Genetic Disorders & Mode of Inheritance

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- An illness caused by one or more abnormalities in the genome
- Abnormalities can range from a small mutation in DNA or addition or deletion of an entire chromosome or set of chromosomes
- Most genetic disease are rare and affect one person in every several thousands or millions

Genetic disorders

- May or may not be heritable
- The defect will only be heritable if genetic disorder occurs in the germ line
- In non-heritable genetic disorders, defects may be caused by new mutations or changes to the DNA

Basic Modes of Inheritance

Chromosmal Disorders

- Trisomy
- Translocation

Single Gene Disorders

- Autosomal dominant
- X-linked recessive

Mitochondrial Disorders

- MERRF
- LOHN

Multifactorial Disorders

- Insulin Dependant Diabetes
- Hypertension
- Spina Bifida, Epilepsy

Somatic Cell Genetic Disorders

- Cancer

1. Chromosomal Disorder

What are chromosome abnormalities?

Results from a change in the number or structure of chromosomes

Syndrome	Abnormality	Incidence
Turner	Monosomy X	2 in 10,000 (female births)
Down's	Trisomy 21	15 in 10,000
Edwards'	Trisomy 18	3 in 10,000
Patau's	Trisomy 13	2 in 10,000
Klinefelter's	XXY	10 in 10,000 (male births)
XXX	XXX	10 in 10,000 (female births)
XYY	XYY	10 in 10,000 (male births)

Numerical Abnormalities

When an individual is **missing one of the chromosomes** from a pair, the condition is called ***monosomy***.

When an individual has **more than two chromosomes** instead of a pair, the condition is called ***trisomy***.

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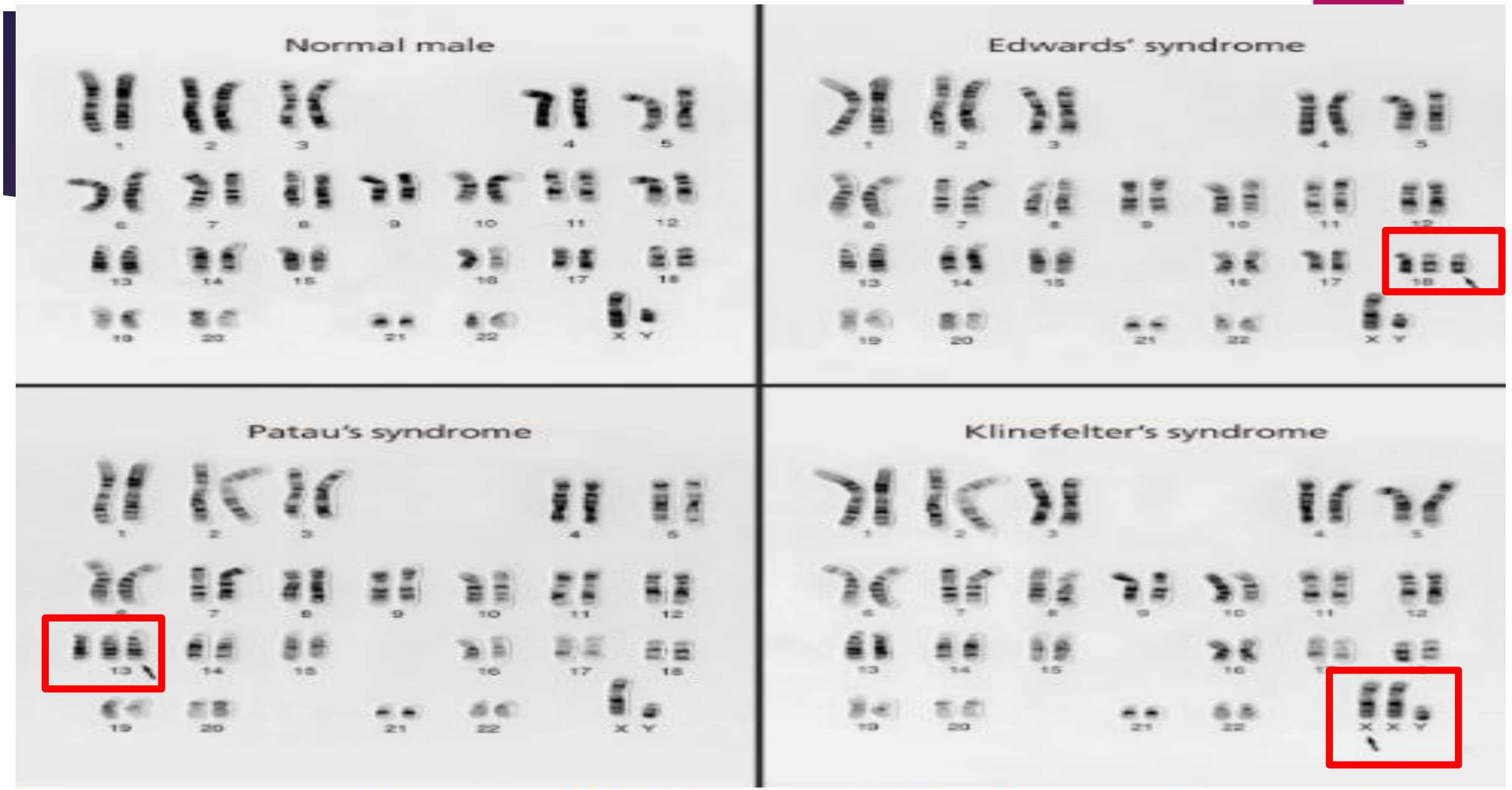


Karyotype images showing different numerical chromosome abnormalities.
Image credit: Wessex Reg. Genetics Centre, Wellcome Images

Structural Abnormalities

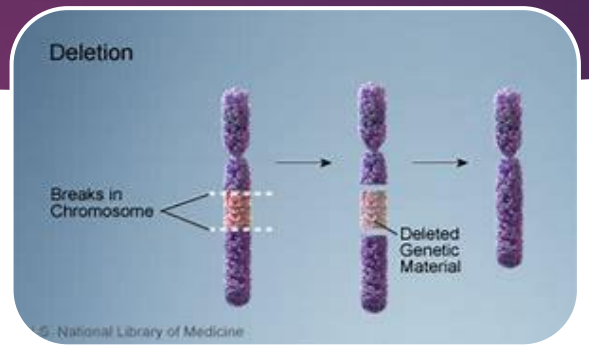
A chromosome's structure can be altered in several ways.

•**Deletions:** A portion of the chromosome is missing or deleted.

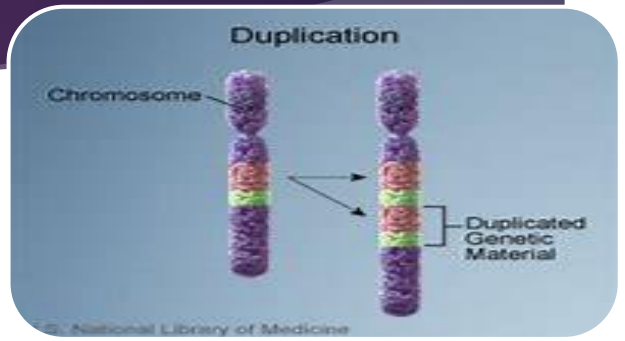
•**Duplications:** A portion of the chromosome is duplicated, resulting in extra genetic material.

•**Translocations:** A portion of one chromosome is transferred to another chromosome.

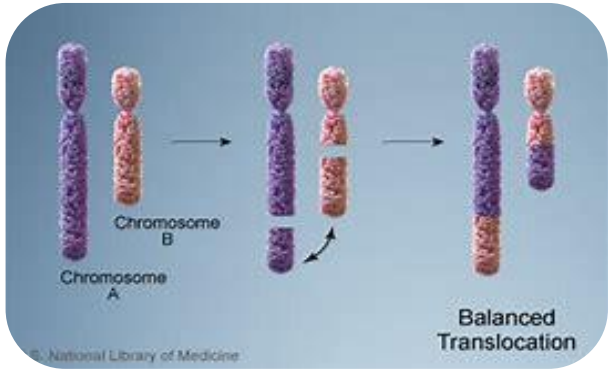
•**Inversions:** A portion of the chromosome has broken off, turned upside down, and reattached. As a result, the genetic material is inverted.



