GENETIC DISORDERS AND MODE OF INHERITANCE

HUMAN GENOME CENTRE

Learning outcome

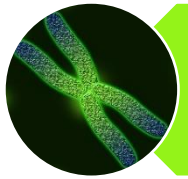
Able to describe the modes of inheritance and several related genetic disorders

Genetic Disorders

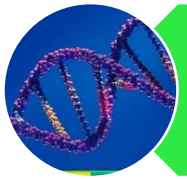
- An illness caused by one or more abnormalities in the genome
- Range from small mutation in DNA or in additional or deletion of entire chromosome or set of chromosomes.
- Most of genetic disease are rare, affected one person in every several thousands or millions
- Heritable (germline) or may not heritable (new mutations or changes in DNA)

Genetic Disorders

Single gene disorder

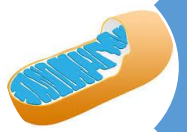


Chromosome abnormalities



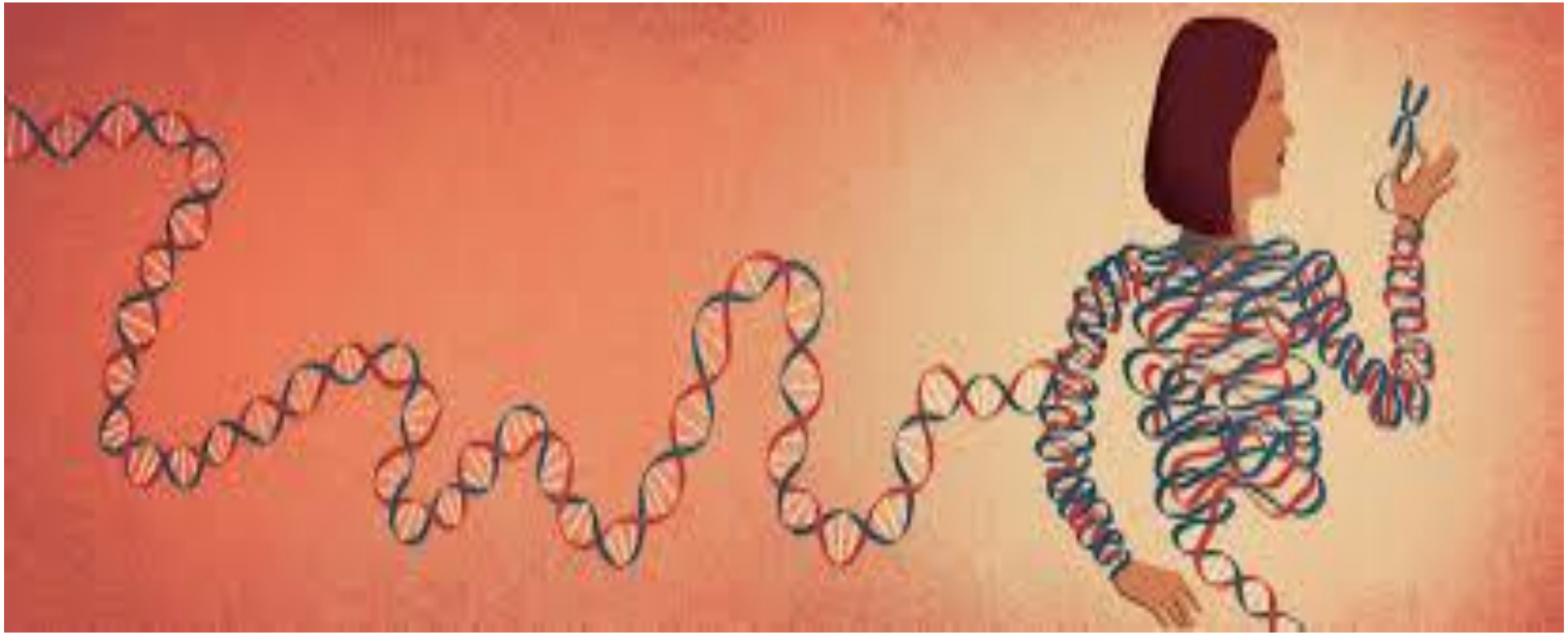
Multifactorial disorder

Acquired somatic disorder



Mitochondrial disorder

1. Single Gene Disorder



Single gene disorder

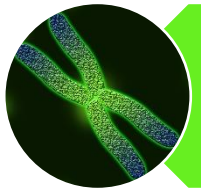
- When a certain gene is known to cause a disease
- Also known as Monogenic/ **Mendelian disorder.**
- Involve mutations in the DNA sequence of single gene, as a result, the protein the gene codes id altered or missing.
- Over 6000 human diseases caused by single gene defect
- Example: Cystic fibrosis, sickle cell disease, Fragile X syndrome, muscular dystrophy, Huntington disease.

Mode of Inheritance

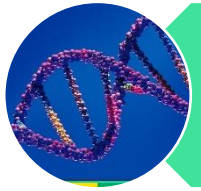
Is the manner in which a genetic trait or disorder is passed from one generation to the next.

Inheritance patterns of single gene disorders

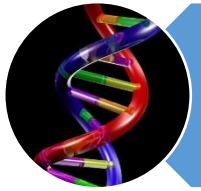
Autosomal dominant



Autosomal recessive

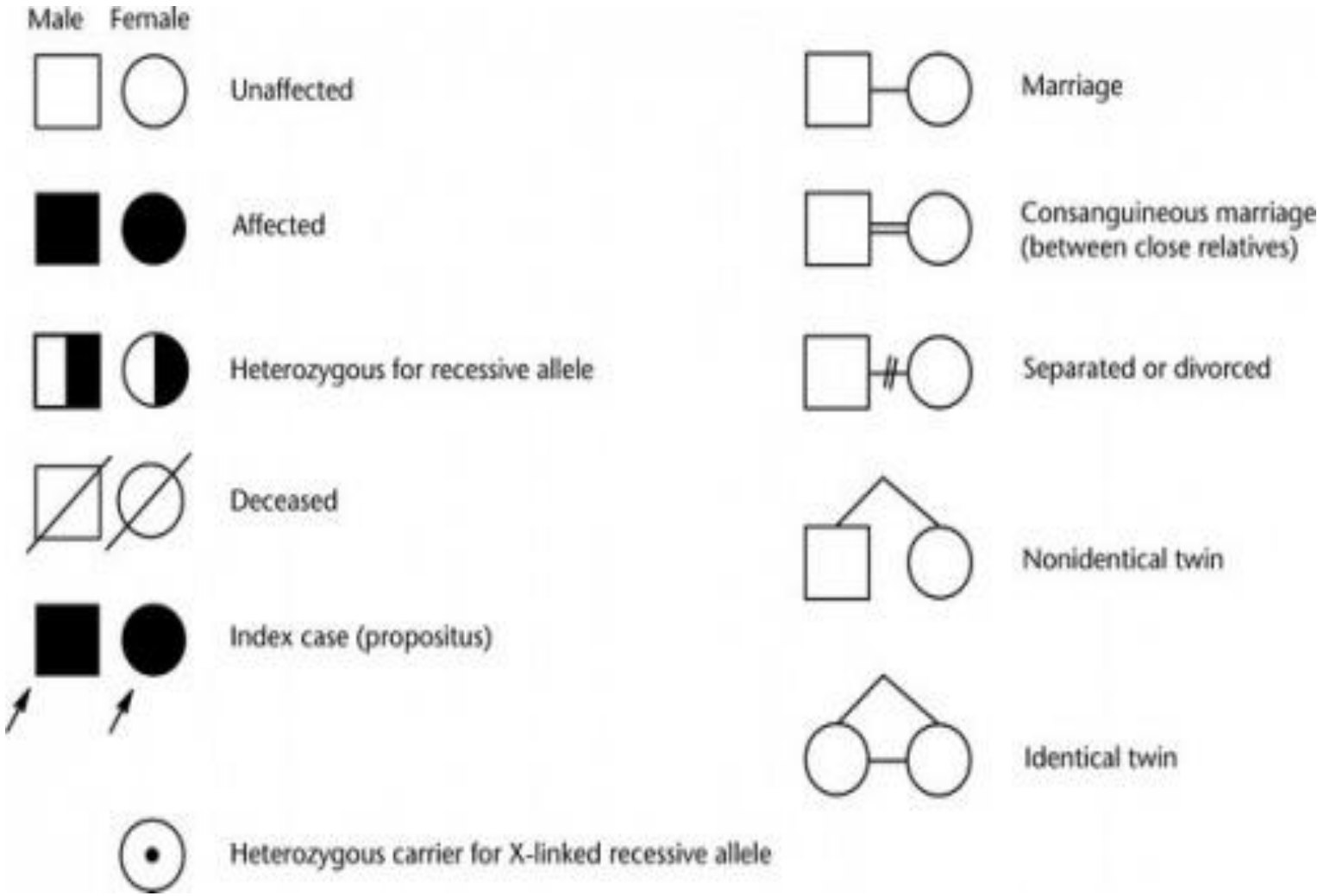


X/Y-linked dominant



X-linked recessive

Pedigree symbol



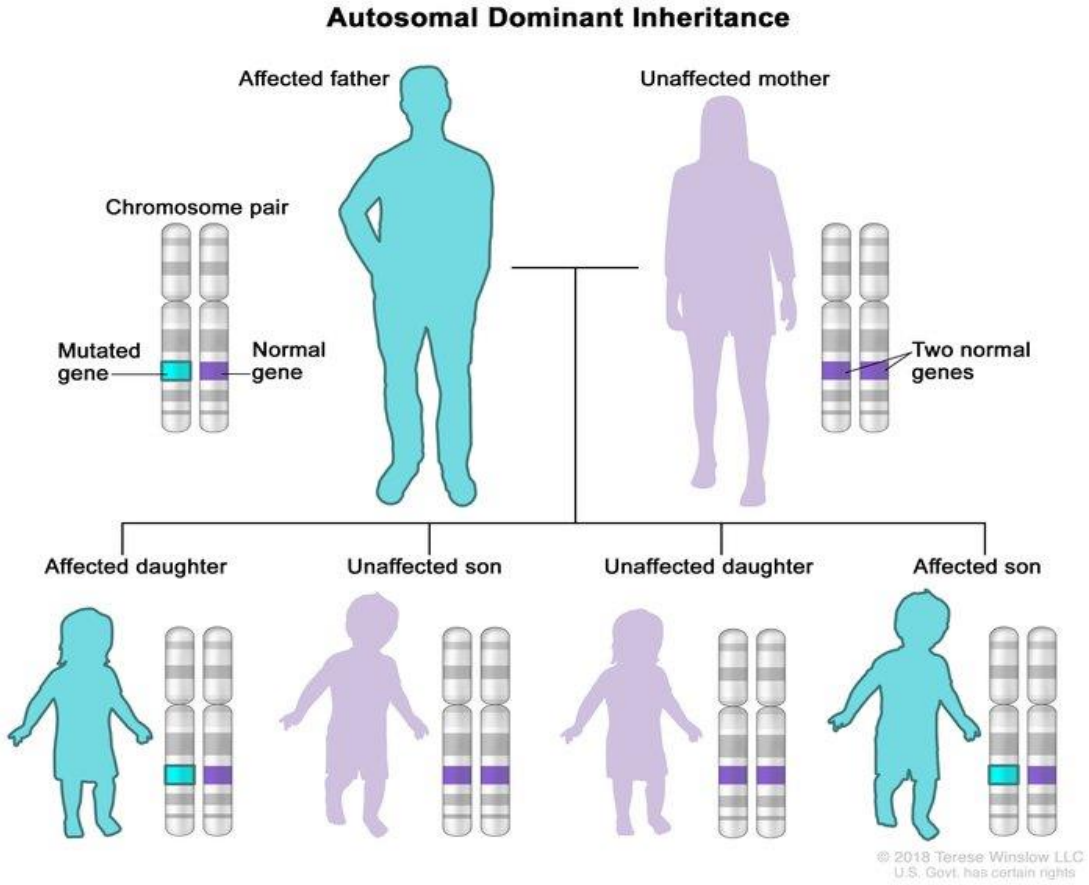
Autosomal dominant

- Abnormal/mutated gene located on one pair of autosome chromosome
- One mutated copy of the gene, is sufficient to cause the disease
- Examples: Noonan disease, Huntington disease, neurofibromatosis, and polycystic kidney disease

