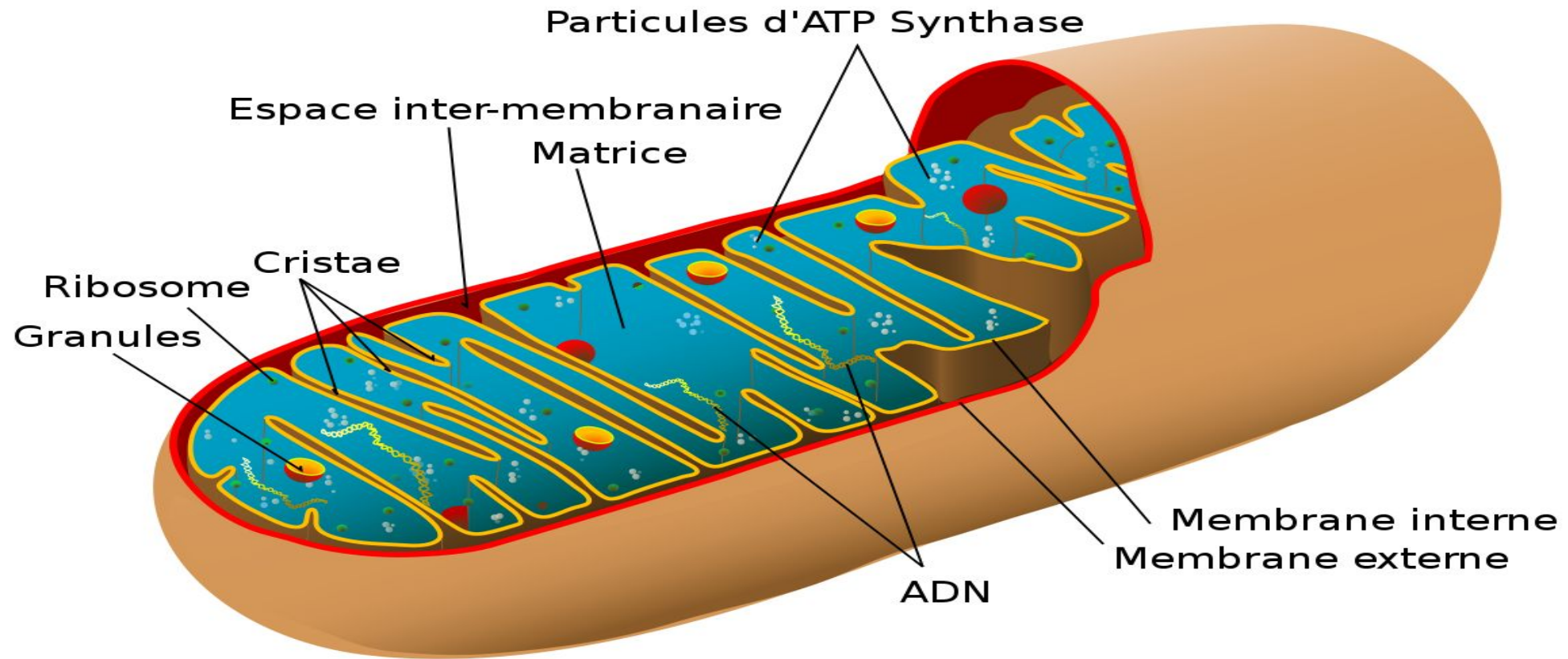


K. Sheets et al, Vibrant Gene Consulting

Sources : [Conclusions de l'étude](#), [IFLscience](#)