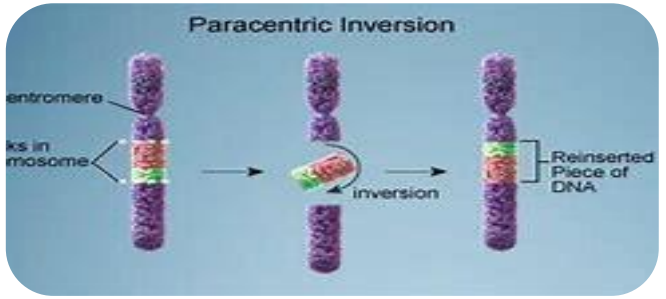
deletion



duplication



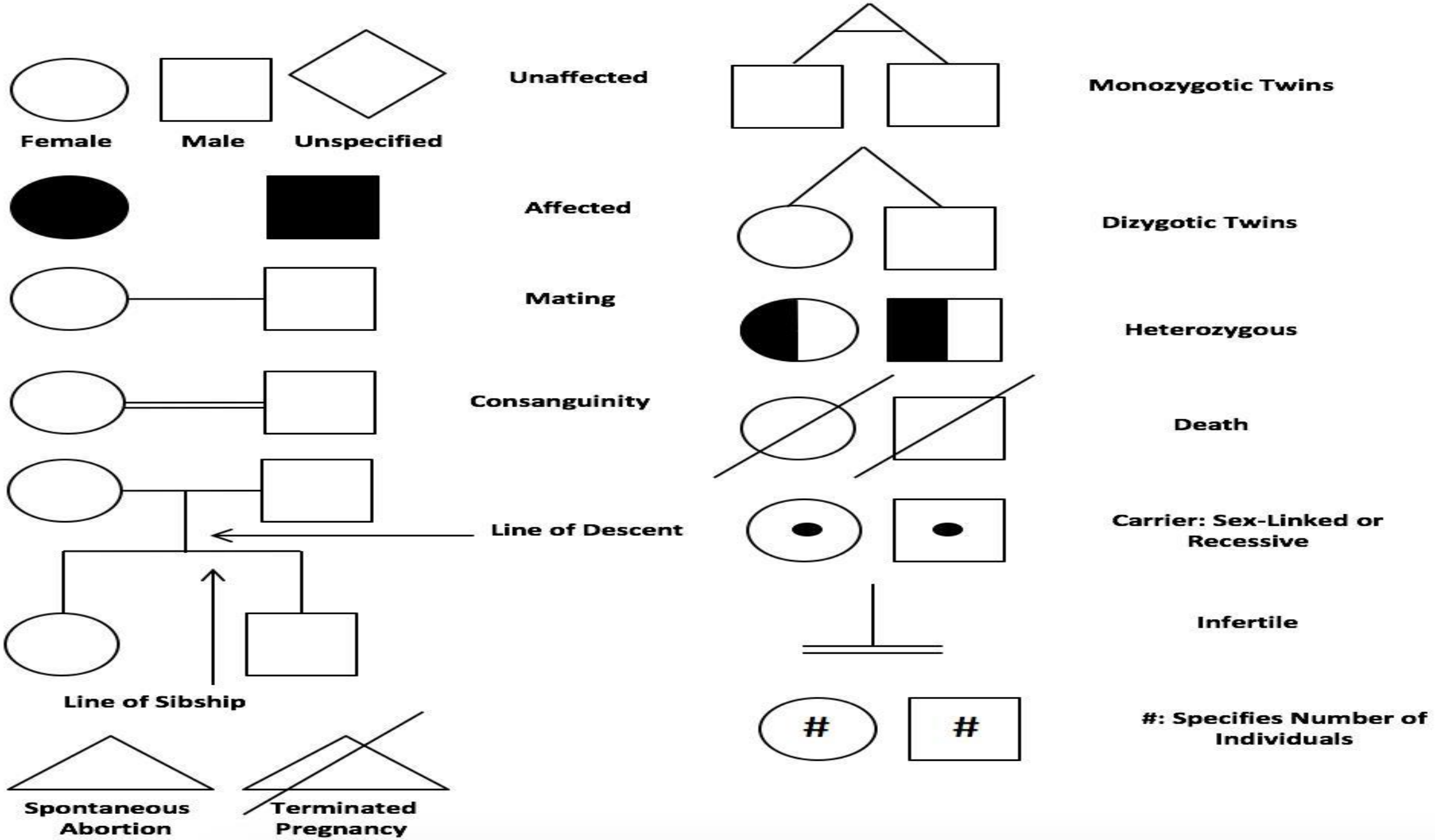
translocation



inversion

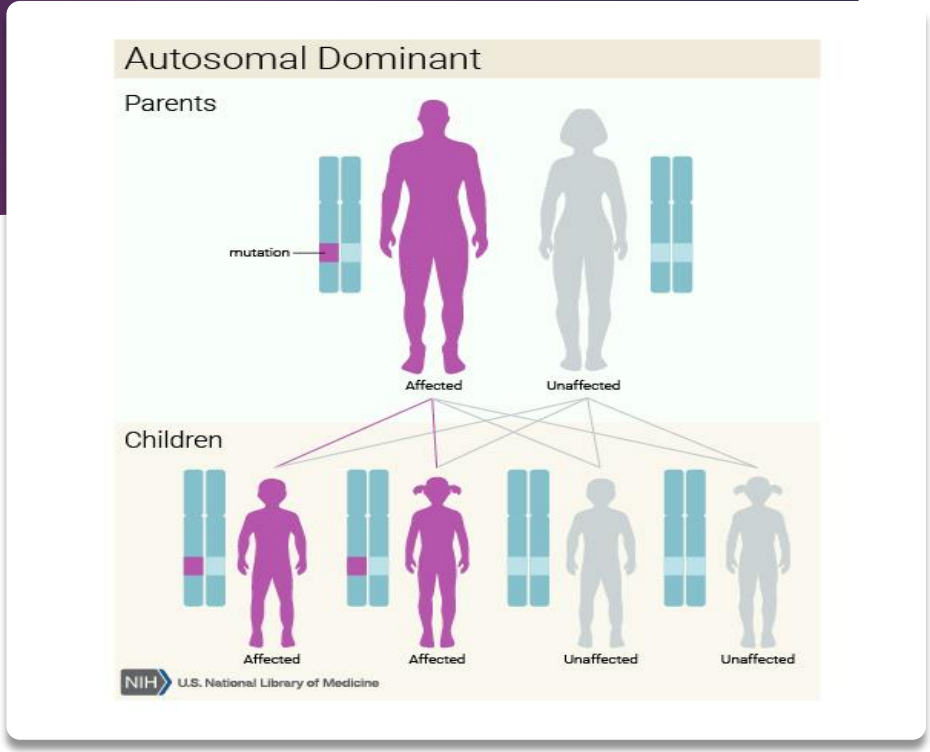
2. Single Gene Disorders

- Also known as monogenic/ Mendelian
- Involve mutations in the DNA sequences of single gene. As a result, the protein the gene codes for is either altered or missing
- Over 6000 human diseases caused by single gene defect
- Single gene disorder:
  - **Autosomal Dominant / Recessive**
  - **X-Linked Dominant / Recessive**
  - **Y-Linked**
  - **Mitochondrial**


Female
Male
Unspecified
Unaffected
Affected
Mating
Consanguinity
Line of Descent
Line of Sibship
Spontaneous Abortion
Terminated Pregnancy
Monozygotic Twins
Dizygotic Twins
Heterozygous
Death
Carrier: Sex-Linked or Recessive
Infertile
#
#
#: Specifies Number of Individuals

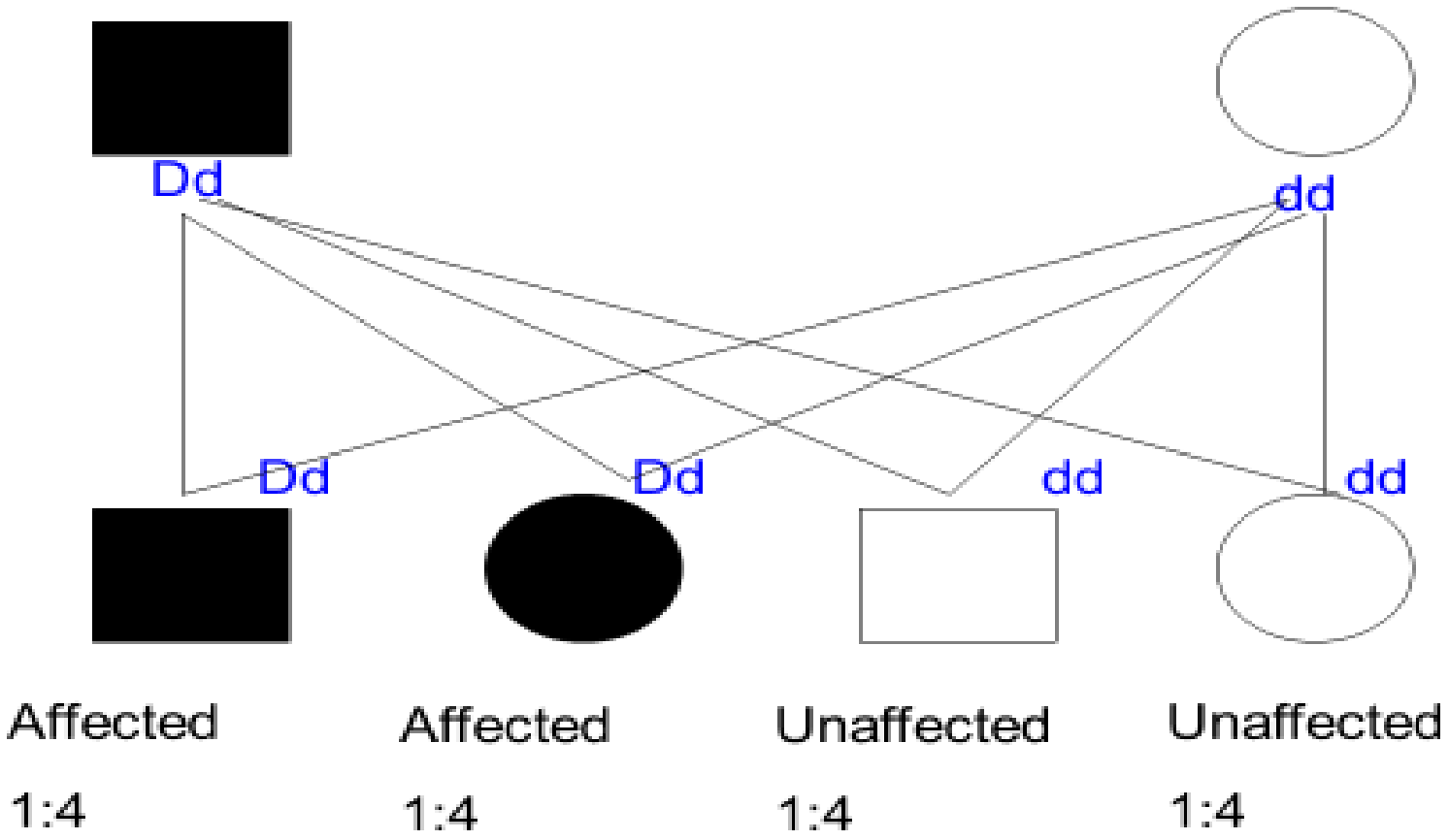
Autosomal Dominant Inheritance

- Abnormal/ mutated gene located on one pair of autosomes
- One mutated copy of the gene is sufficient to cause the disease
- Features:
  - affect both males & females
  - males & females affected with equal frequency and severity
  - appears in every generations
  - transmission by the mother or father
  - vertical transmission
  - unaffected parent cannot transmit to children
  - the chance a child will inherit the mutated gene is 50%
- Examples: Noonan disease, Huntington disease, neurofibromatosis, and polycystic kidney disease