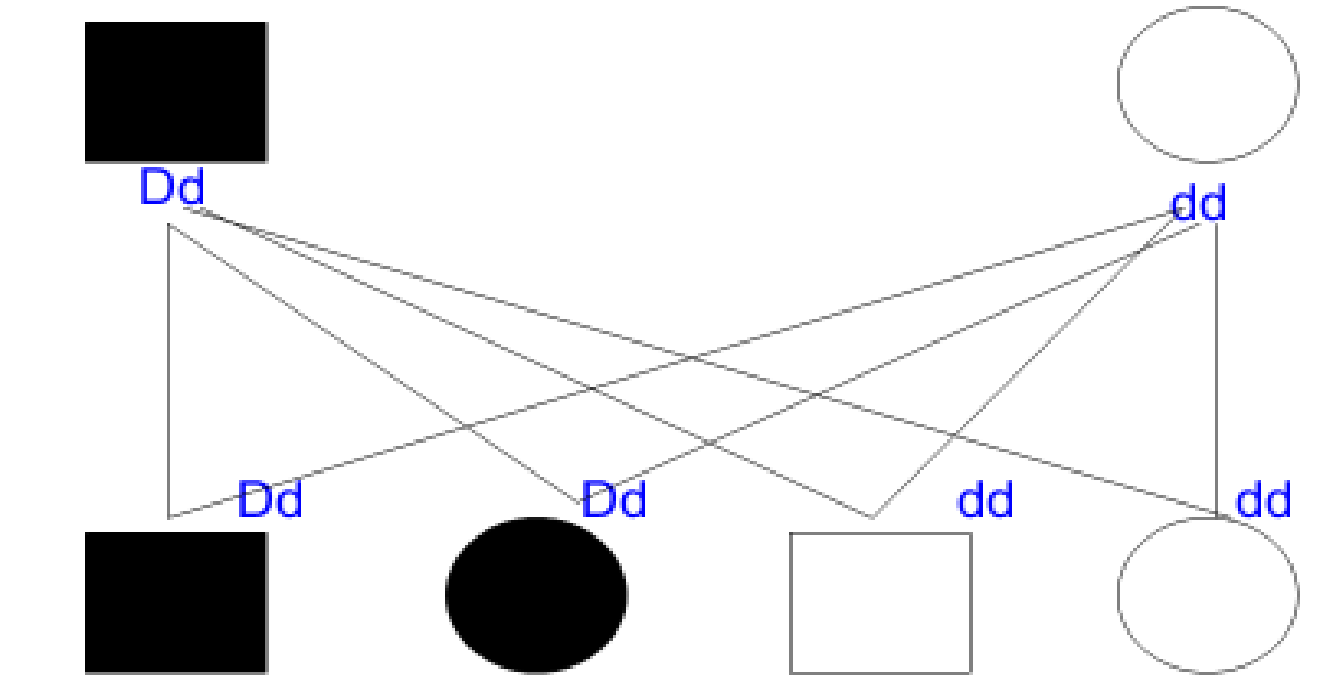
i. Autosomal dominant

Features:

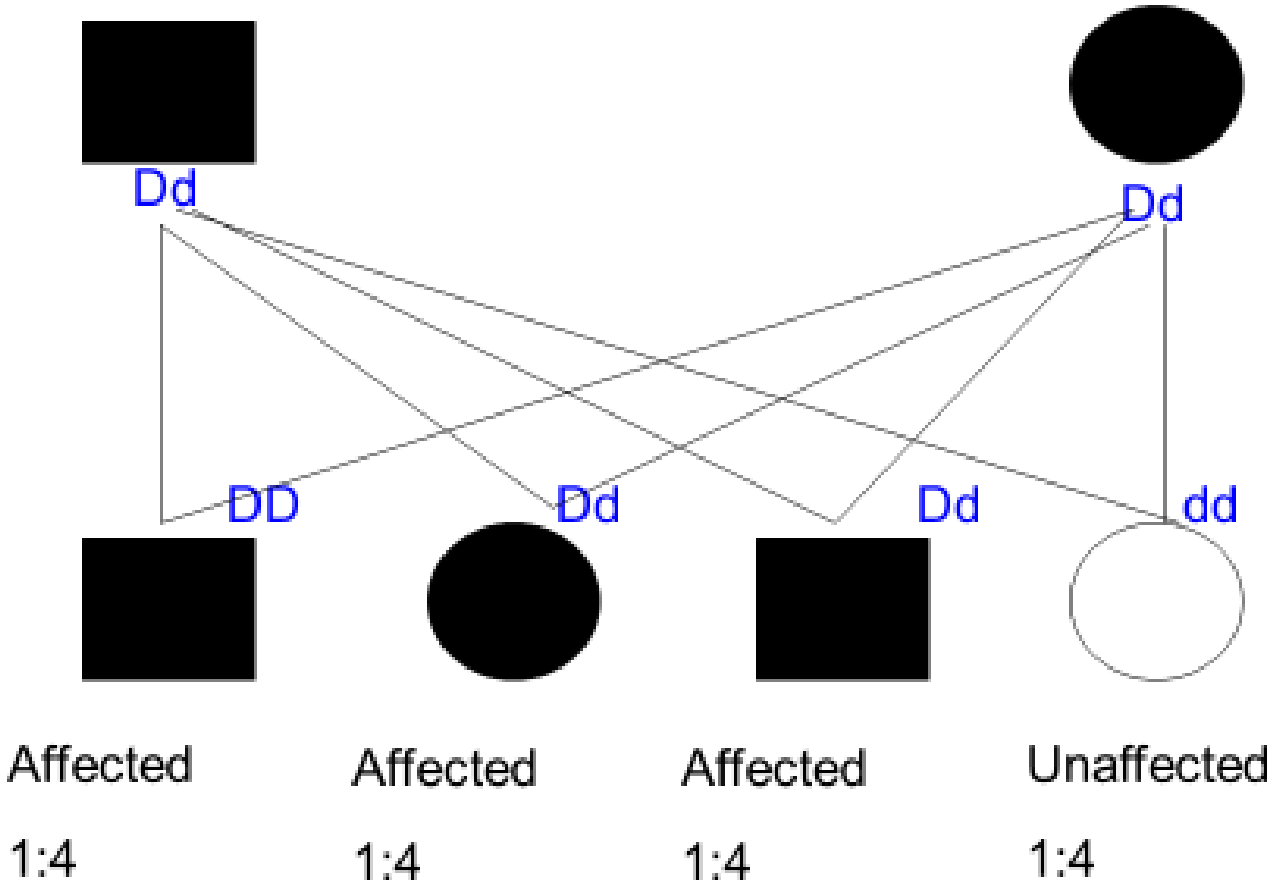
- affect both males & females
- males & females affected with equal frequency and severity
- appears in every generations
- transmission by the mother or father
- vertical transmission
- unaffected parent cannot transmit to children
- the chance a child will inherit the mutated gene is 50%

