# Different modes of inheritance

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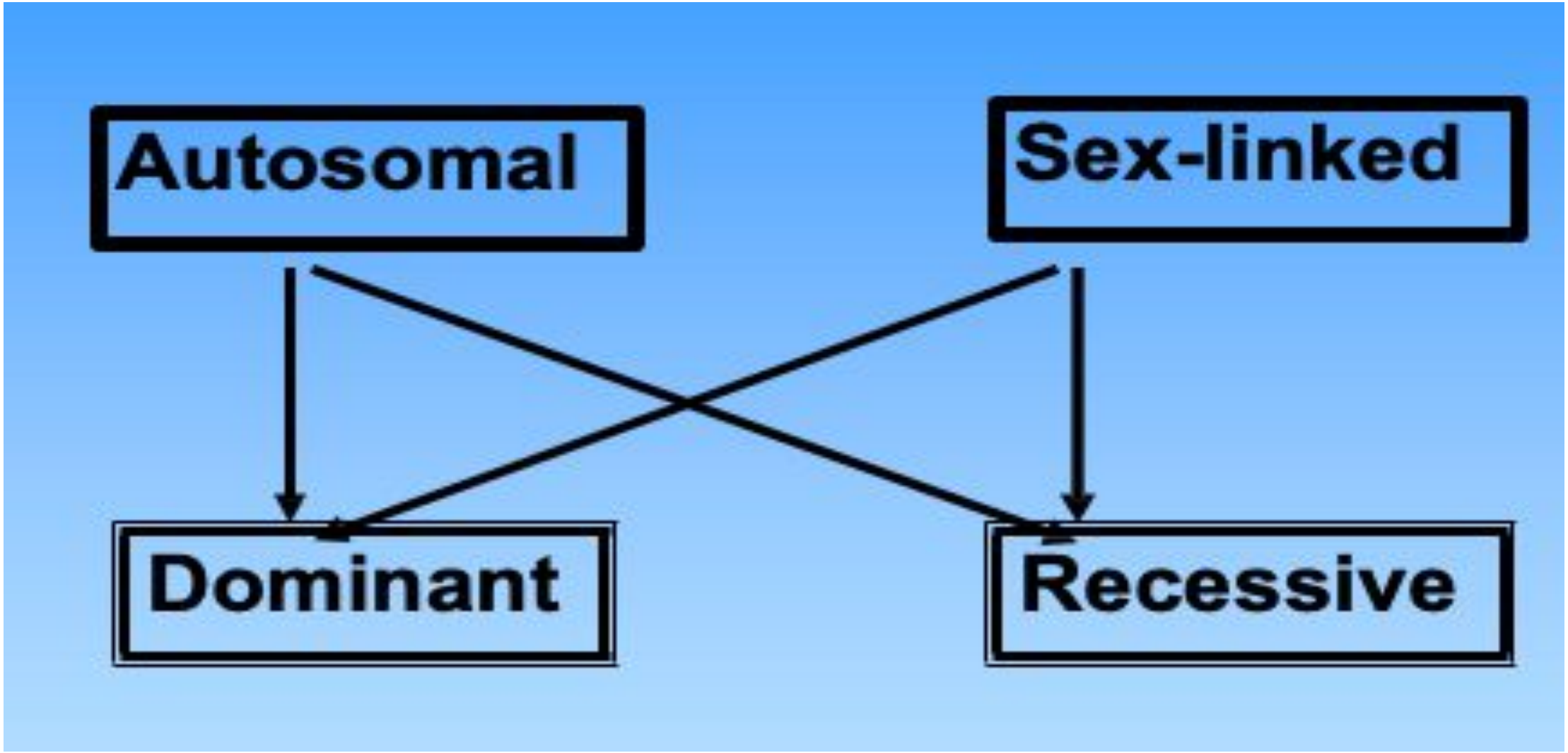
# Objectives

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

# Mendelian inheritance /Monogenic /monofactorial



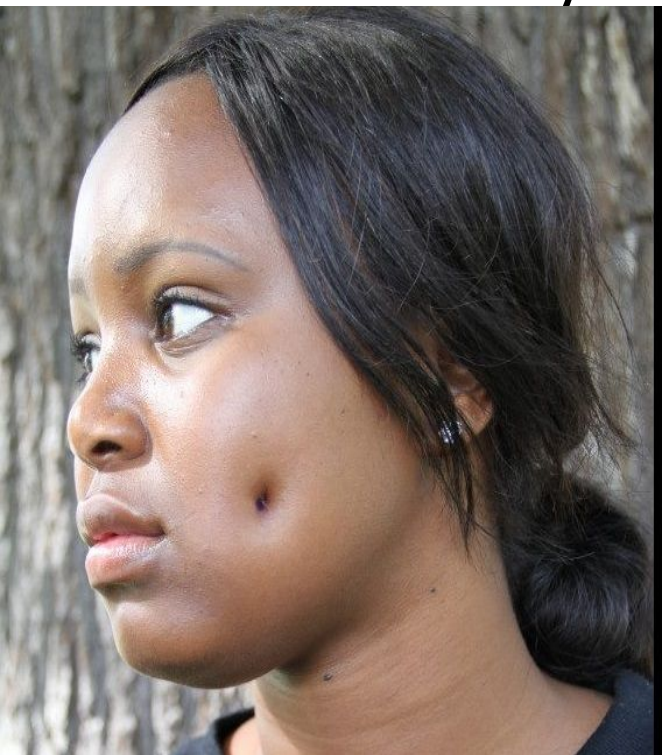
# Autosomal dominant  inheritance

- Phenotypic trait determined by a dominant allele:

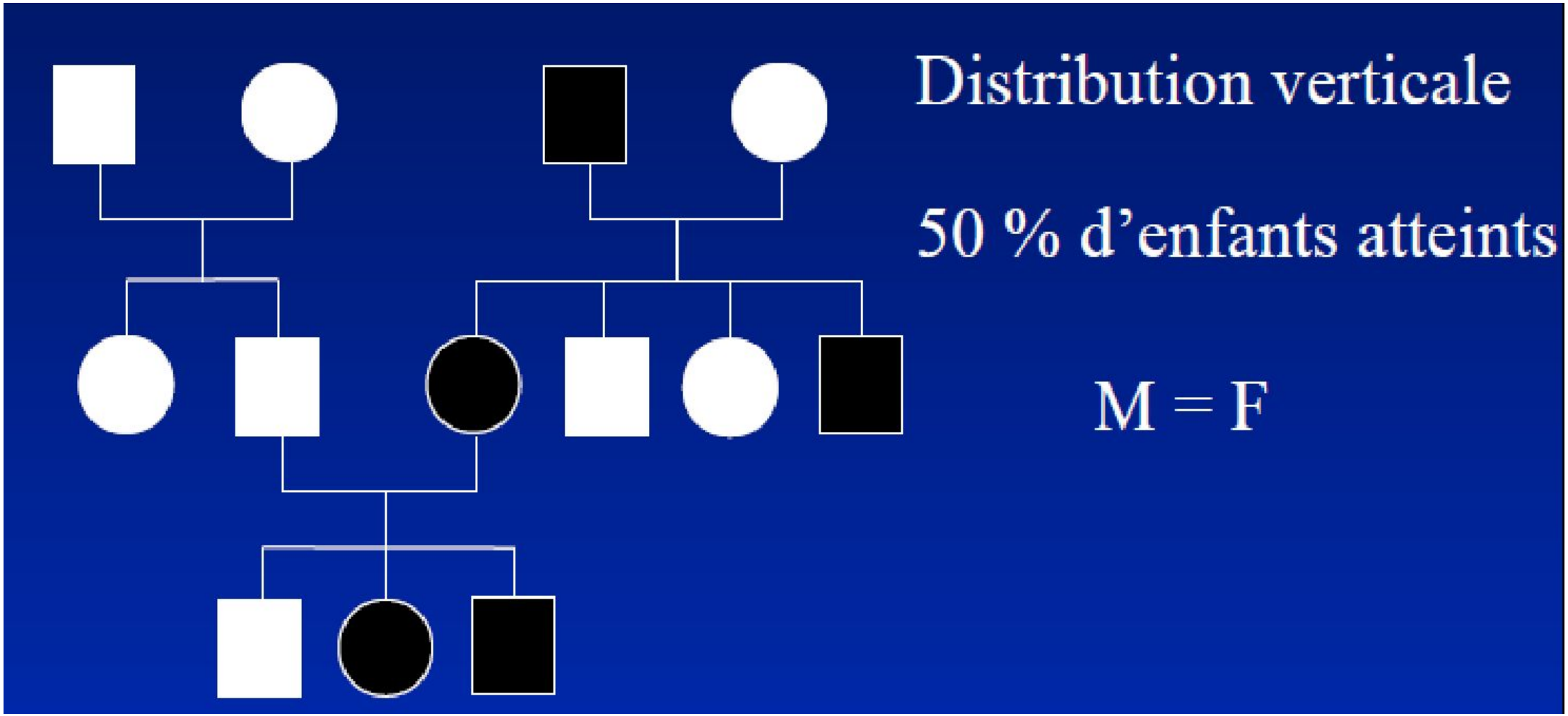
1- Freckles

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

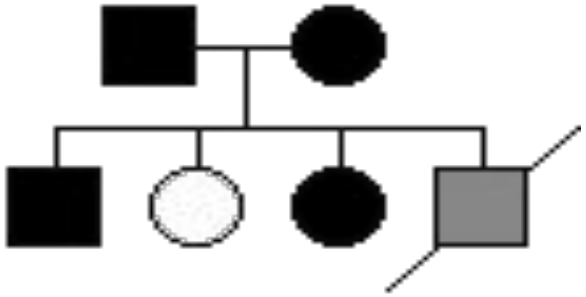
**Ectrodactyly**

***Variable expression:*** **the manifestation of the disorder varies**

**Tibial aplasia / ectrodactyly**

# Are 2 dominant mutations worse than 1?

**Usually yes…**

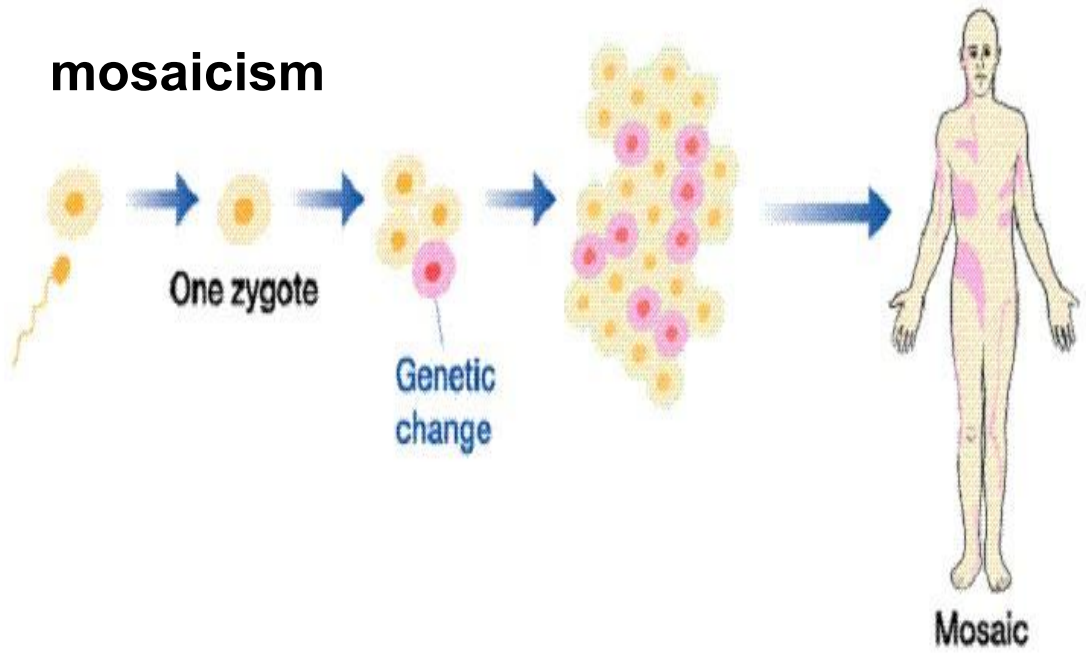


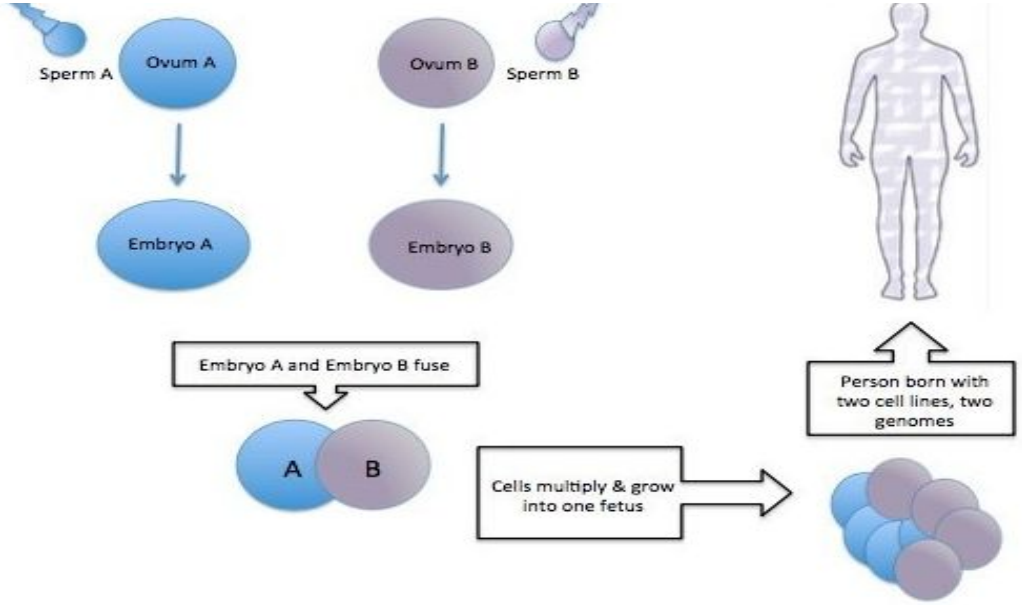
**Achondroplasia**

**Huntington Disease**

# Are 2 dominant mutations worse than 1?

- But sometimes no…
  - New dominant mutations (parents not affected)



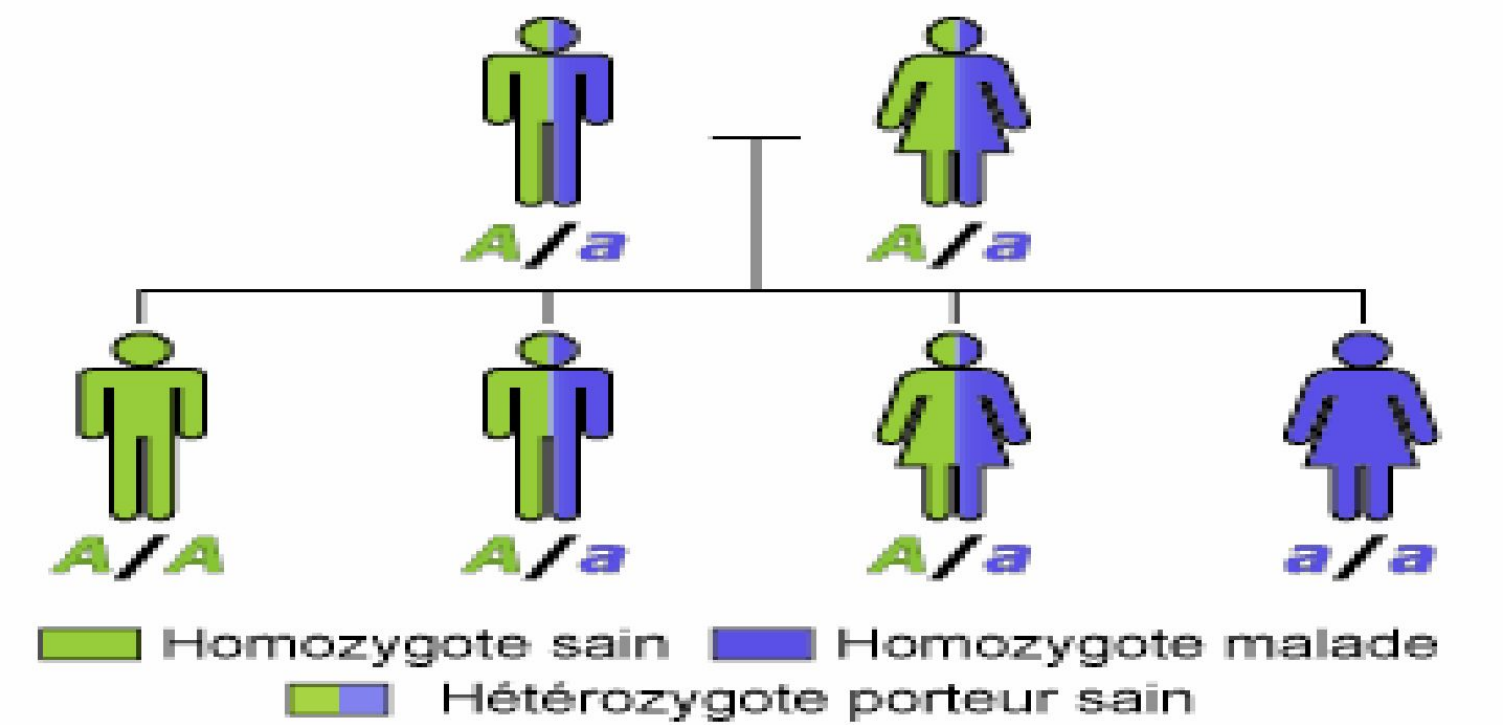




***chimera***

K. Sheets et al, Vibrant Gene Consulting

rces : Conclusions de l'étude, IFLscience

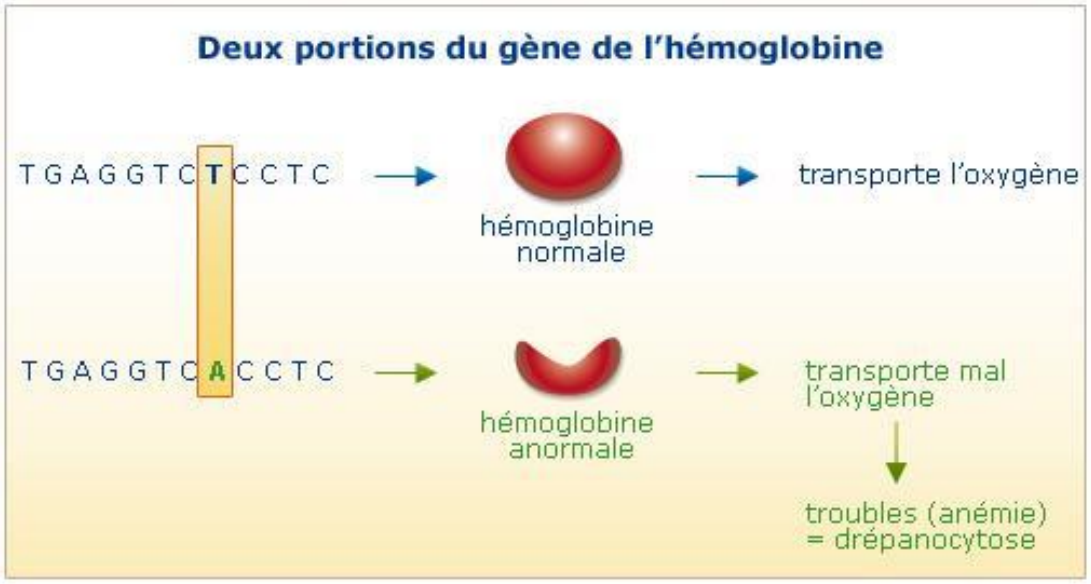
# Autosomal recessive inheritance




- Parents unaffected carrier 25% risk for child to be a/a

50% probability to be A/s ; 25% probability to be A/A

# Sickle cell disease




# mucoviscidose



Génotype [mm]

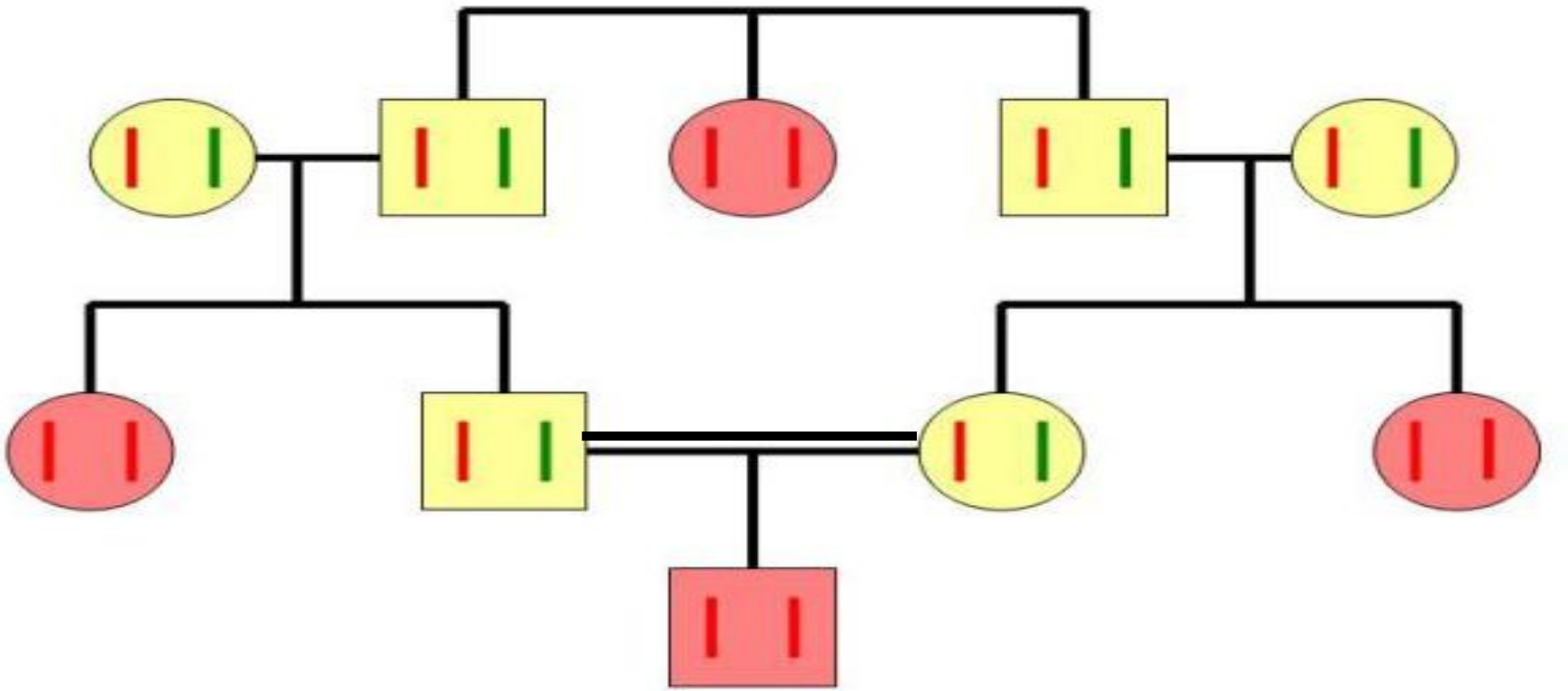
Une espérance
de vie désormais
**supérieure**
**à 40 ans**
et qui devrait
encore progresser