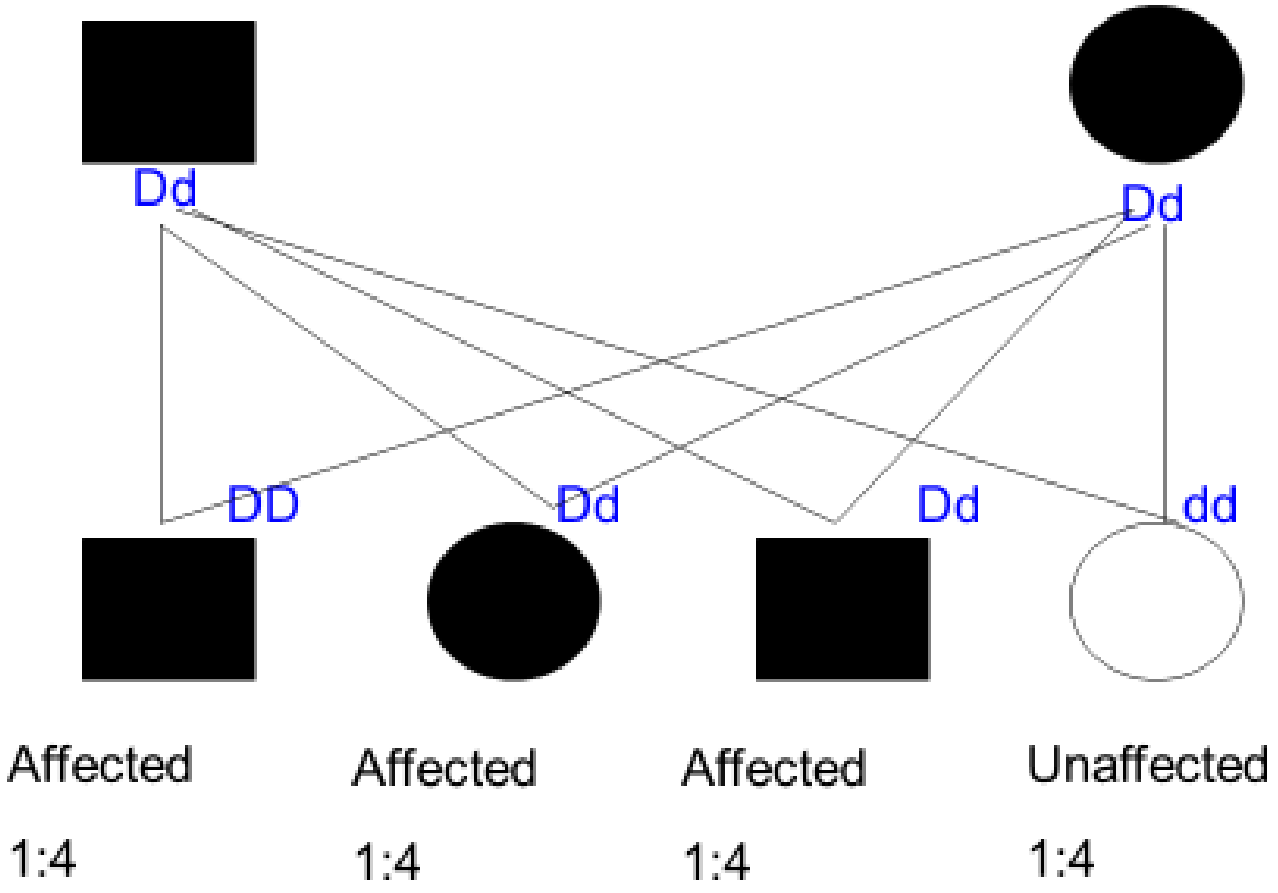


- 50% offspring will inherit the disease allele
- 50% offspring unaffected

A) One parent has a dominant mutation

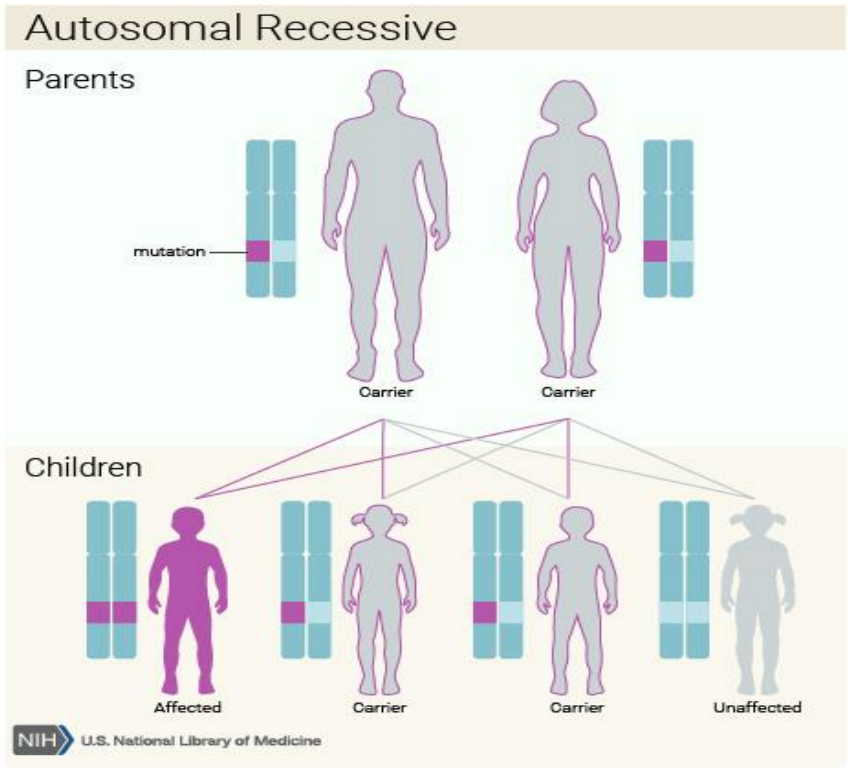


B) Both parents have a dominant mutation



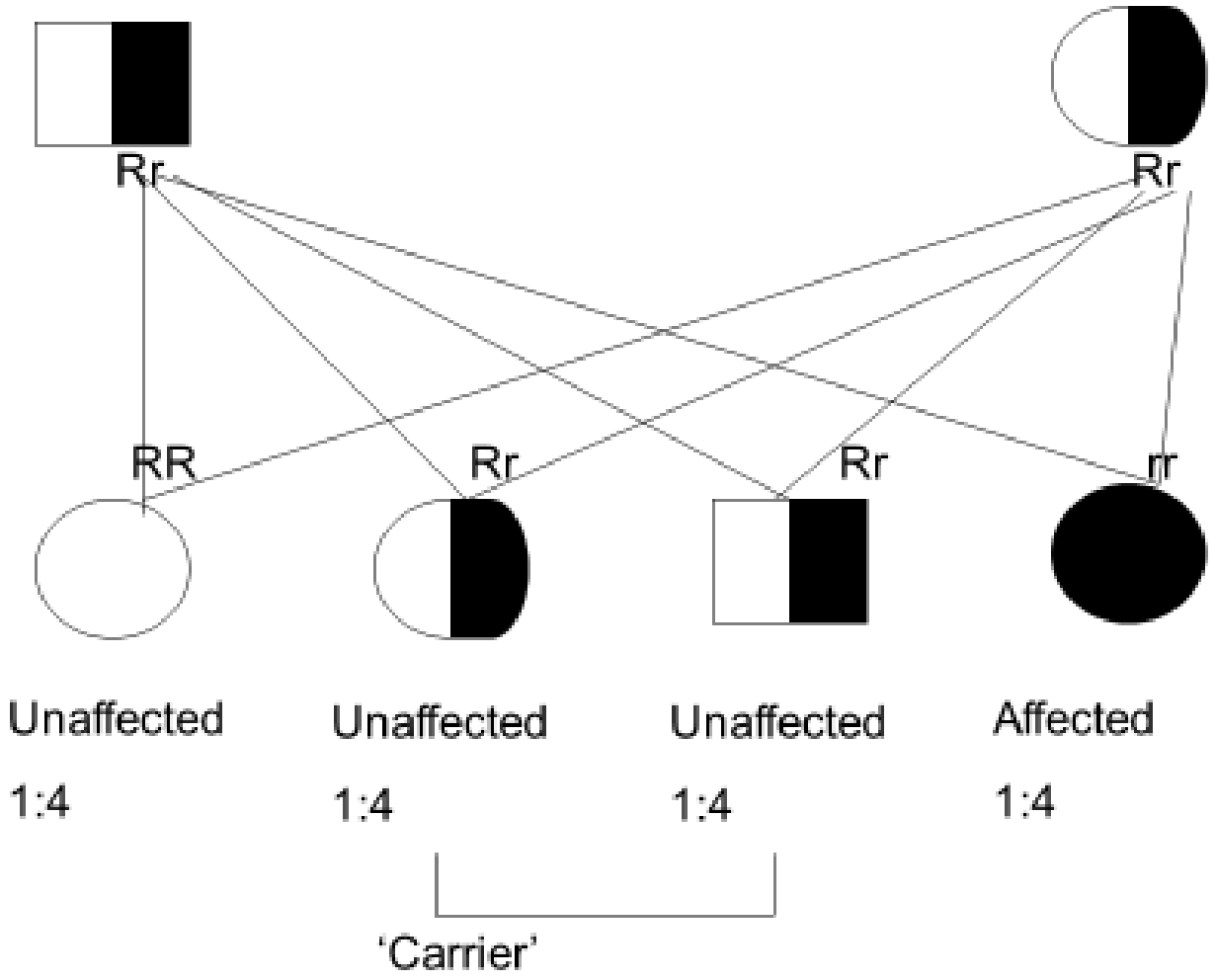
Autosomal Recessive Inheritance

- Two copies of the gene must be mutated for a person to be affected
- Features:
  - - both parents carry the same recessive genes (both are heterozygous carrier)
  - - parents do not express the abnormalities
  - - parents of affected children often consanguineous
  - - horizontal transmission
- Examples: cystic fibrosis (CF), sickle cell anemia (SC), Tay Sachs disease