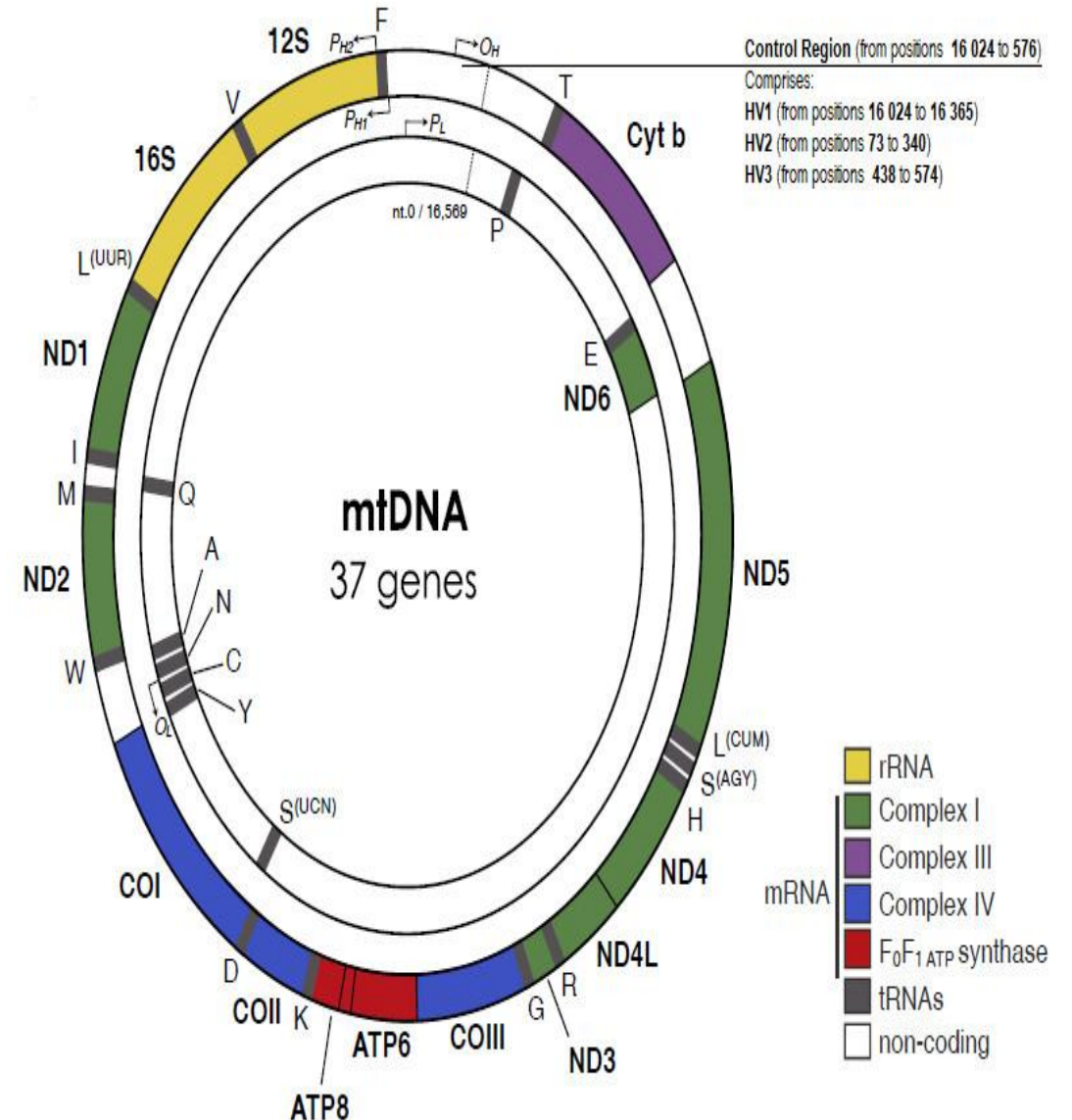
Mitochondrial inheritance

- Mitochondria: energy source organelle with their own DNA.



