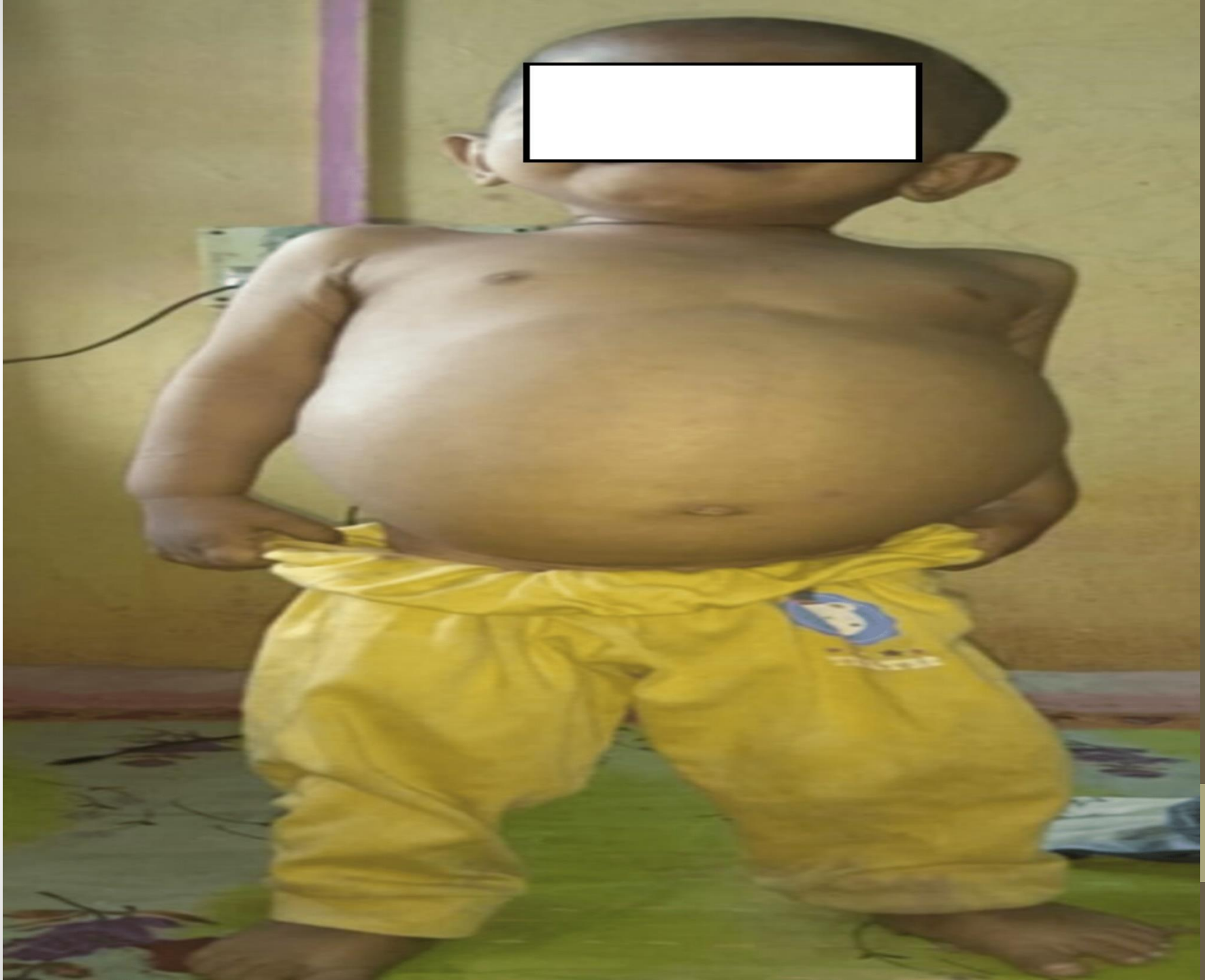
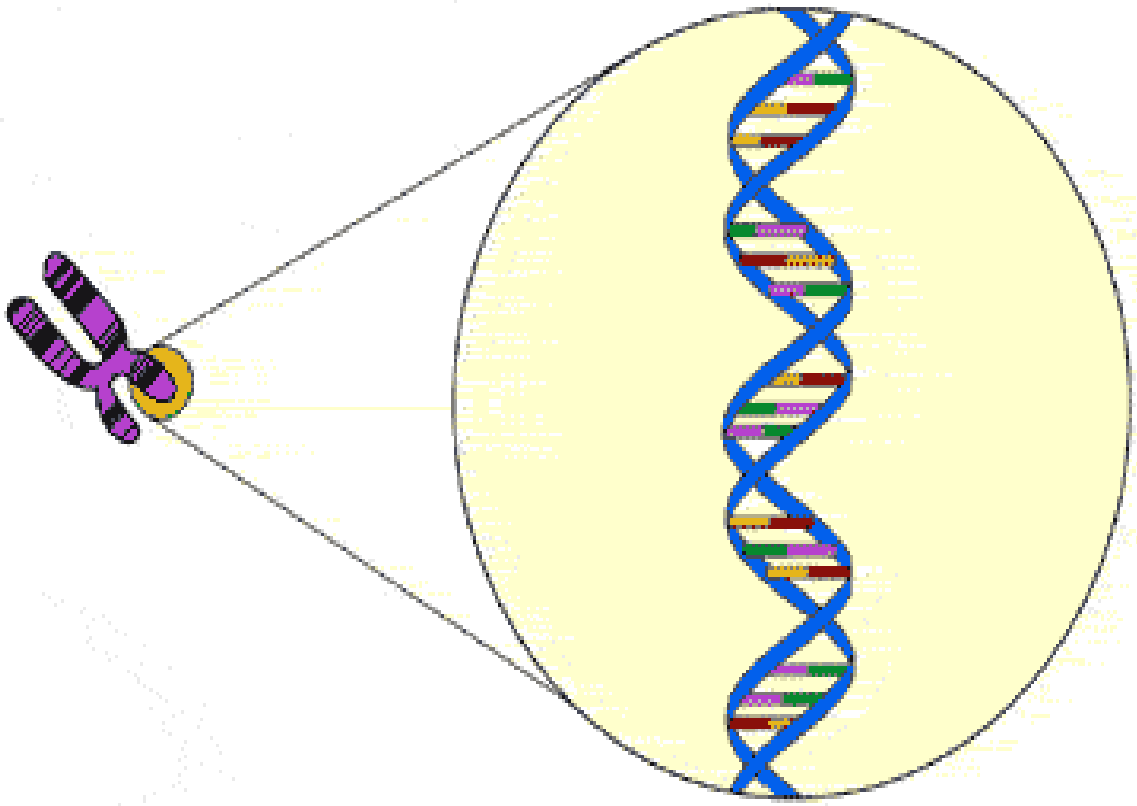
# TRANSMISSION PATTERN OF SINGLE GENE DISORDERS

By DR Wajeeha Rahman



Chromosome → Gene → Protein Product



Each chromosome is composed of one large DNA molecule.