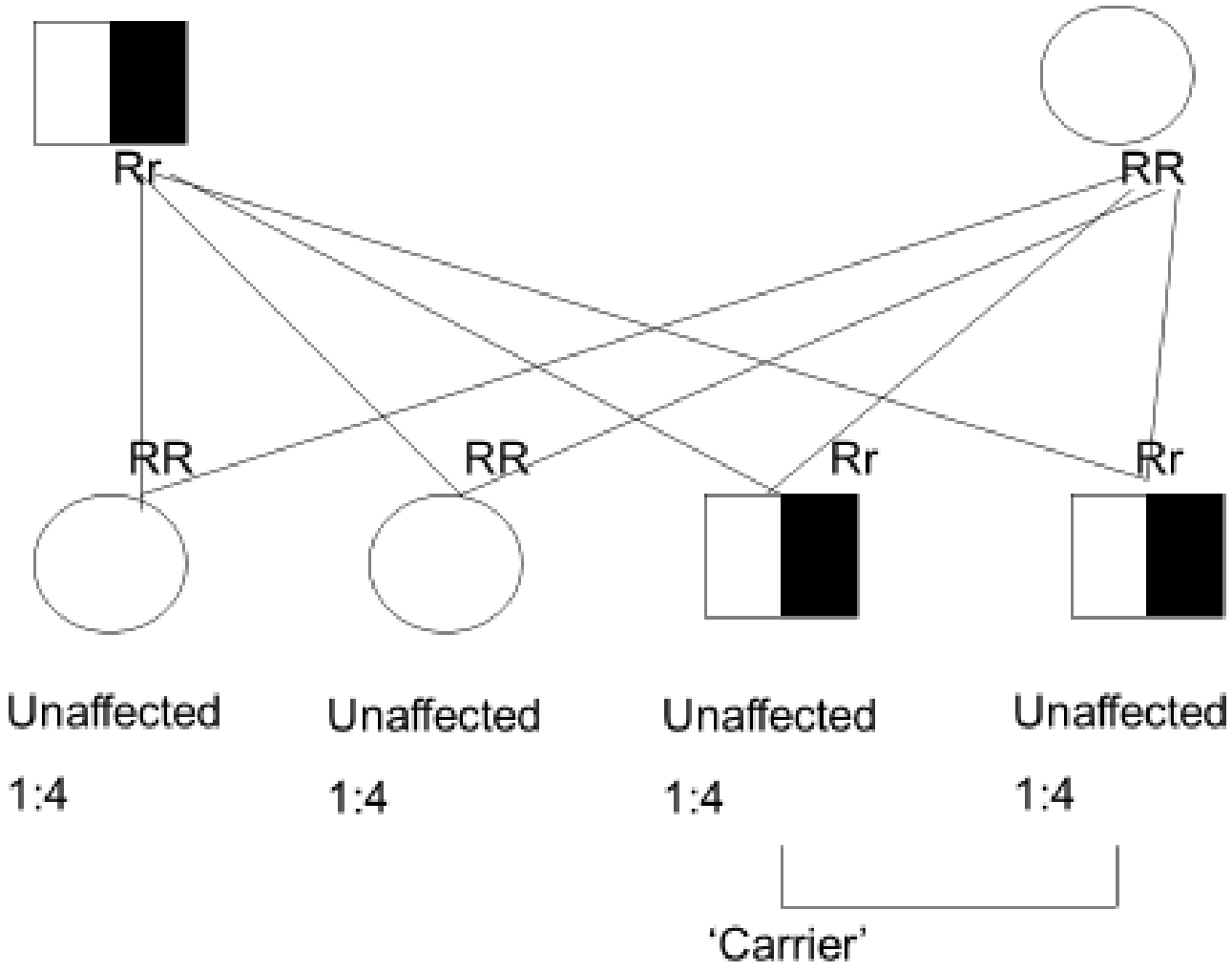


- ❑ 25% offspring will inherit 2 copies of disease allele
- ❑ 50% offspring will inherit 1 copy of disease allele
- ❑ 25% offspring unaffected (normal)

A) Both parents carry of the same recessive gene



B) One parent is a carrier of a recessive gene



X-LINKED INHERITANCE

Genes located on the X chromosome are called X-linked genes.

Recessive

- Male display disorder or not

  X: mother

  Y: father

- Female commonly carrier

e.g. haemophilia, Duchenne and Becker types of muscular dystrophy

Dominant

-Male display disorder (lethal)

e.g. Rett syndrome,

fragile X syndrome

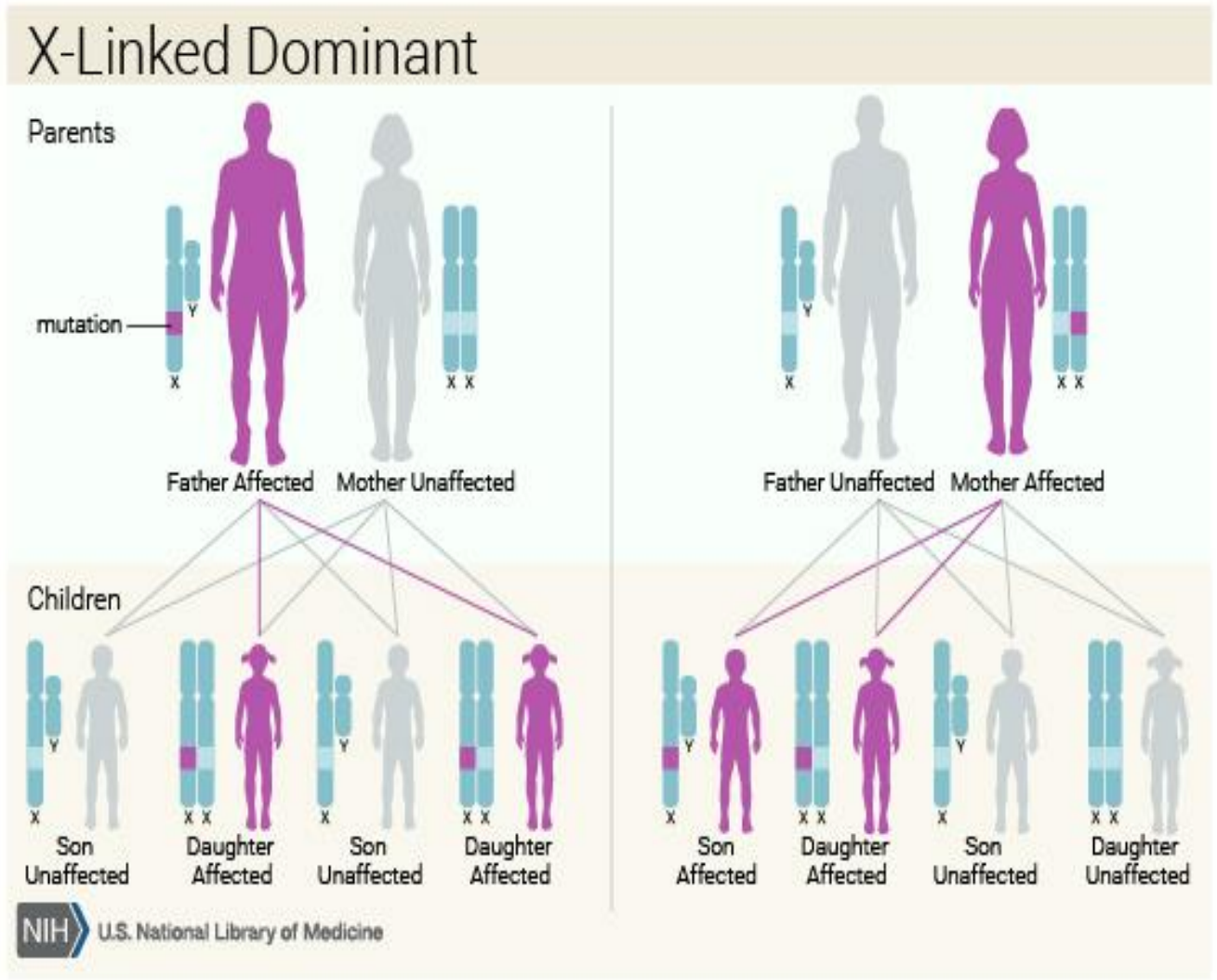
X-Linked Dominant Inheritance

- Caused by mutations in genes on the X chromosome
- Features:

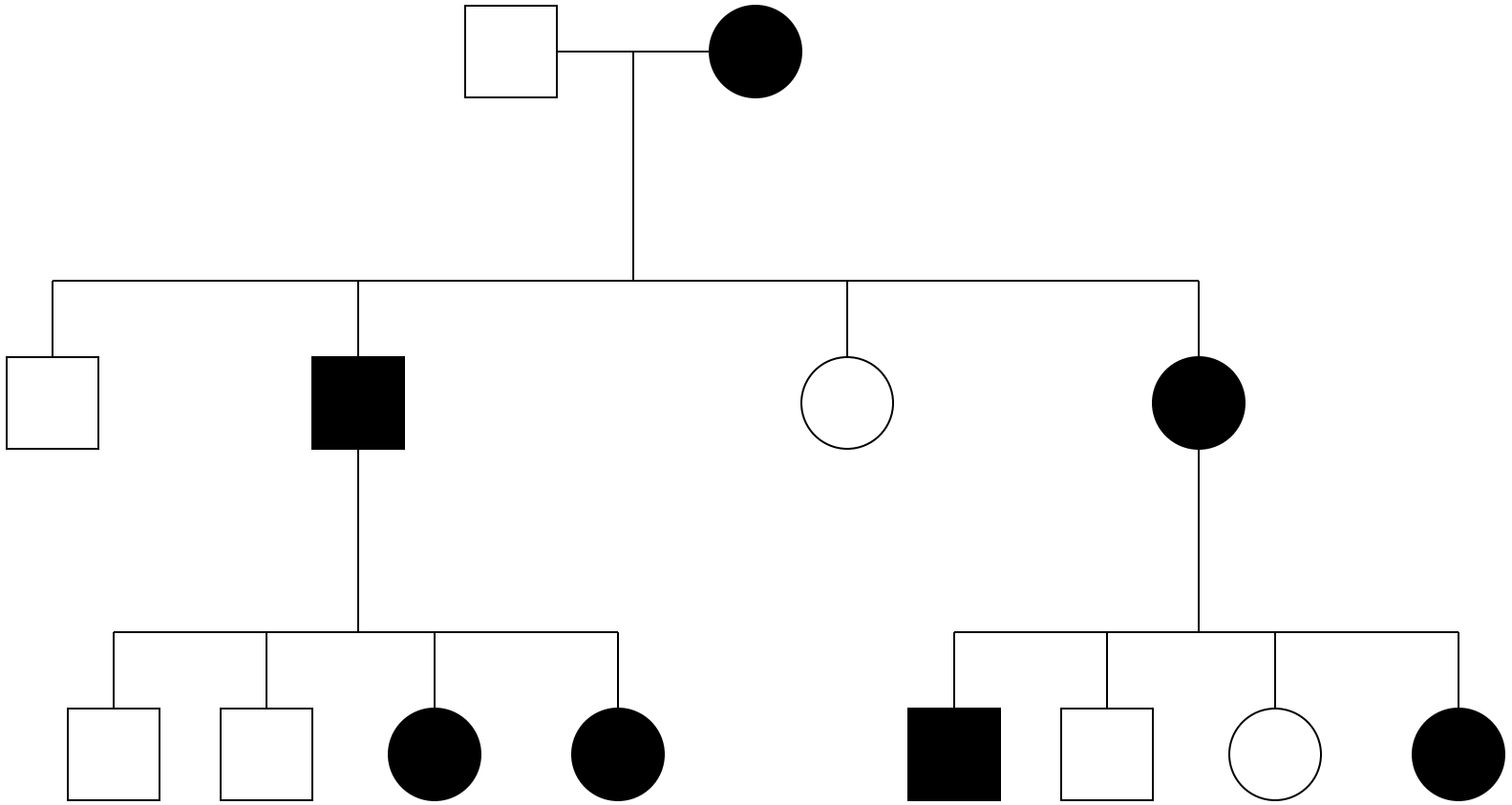
  - males and females are both affected, with males typically being more severe

  - father-to-son does not occur

  - vertical transmission
- Examples: Vitamin D resistant rickets:X-linked hypophosphatemia
  - Rett syndrome
  - Fragile X syndrome

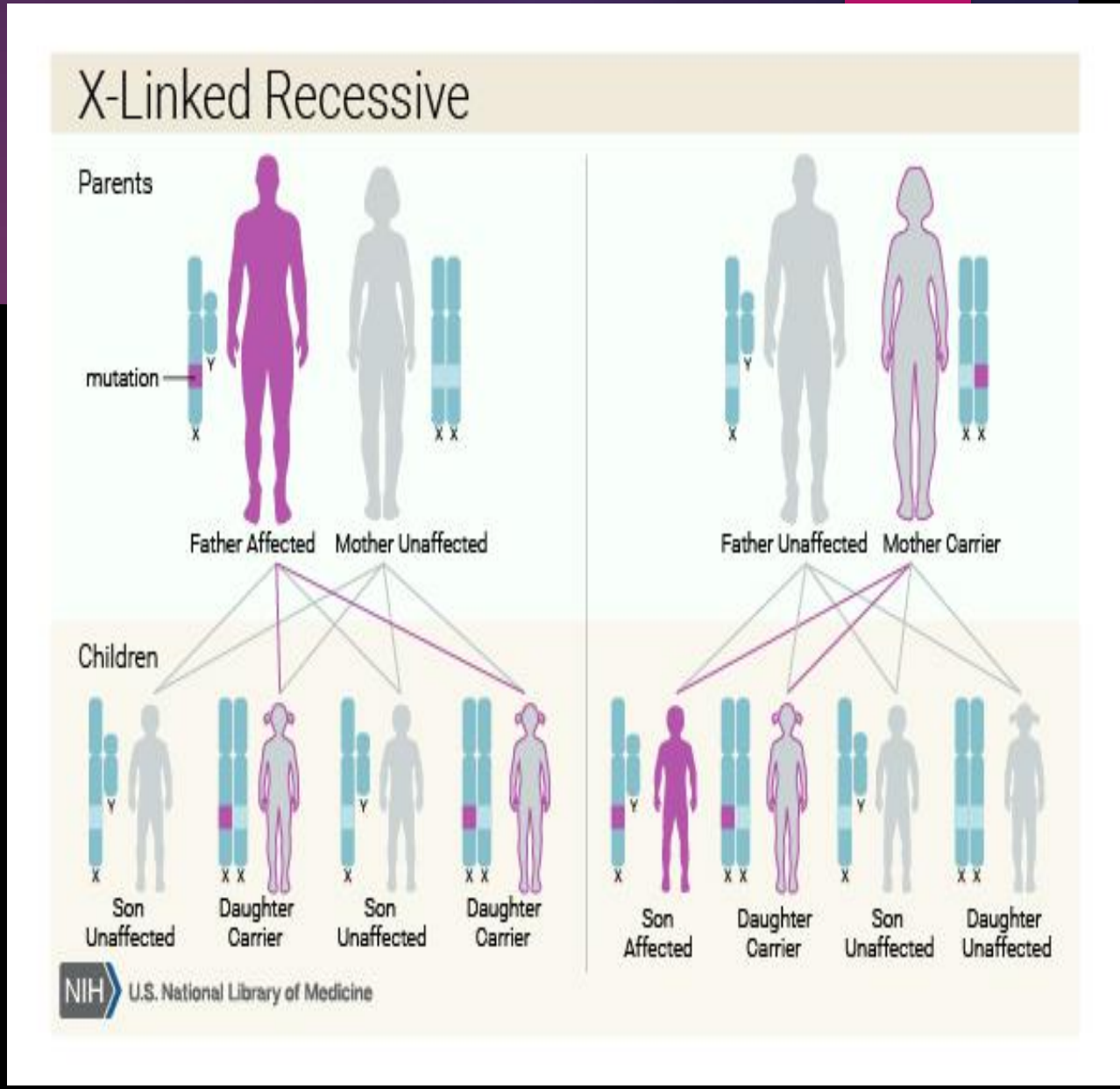


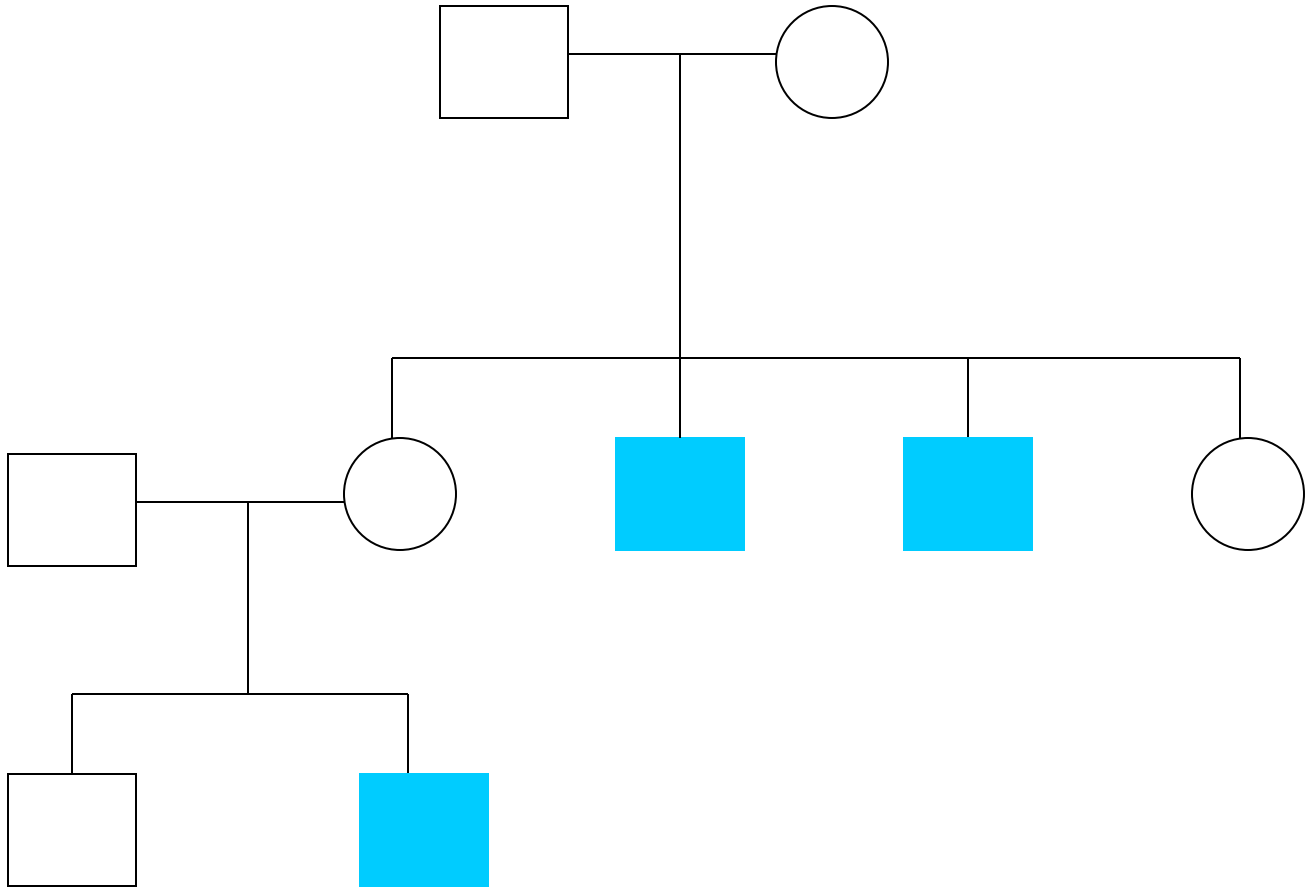
X linked dominant disorders



X-Linked Recessive Inheritance

- Mutations in genes on the X chromosomes
- Features:
  - Observed mostly in males (affected homozygous females are rare)
  - Family pedigree shows skipped generation
  - Father-to-son transmission does not occur
- Eg: DMD,red green colour blindness, Haemophilia