Mitochondrial inheritance

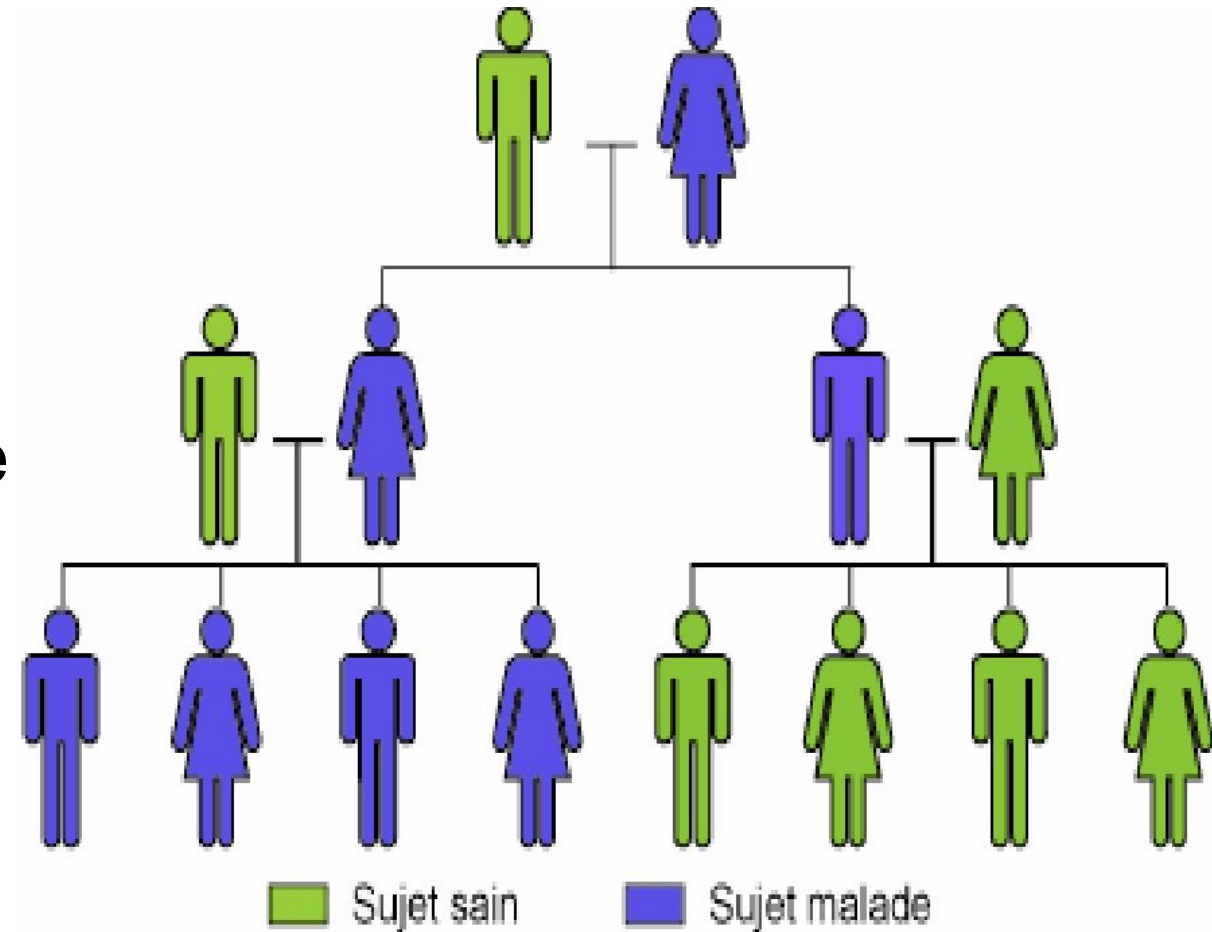
- 16 kb circular DNA,
- 37 genes coding for 13 proteins, ribosomal RNAs, and transfer RNAs.
- With a code different from the universal code:
 - Mito. Univ. UGA Trp STOP AUA
 - Met Ile AGA/AGG STOP Arg
- mutations in these genes are common