A gene is a segment of DNA that makes a protein product.

# What are the different ways a genetic condition can be inherited?

- Some genetic conditions are caused by variants (also known as mutations) in a single gene. These conditions are usually inherited in one of several patterns, depending on the gene involved:

- There are five basic modes of inheritance for single-gene diseases: autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, and mitochondrial. Genetic heterogeneity is a common phenomenon with both single-gene diseases and complex multi-factorial diseases.

# Autosomal dominant

- One altered copy of the gene in each cell is sufficient for a person to be affected by an autosomal dominant disorder. In some cases, an affected person inherits the condition from an affected parent. In others, the condition may result from a new variant in the gene and occur in people with no history of the disorder in their family.

- Huntington disease, Marfan syndrome

# Autosomal recessive

- In autosomal recessive inheritance, variants occur in both copies of the gene in each cell. The parents of an individual with an autosomal recessive condition each carry one copy of the altered gene, but they typically do not show signs and symptoms of the condition. Autosomal recessive disorders are typically not seen in every generation of an affected family.

- cystic fibrosis, sickle cell disease

# X-linked dominant

- X-linked dominant disorders are caused by variants in genes on the X chromosome. In males (who have only one X chromosome), a variant in the only copy of the gene in each cell causes the disorder. In females (who have two X chromosomes), a variant in one of the two copies of the gene in each cell is sufficient to cause the disorder. Females may experience less severe symptoms of the disorder than males. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).

- fragile X syndrome

# X-linked recessive

- X-linked recessive disorders are also caused by variants in genes on the X chromosome. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a variant would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).

- hemophilia, Fabry disease

# X-linked

- Because the inheritance pattern of many X-linked disorders is not clearly dominant or recessive, some experts suggest that conditions be considered X-linked rather than X-linked dominant or X-linked recessive. X-linked disorders are caused by variants in genes on the X chromosome, one of the two sex chromosomes in each cell. In males (who have only one X chromosome), an alteration in the only copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), one altered copy of the gene usually leads to less severe health problems than those in affected males, or it may cause no signs or symptoms at all. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).

- glucose-6-phosphate-dehydrogenase-deficiency, X-linked thrombocytopenia

# Y-linked

- A condition is considered Y-linked if the altered gene that causes the disorder is located on the Y chromosome, one of the two sex chromosomes in each of a male's cells. Because only males have a Y chromosome, in Y-linked inheritance, a variant can only be passed from father to son.

- Y chromosome infertility, some cases of Swyer syndrome

# Codominant

- In codominant inheritance, two different versions (alleles) of a gene are expressed, and each version makes a slightly different protein. Both alleles influence the genetic trait or determine the characteristics of the genetic condition.

- ABO blood group, alpha-1 antitrypsin deficiency

# Mitochondrial

- Mitochondrial inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA. Mitochondria, which are structures in each cell that convert molecules into energy, each contain a small amount of DNA. Because only egg cells contribute mitochondria to the developing embryo, only females can pass on mitochondrial variants to their children. Conditions resulting from variants in mitochondrial DNA can appear in every generation of a family and can affect both males and females, but fathers do not pass these disorders to their daughters or sons.

- Leber hereditary optic neuropathy (LHON)

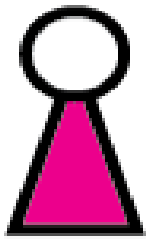
- Many health conditions are caused by the combined effects of multiple genes (described as polygenic) or by interactions between genes and the environment. Such disorders usually do not follow the patterns of inheritance listed above. Examples of conditions caused by variants in multiple genes or gene/environment interactions include heart disease, type 2 diabetes, schizophrenia, and certain types of cancer.

- Even though these diseases are primarily caused by a single gene, several different mutations can result in the same disease but with varying degrees of severity and phenotype. But even the same mutation can result in slightly different phenotypes. This may be caused by differences in the patient's environment and/or other genetic variations that may influence the disease phenotype or outcome. For example, other genes have been shown to modify the cystic fibrosis phenotype in children who carry the same CFTR mutation. In addition, for some disorders such as galactosemia, mutations in different genes can result in similar phenotypes.

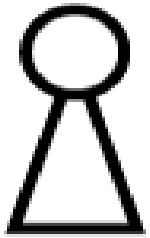
- Penetrance refers to how often a trait is expressed in people with the gene for that trait. Penetrance may be complete or incomplete. A gene with incomplete penetrance is not always expressed even when the trait it produces is dominant or when the trait is recessive and present on both chromosomes. If half the people with a gene show its trait, its penetrance is said to be 50%.

- Expressivity refers to how much a trait affects a single person, that is, whether the person is greatly, moderately, or mildly affected