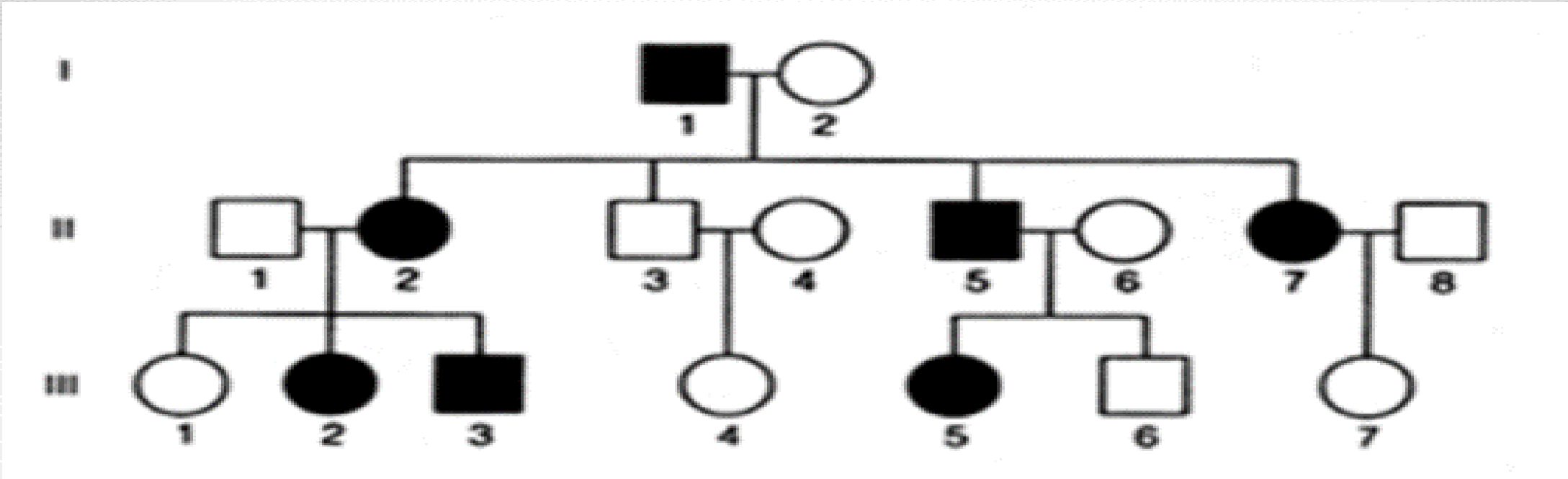


A) One parent has a dominant mutation



B) Both parents have a dominant mutation



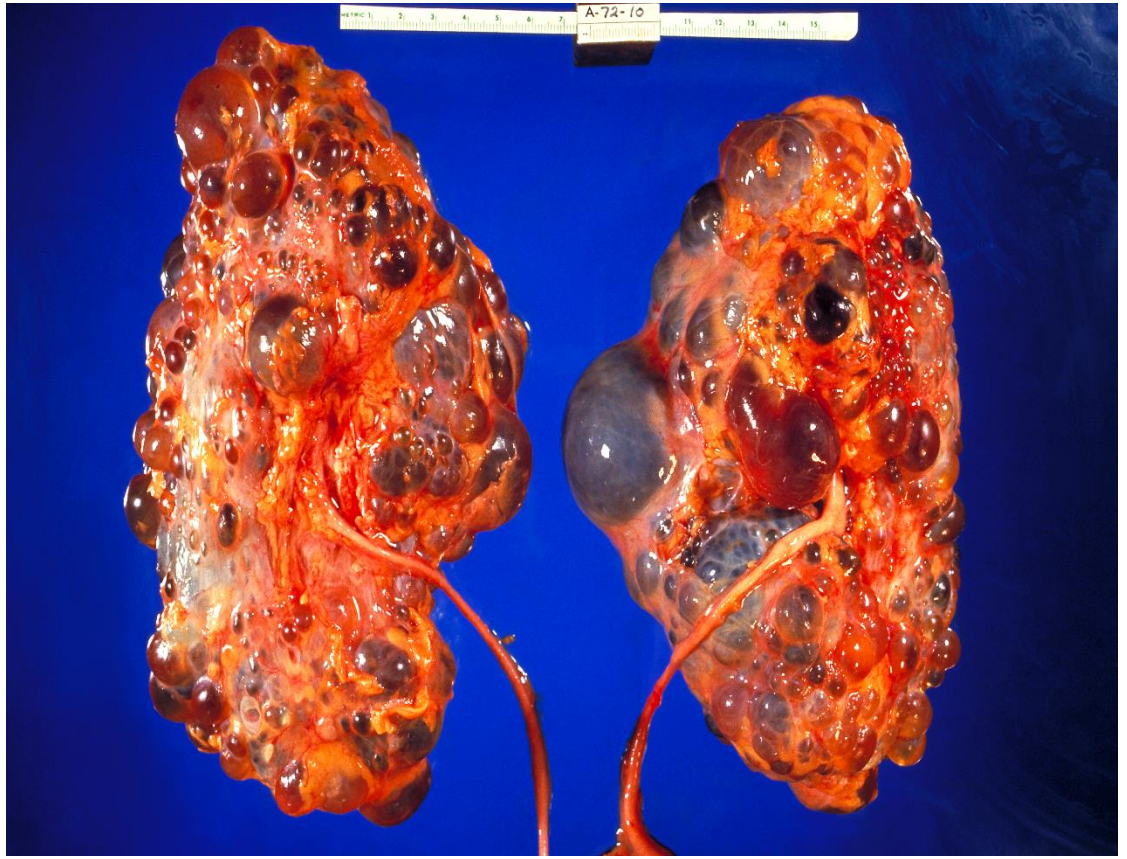


1. Vertical transmission
2. Male and female affected
3. Mum and dad can transmit to male and female child
4. Skip generation
5. Variable penetrance

Autosomal dominant

Treacher Collins syndrome- due to mutation *TCOG1* gene

Polycystic kidney disease (PKD) due to mutation in *PKD1* and *PKD2* gene

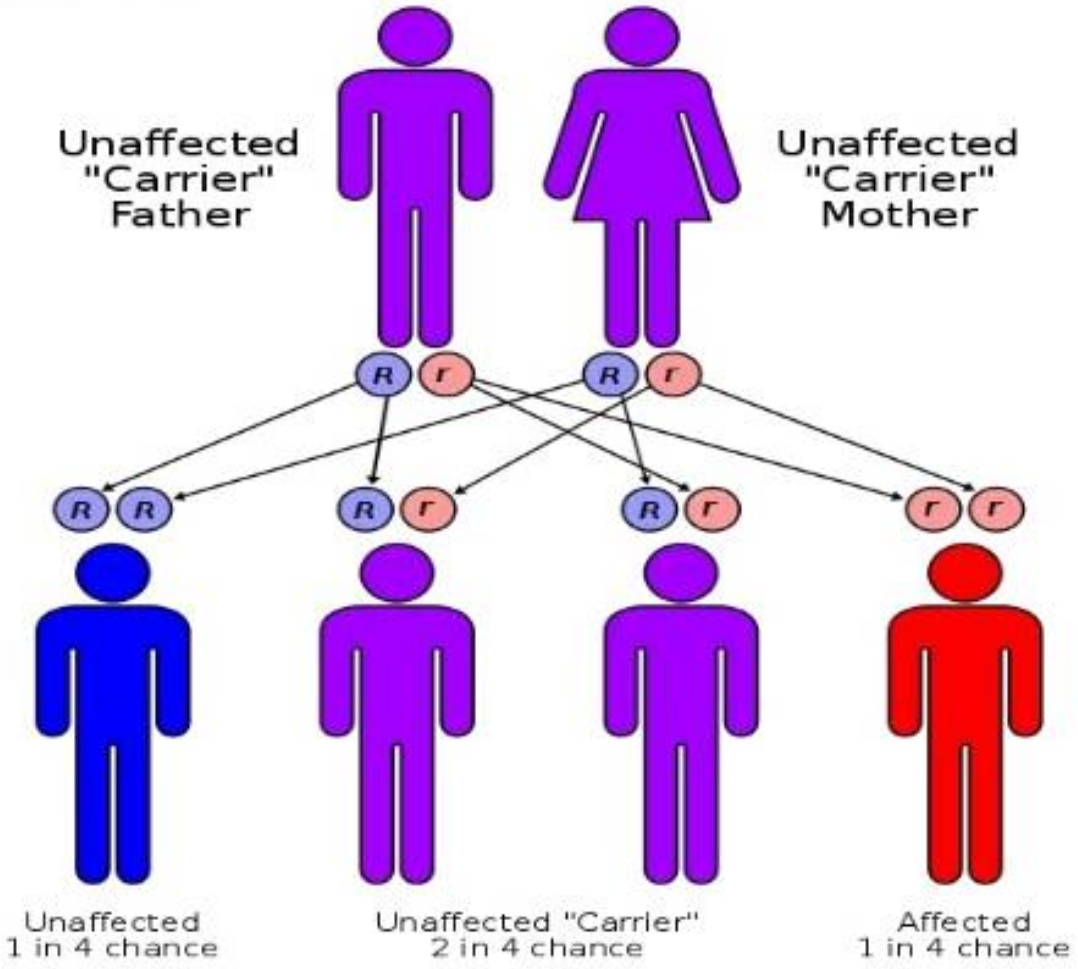


ii. Autosomal recessive

Two copies of the gene must be mutated for a person to be affected

The parents are called carriers of the disorder because they have one normal copy of the gene and one mutated copy of the gene

But they do not show symptoms of the disorder.



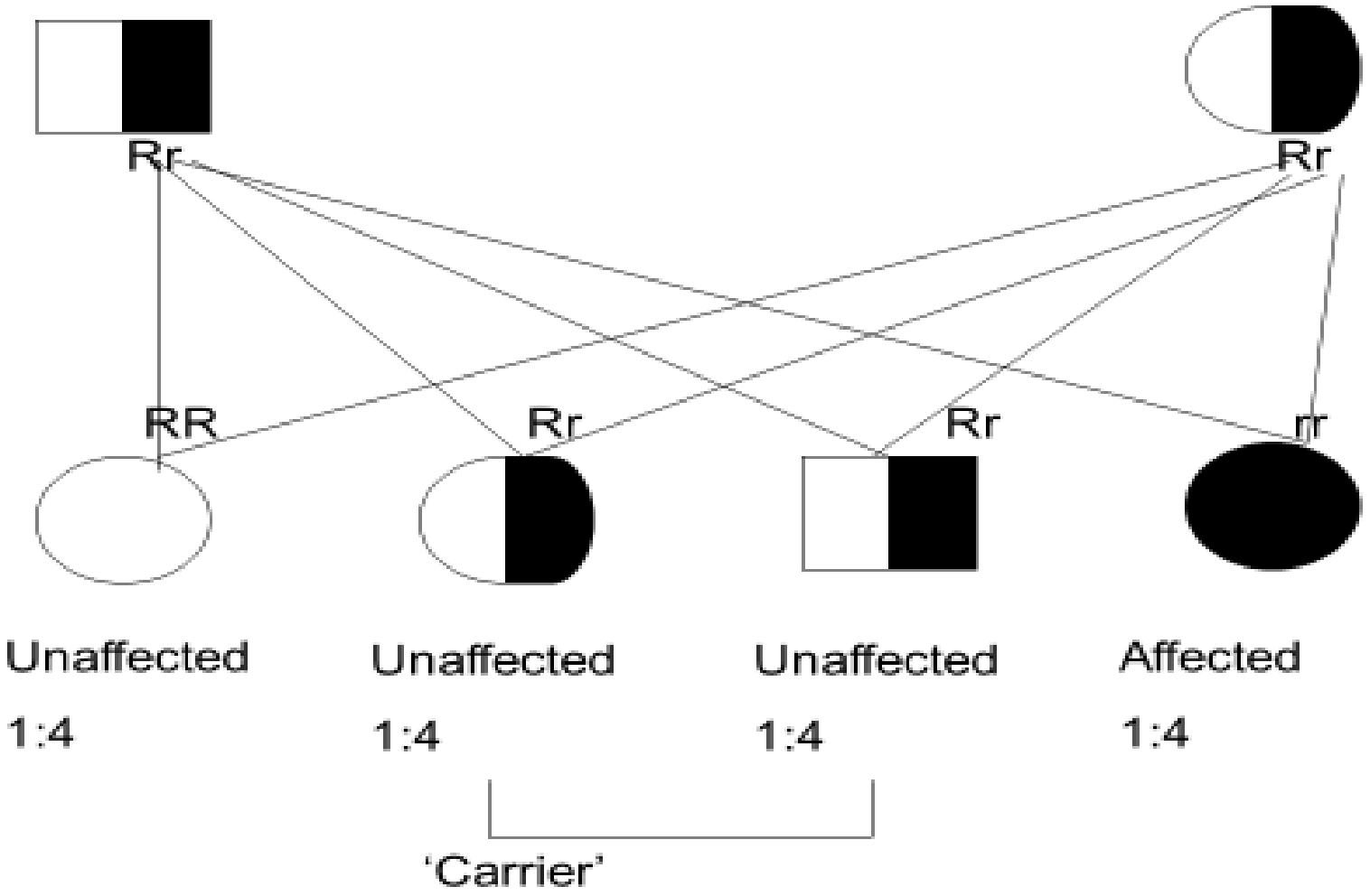
Autosomal recessive

Features:

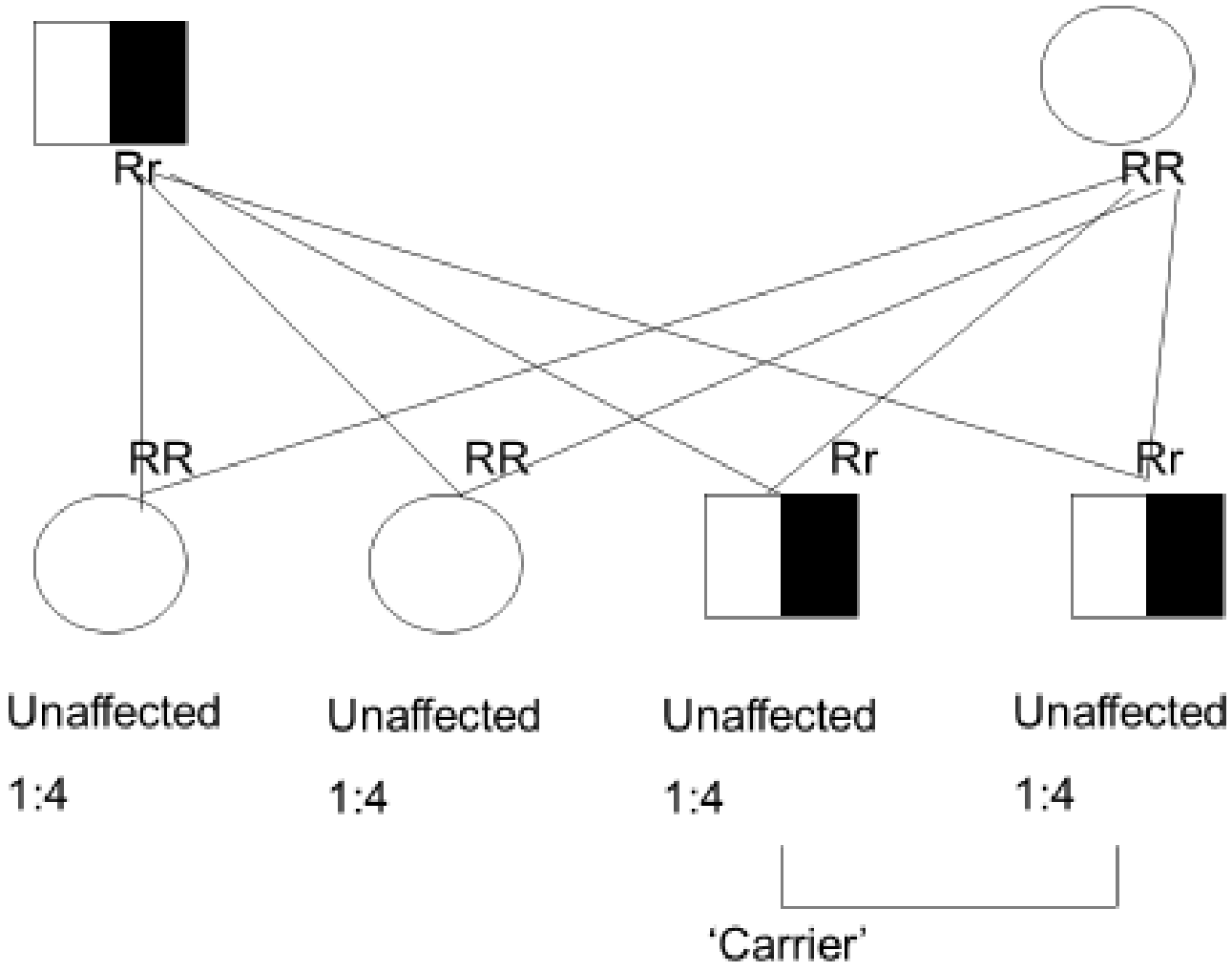
- both parents carry the same recessive genes (both are heterozygous carrier)
- parents do not express the abnormalities
- parents of affected children often consanguineous
- horizontal transmission

Examples: cystic fibrosis (CF), sickle cell anemia (SC), Tay Sachs disease

A) Both parents carry of the same recessive gene



B) One parent is a carrier of a recessive gene



Autosomal Recessive Disorder	
Metabolic	Cystic fibrosis , Phenylketonuria Galactosemia , Homocystinuria Glycogen storage disease
Hematopoietic	Sickle cell anaemia Thalassemias
Endocrine	Congenital Adrenal hyperplasia
Skeletal	Alkaptonuria
Nervous	Friedrich ataxia Spinal muscular atrophy

Sickle cell anemia

Inheritance Pattern:

-Autosomal recessive

Physical Effects:

-Shortness of breath, fatigue, delayed growth and development in children

-May experience painful episodes of anemia resulting in organ damage

iii. Sex-linked Inheritance

- Refers to the pattern of inheritance shown by genes that are located on either of the sex chromosome (X or Y).

- Genes carried on the X chromosome are referred to as being X-linked, and those carried on the Y chromosome are referred to as exhibiting Y-linked

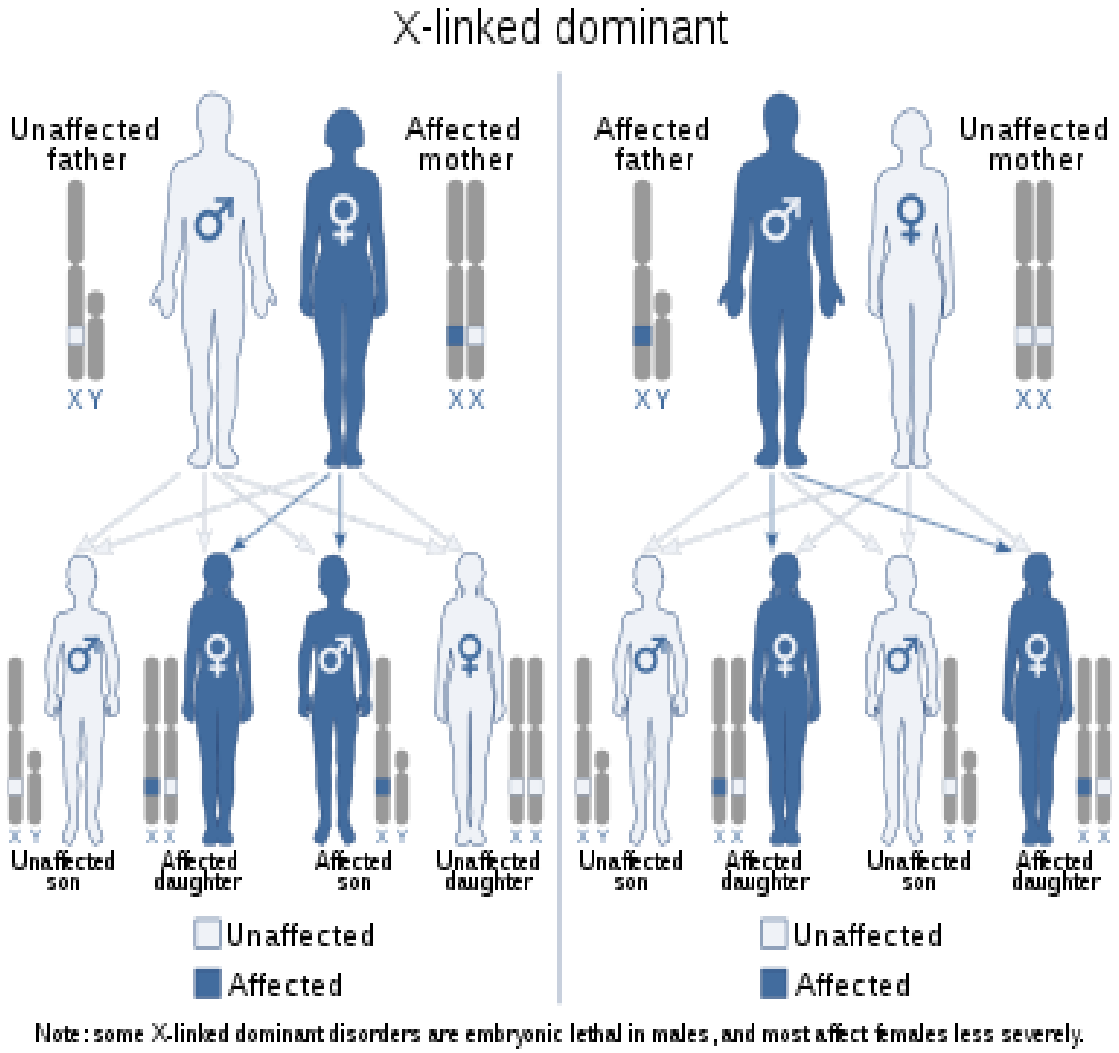
- X-linked Dominant
- X-linked Recessive
- Y-linked

iii(a1). X-linked dominant

- **Manifest in the heterozygous female as well as in the male who has the mutant allele on is single X chromosome.** ***(A single copy of the mutation is enough to cause the disease in both males (who have one X chromosome) and females (who have two X chromosomes).***

- **Very rare.**
- **Superficially resemble AD trait bcoz both the daughters and sons of an affected female have 50% chance of being affected.**

- **But, affected male transmits the trait to all daughter and none to his sons.**

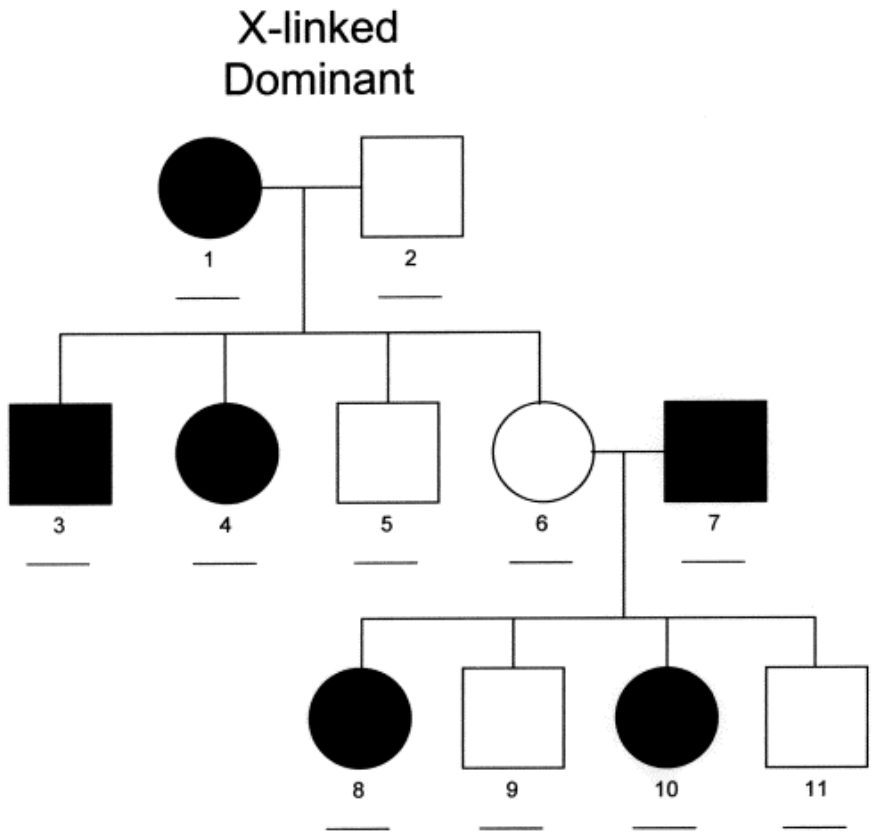


X-linked dominant

- **There is an excess of affected females and direct male to male transmission cannot occur.**

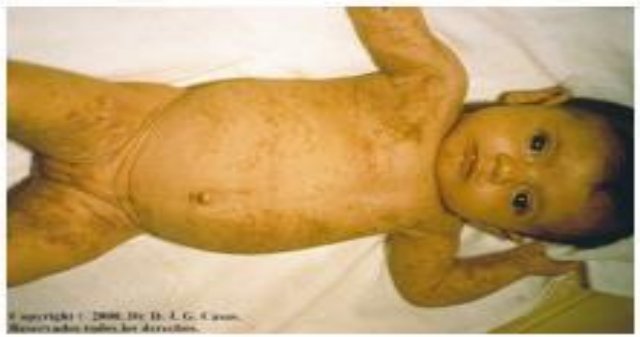
- **In some disorder, it is lethal in hemizygous males (resulting in no males in that family and excess of females, half of whom will be affected)- due to absence of functional X genes**

