

Genetic Pathology

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Genetic diseases are classified into:

1. Classical genetic disease: are divided into:

- A. Chromosomal diseases.
- B. Single gene diseases .
- C. Multifactorial diseases.

2. Non-Traditional diseases: are divided into:

- A. Mitochondrial diseases.
- B. Gonadal diseases.
- C. Uni-parental diseases.

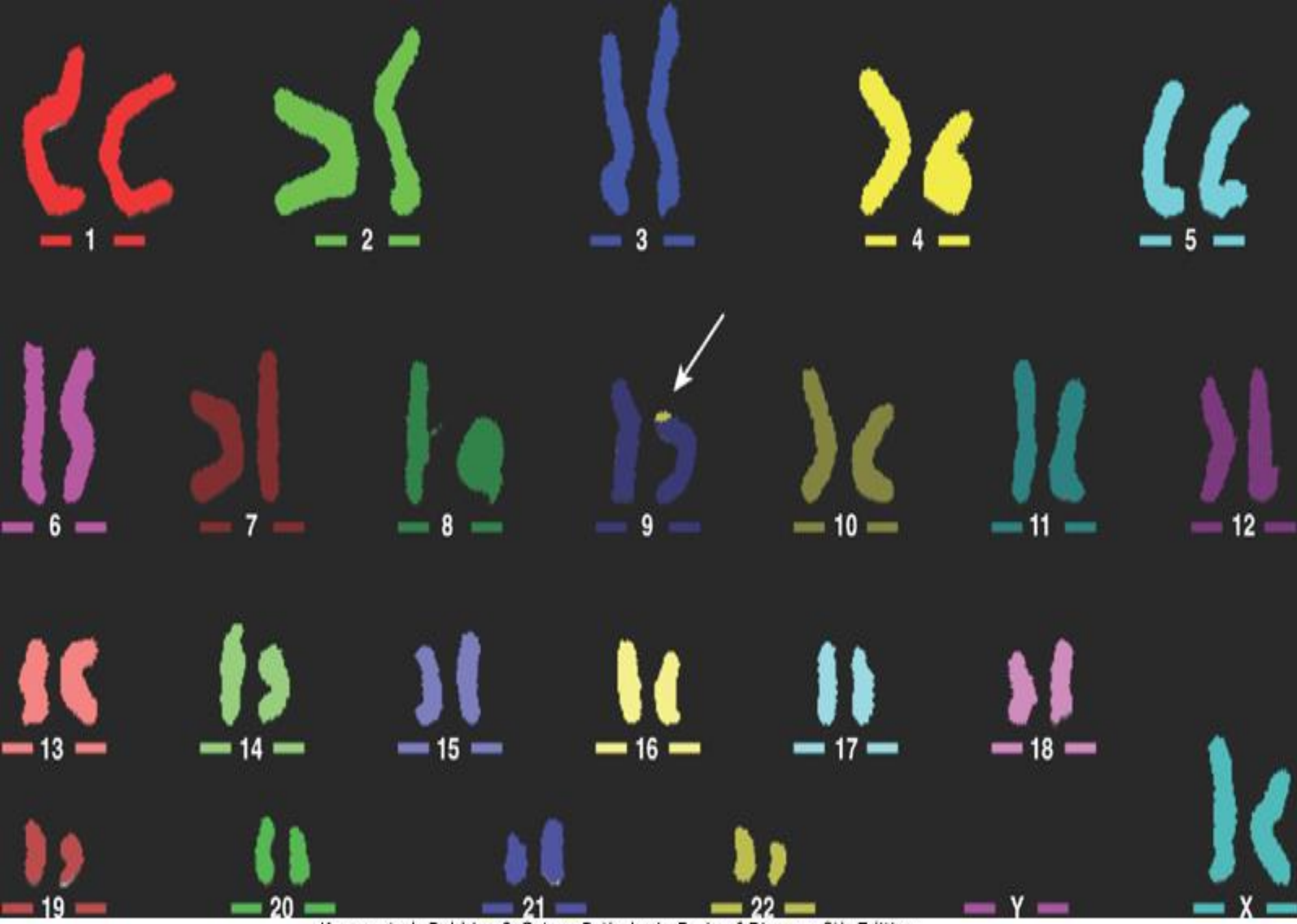
Chromosomal disease:

These may be due to:

- 1. Numerical abnormalities** (i.e. Alternation in numbers of chromosome).
- 2. Structural abnormalities** (i.e. Alternation in structure of chromosome).