# 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

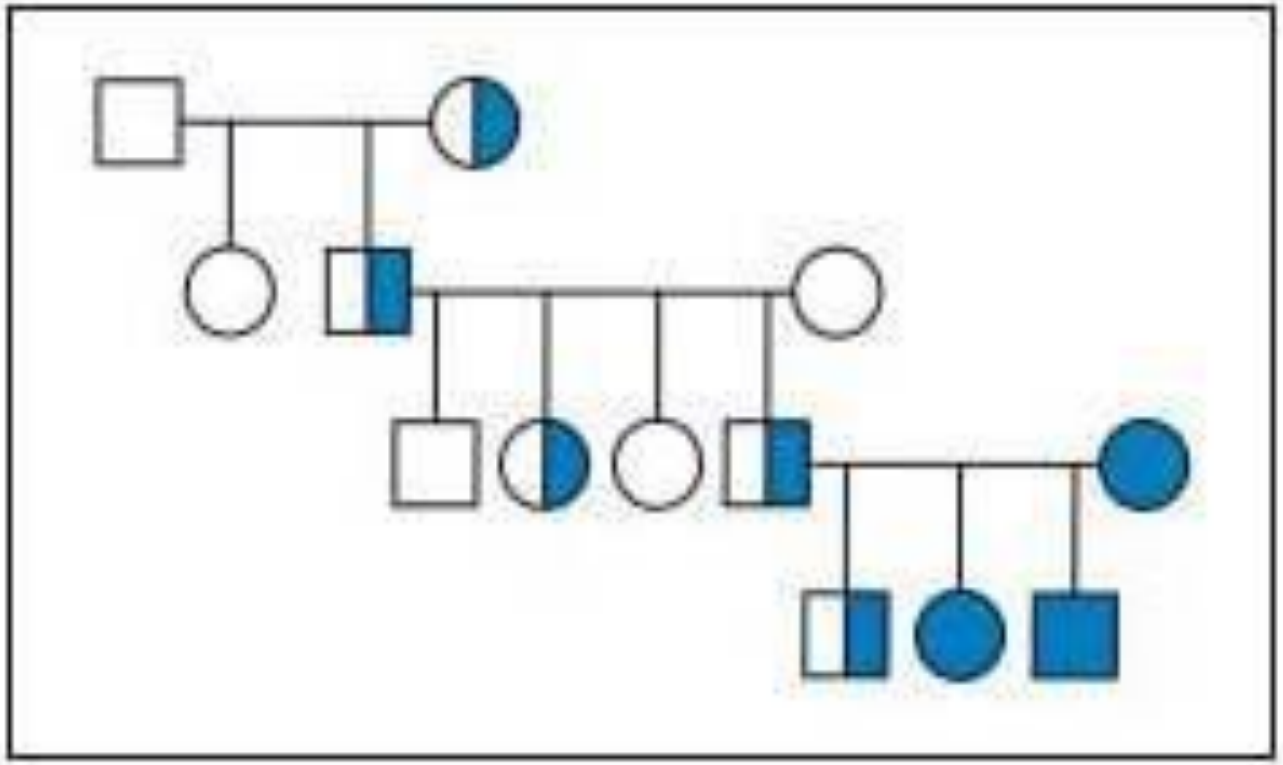
## 2) Genetic heterogeneity

**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 recesssive “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