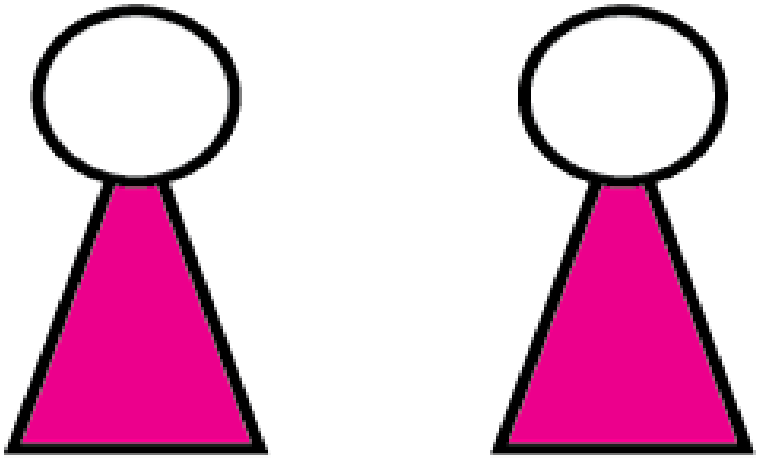
Key



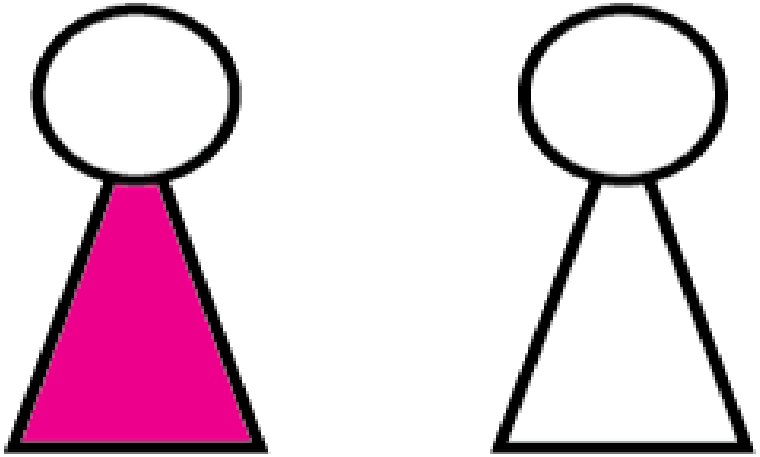
= Penetrance



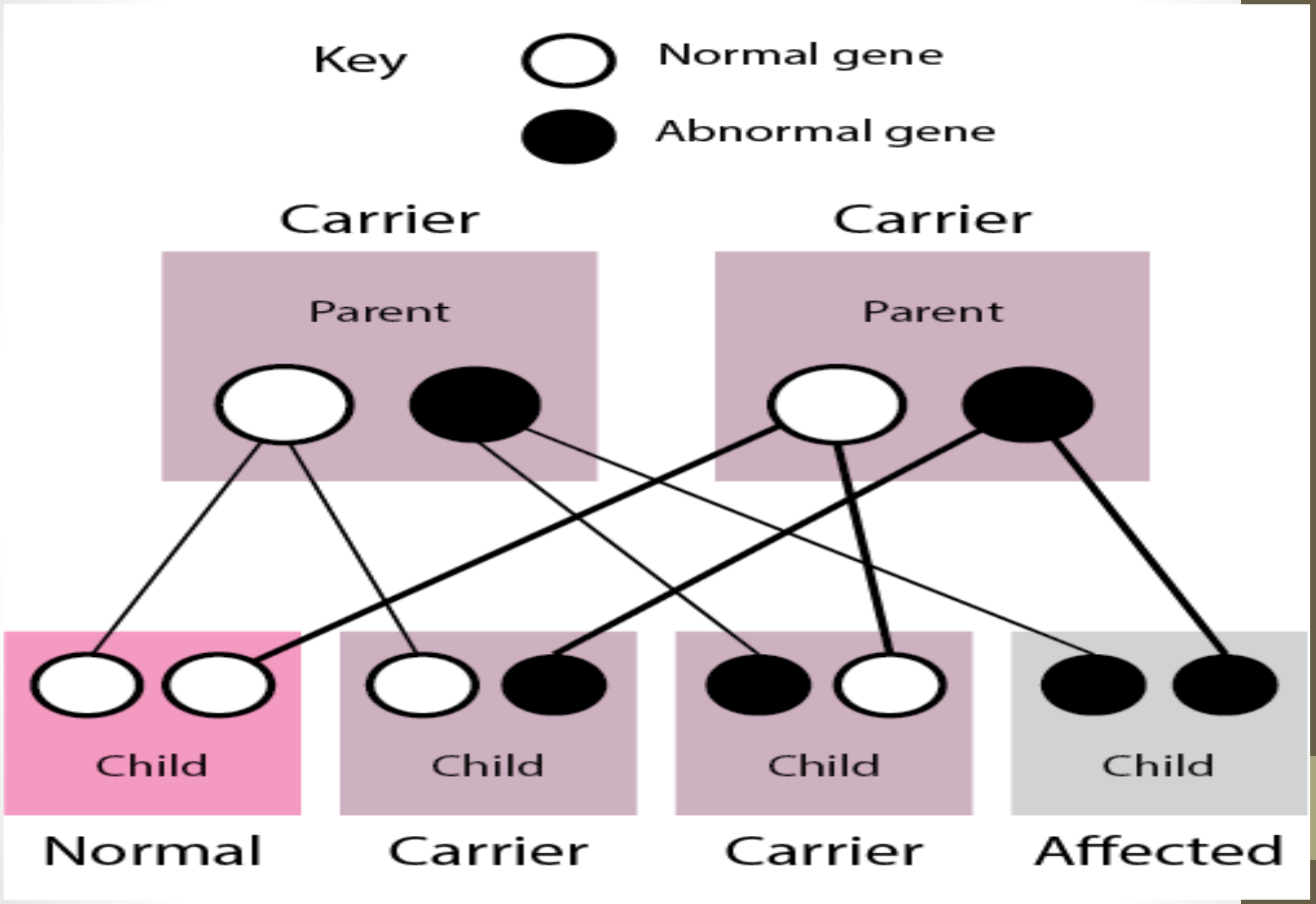
= No penetrance



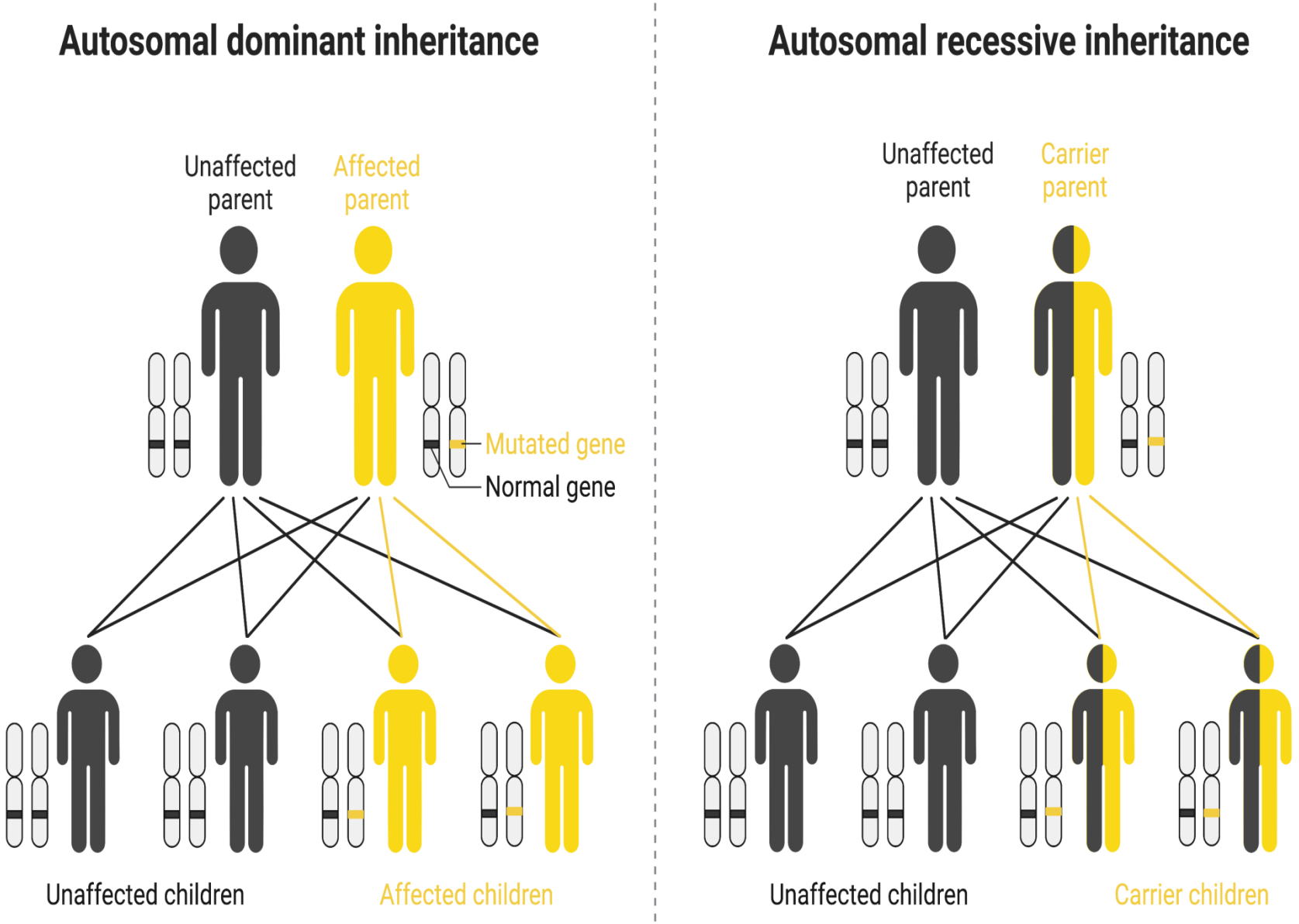
100% Penetrance

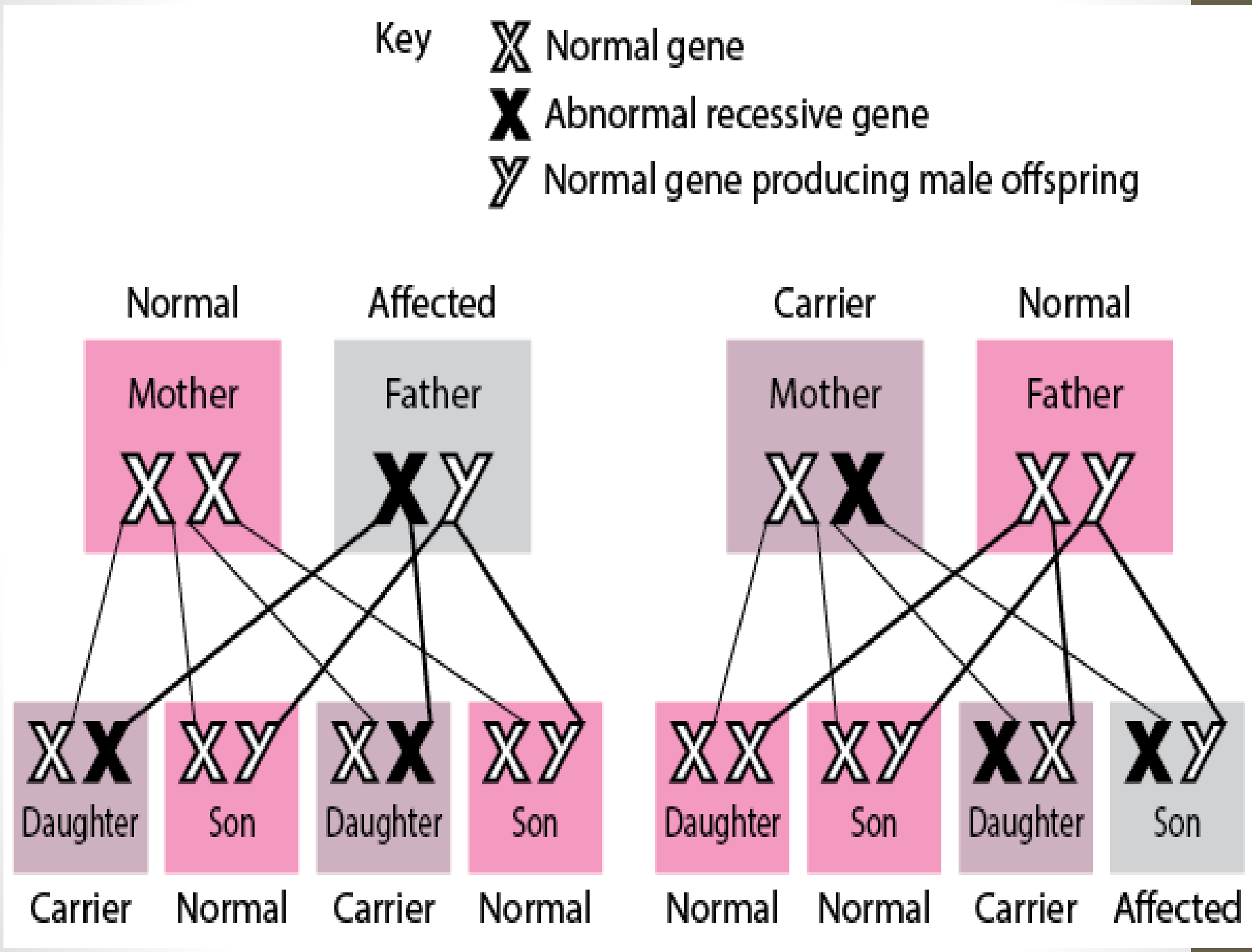


50% Penetrance


Key
Normal gene
Abnormal gene
Carrier
Carrier
Parent
Parent
Child
Child
Child
Child
Normal
Carrier
Carrier
Affected

- Genetic testing is available for many single-gene disorders, however, the clinical examination is extremely important in the differential diagnosis particularly in patients with no family history. For some genetic conditions, patients can often be treated for their symptoms or modify their diets to prevent the onset of symptoms if diagnosed at an early age (newborn screening). However, despite advancements in the understanding of genetic etiology and improved diagnostic capabilities, no treatments are available to prevent disease onset or slow disease progression for a number of these disorders.