Mitochondrial inheritance

Characteristics

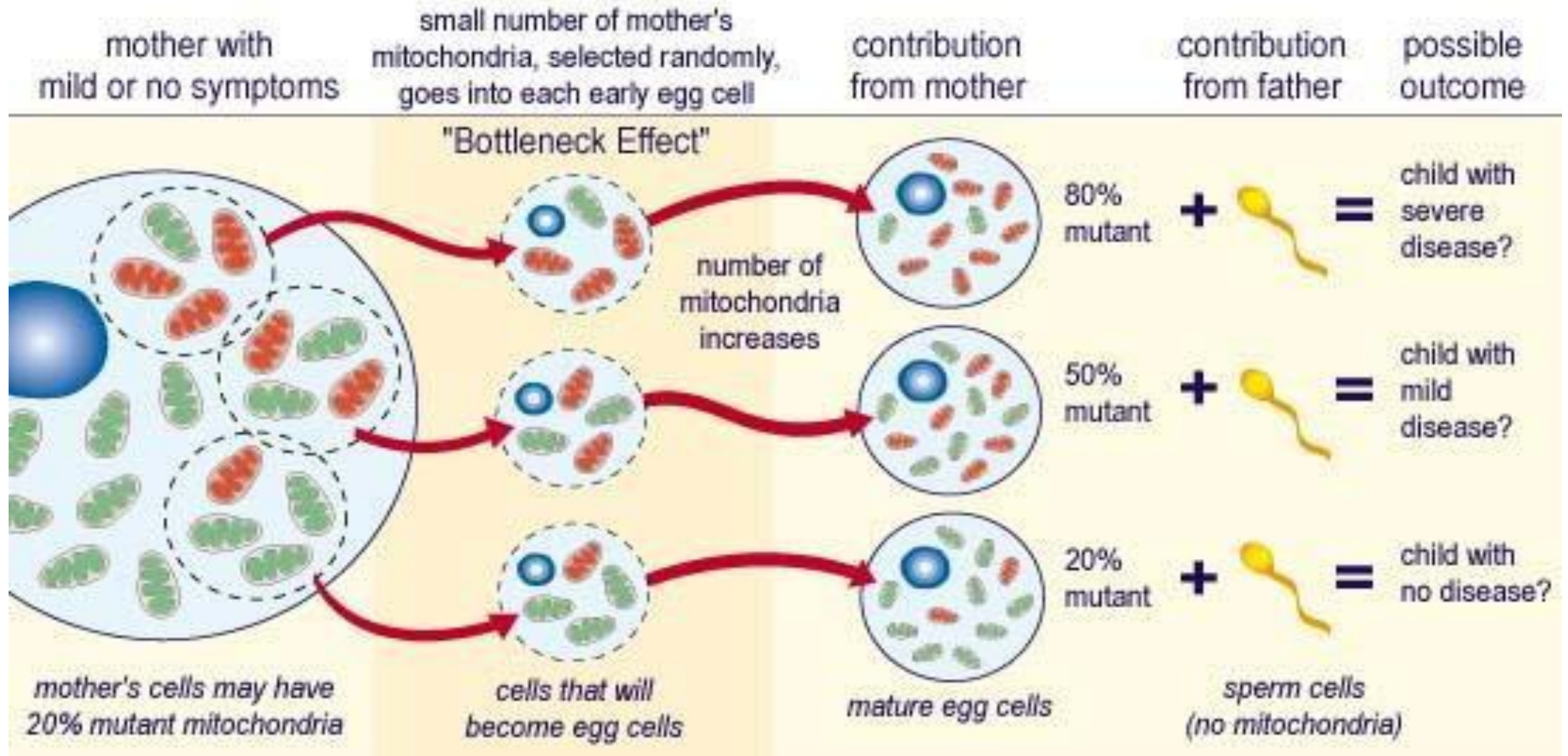
- Male and females inherit the mutation
- Only females pass it on
- Sick men do not pass on the disease to any of their children.



Characteristics

- The disease can have moderate or severe forms.
- People with a severe form only have children with a severe form.
- Those with a moderate form may have children:
 - not affected,
 - with a moderate form or
 - with a severe form.