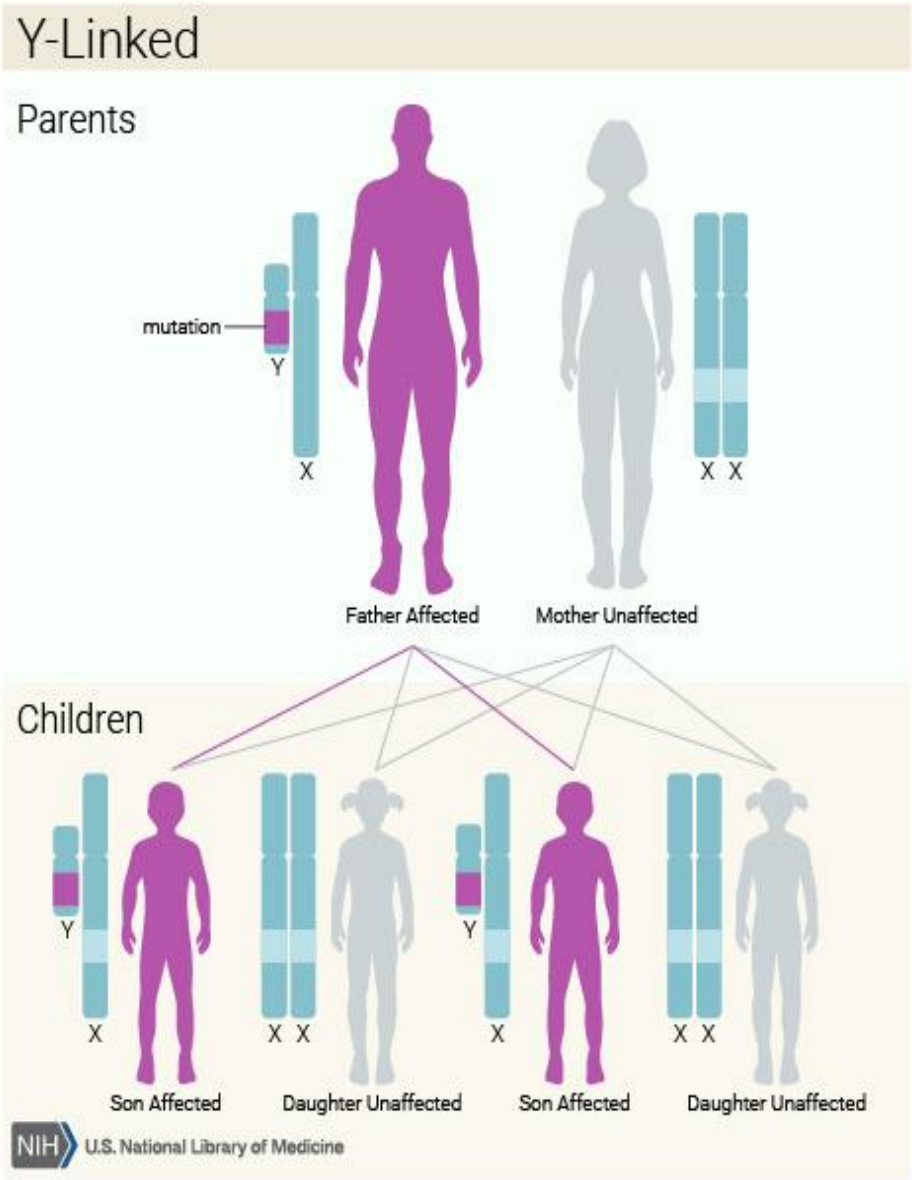




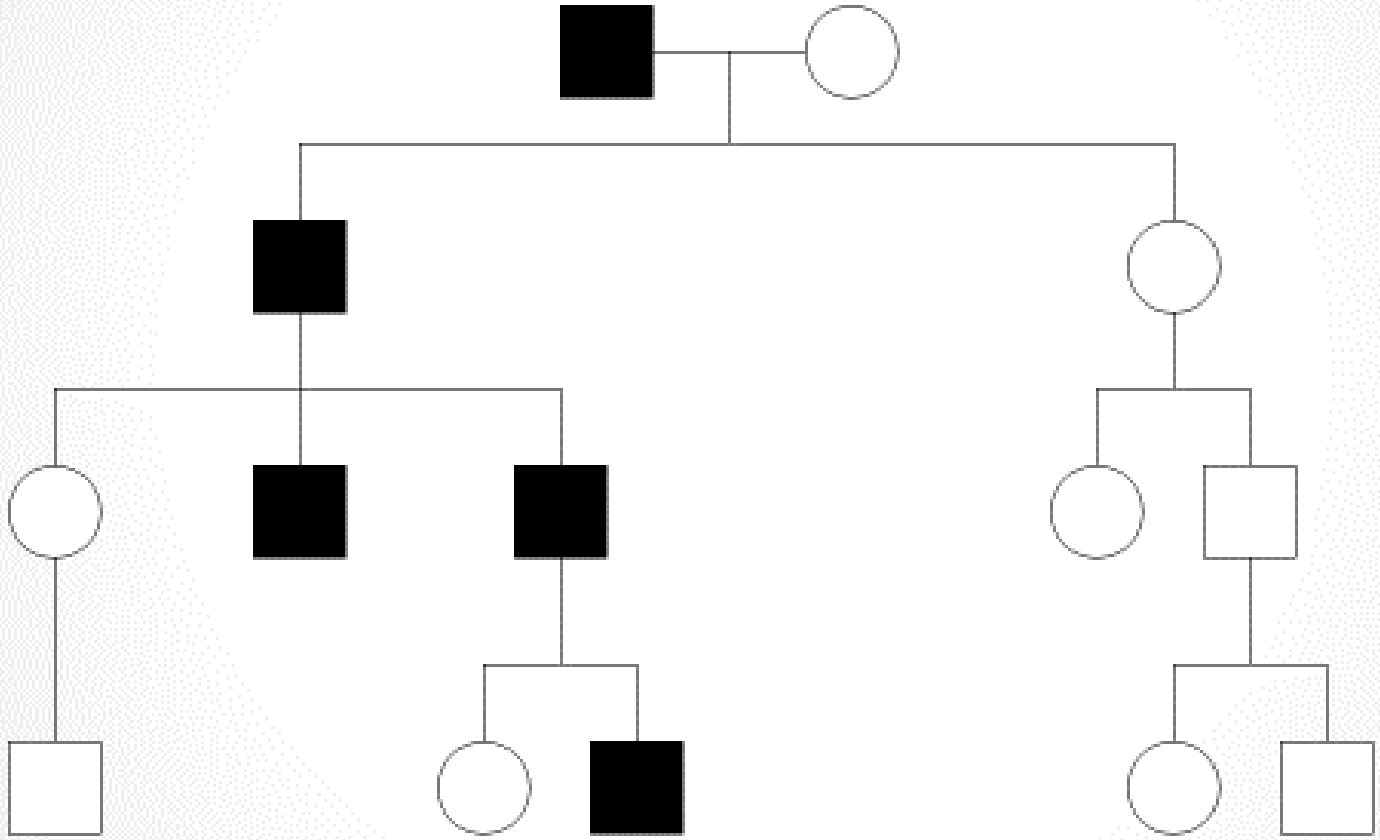
An X-linked recessive family tree

Y-Linked Disorders

- Only males are affected
- Transmission directly from father to son
- Examples:-
  - hairy ears
  - porcupine skin
  - webbed toes