Autosomal dominant inheritance
Unaffected parent
Affected parent
Mutated gene
Normal gene
Unaffected children
Affected children
Autosomal recessive inheritance
Unaffected parent
Carrier parent
Unaffected children
Carrier children


Key
Normal gene
Abnormal recessive gene
Normal gene producing male offspring
Normal
Affected
Mother
Father
Daughter
Son
Daughter
Son
Carrier
Normal
Carrier
Normal
Carrier
Normal
Mother
Father
Daughter
Son
Daughter
Son
Normal
Normal
Carrier
Affected

# Tay-Sachs Disease

- The disease occurs when harmful quantities of cell membrane components known as gangliosides (glycosphingolipids) accumulate in the nerve cells of the brain, eventually leading to premature death of those cells.

- There is no cure or treatment.

# Duchenne and Becker Muscular Dystrophies (x-linked recessive)

- Are a group of genetic conditions characterized by progressive muscle weakness and wasting (atrophy).
- The Duchenne and Becker types of muscular dystrophy primarily affect the skeletal muscles, which are used for movement, and the muscles of the heart.
- These conditions predominantly affect males.

# Becker Muscular Dystrophy

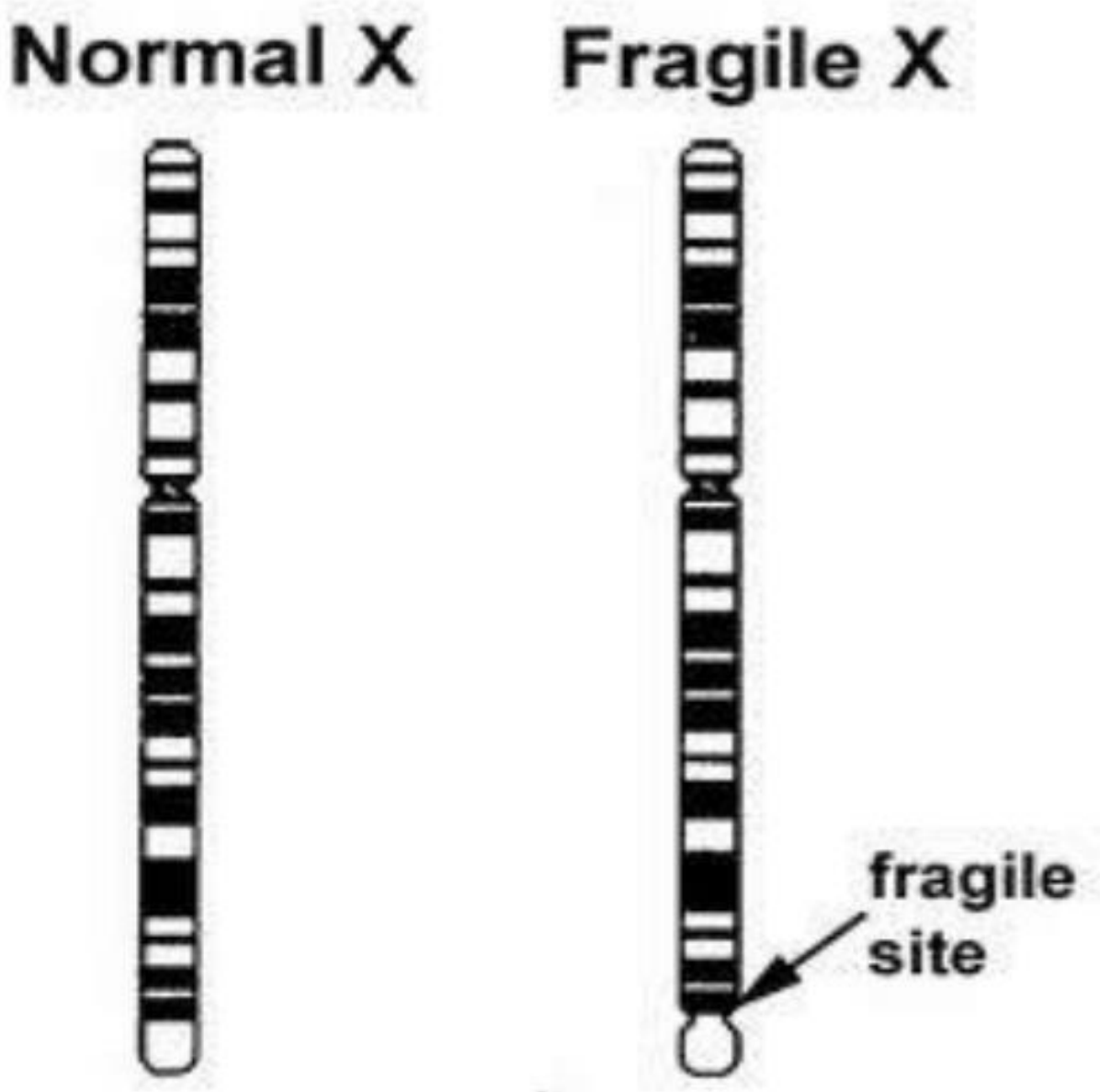
- Becker muscular dystrophy is very similar to Duchenne muscular dystrophy, except that it gets worse at a much slower rate.

- Having a family history of the condition raises your risk.

# Fragile X Syndrome

- The Fragile X syndrome is caused by a "fragile" site at the end of the long arm of the X-chromosome.

- It is a genetic disorder that manifests itself through a complex range of behavioral and cognitive phenotypes.