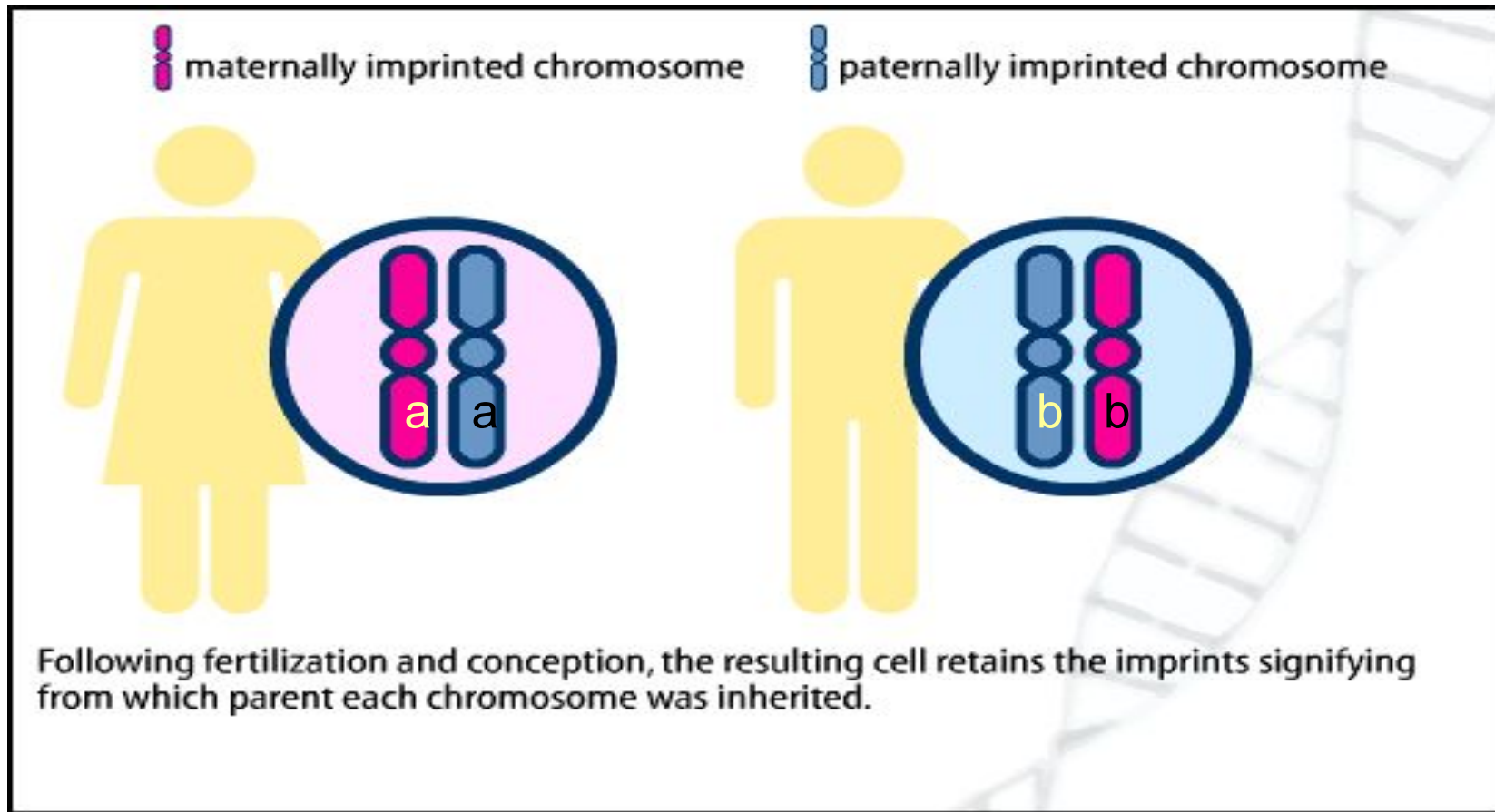
Heteroplasmy



Genetic counselling nightmare!!

Genomic Imprinting

- It is a selective inactivation of a few genes during gametogenesis, so that the diploid genome resulting from fertilisation is functionally haploid for these genes (functional haploidy)
- Genes where either the maternal OR the paternal copy is expressed the other is “silenced” not both
- Maintained largely by methylation
- Clustering of imprinted genes
- Differential expression depending on parental origin of gene
- Mom “on” / dad “off” or vice versa



- So if both copies of an imprinted gene are inherited
i.e one from mom, one from dad
one is “on” one is “off”..... All is well but...

If one copy missing the problem will depend on whether the missing one was meant to be the “on” one or not..

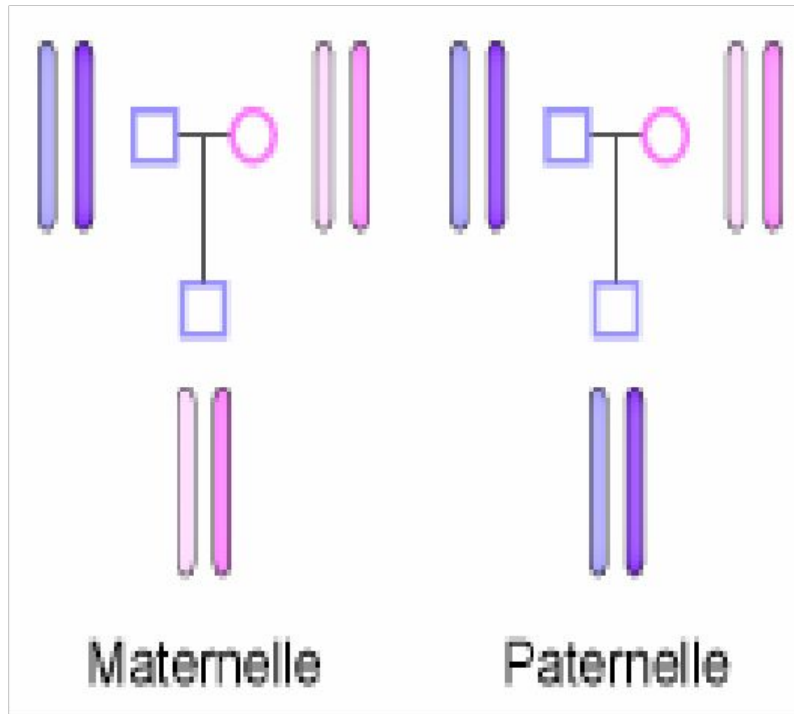
**A occurs in absence
of MATERNALLY
expressed gene**