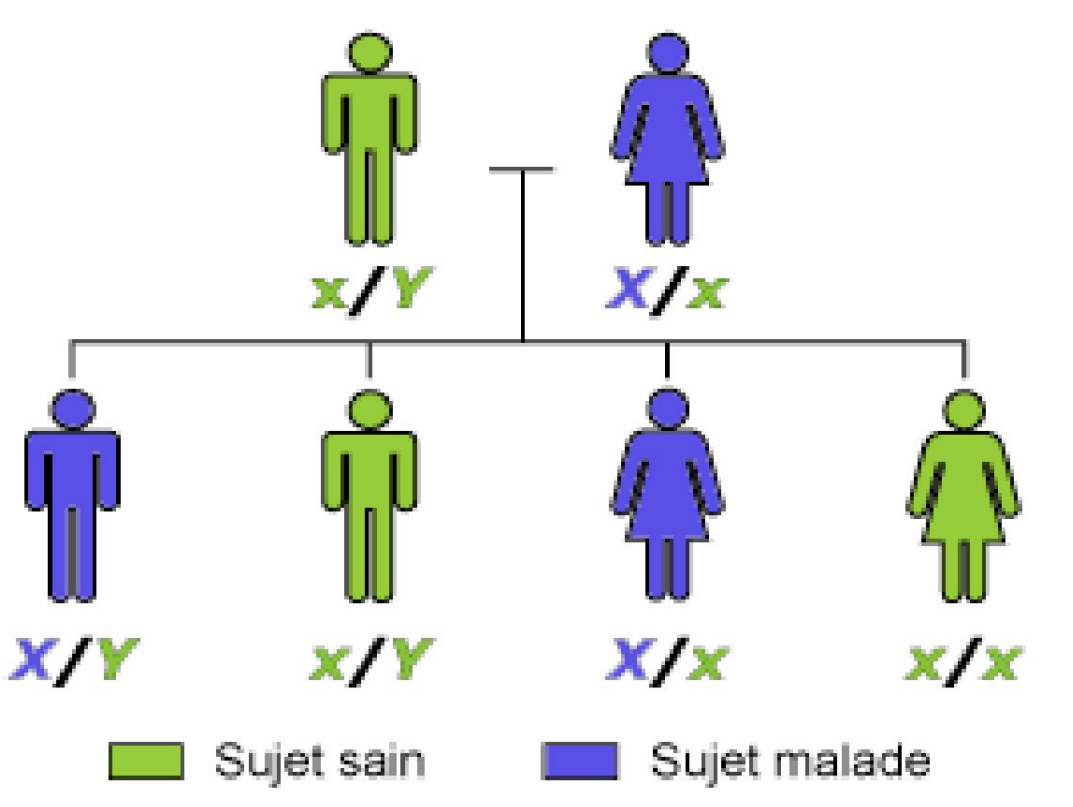
## X-linked heredity

- 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.**

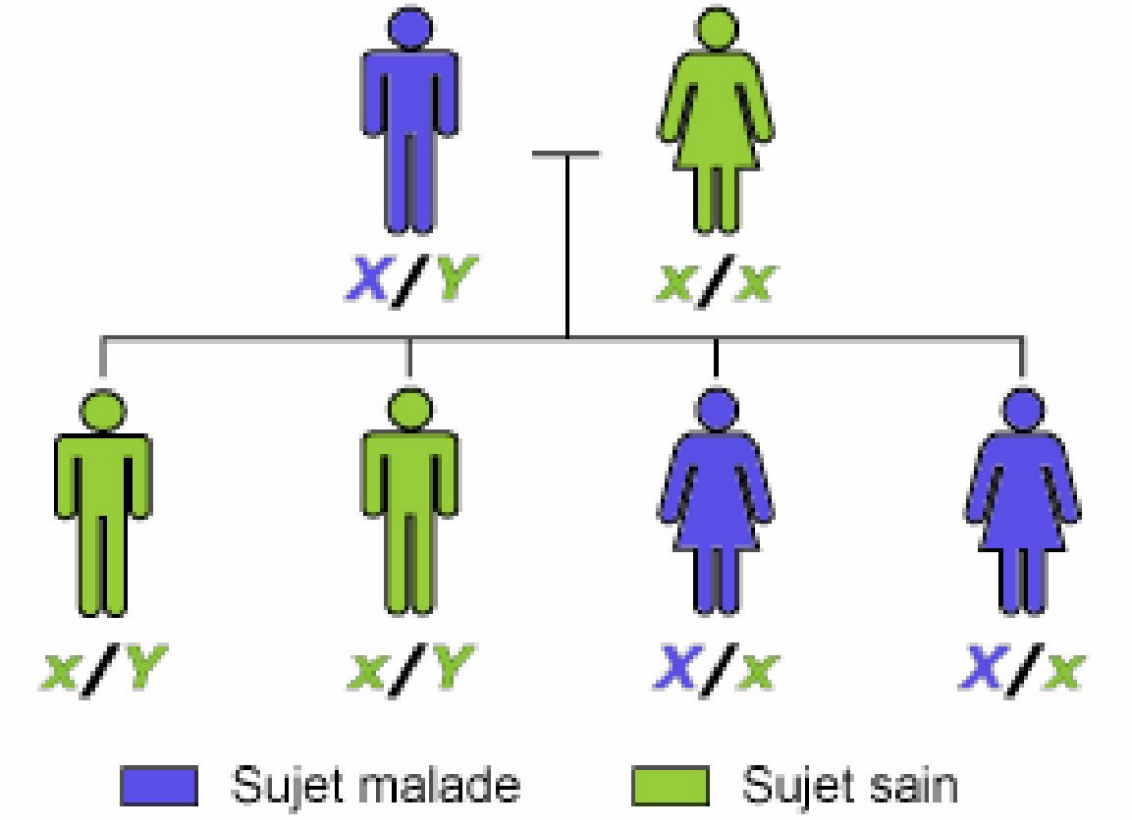
# X linked - Dominant

**Case of a sick mother and a healthy father**



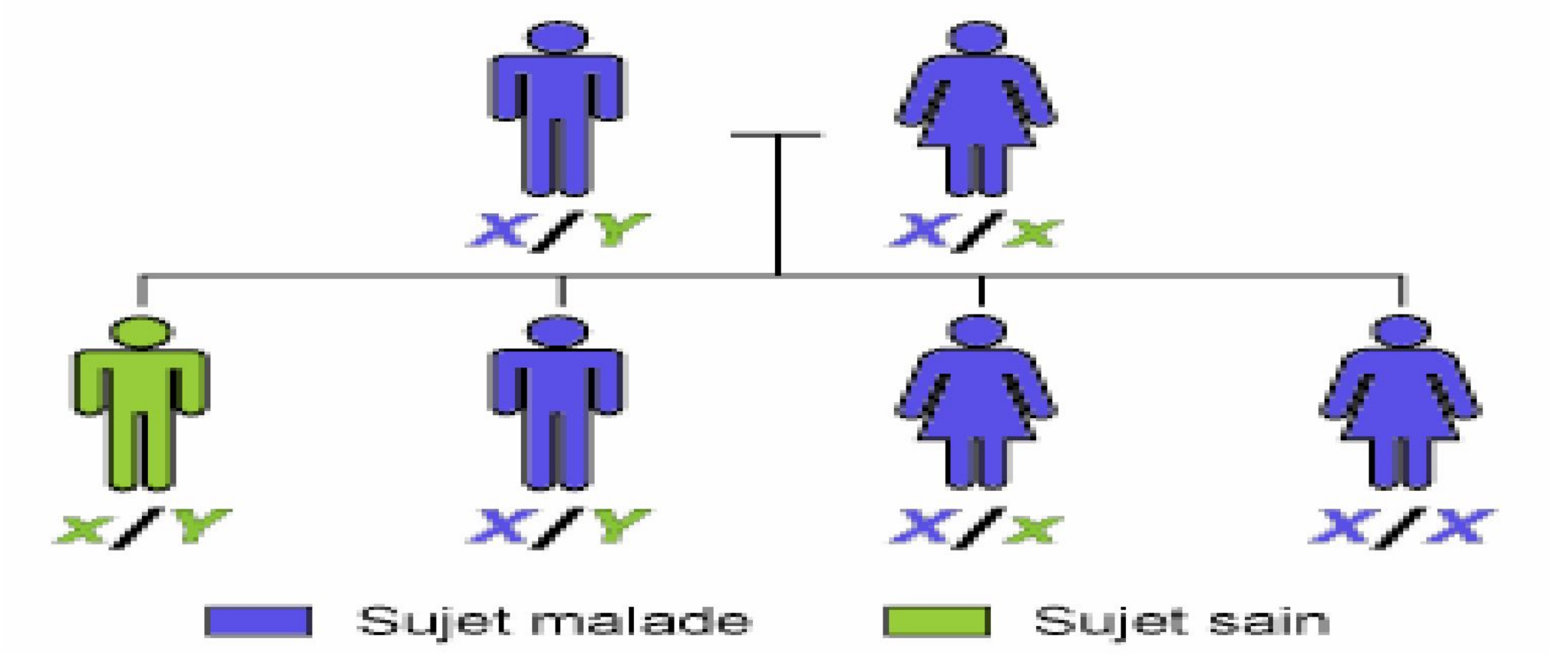

Risk for offspring :
- that a boy will be ill is 50%.
- that a girl will be ill is 50%.

**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 :

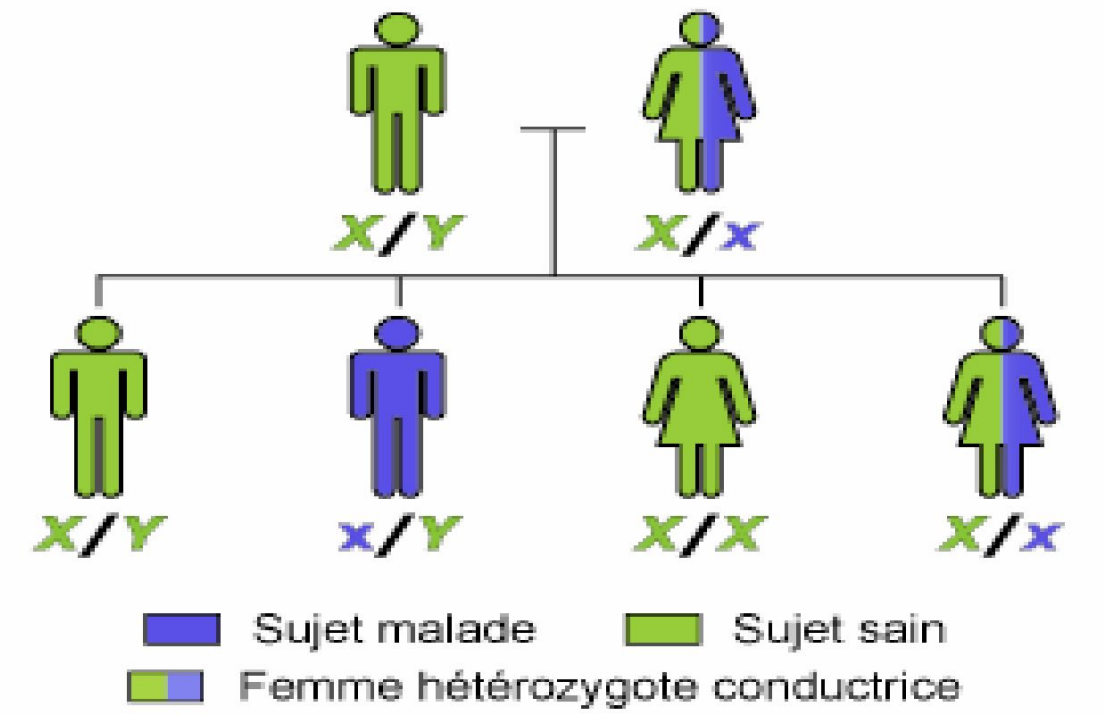
- that a boy will be ill is 50%.

- that a girl will be ill is 100%.

# X linked - recessive

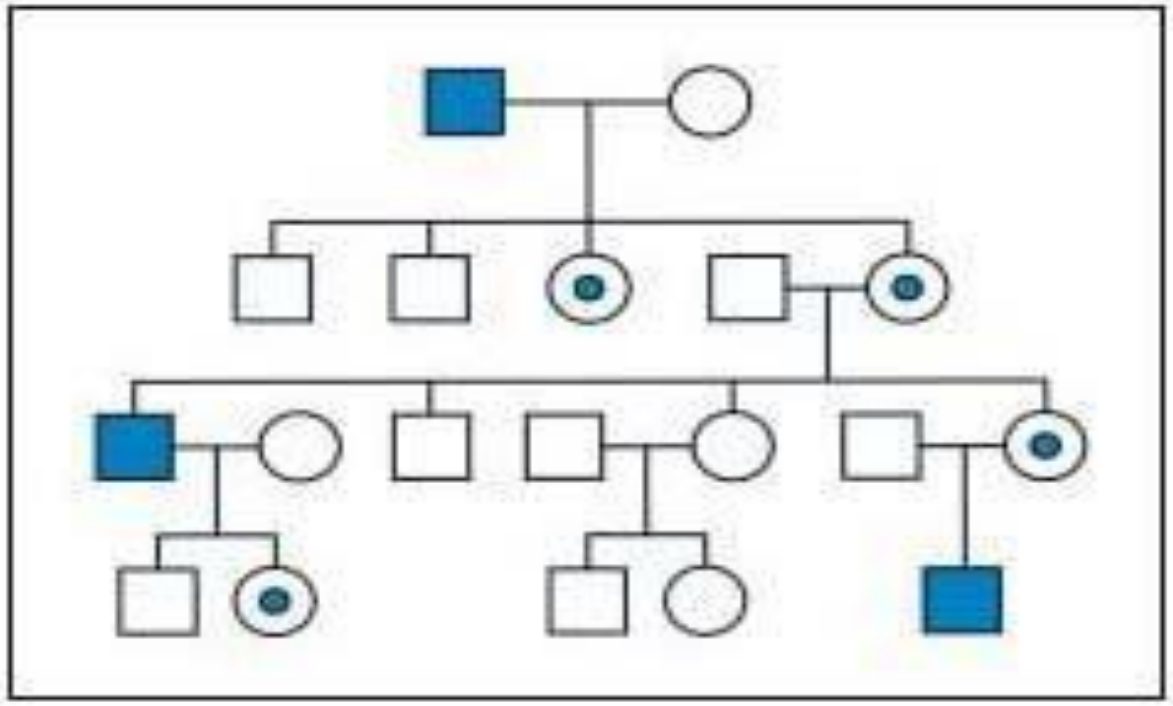
- Only boys are affected.
- There are no affected individuals in the paternal line and father-son transmission is never observed.

## Maternal transmission



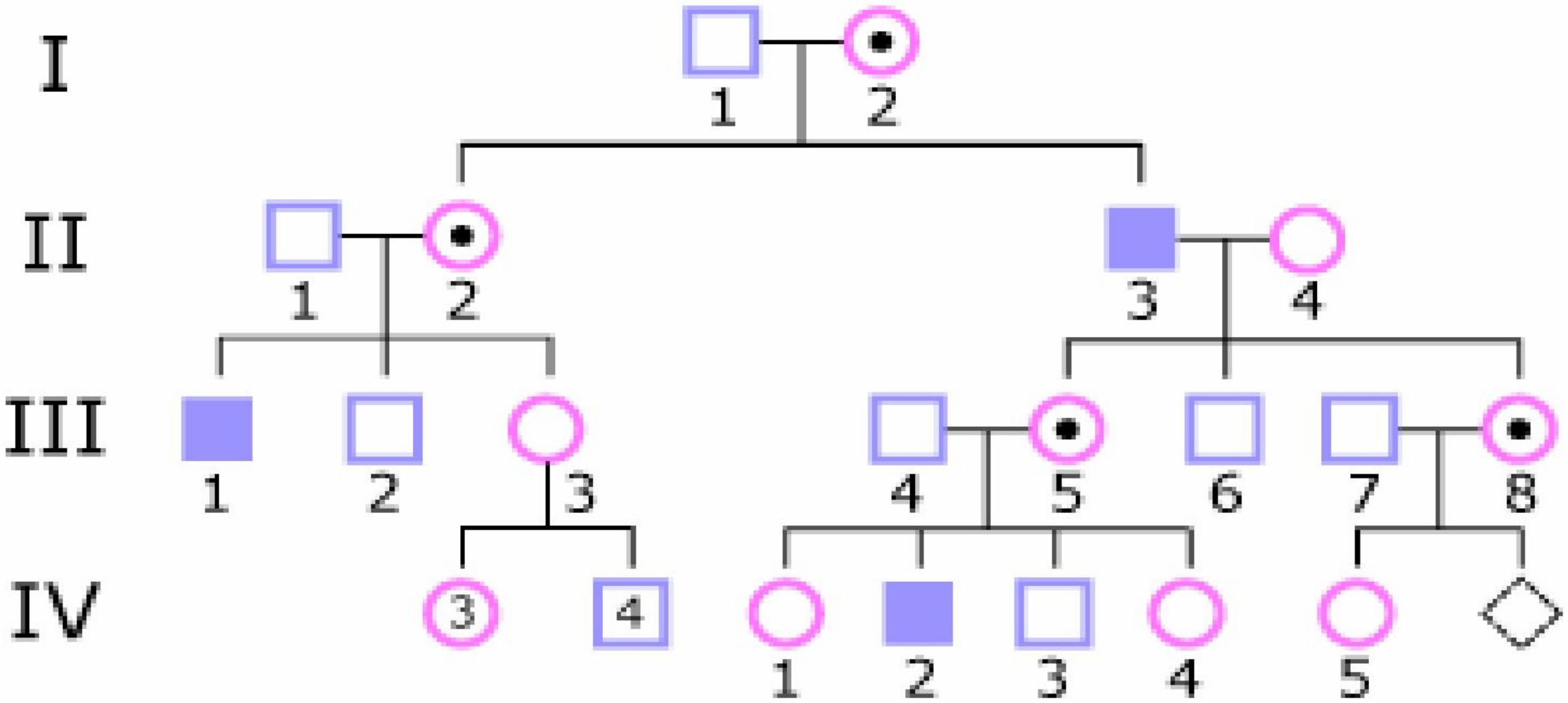

The risk for a boy to be sick is 50%.
- For  a girl to be a carrier is 50%.