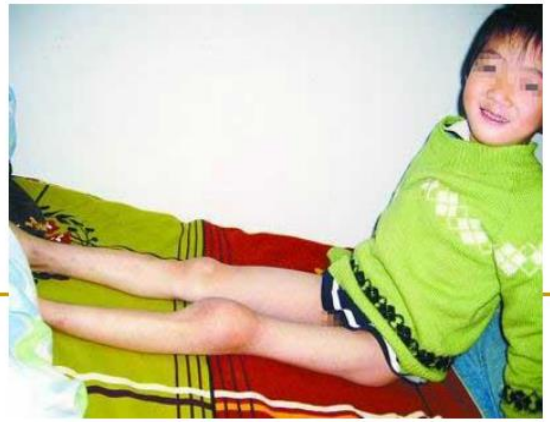

Normal X
Fragile X
fragile
site

# Single gene Disorders

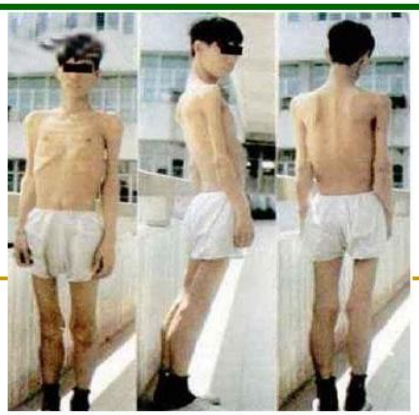
**Huntington's disease**
亨廷顿氏舞蹈症

**Albinism**
白化病

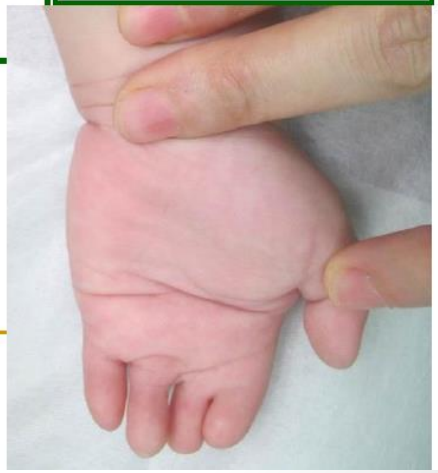
**Hemophilia**
血友病



**Duchenne muscular dystrophy**
杜氏肌营养不良



**Brachydactyly**
短指症



# A ROYAL DISEASE

- Queen Victoria of England, who ruled from 1837-1901, is believed to have been the carrier of hemophilia B, or factor IX deficiency. She passed the trait on to three of her nine children. Her son Leopold died of a hemorrhage after a fall when he was 30.

# Members of the Royal Family with Hemophilia and Carriers of Hemophilia

With Hemophilia

Carriers of Hemophilia

Queen Victoria
5/4/1819 - 1/22/1901
Age 81

Princess Alice,
Grand Duchess,
4/25/1843 - 12/14/1878
Age 35

Prince Leopold,
Duke of Albany
4/7/1853 - 3/28/1884
Age 31

Princess Beatrice
of Battenberg
4/14/1857 - 10/26/1944
Age 87

Princess Irene
of Hesse and by Rhine
7/11/1866 - 11/11/1953
Age 87

Prince Friedrich
of Hess
10/7/1870 - 5/29/1873
Age 2 1/2

Princess
Alexandra
6/6/1872 - 7/17/1918
Age 46

Princess Alice,
Countess of Athlone
2/25/1883 - 1/3/1981
Age 97

Prince Leopold
Mountbatten
5/21/1889 - 4/23/1922
Age 32

Prince Maurice
of Battenberg
10/3/1891 - 10/27/1914
Age 23

Princess Victoria
Eugenia of Battenberg
10/24/1887 - 4/15/1969
Age 81

Prince Waldemar
of Prussia
3/20/1889 - 5/2/1945
Age 56

Prince Heinrich
of Prussia
1/9/1900 - 2/26/1904
Age 4

Tsarevich
Nikolaevich Alexei
12/12/1904 - 7/17/1918
Age 13

Prince Rupert
of Teck
4/24/1907 - 5/15/1928
Age 20

Alfonso,
Prince of Asturias
5/10/1907 - 9/6/1938
Age 31

Infante Gonzalo
of Spain
10/24/1914 - 3/13/1934
Age 19

# HOUSE OF SAXE-COBURG-GOTHA/ WINDSOR


VICTORIA


PRINCE ALBERT
OF SAXE-COBURG-GOTHA


VICKI, PRINCESS ROYAL
EMPRESS OF GERMANY
QUEEN OF PRUSSIA


EDWARD VII


ALICE,
GRAND DUCHESS
OF HESSE


ARTHUR
DUKE OF
CONNAUGHT


LEOPOLD,
DUKE OF ALBANY


ALFRED,
DUKE OF SAXE-
COBURG- GOTHA


BEATRICE,
PRINCESS HENRY
OF BATTENBURG


WILHELM II


SOPHIE
QUEEN OF
GREECE


MAUD,
QUEEN OF
NORWAY


GEORGE V


VICTORIA
PRINCESS LOUIS
OF BATTENBURG


MARGARET
CROWN PRINCESS
OF SWEDEN


CHARLES EDWARD
DUKE OF SAXE-
COBURG-GOTHA


MARIE
QUEEN OF
ROMANIA


VICTORIA
EUGENIE
QUEEN OF SPAIN


VICTORIA LOUISE
DUCHESS OF
BRUNSWICK


OLAV V


GEORGE VI


ALICE
PRINCESS ANDREW
OF GREECE


INGRID
QUEEN OF
DENMARK


PRINCE
ADOLF GUSTAF
OF SWEDEN


IRENE
PRINCESS OF
SWEDEN


MARIE
QUEEN OF
YUGOSLAVIA


INFANTE JUAN,
COUNT OF BARCELONA


QUEEN
FREDERICA
OF GREECE


PAUL OF
GREECE


HELENE
QUEEN OF
ROMANIA


PETER III


JUAN CARLOS I


QUEEN
SOFIA OF
SPAIN


CONSTANTINE
II


MICHAEL I


HARALD V


ELIZABETH II


PRINCE PHILLIP
DUKE OF
EDINBURGH


ANNE-MARIE
QUEEN OF
GREECE


MARGRETHE
II


CARL XVI
GUSTAV


CROWN
PRINCE
ALEXANDER

# GENETIC DISORDER

## Mendelian disorders

- alteration or mutation in the single gene
- transmitted to the offspring
- can be traced in a family by the pedigree analysis
- Examples -
- Haemophilia, Cystic fibrosis, Sicklecell anaemia, Colour blindness, Phenylketonuria, Thalassemia