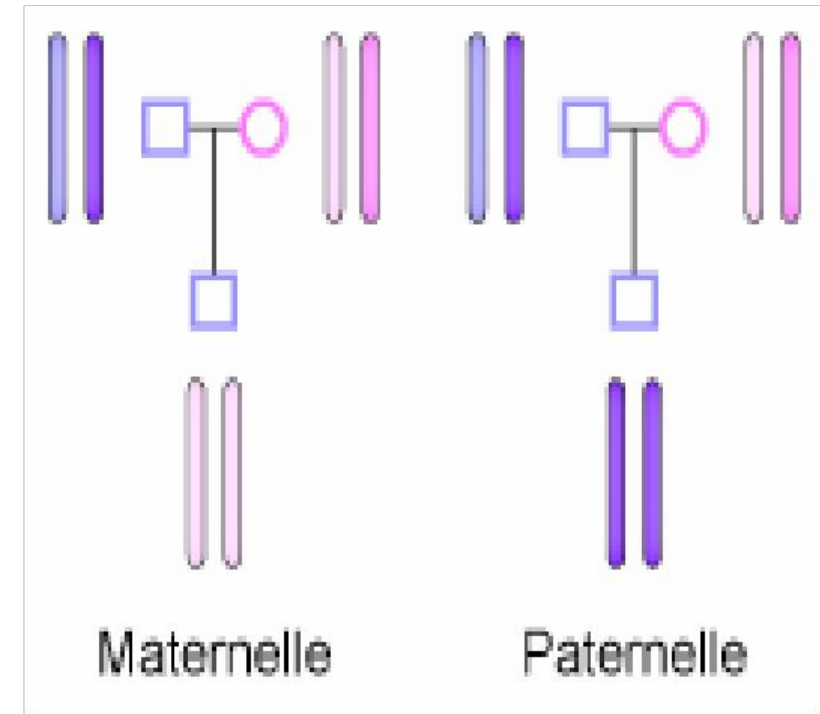
PW occurs in absence of
PATERNALLY expressed
genes