Chromosome nomenclature:

- The ***normal somatic cell*** has **46 chromosomes** and this is called ***diploid***.
- ***Ova*** or ***sperm*** have **23 chromosomes** and this is called ***haploid***.
- The ***chromosomes*** arrange in ***pairs*** and are number from **1-22 in decreasing size orders**.
- There are ***two sex chromosome; XX in females*** and ***XY in males***.



- **Karyotype** is the term used to describe the chromosomes derived from mitotic cells which have been set out in numerical order.
- **Aneuploid**: Somatic cells with *more* or *less* than **46 chromosomes**.
- **Hyper diploid**: Somatic cells with *more* than **46 chromosomes**.
- **Hypo diploid**: Somatic cells with *less* than **46 chromosomes**.

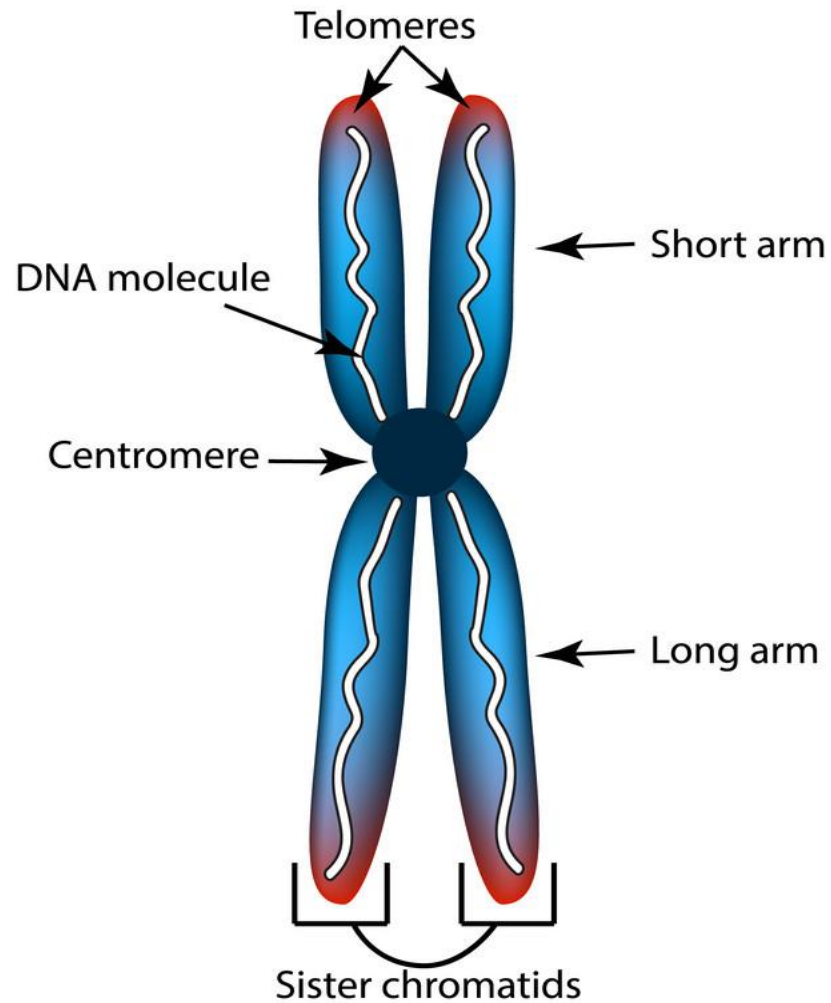
Each chromosome has two arms:

1. **Short arm** called "**P**".

2. **Long arm** called "**q**".

- Both arms meet at the region called **Centromere** and the end of chromosome called **Telomeres**.
- On staining, each arm divided into **regions** numbered outwards from the Centromere and each region divided into **bands**.