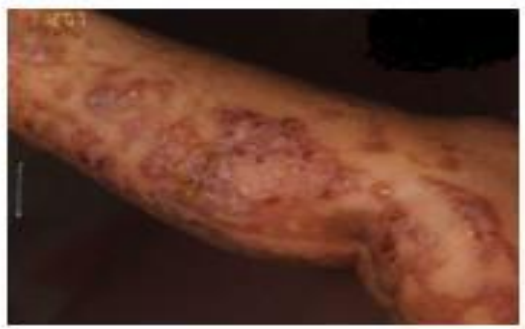
- **Example: X- linked hypophosphatemia, X-linked Charcot-Marie-Tooth, Incontinentia pigmenti**

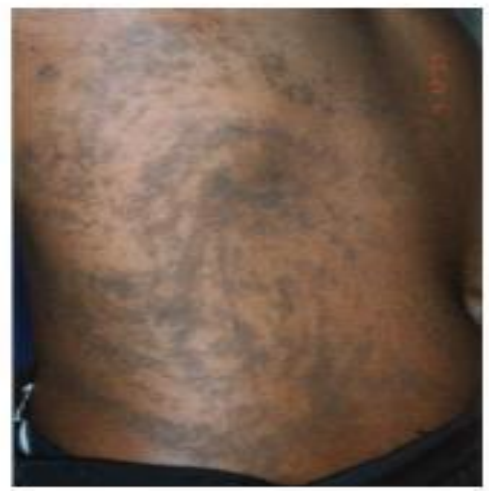


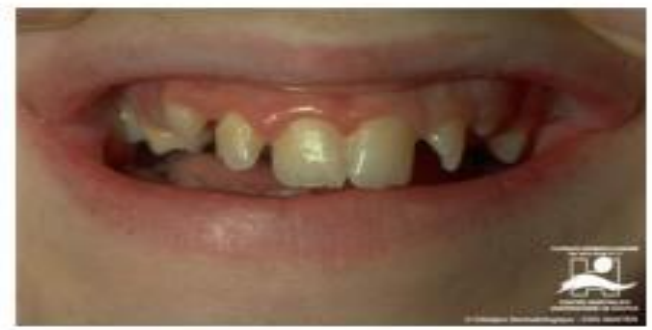
Incontinentia pigmenti

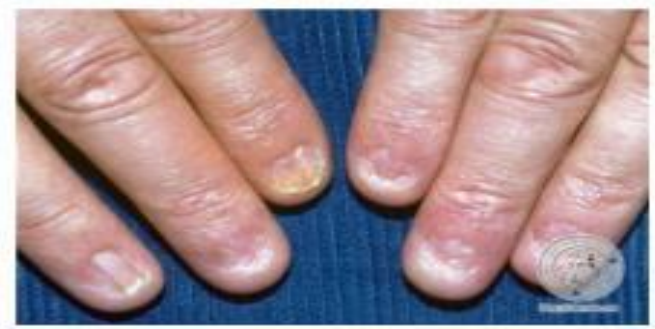
- severe X-linked genodermatosis, associated with mutations in **the *NEMO* gene** (NFkB essential modulator),
- affects almost exclusively females (males die *in utero* before the second trimester),
- highly variable in clinical manifestations but always associated with skin defects.





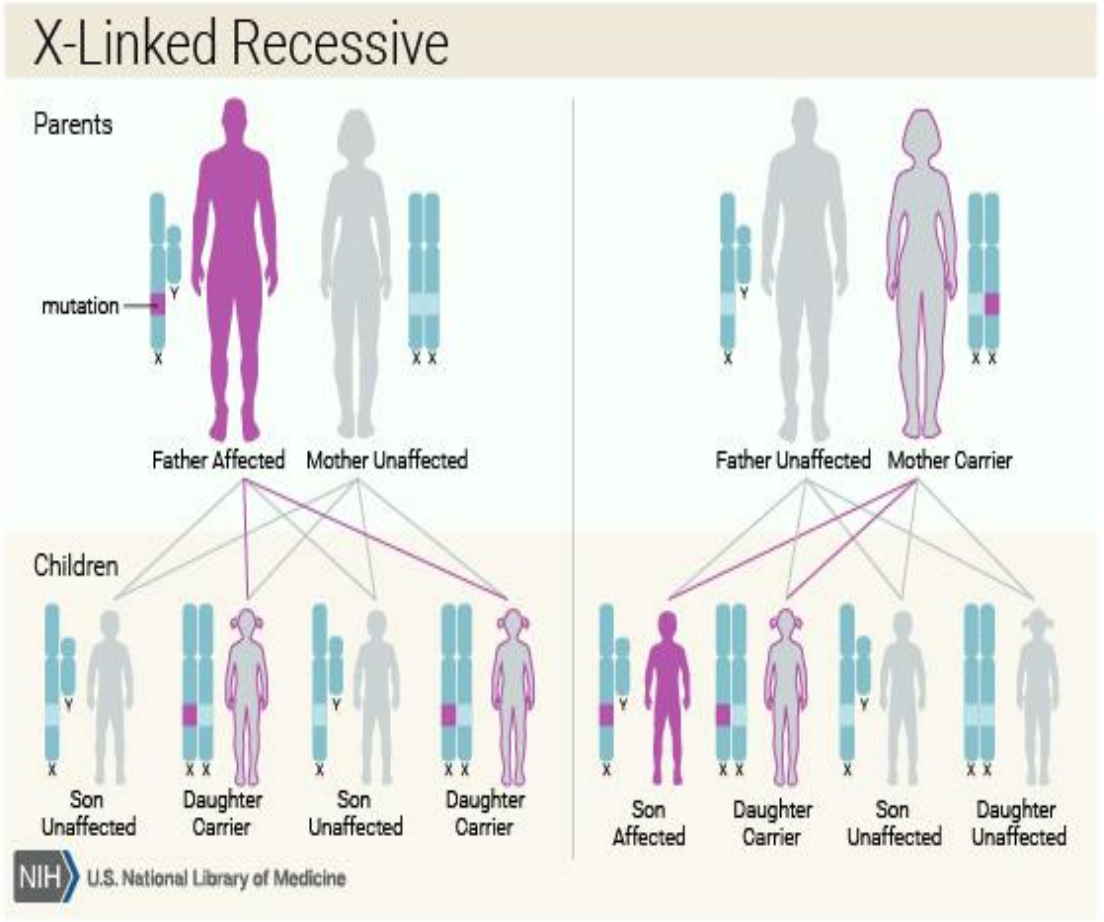






iii(a2). X-linked recessive

- **Are usually only seen in males.**
- **Males only have one X chromosome, so if a male inherits a changed gene on his X chromosome (which is always inherited from his mother), then he does not have another copy of the working gene to compensate.**
- **Females with one copy of a changed gene on one X chromosome are called carriers of X-linked recessive disorder. It is rare for a female to have the changed gene on both her X chromosomes.**



- **In most cases, females who are carriers do not show symptoms because the working copy of the gene compensates for the non-working copy of the gene.**

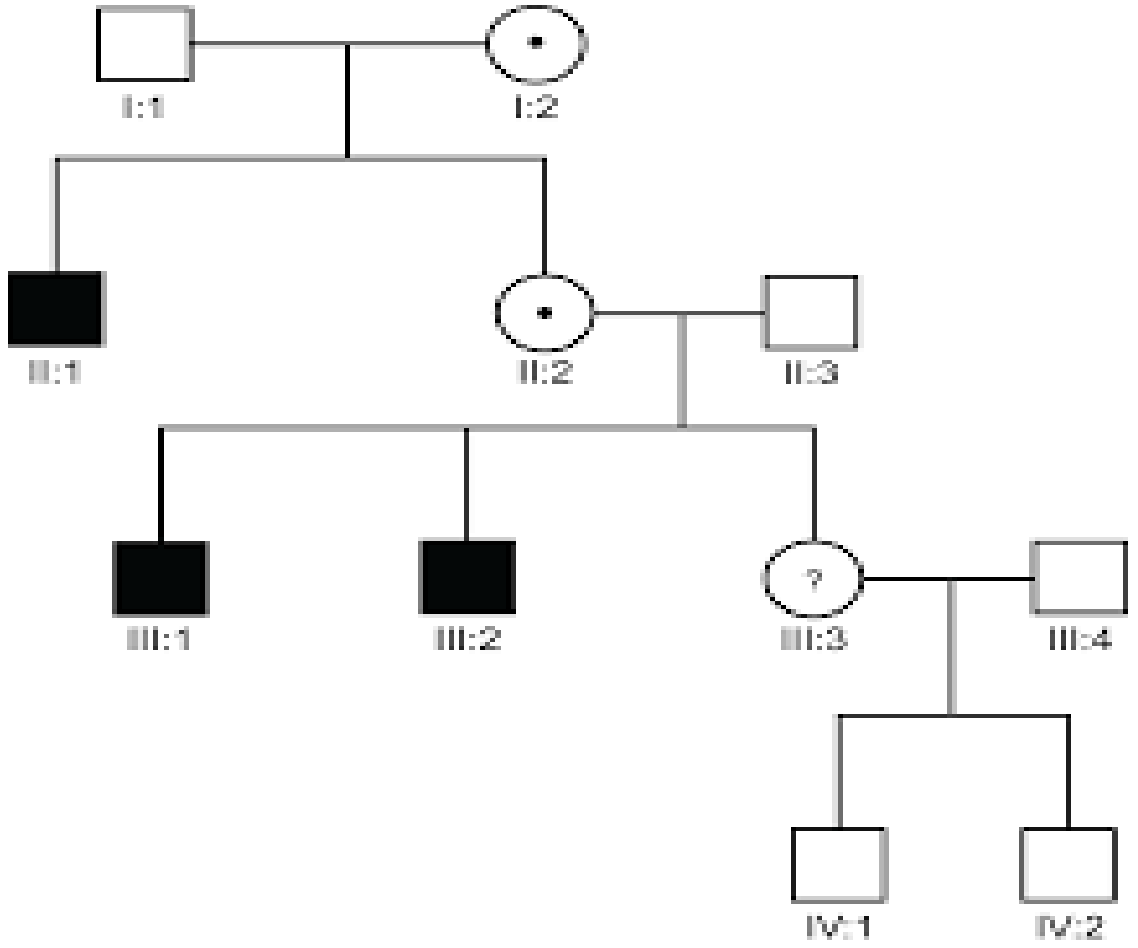
- **Carrier females have a 25% of having a son with the disorder, a 25% chance of having a son without the disorder, a 25% chance of having a carrier daughter and a 25% chance of having a daughter who is not a carrier.**

- **Males with an X-linked recessive disorder cannot pass the disorder to their sons, but 100% of their daughters will be carriers. *‘knight’s move’***

X linked recessive

more than one generation involved with the disease

Example: hemophilia, Duchenne muscular dystrophy, red-green clolour blindness, X linked icthyosis