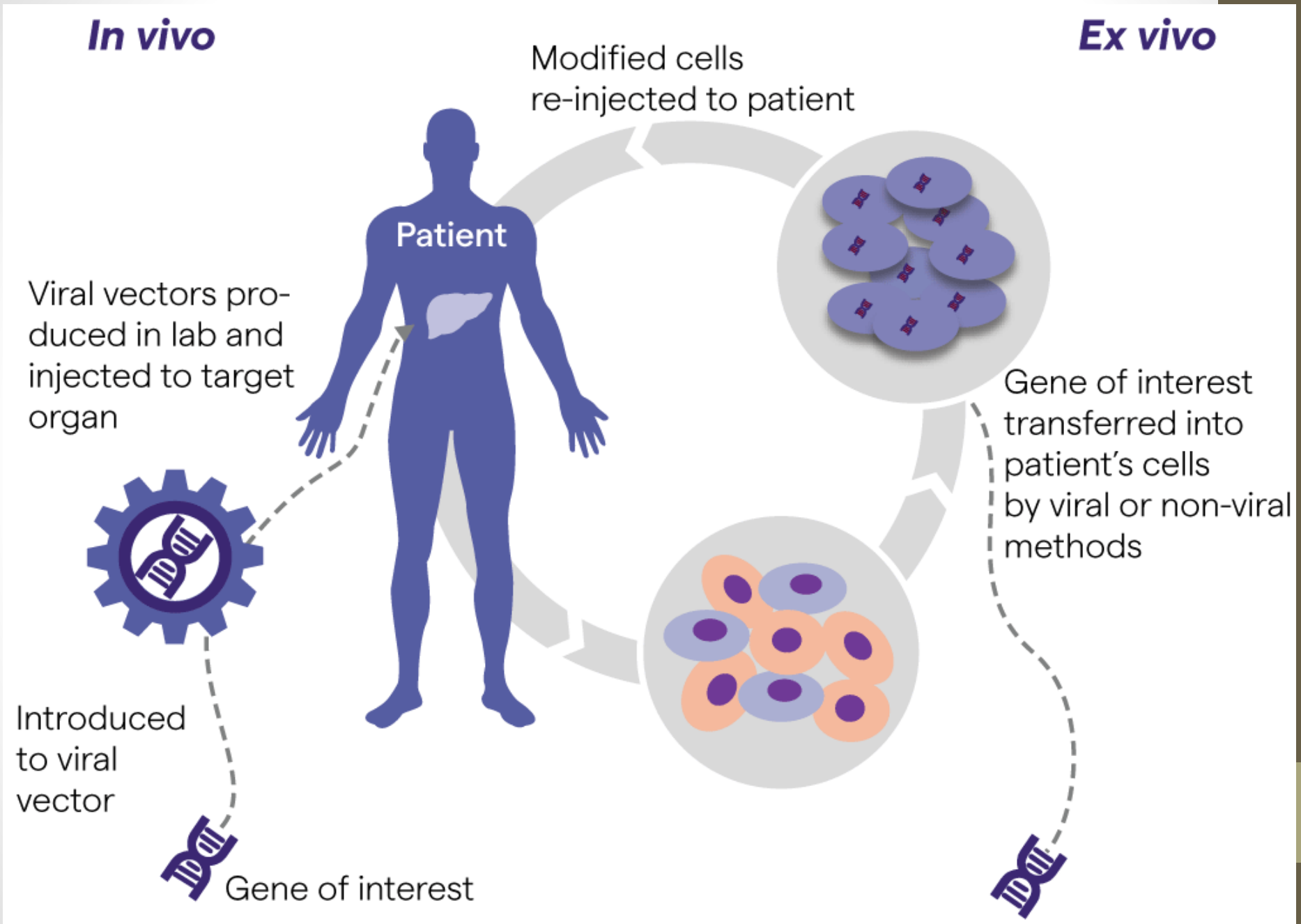
## Chromosomal disorders

- due to absence / excess / abnormal arrangement of one or more chromosomes
- Failure of segregation of chromatids in cell division cycle results in the gain / loss of a chromosome(s), called Aneuploidy
- Down's Syndrome
- Klinefelter's Syndrome
- Klinefelter's Syndrome

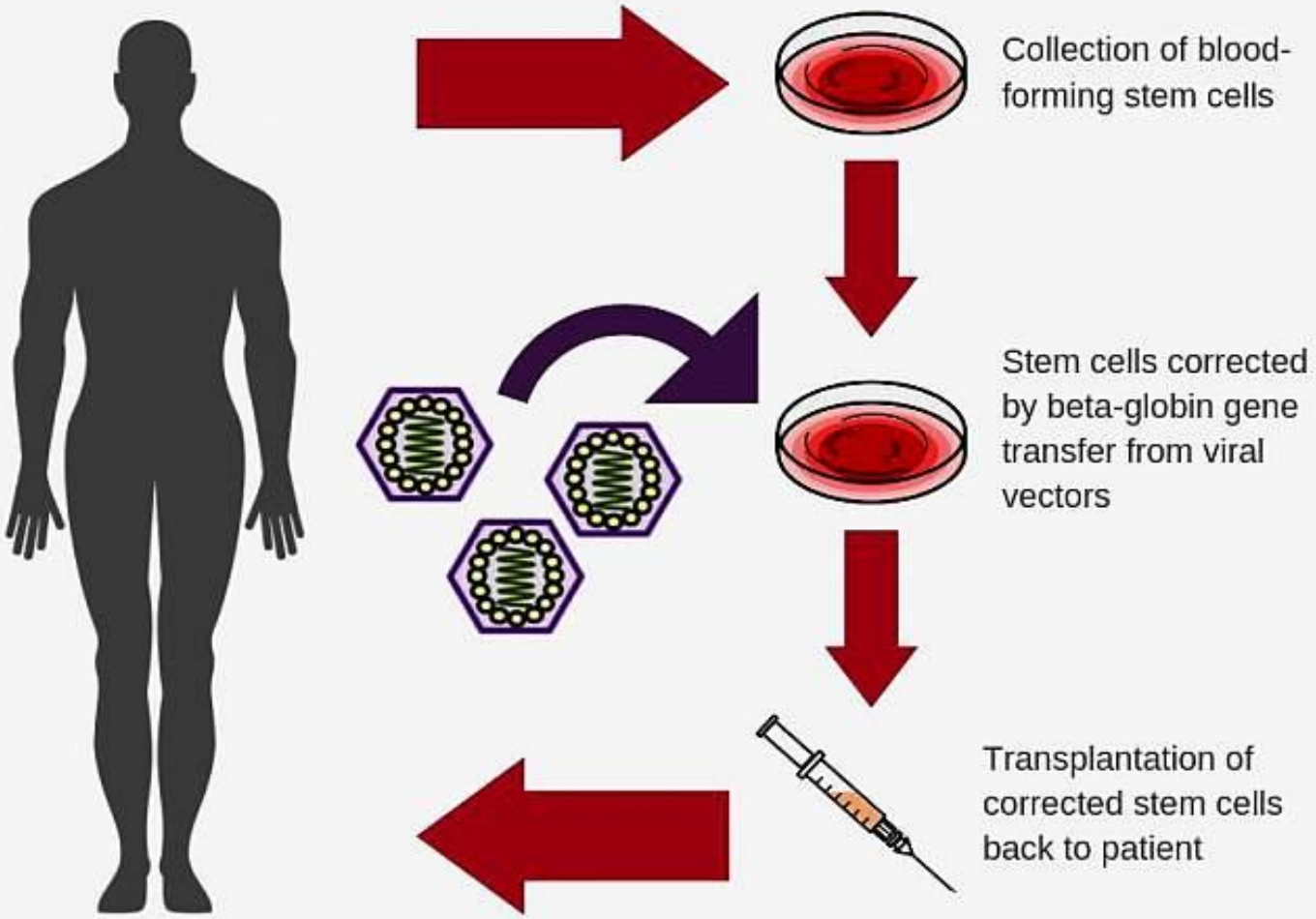
# Monogenic Disorders vs Chromosomal Disorders