Chromosome X



- When whole chromosome is ***lost*** or ***gain***, a ***–*** or ***+*** is put in front of chromosome number.
- If part of chromosome is ***lost***, it's prefixed with ***del*** for ***deletion***.
- If there is ***extra material*** replacing part of chromosome, the prefixes ***add*** for ***additional*** material is used.
- ***Chromosome translocation*** are denoted by ***t***, the chromosome involved ***placed in brackets*** with the ***lower number*** chromosome ***first***.
- The prefix ***inv*** describes an ***inversion*** where part of chromosome has been inverted to run in apposite direction.

Chromosomal diseases:

1. Numerical abnormalities: Which defined as **again or loss** of whole chromosome from the usual number of chromosome in Karyotype (i.e. 46 chromosomes).

Gain or **loss** of **sex chromosome** especially the -
X-chromosome is **compatible with life** and is **relatively common**.

- **While** **loss** of an **Autosomal chromosome** is usually **incompatible with life** and a **fertilized ovum carrying such Karyotype** could **not sustain pregnancy to full term** and usually are lost very early in pregnancy i.e. **abortion**.

- ***Gain of an Autosomal chromosome*** is a state known as ***Trisomy***.

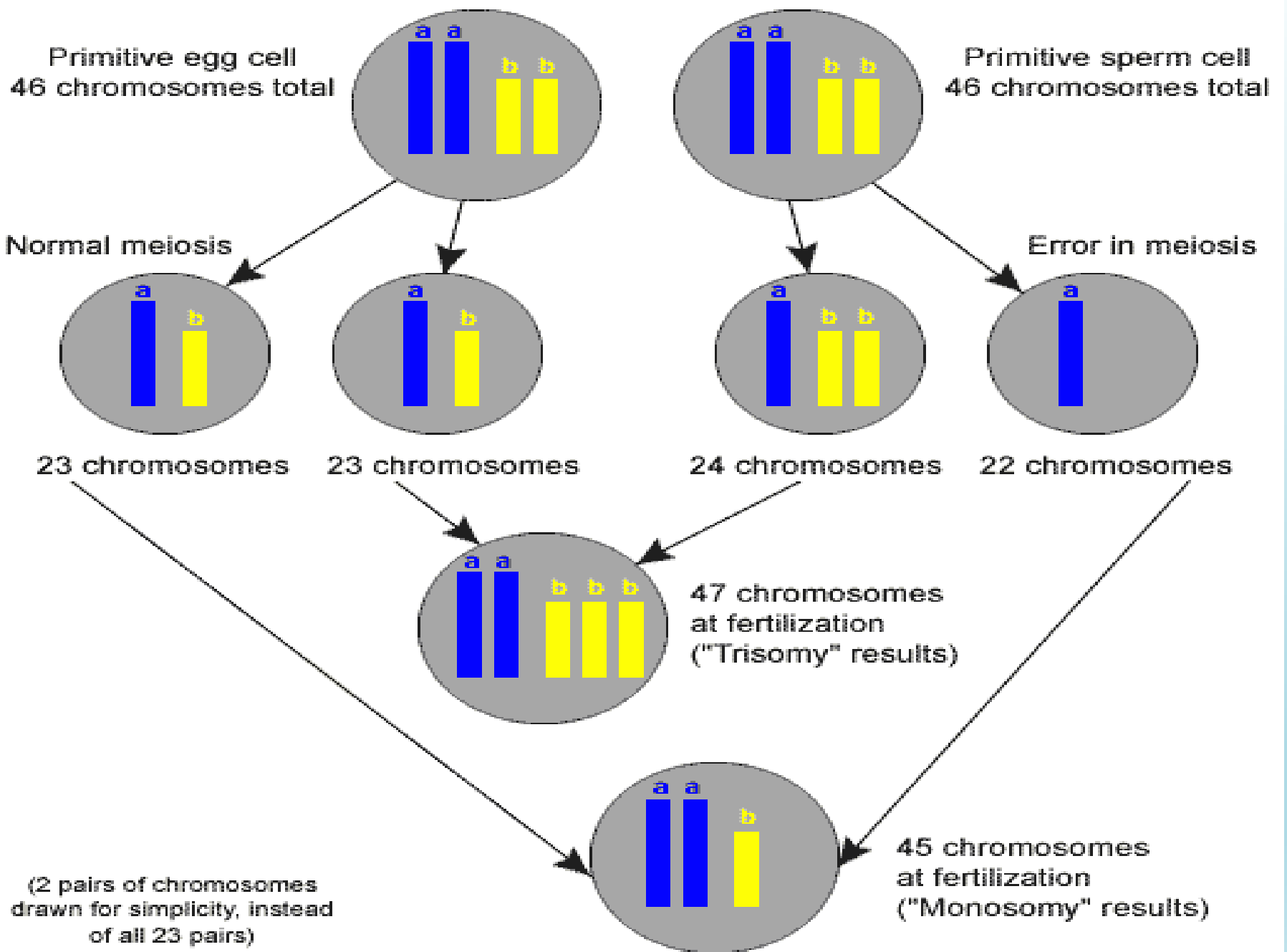
e.g. _ ***Trisomy 21*** or called ***Down's syndrome***.