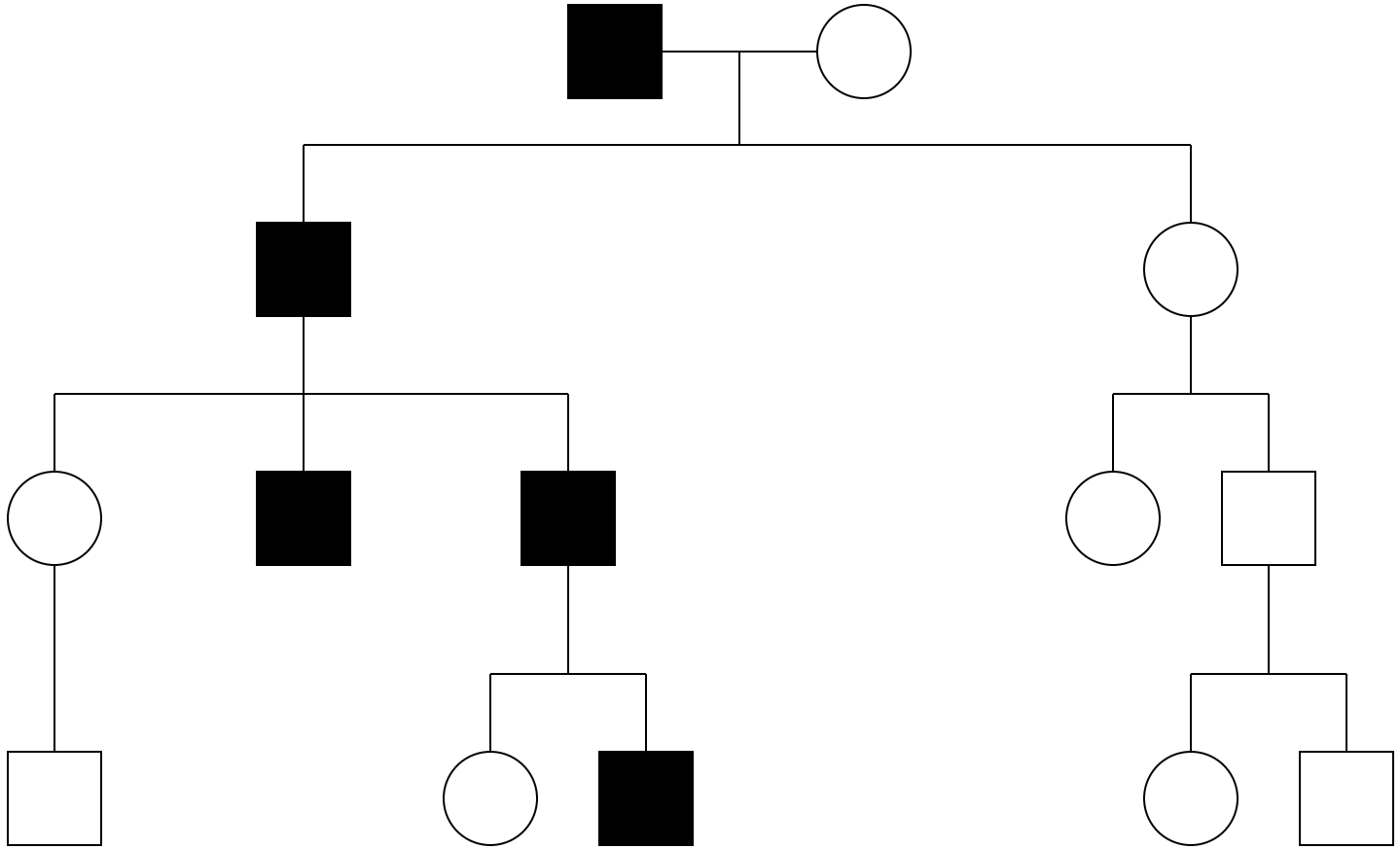
X-linked recessive

- **Duchenne muscular dystrophy** (**DMD**) and Becker muscular dystrophy are caused by **mutations** in the dystrophin-encoding **DMD gene**.

iii (b). Y-linked Inheritance

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

Y linked disorders



2. Chromosomal Disorders

What is chromosome abnormalities?

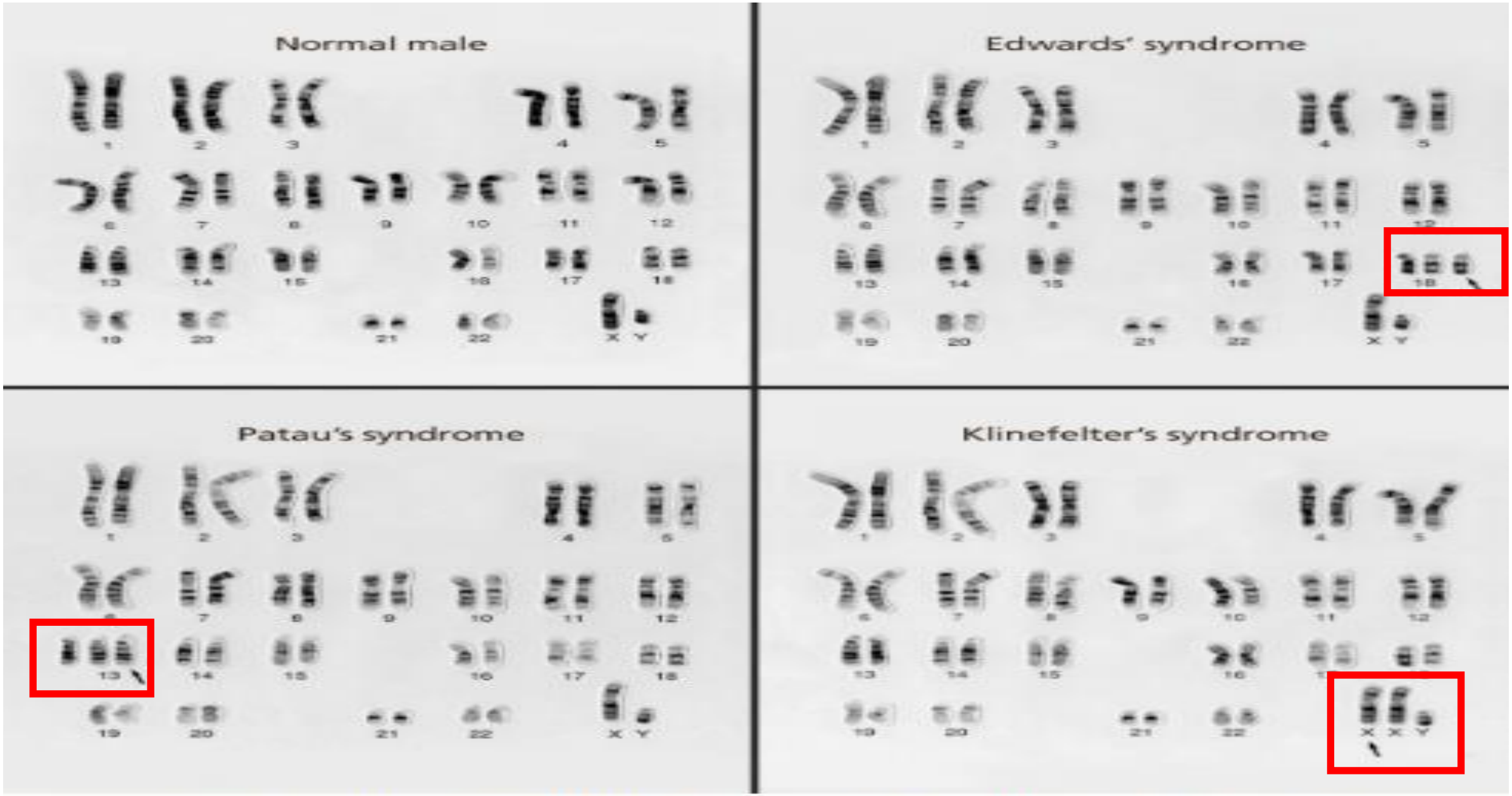
Results from a change in the number or structure of chromosomes

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***.

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)



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

Structural Abnormalities

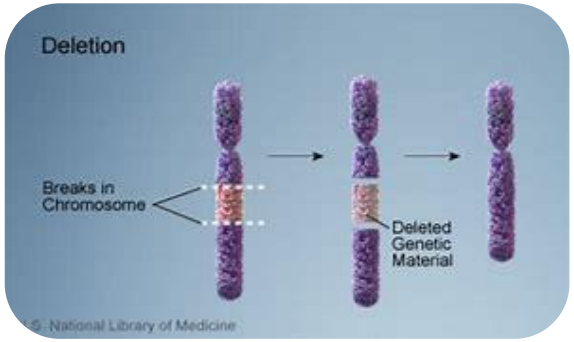
A chromosome's structure can be altered in several ways.

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

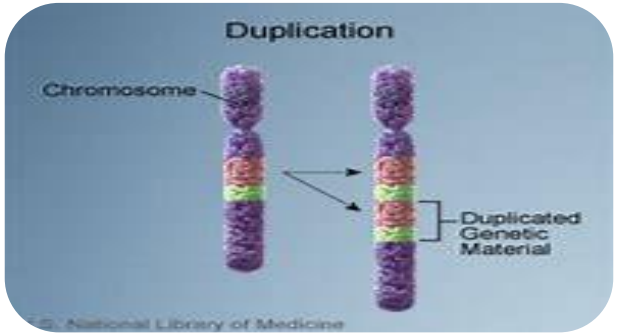
•**Duplications:** A portion of the chromosome is duplicated, resulting in extra genetic material.

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

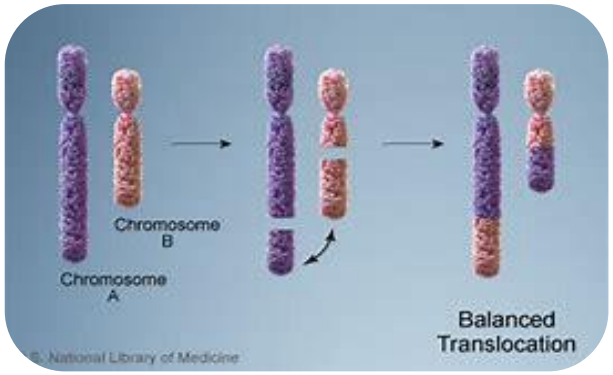
•**Inversions:** A portion of the chromosome has broken off, turned upside down, and reattached. As a result, the genetic material is inverted.