More Information Online WWW.DIFFERENCEBETWEEN.COM

| | Monogenic Disorders | Chromosomal Disorders |
|---|---|---|
| DEFINITION | Monogenic disorder is a genetic disorder caused by a single mutated gene | Chromosomal disorder is a genetic disorder caused by missing, extra or changed DNA of a chromosomal part |
| CHANGE HAPPENS IN | A single gene | A chromosome or a part of a chromosome |
| NUMBER OR STRUCTURE OF CHROMOSOME | Does not change | Changes |
| NUMBER OF GENES INVOLVED | One | More than one gene |
| CAUSE | Mutation | Error in cell division following meiosis or mitosis |
| DETECTION | Analyzing inheritance patterns | Examination of karyotype |
| EXAMPLES | Sickle cell anaemia, cystic fibrosis, Huntington disease, and Duchenne muscular dystrophy, etc. | Down syndrome, Turner's syndrome, Wolf-Hirschhorn syndrome and Jacobsen syndrome, etc. |

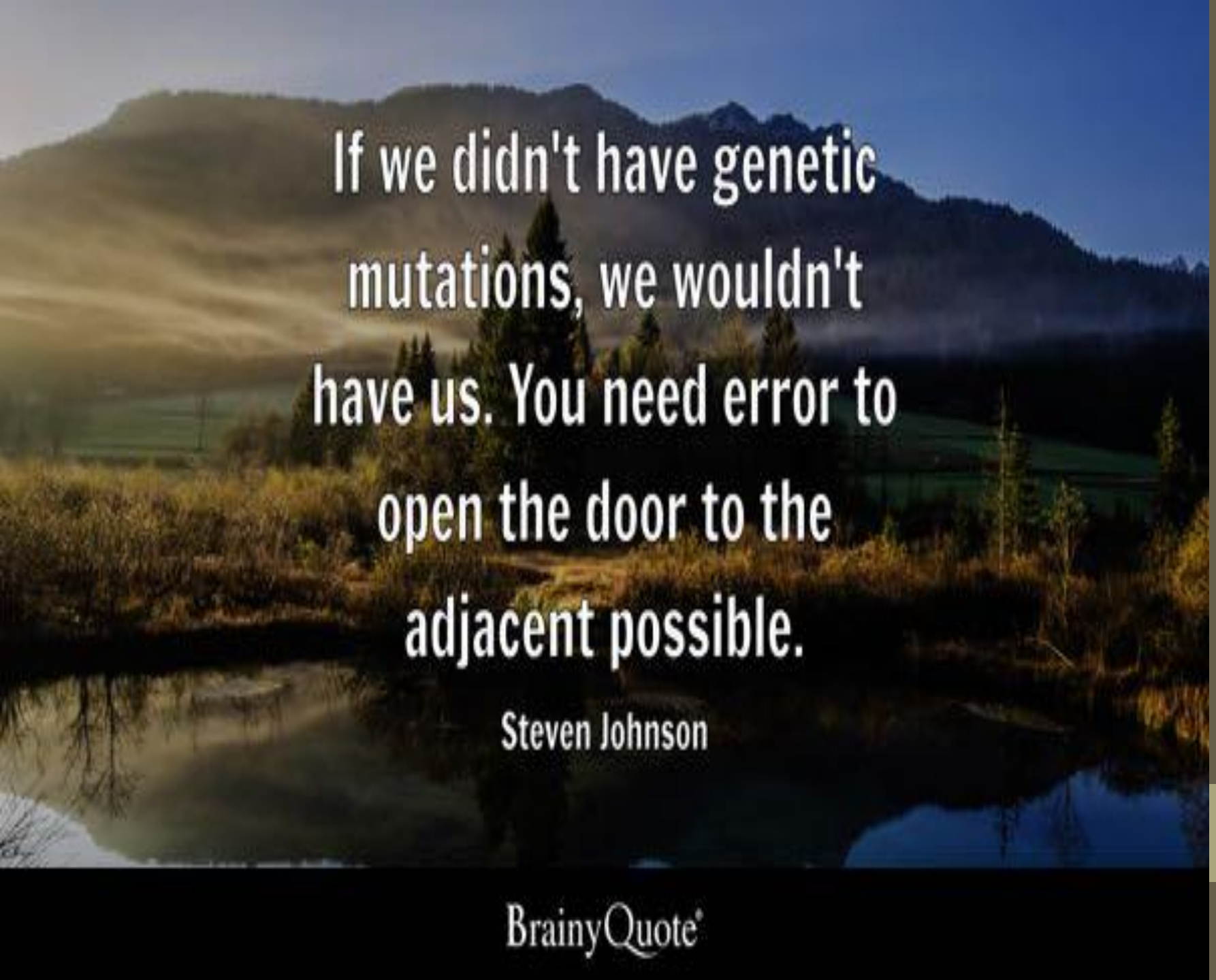

In vivo
Ex vivo
Modified cells
re-injected to patient
Patient
Viral vectors pro-
duced in lab and
injected to target
organ
Gene of interest
transferred into
patient's cells
by viral or non-viral
methods
Introduced
to viral
vector
Gene of interest

# Gene therapy for sickle cell disease



# Fact 236:

Having blue eyes is actually a mutation. Before the mutation occurred, all humans had brown eyes.


If we didn't have genetic mutations, we wouldn't have us. You need error to open the door to the adjacent possible.
Steven Johnson
BrainyQuote