## Paternal transmission

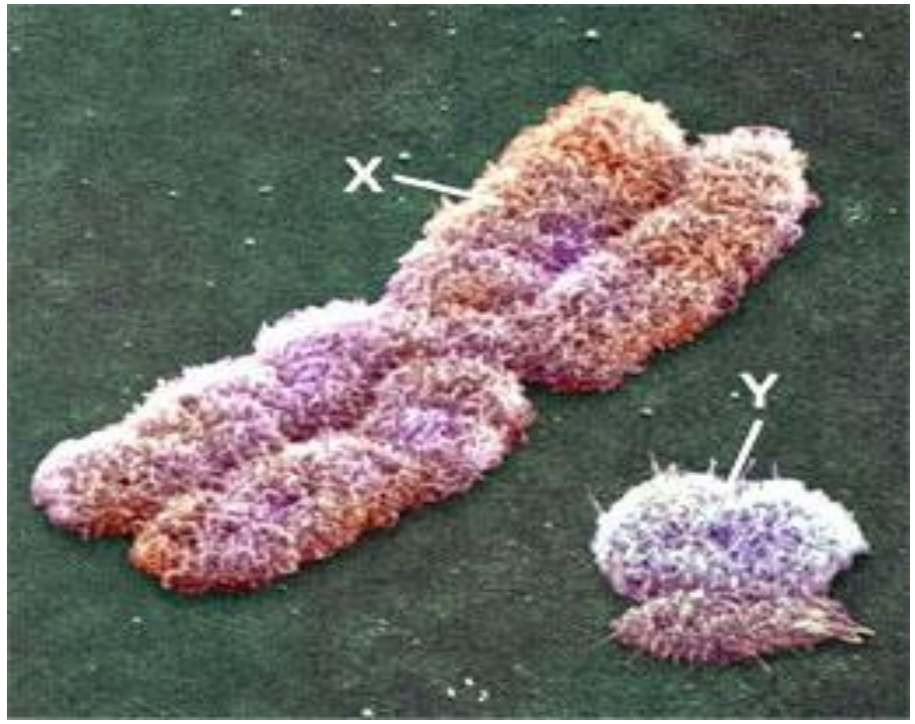


**All daughters carriers**
**All sons normal**

# Haemophilia



# Y – linked transmission?

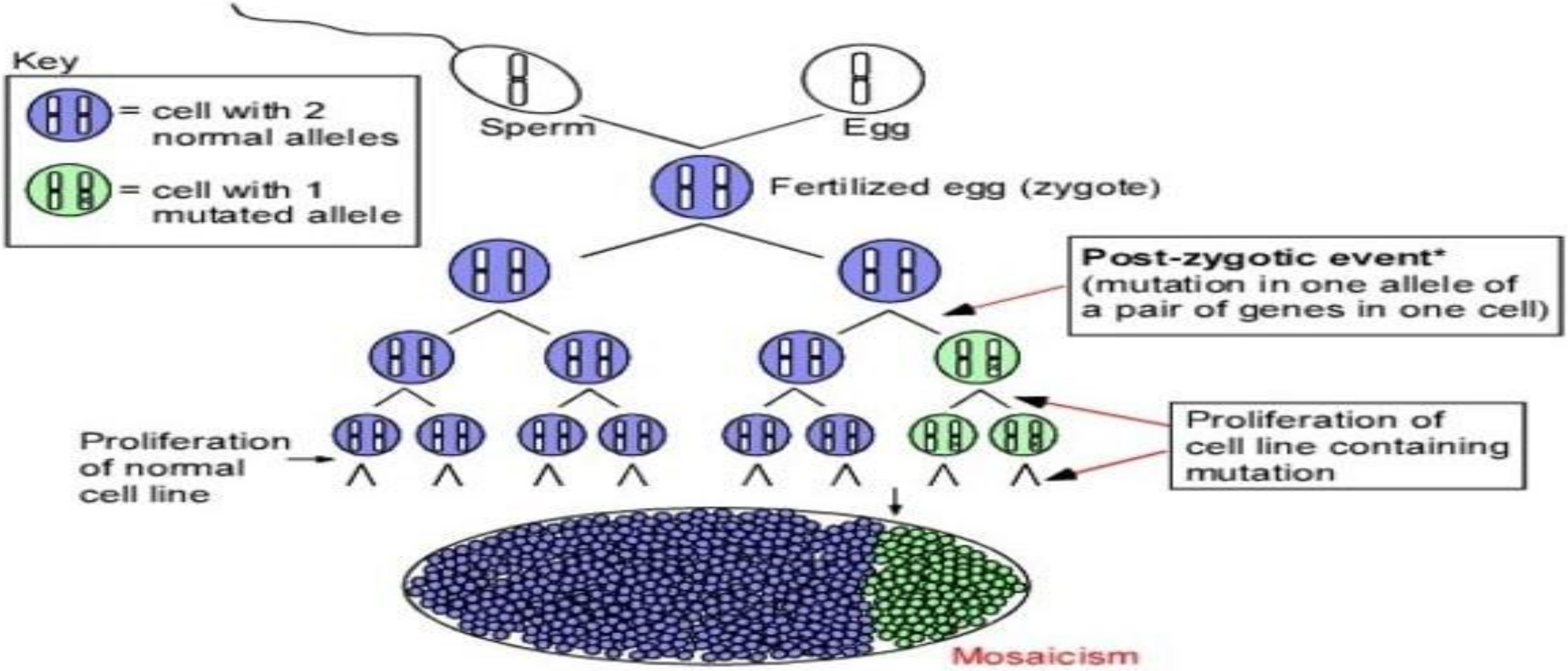



Gene poor
Infertility and ICSI…
Transmit to all sons but not to daughters

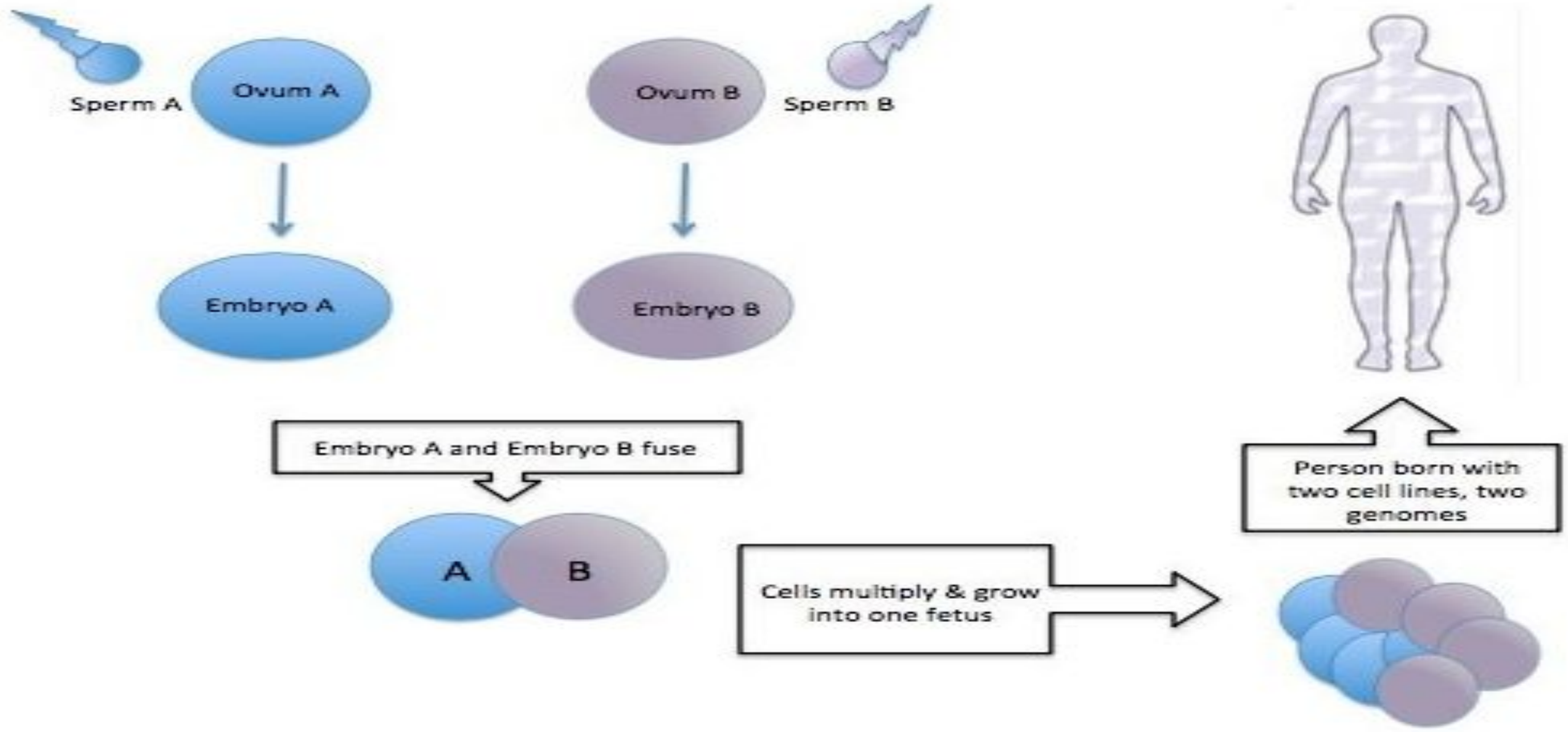
# Non-conventional heredity

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

Mosaisim: 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

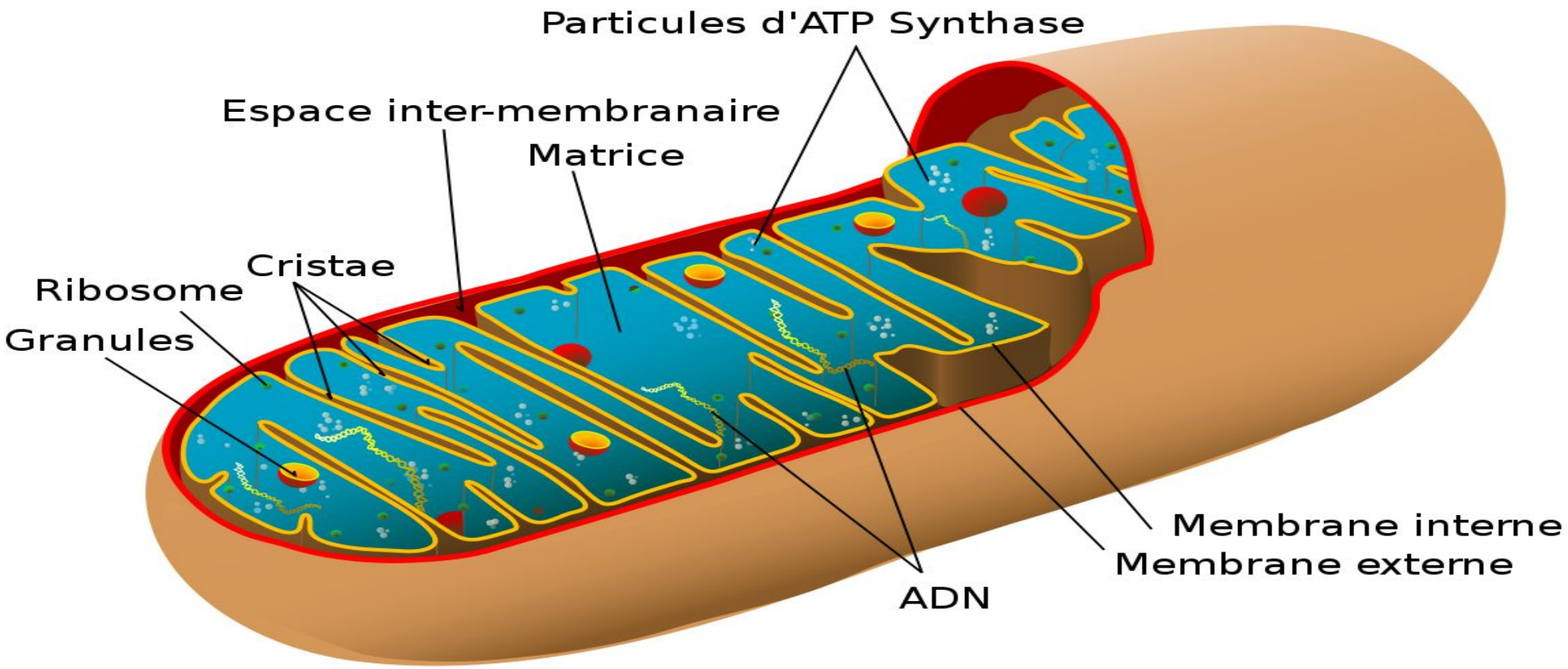



K. Sheets et al, Vibrant Gene Consulting

Sources : Conclusions de l'étude, IFLscience

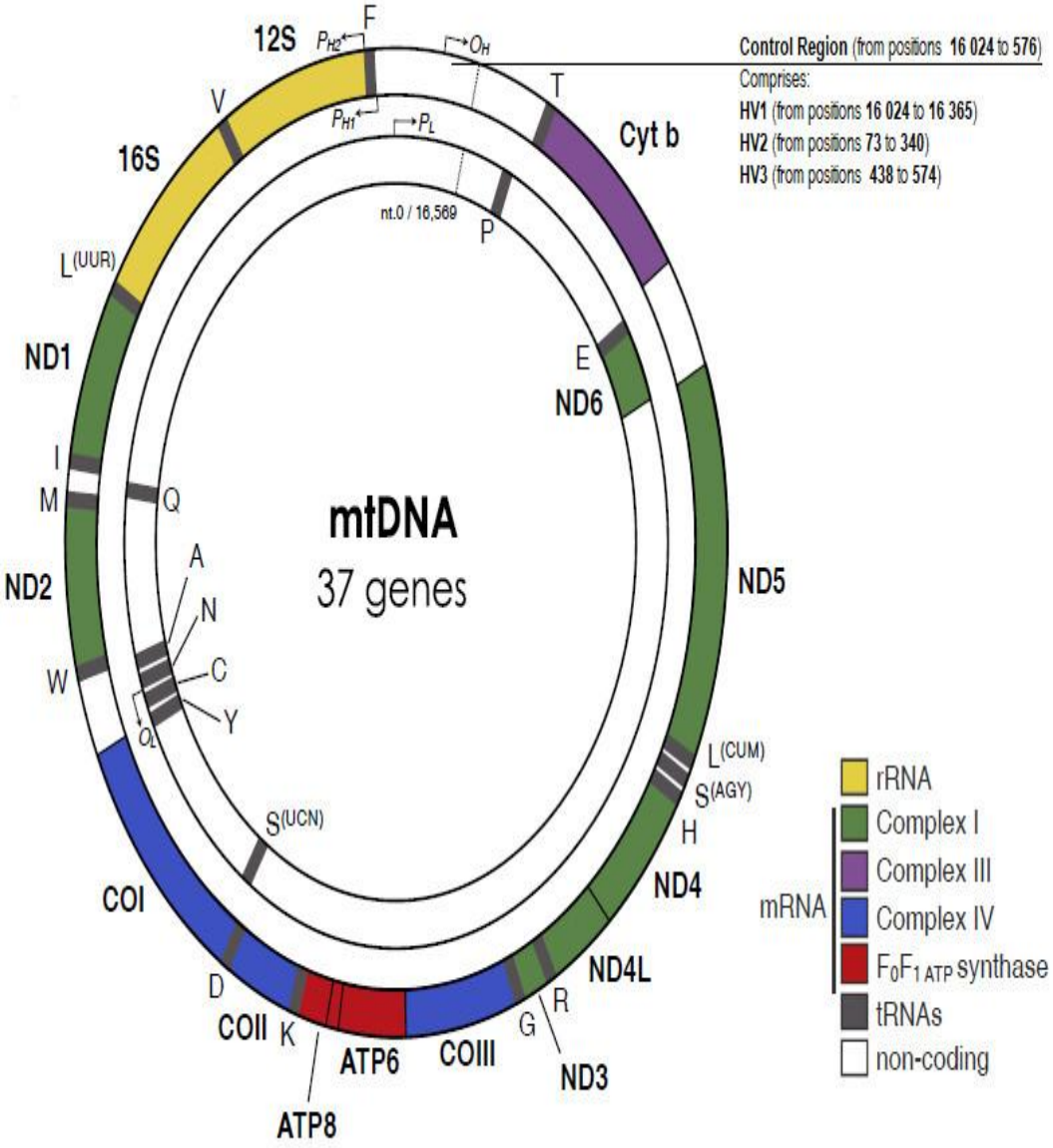