_ ***Trisomy 18*** or called ***Edward's syndrome***.

_ ***Trisomy 13*** or called ***Patau's syndrome***.

- ***Loss of an Autosomal chromosome*** is a state known as ***Monosomy*** , so Monosomy of sex chromosome occurs when females loses ***one X- chromosome*** resulting in ***Turners syndrome (45 X) known as aneuploidy.***

Aneuploidy is one of the commonest changes occur in malignant tissues.



2. Structural abnormalities: Here the suffering cells or the carrier cell of ***structurally*** and ***morphologically*** abnormal chromosome (S) ***has the normal number of 46.***

Structural abnormalities usually result from a **translocation** between two non-homologous chromosome i.e. aberrant crossing over, which is the normal process where the sister chromatids or the pair of homologous chromosomes exchanges segment among them. This process usually is preceded by physical breaks in the chromosomes.

They are of different types:

A. Deletion: (i.e. refers to loss of a piece of chromosome), this of two types:

1. Terminal deletion: Where the piece of chromosome behind the breaks will be lost.

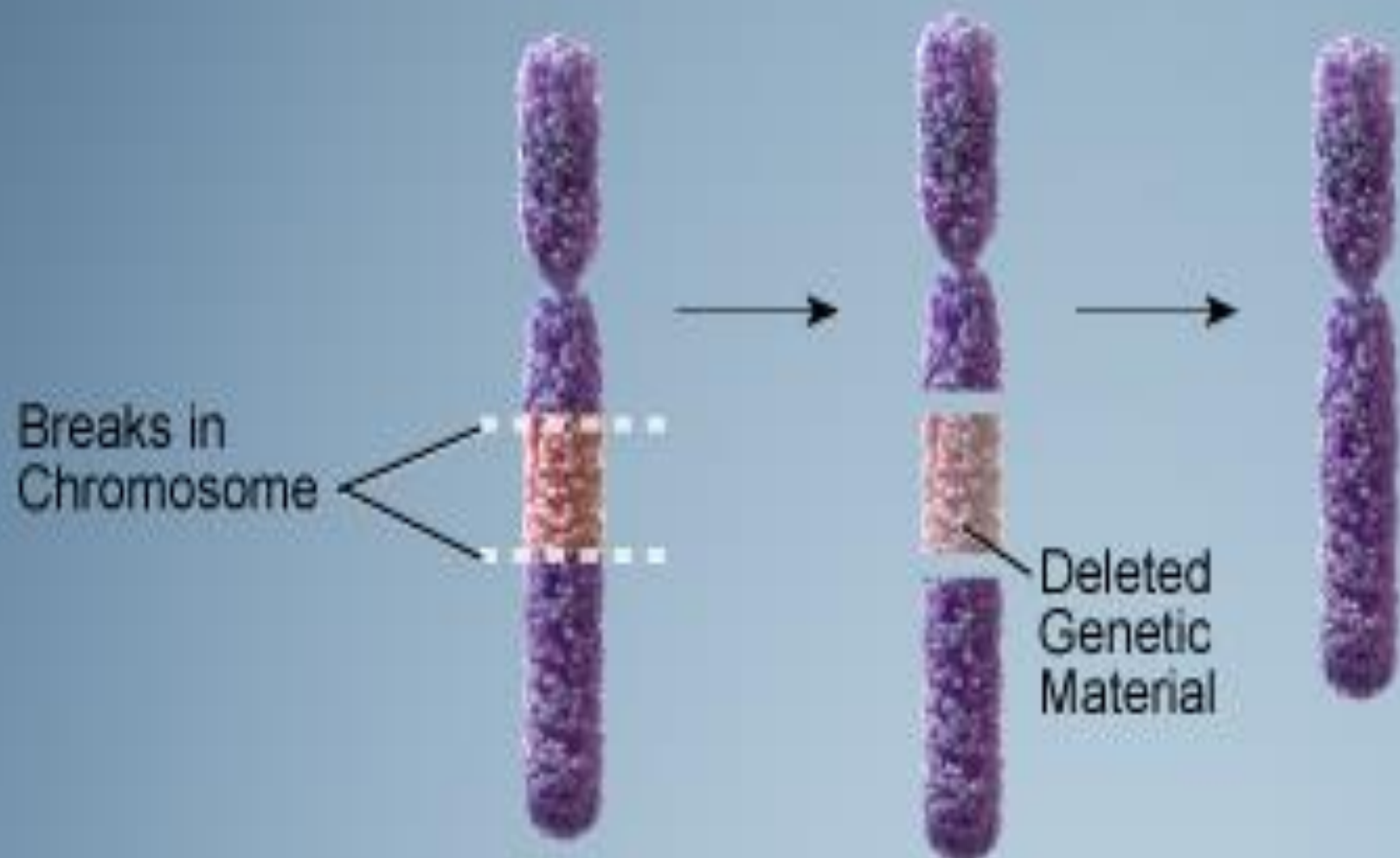
2. Interstitial deletion: Where the piece of chromosome between two breaks will be lost resulting in syndrome e.g. ***Cri du chat syndrome (loss of short arm of chromosome 5)***.

The sequences of this deletion are that sometimes the piece lost carries a gene so the patient will lose this gene or genes. Most of the genes known as oncogenes are lost from the cells during deletion and their loss will result in development of malignancy of certain tissues e.g. ***loss of retinoblastoma gene*** by interstitial deletion of the long arm of ***chromosome 13*** i.e. 13 q and newborn carrying this deletion will develop ***retinoblastoma***.

Another oncogenes is lost in ***deletion of short arm of chromosome 11*** which results in development of ***Wilms's tumor***.

But deletion is not always followed by oncogenes deletion and development of malignancy. Sometimes the piece lost carries no gene and therefore it causes no abnormality

Deletion



B. Inversion: This abnormality results from two breaks in the chromosome and the piece between two breaks will rotate 180 before its return to its place.