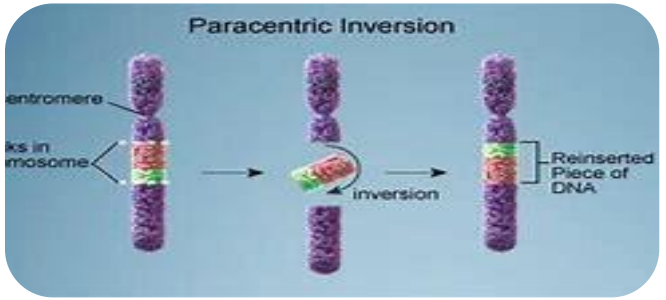
deletion



duplication

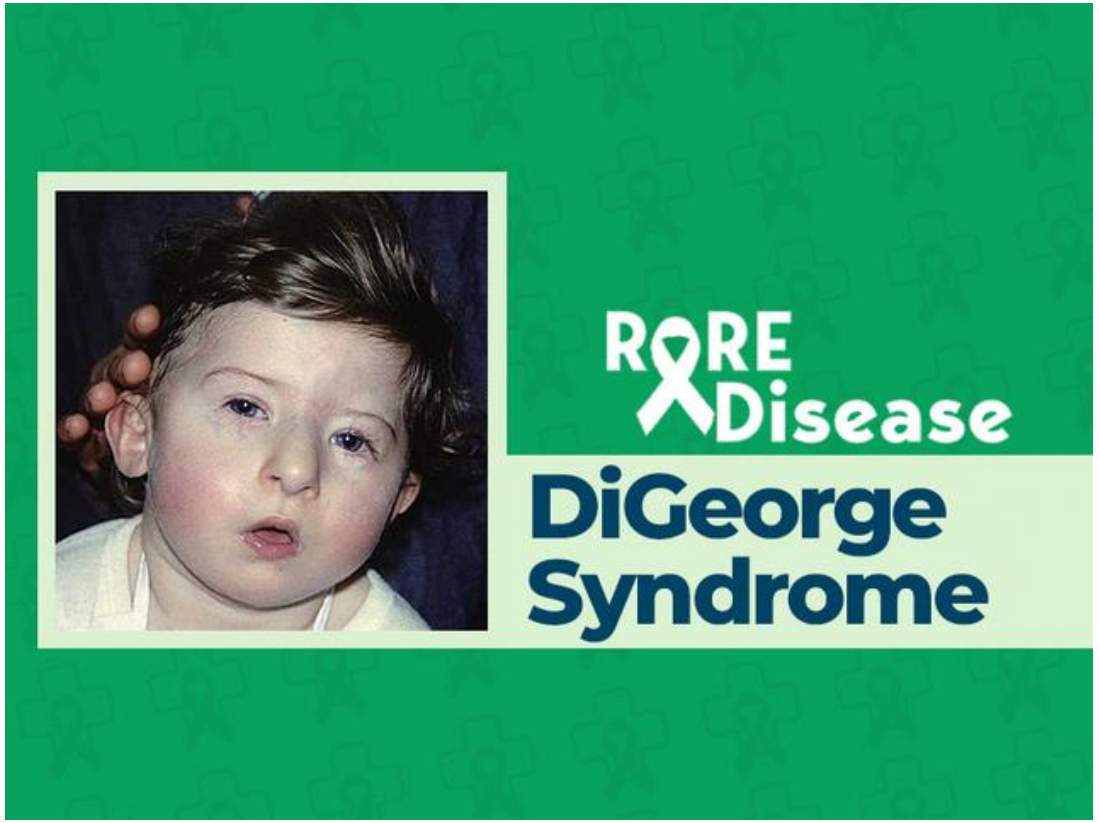


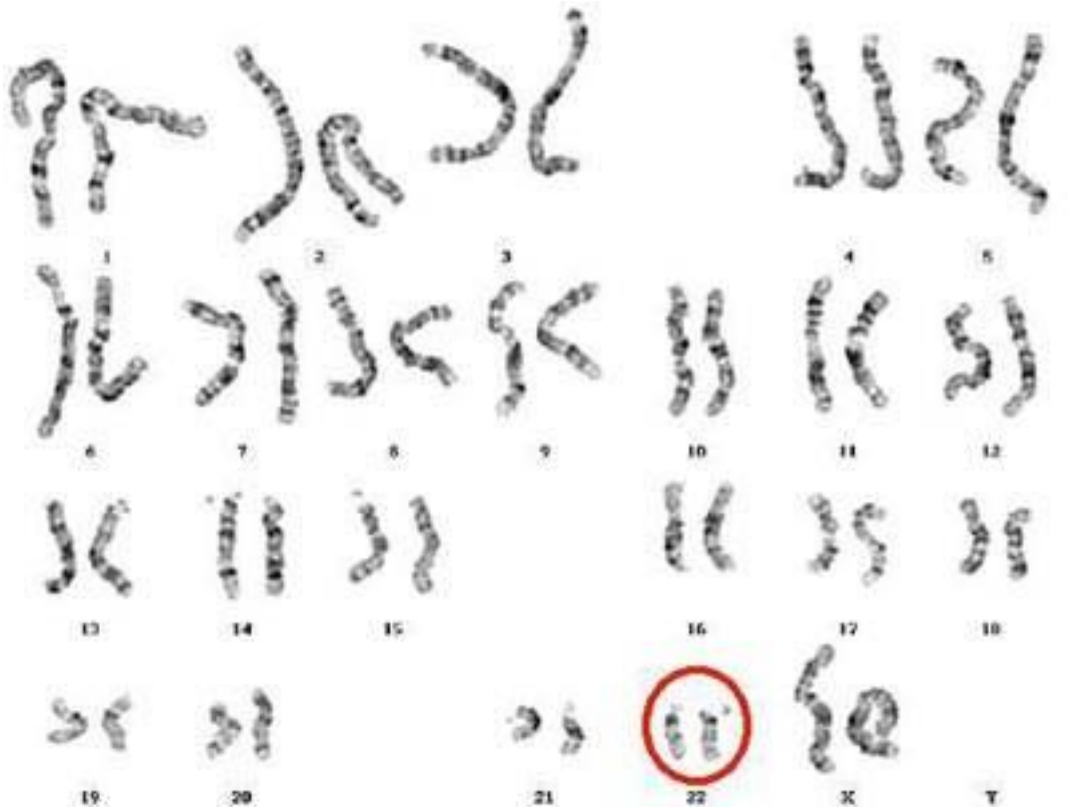
translocation



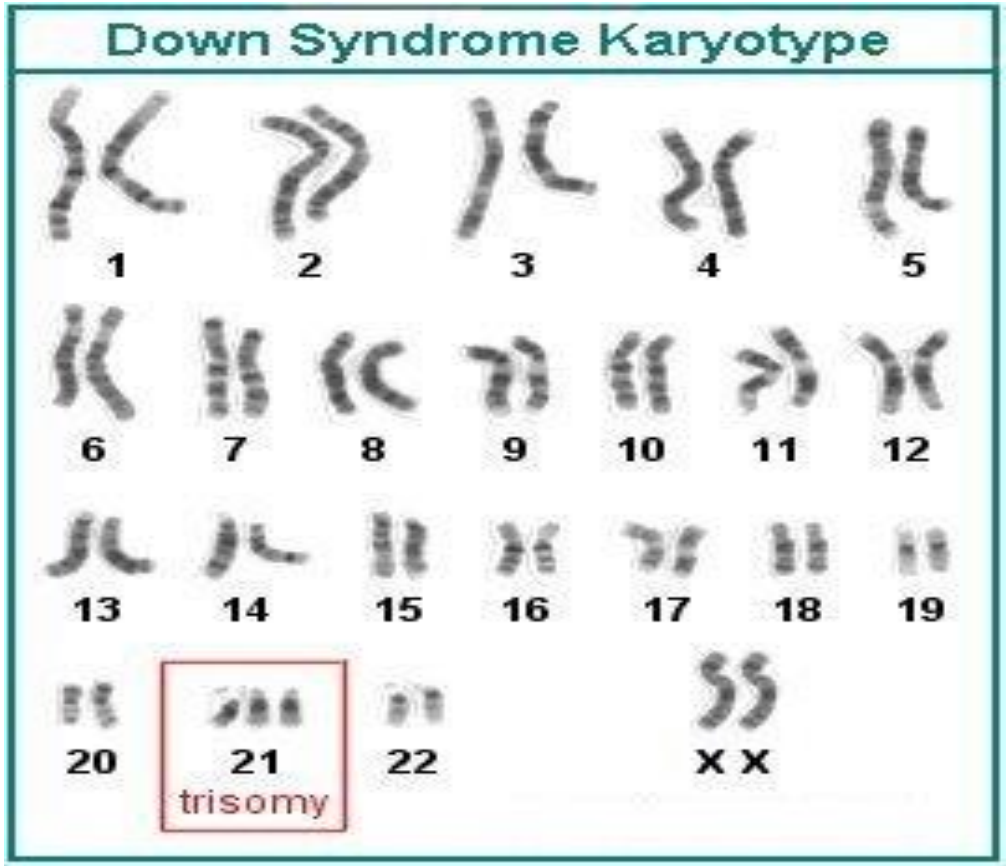
inversion

Microdeletion syndrome-DiGeorge synd-deletion 22q11.2





Chromosomal aneuploidy



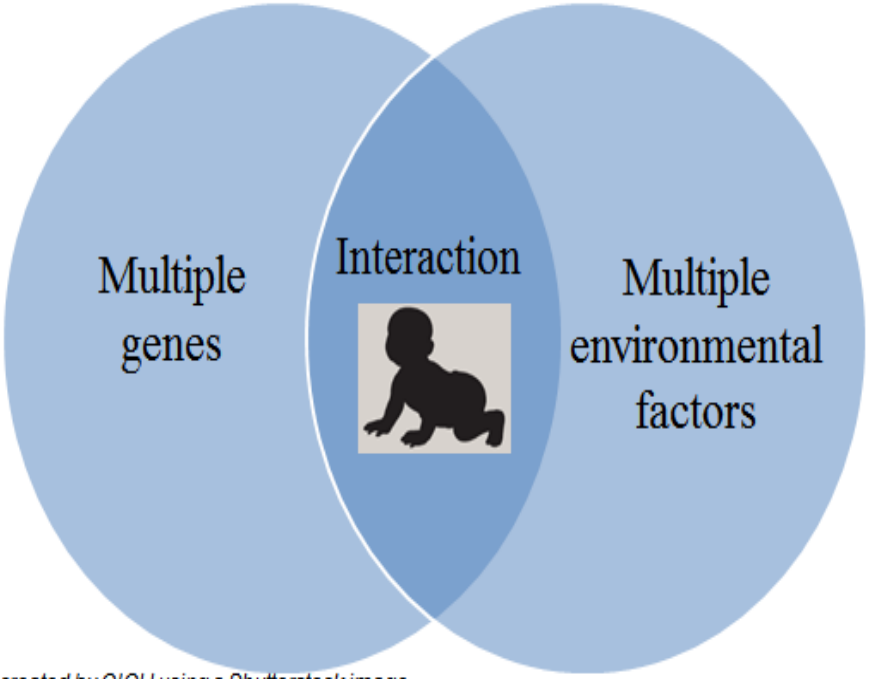
Disorder	Cause	Chromosomes
Down Syndrome	Extra copy of chromosome 21	
Patau Syndrome	Extra copy of chromosome 13	
Edward's Syndrome	Extra copy of chromosome 18	
Triple X Syndrome	Extra X chromosome in females	
Turner Syndrome	One X chromosome missing in females	
Klinefelter Syndrome	Extra X chromosome in males	
XYY Syndrome	Extra Y chromosome in males	
Cri-du-Chat Syndrome	Deletion on chromosome 5	
Fragile X Syndrome	Duplications on X chromosome	
Acute Myelogenous Leukemia	Translocation in which part of chromosome 22 moved to 9	

3. Multifactorial disorder

Multifactorial disorder

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

Fig. 2.1.3 Multifactorial Disorders or Complex Traits



Graphic created by CICH using a Shutterstock image.