# Mitochondrial inheritance

- Mitochondria: energy source organelle with their own DNA.



# Mitochondrial inheritance

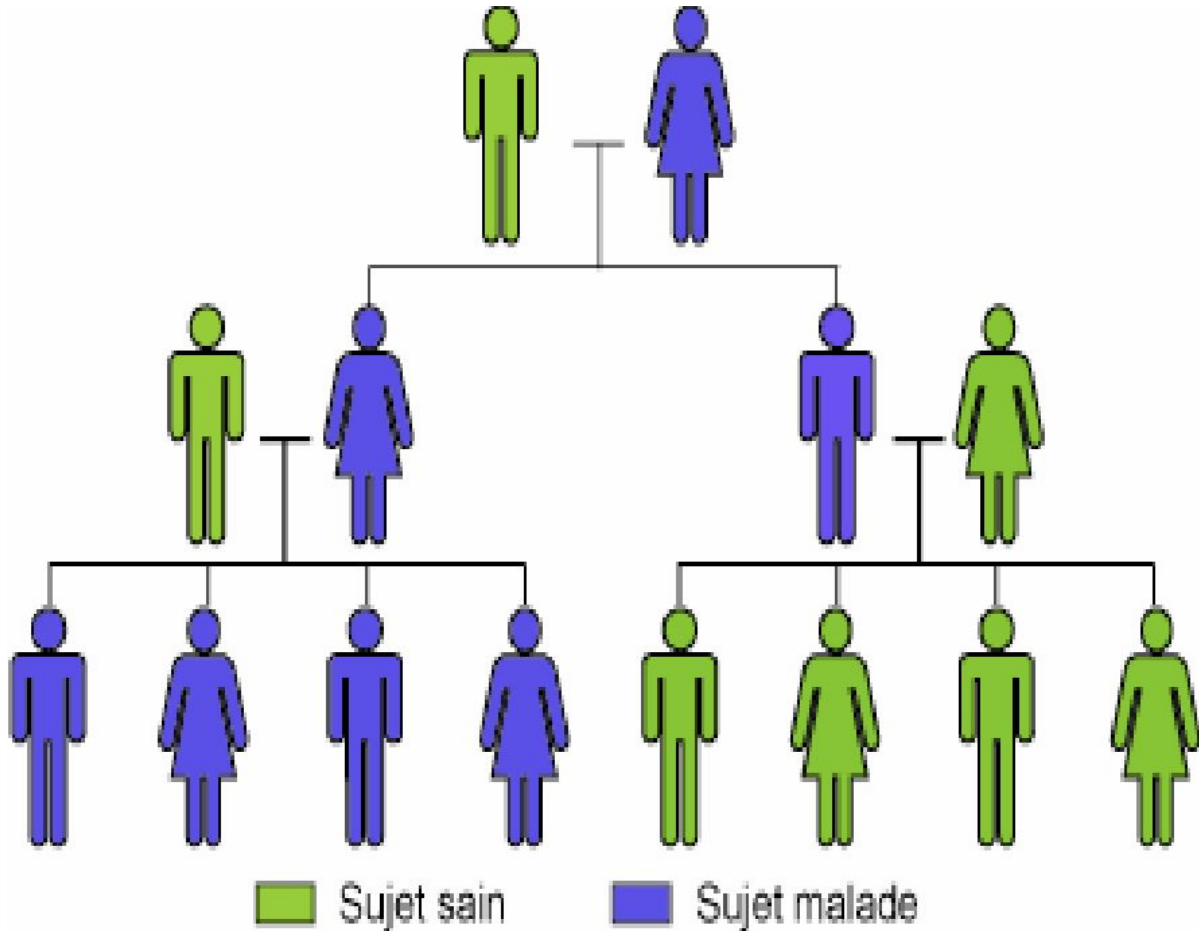
- 16 kb circular DNA,
- 37 genes coding for 13 proteins, ribosomal RNAs, and transfer RNAs.
- With a code different from the universal code:
  - Mito. Univ. UGA Trp STOP AUA Met Ile AGA/AGG STOP Arg
- mutations in these genes are common



# Mitochondrial inheritance

## Characteristics

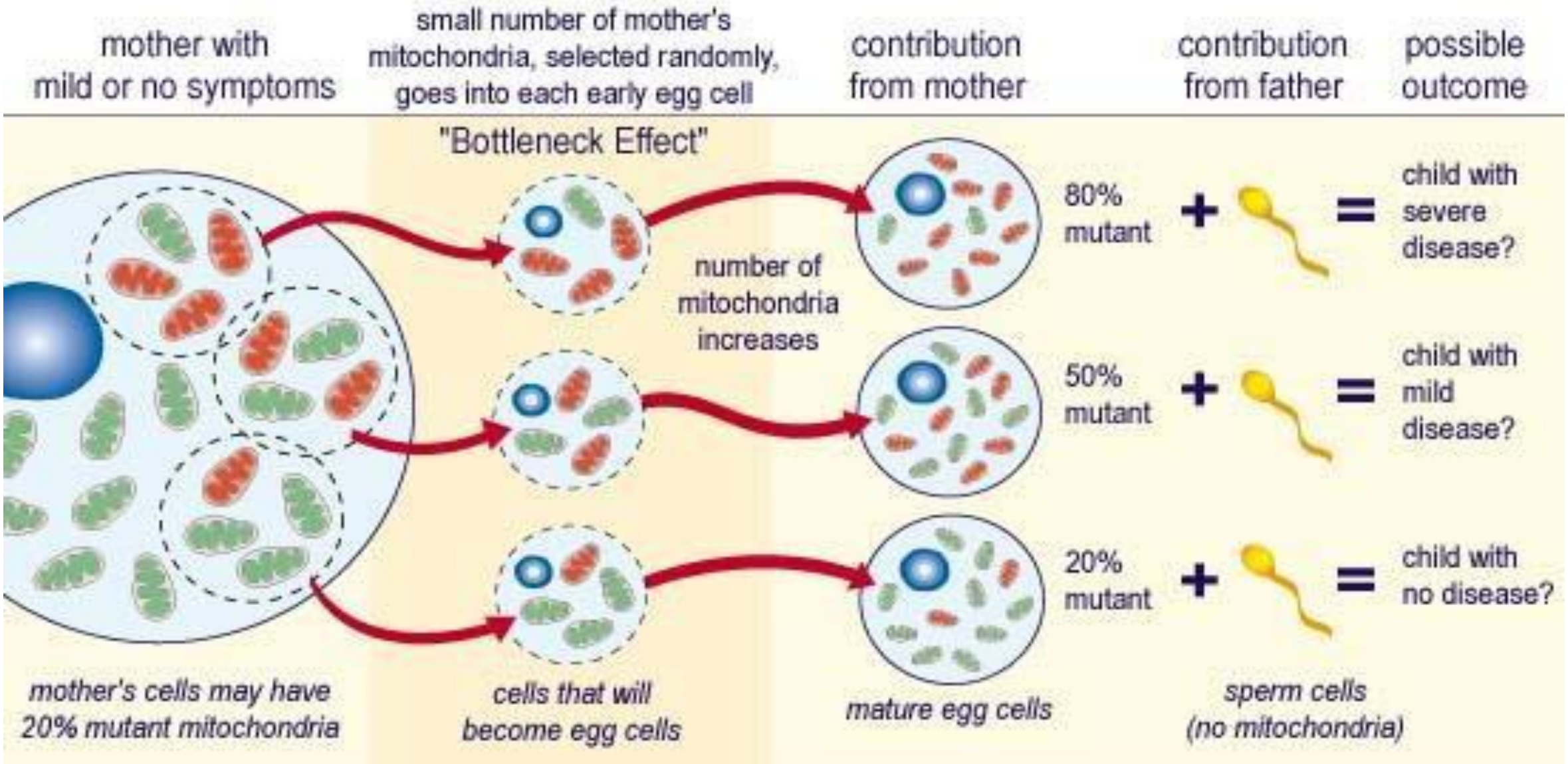
- Male and females inherit the mutation
- Only females pass it on
- Sick men do not pass on the disease to any of their children.