Uniparental disomy

Both copies of a chromosome pair same parental origin



Hétérodisomie parentale



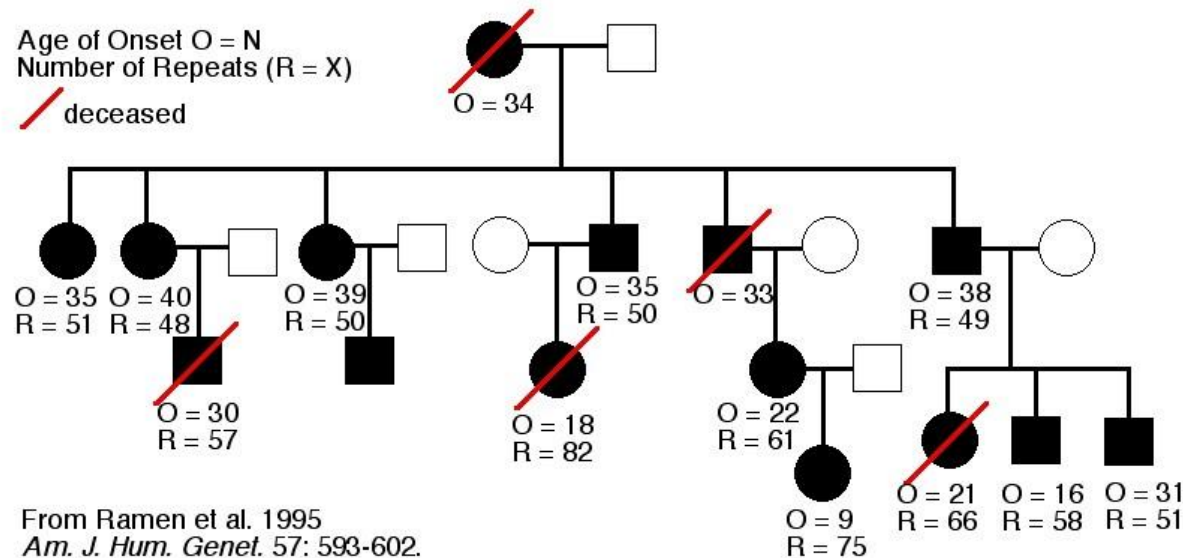
Isodisomie parentale

Dynamic Mutation Disorders

DNA sequence repeats Usually triplets

Unstable beyond threshold

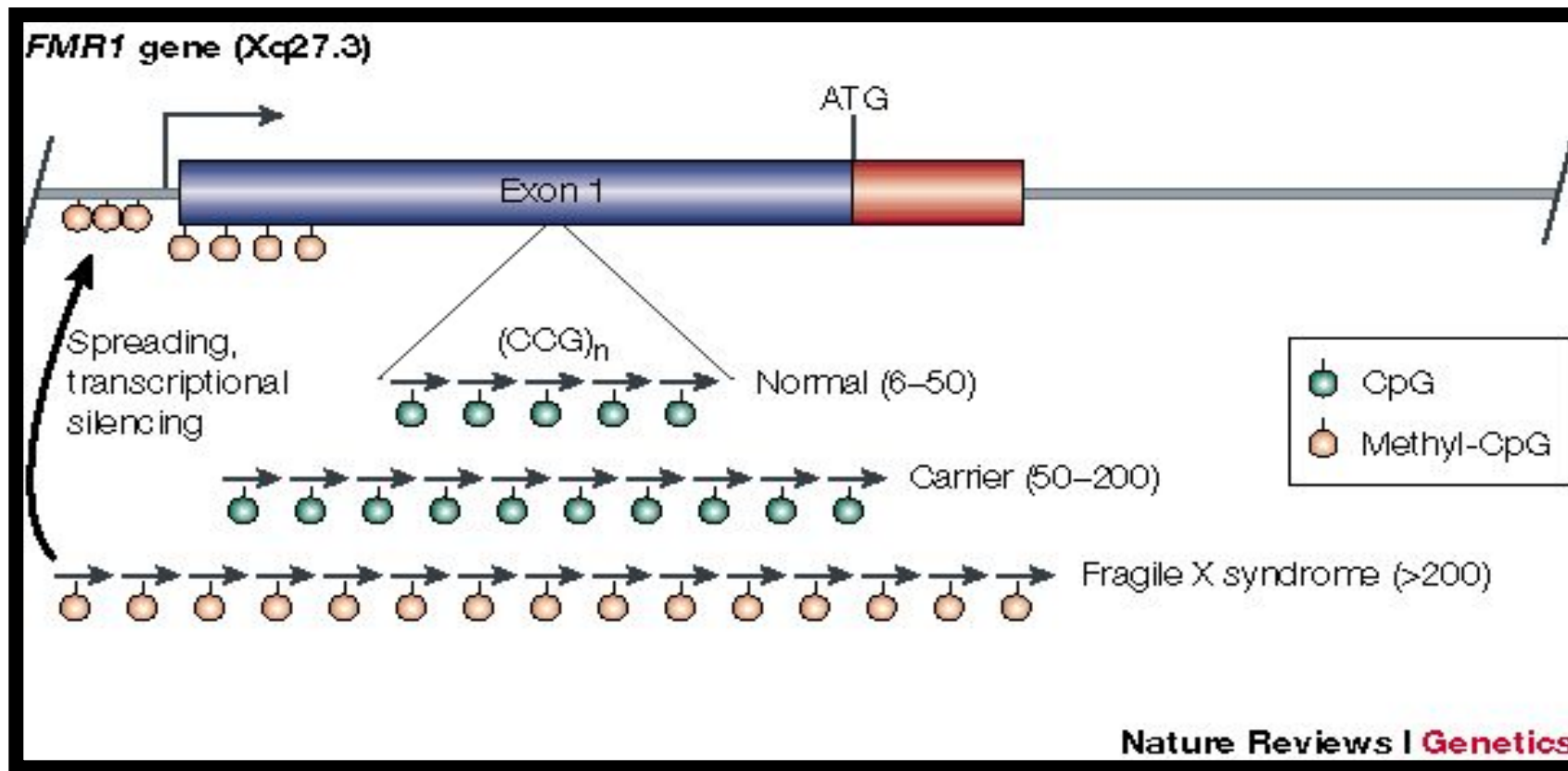
Anticipation



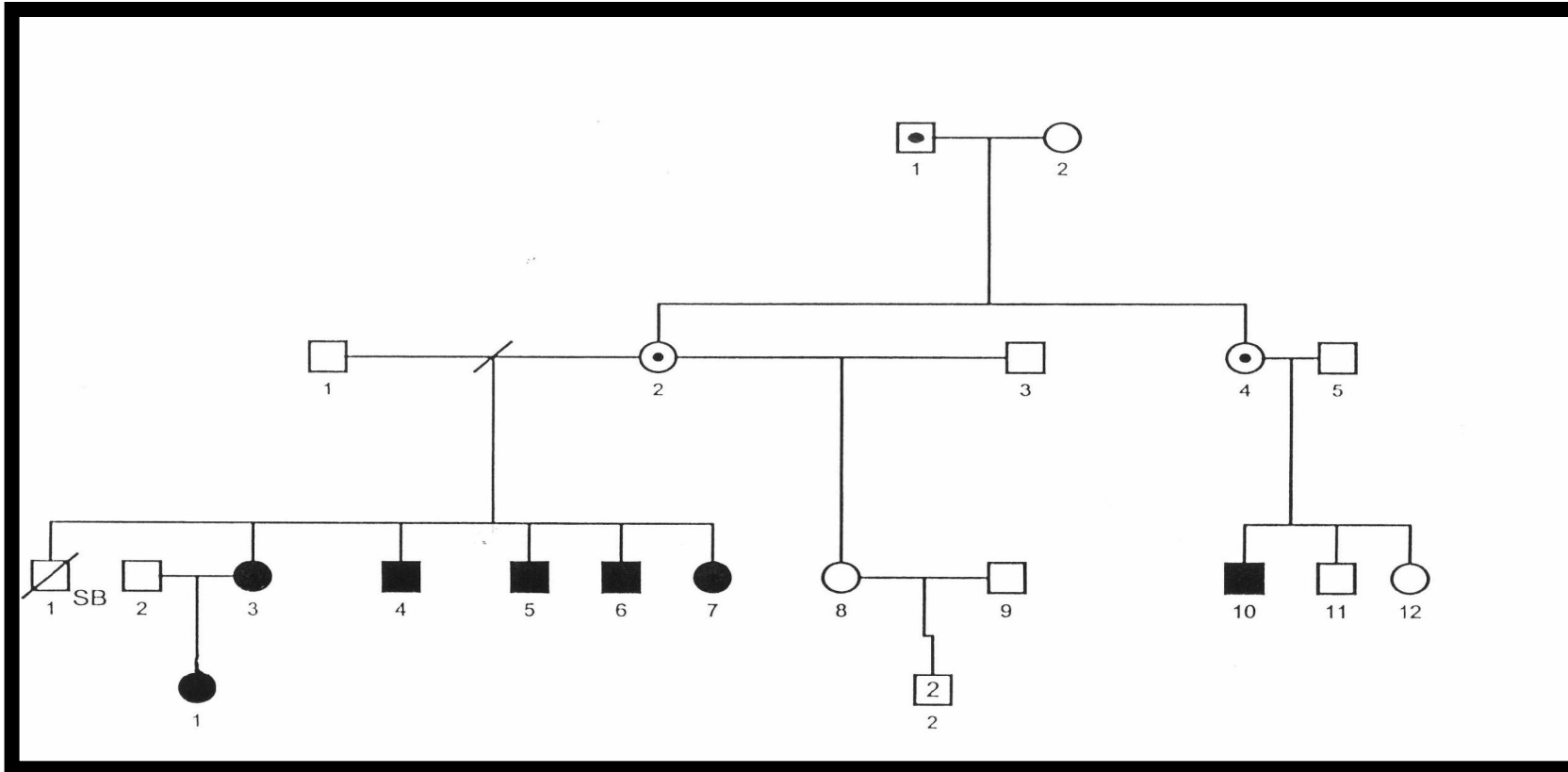
Parent of origin effects on instability and tendency for expansion

Ex: Fragile X syndrome

- Premutation 50 – 200
 - Gain of function phenotypes
- Full mutation (> 200 repeats)
 - Methylation with loss of function



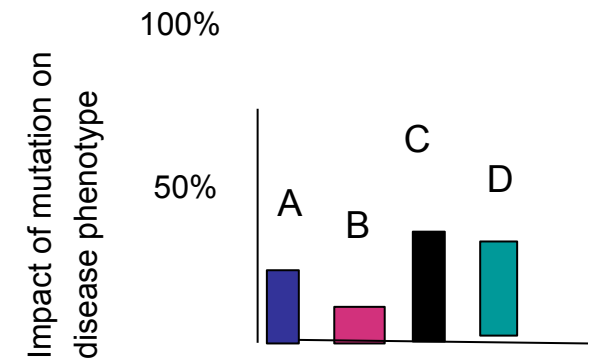
- Premutation stable during paternal transmission
- Expansion during maternal transmission



X linked “semi dominant / ”Atypical” X linked inheritance

Complex /Multifactorial Inheritance

- Interactions of both genetic and environmental factors
- Many genes Incomplete penetrance
- Recurrence risk:
 - Can't be calculated by “rules”
 - Lower than with Mendelian conditions (usually 3-10% range)
- Increases with:
 - Number of affected family members
 - Frequency of condition in the population



The 'risk' of any given genetic variant is small and can be modified by the environment often common variants