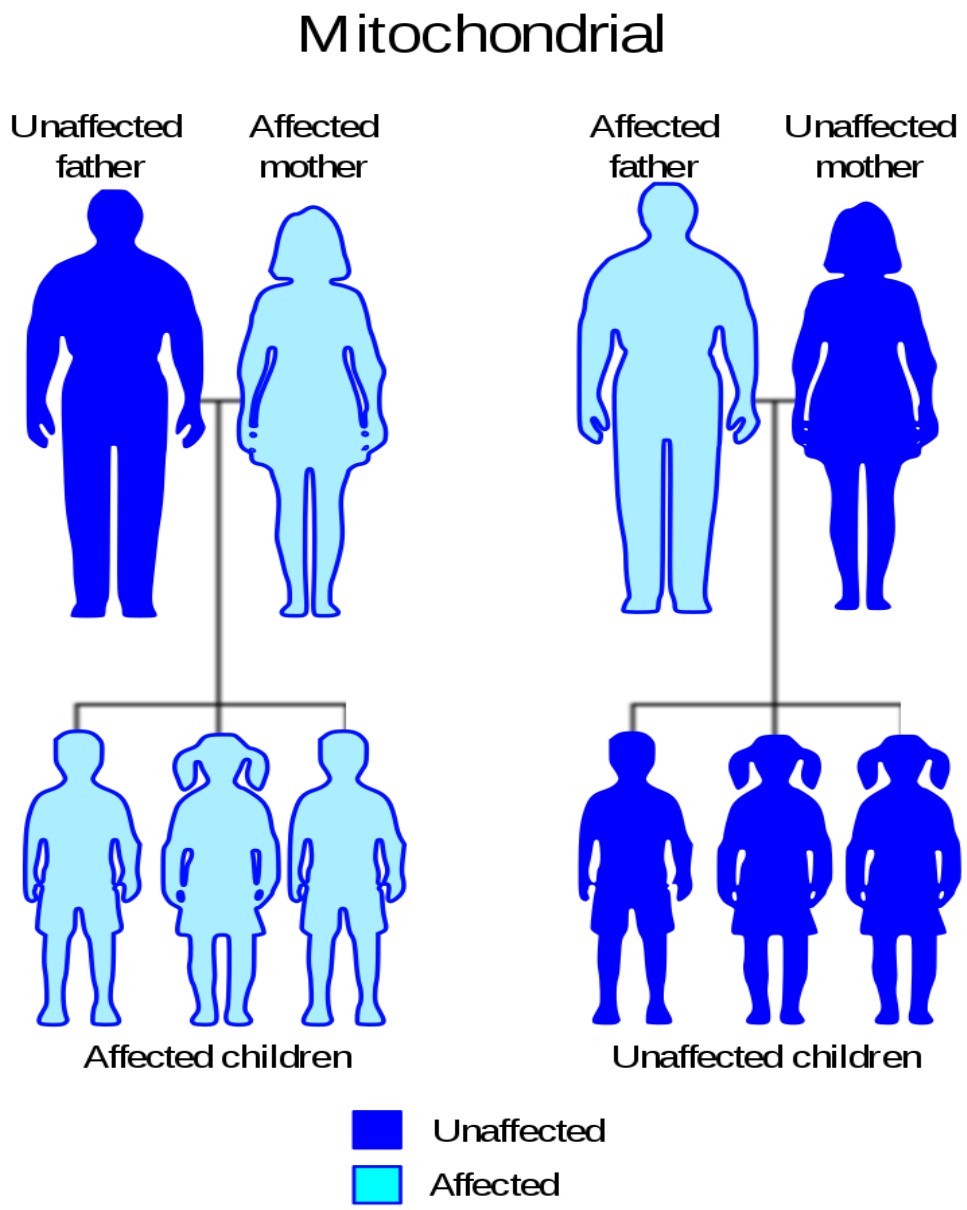
Y linked disorders

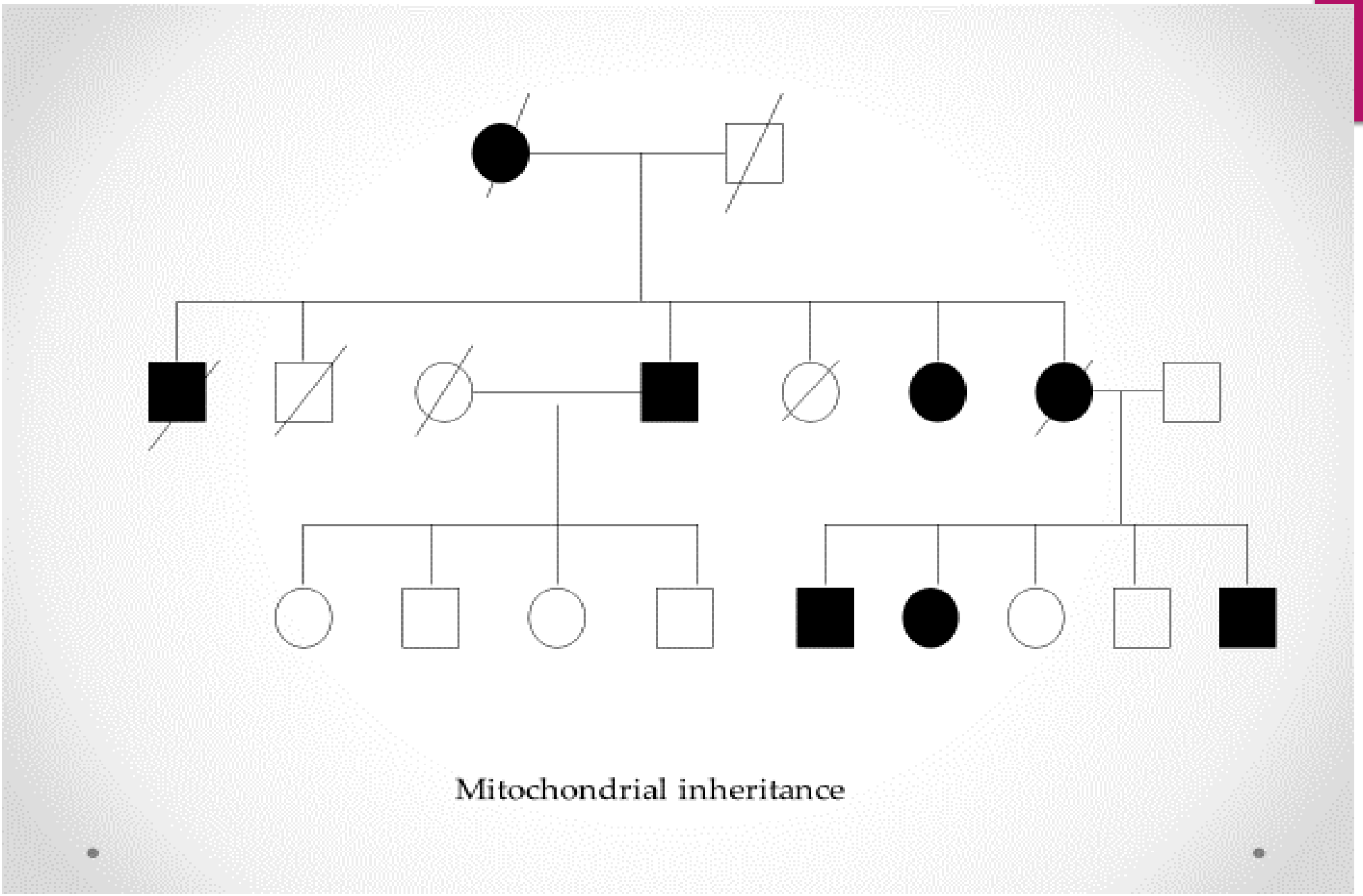


3. Mitochondrial Inheritance

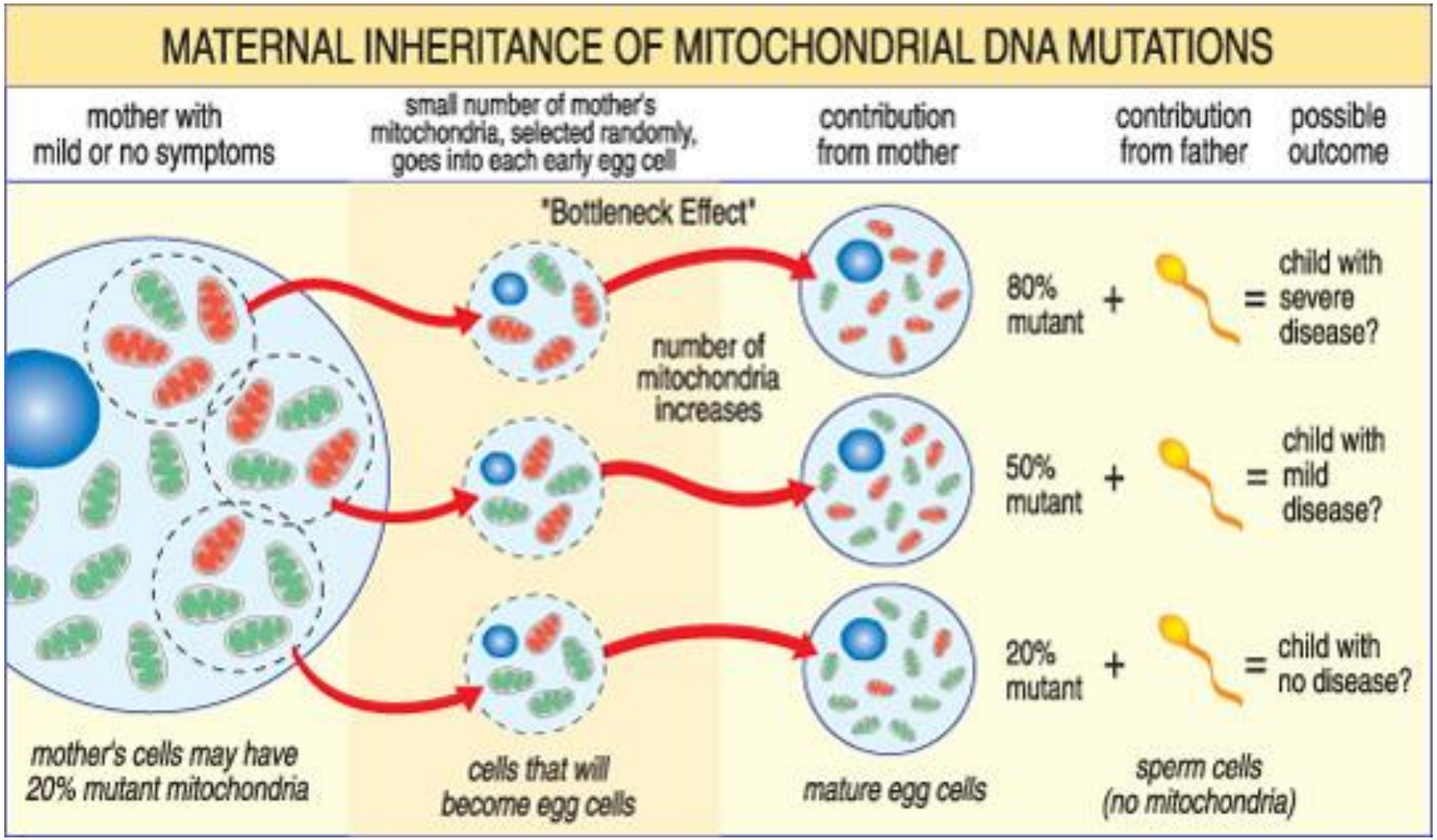
- Also known as maternal / extranuclear inheritance, applies to genes encoded by mitochondrial DNA

- Features:
  - - occurs in both females and males equally who have an affected mother
  - - family pedigree is vertical
  - - maternal transmission only
  - - ranges of phenotypes are seen in affected males and females
  - - high mutation rate





Mitochondrial inheritance



The severity of a mitochondrial disease in a child depends on the percentage of abnormal (mutant) mitochondria in the egg cell that formed them.