## 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

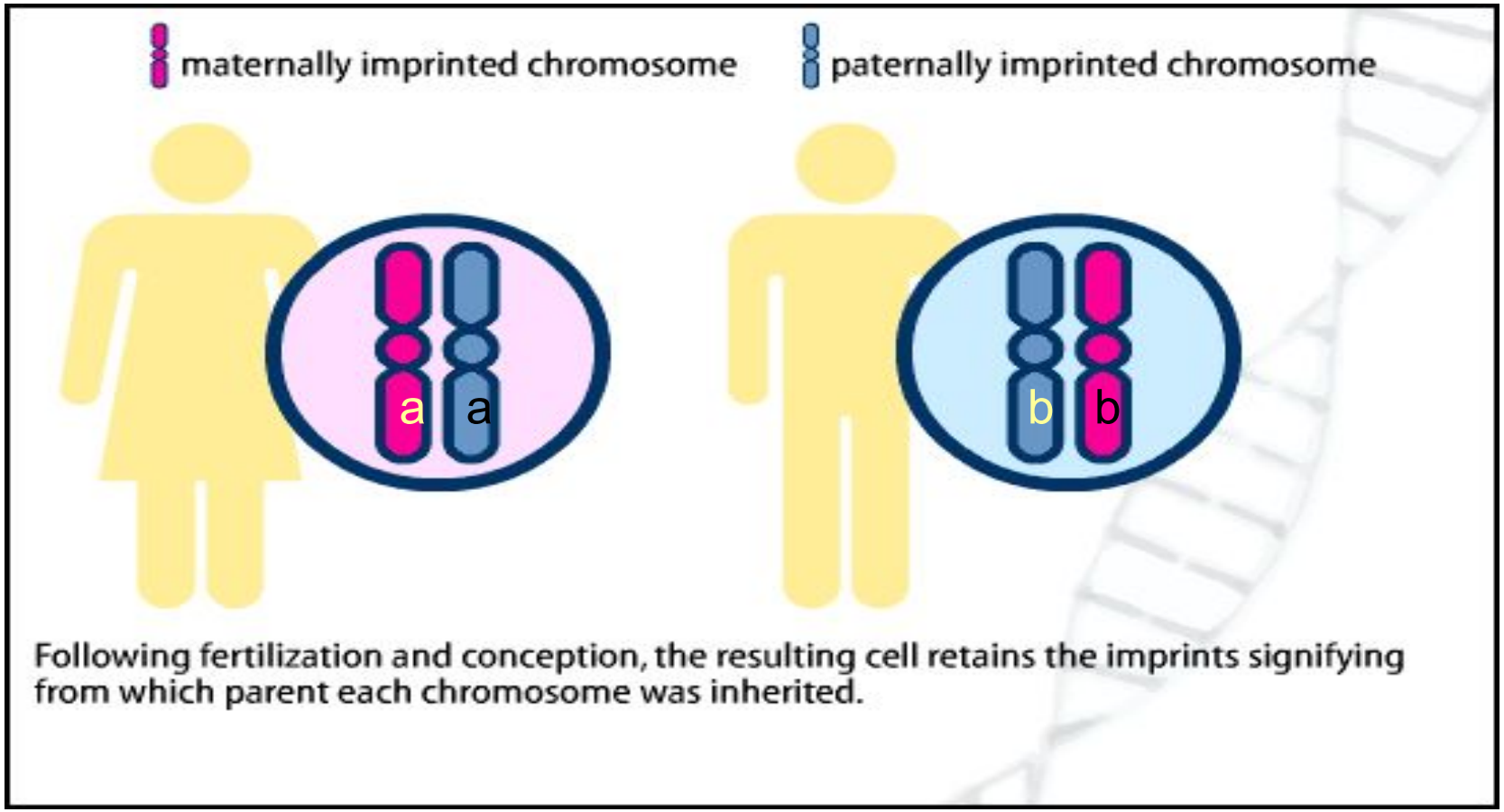



**Genetic counselling nightmare!!**

# 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…

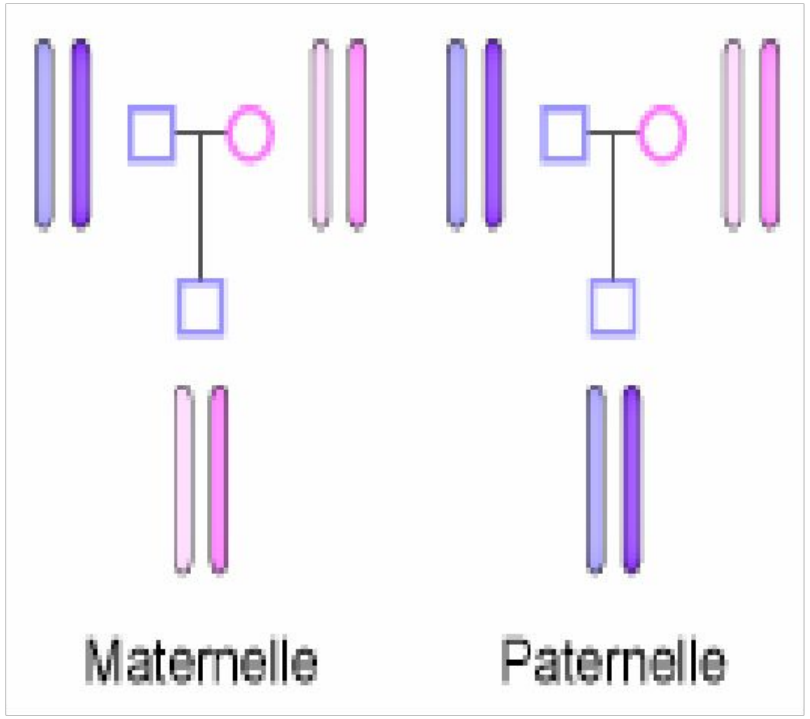
If one copy missing the problem will depend on whether the missing one was meant to be the “on” one or not..

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

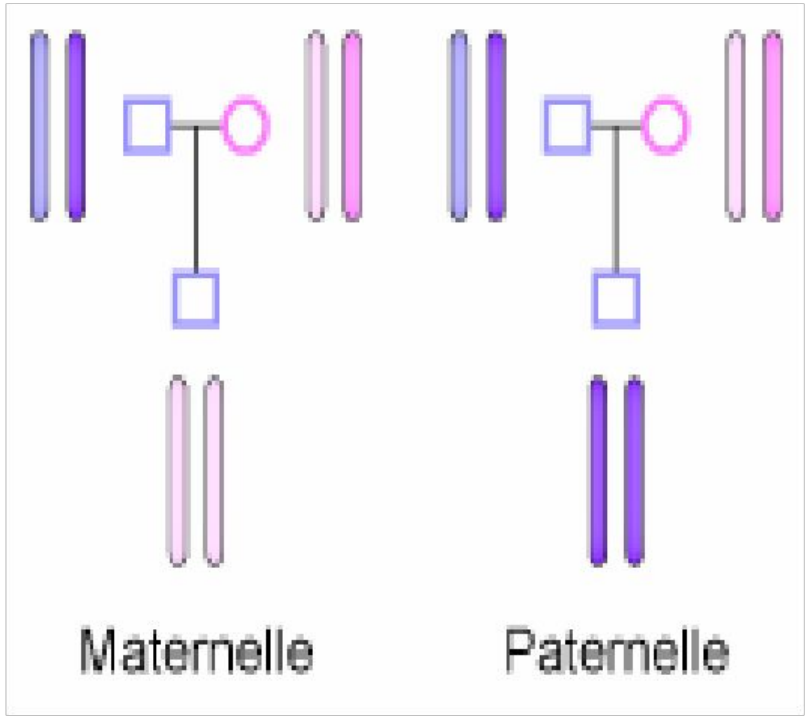
PW occurs in absence of PATERNALLY expressed genes