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.

4. Acquired Somatic Disease

- **Not all genetic errors are present from conception.**

- **Many billions of cell divisions (mitoses) occur in the course of an average human lifetime.**

- **During each mitosis, there is opportunity for both single gene mutations to occur because of DNA copy errors, and for numerical chromosome abnormalities to arise as a result of chromosome separation.**

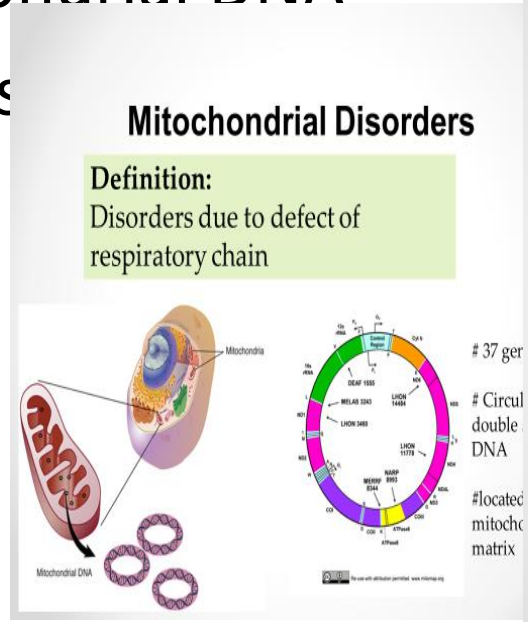
- **Accumulating somatic mutations and chromosomal abnormalities are now known to play a major role in causing cancer.**

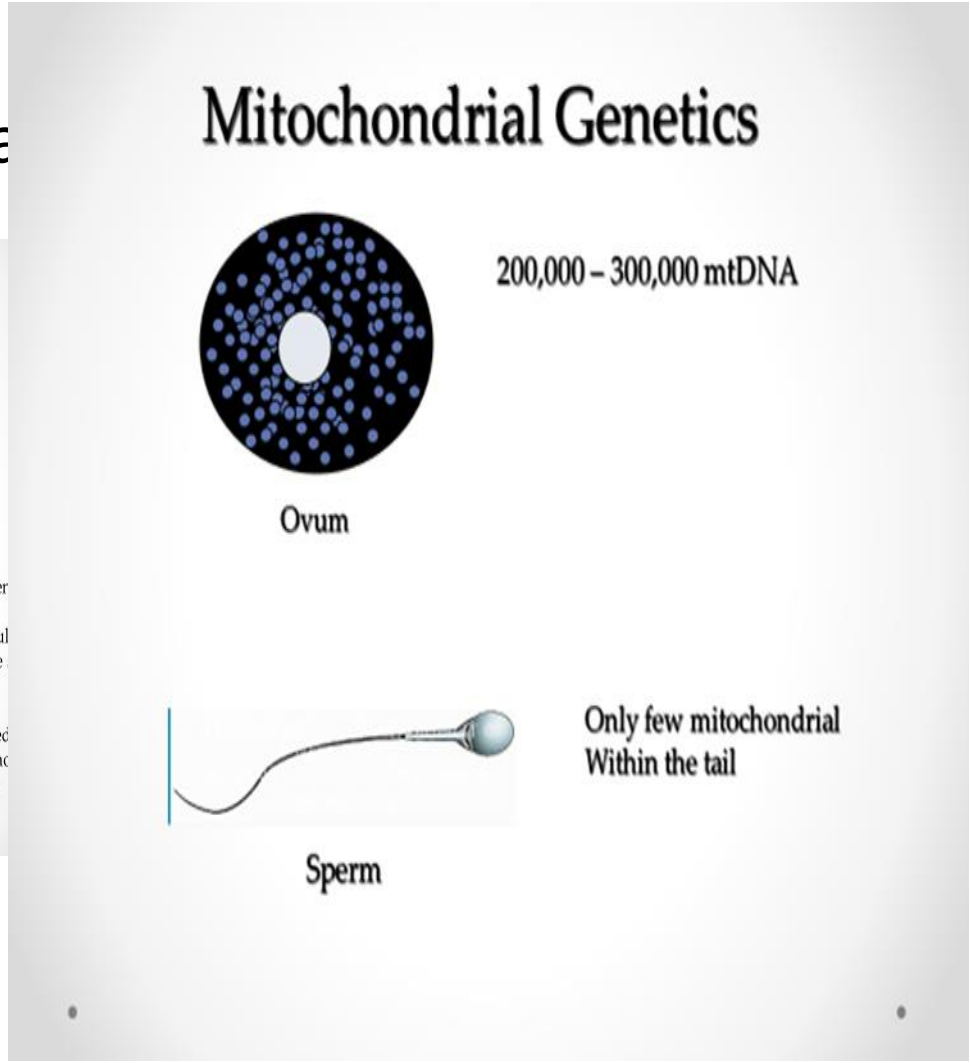
- **They probably also explain the serious illnesses as well as the aging process itself.**

- **It is therefore necessary to appreciate that not all disease with a genetic basis is hereditary.**

Mitochondrial inheritance

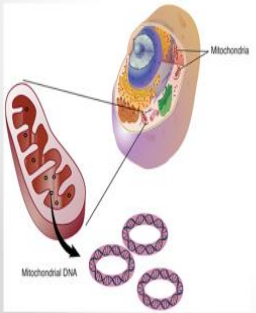
- Also known as maternal / extranuclea
  encoded by mitochondrial DNA
- Due to defects of res

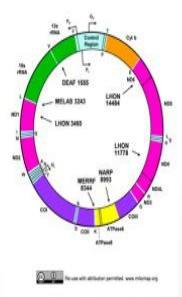




Mitochondrial Disorders

Definition:
Disorders due to defect of respiratory chain



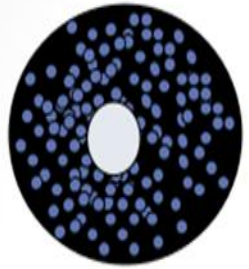


37 genes

Circular piece of double stranded DNA

#located in mitochondrial matrix

Mitochondrial Genetics



200,000 – 300,000 mtDNA

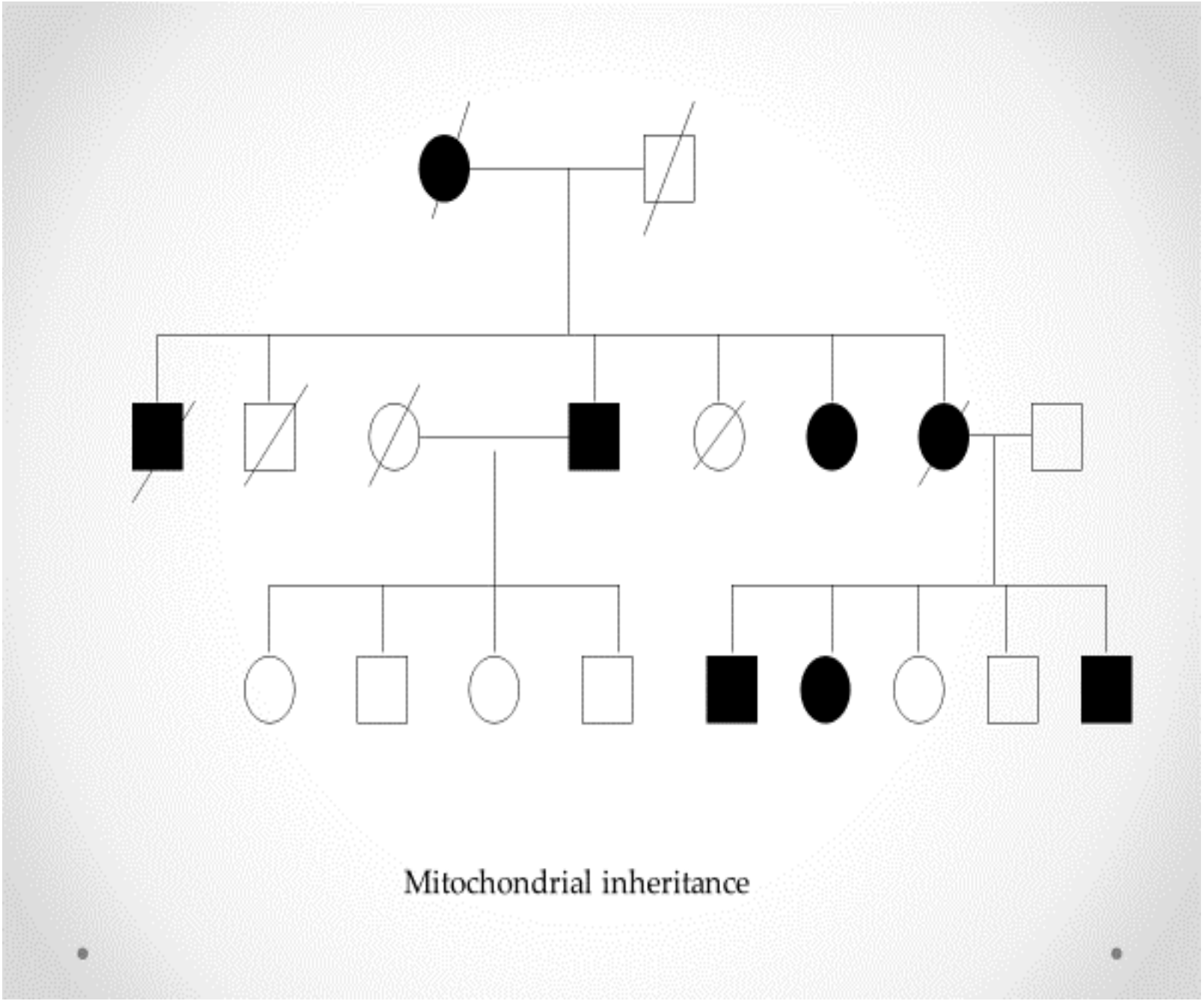
Ovum

Only few mitochondrial
Within the tail

Sperm

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

Mitochondrial trait

Trait	Phenotype
Kearns-Sayre syndrome	Short statue, retinal degeneration
Leber optic atrophy (LHON)	Loss of vision in centre of visual field: adult onset
MELAS syndrome	Episodes of vomiting,seizures,and stroke-like episodes
MERRF syndrome	Deficiencies in the enzyme complexes associated with energy transfer
Oncocytoma	Benign tumours of kidney

Recap....

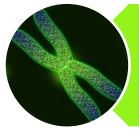
- 5 types of genetic disease:

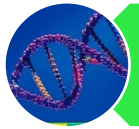
- 4+1 types of mode of inheritance

Recap…

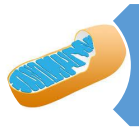
5 types of genetic disease


Single gene disorder


Chromosome abnormalities

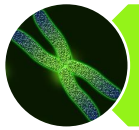

Multifactorial disorder

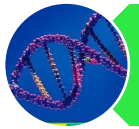

Acquired somatic disorder

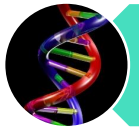

Mitochondrial disorder

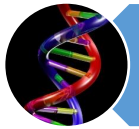
4+1 types of mode of inheritance


Autosomal dominant


Autosomal recessive


X/Y-linked dominant


X-linked recessive


Mitochondrial inheritance


thank you!