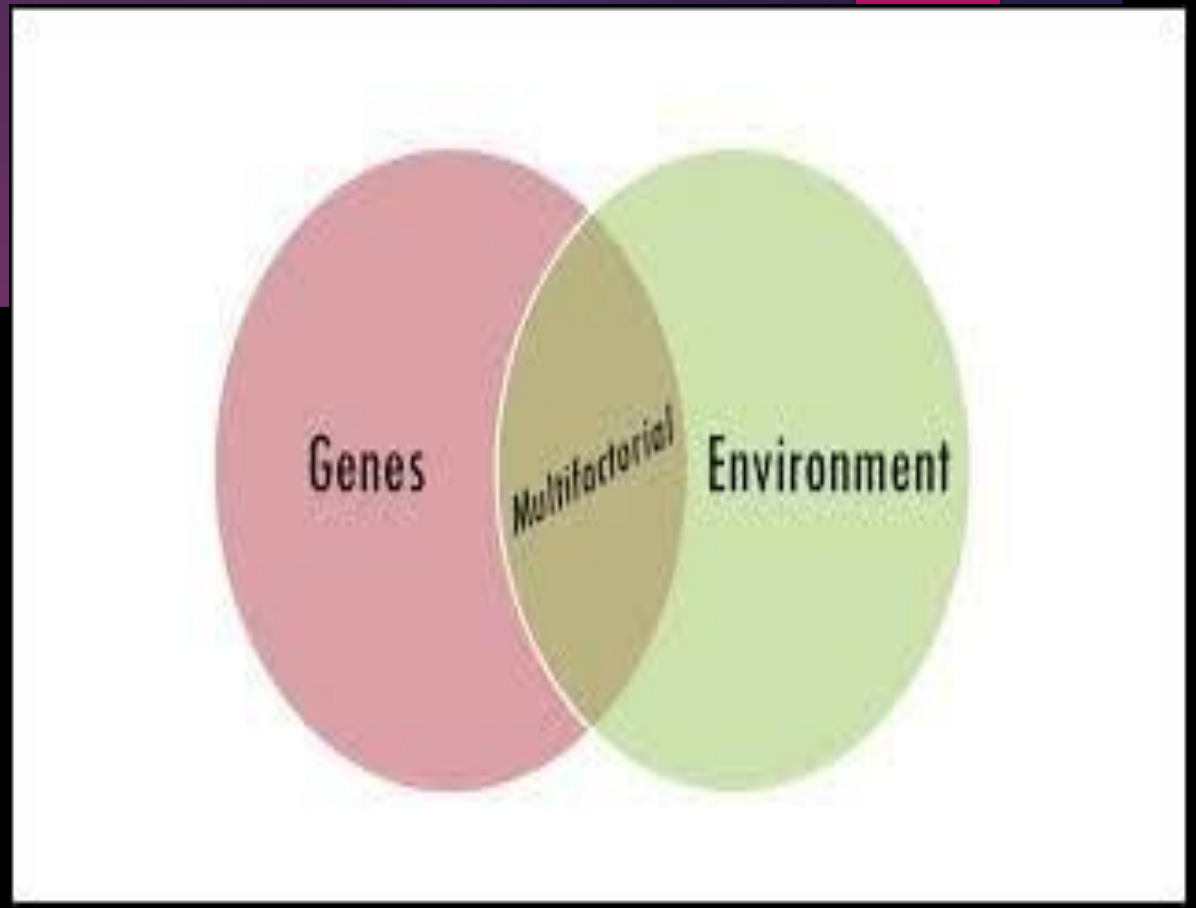
Mitochondrial disorders

- **MERRF syndrome** (or myoclonic epilepsy with ragged red fibre) has symptoms of myoclonus, seizures, cerebellar ataxia, myopathy, and ragged red fibers (RRF) on muscle biopsy.
- Four point mutations in the genome are associated with MERRF: m.A8344G, m.T8356C, m.G8361A, and m.G8363A.

- **Leber's hereditary optic neuropathy (LHON)** is a degeneration of retinal ganglion cells (RGCs) and their axons that leads to an acute or subacute loss of central vision.
- These mutations are at nucleotide positions 11778 G to A, 3460 G to A and 14484 T to C, respectively in the ND4, ND1 and ND6 subunit genes of complex I of the oxidative phosphorylation chain in mitochondria.

4. Multi Factorial Diseases

- Also known as polygenic/ mutations
- These disorders involve variations in multiple genes, often coupled with environmental causes
- Examples: diabetes mellitus, asthma, heart disease, hypertension



Type 2 diabetes mellitus

- As of 2011 more than 36 genes have been found that contribute to the risk of type 2 diabetes
- GWAS has revealed 65 different loci (where single nucleotide sequences differ from the patient and control group's genomes), and genes associated with type 2 diabetes, including TCF7L2, PPARG, FTO, KCNJ11,NOTCH2, WFS1, IGF2BP2, SLC30A8, JAZF1, HHEX, DGKB, CDKN2A, CDKN2B, KCNQ1, HNF1A, HNF1B MC4R, GIPR, HNF4A, MTNR1B, PARG6, ZBED3, SLC30A8, CDKAL1, GLIS3, GCKR, among others.

How to approach?

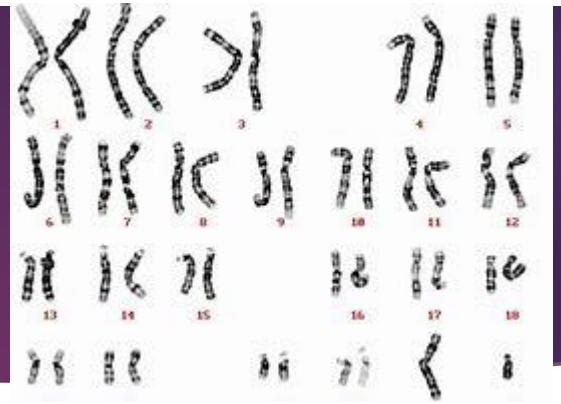
- Family history
  - Significant of pedigree
- Features/ findings
- Known/unknown disease/disorders
- Investigations
- Treatment / management offered
- Family planning

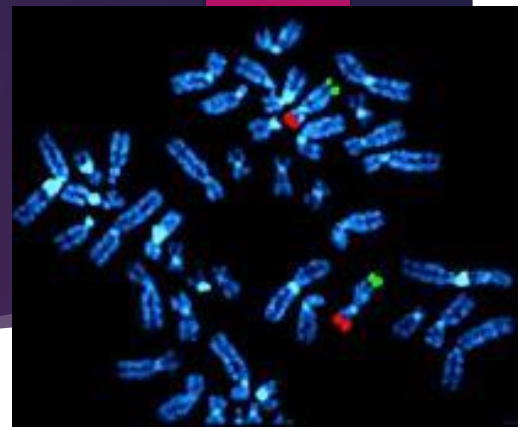
Genetic counselling

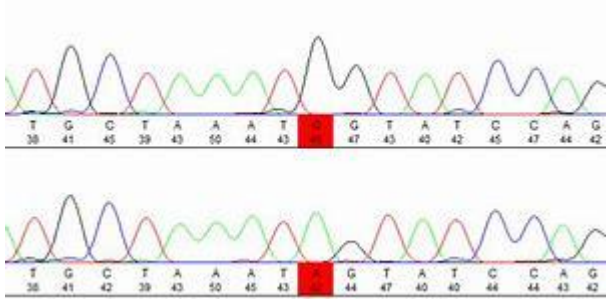
a process of communication and education that addresses concerns relating to the development and/or transmission of a hereditary disorder

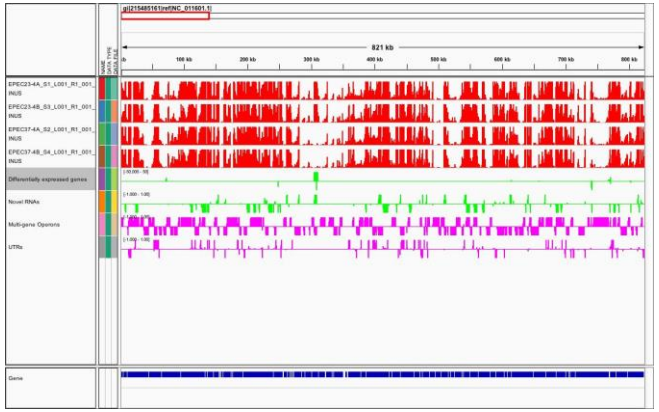
Investigations

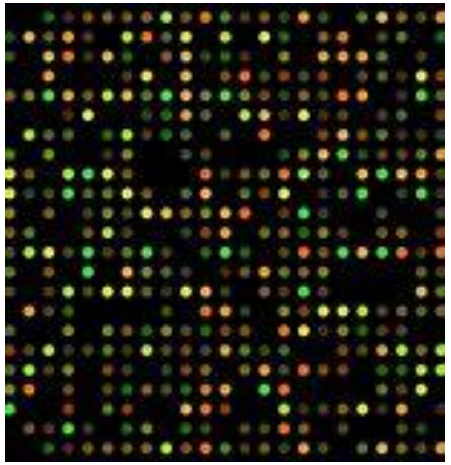
- Cytogenetic analysis
- Fluorescent *in situ* hydridization (FISH)
- Polymerase chain reaction (PCR)
- Sanger sequencing
- Microarray
- Next generation sequencing











Somatic Cell Disorder- Cancer

Conclusion

- Genetic disorders
  - Single gene disorders
  - Chromosomal disorders
  - Multifactorial disorders
- Principles of inheritance
  - Autosomal dominant, autosomal recessive, X-linked, Y-linked, mitochondrial
- Common genetic disorders/syndromes