# Uniparental disomy

Both copies of a chromosome pair same parental origin




Hétérodisomie parentale



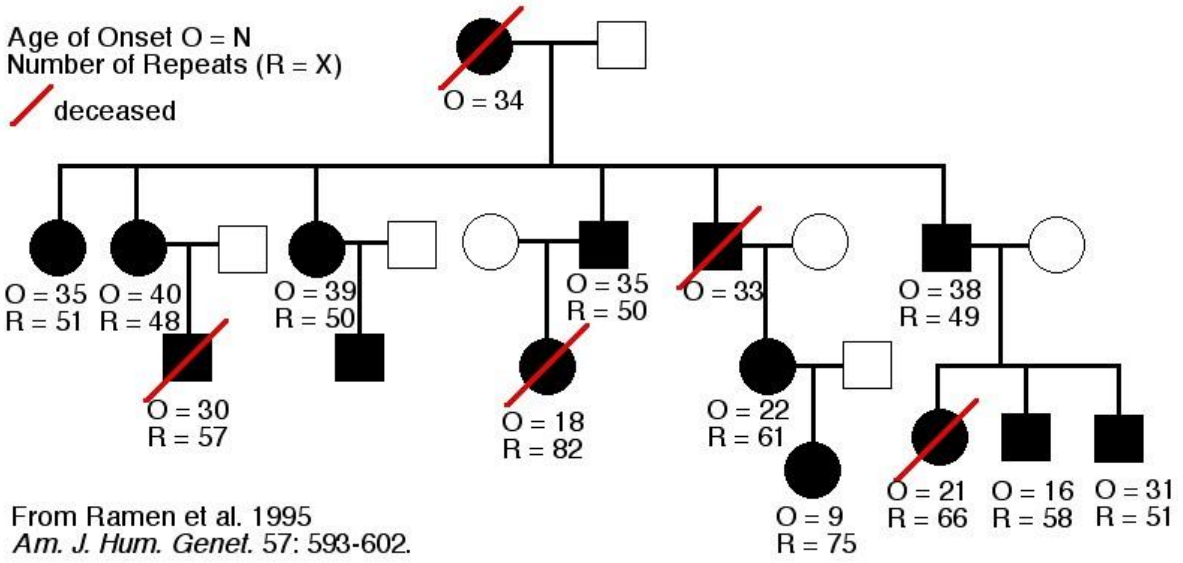

Isodisomie parentale

# Dynamic Mutation Disorders

DNA sequence repeats  Usually triplets

Unstable beyond threshold

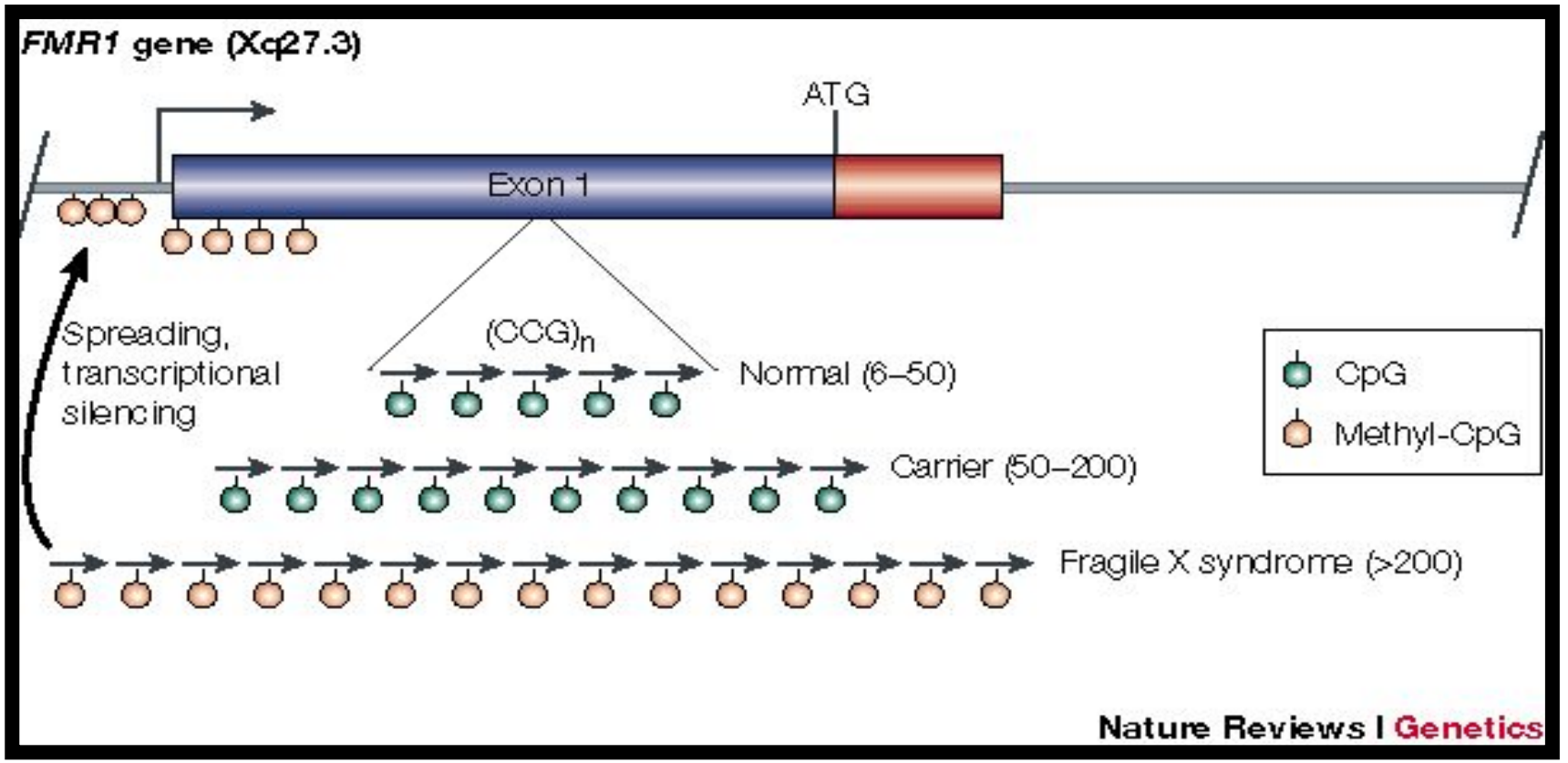
***Anticipation***



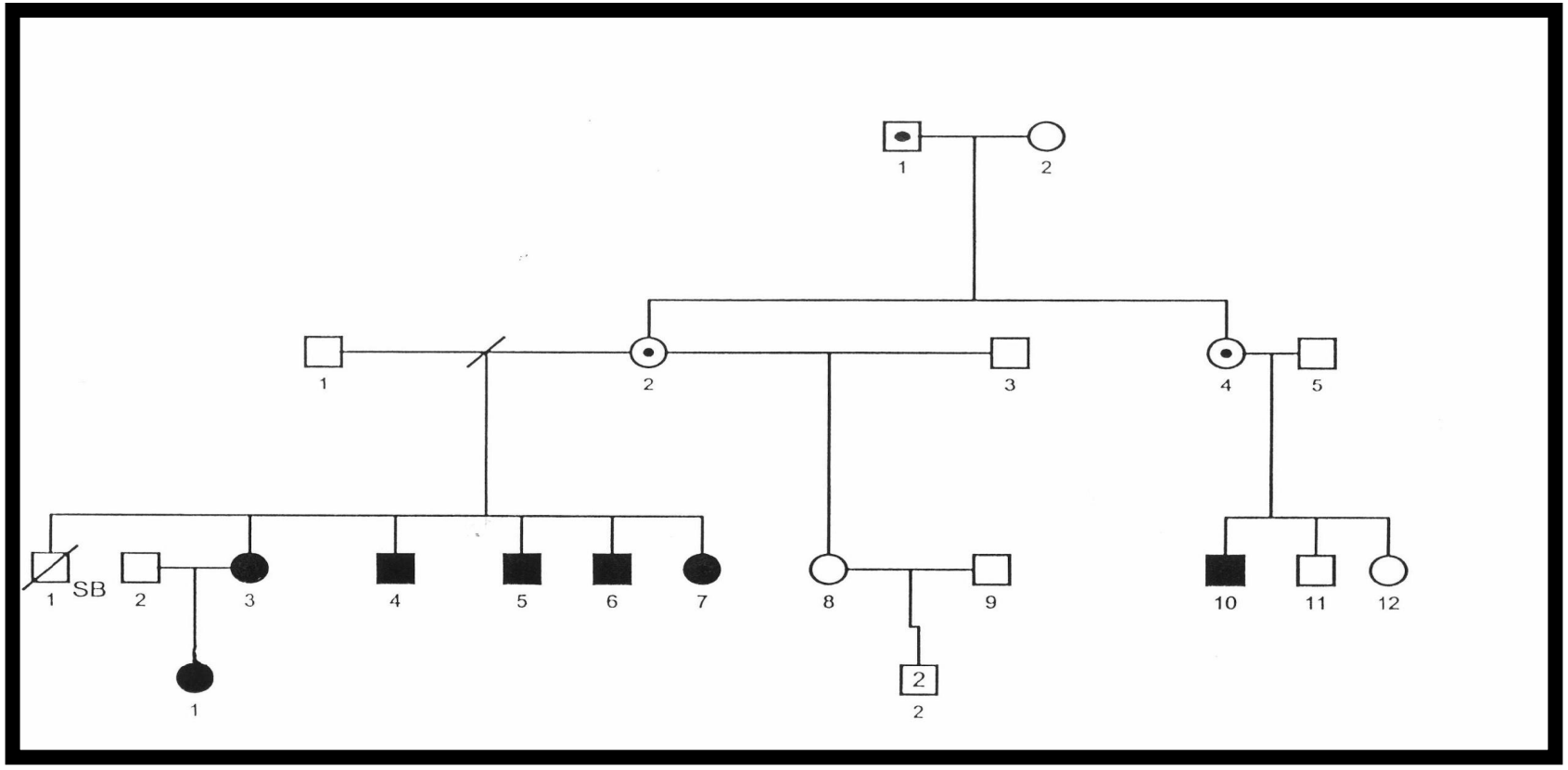

Parent of origin effects on instability and tendency for expansion

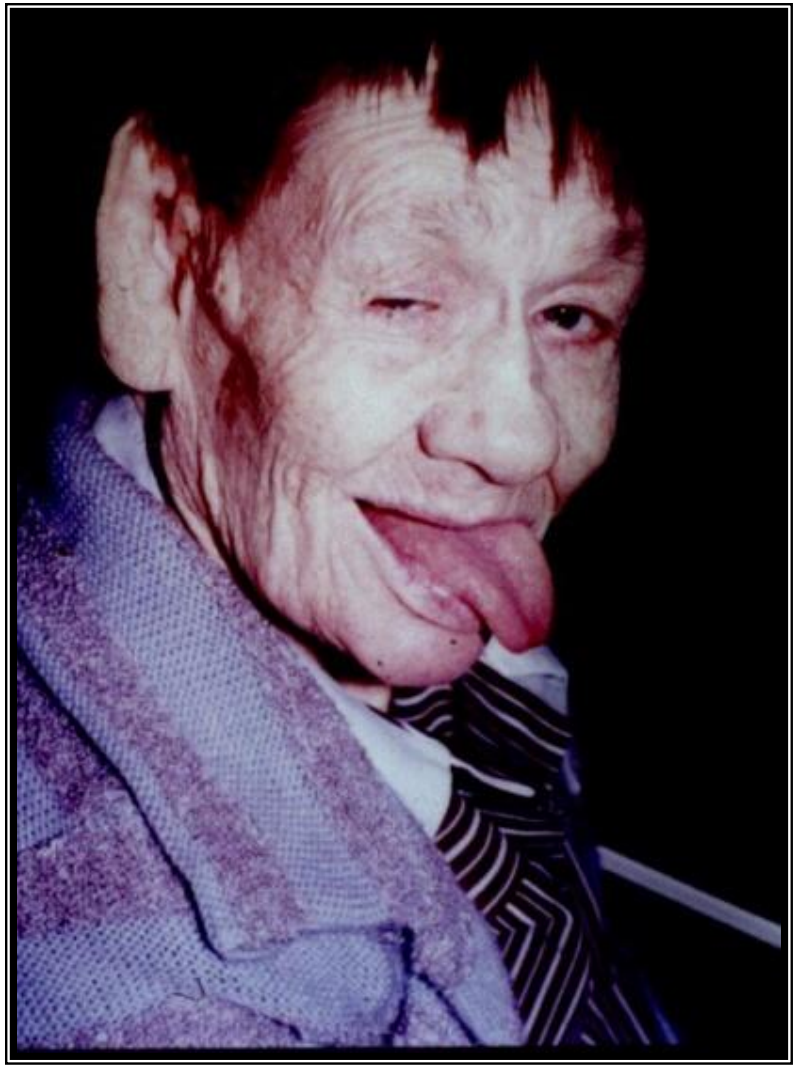
# Ex: Fragile X syndrome

- 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

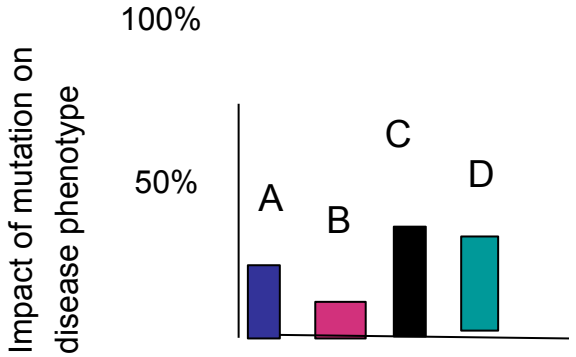


**X linked “semi dominant / ”Atypical” X linked inheritance**

# 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 inthepopulation




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