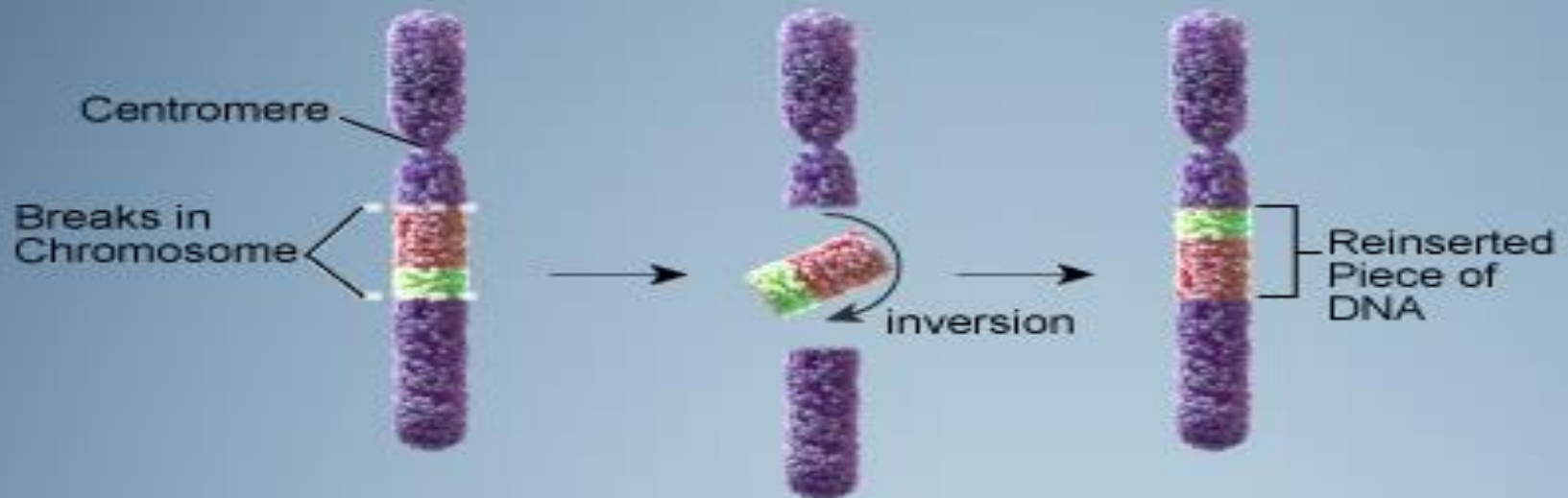
The breaks may involve either the short arm and the inversion is called

Para centric or the breaks involve both arms and the inversion called ***Peri centric*** Which is ***more sever***.

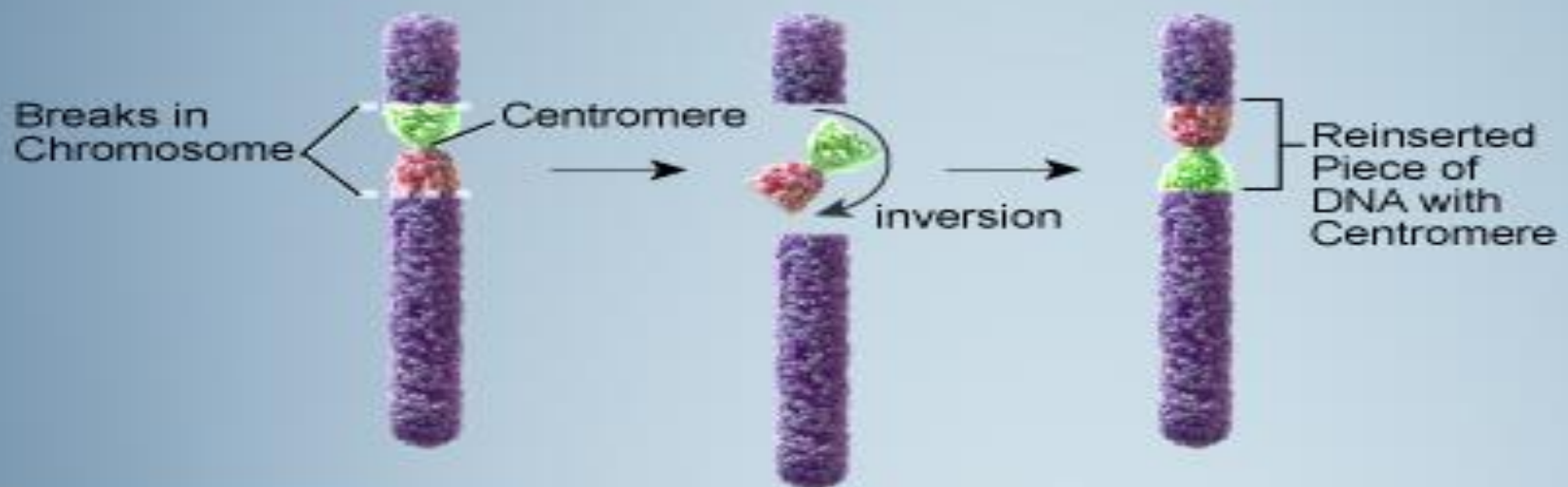
The sequences of both types of inversion are creation of unbalanced homologous chromosome one carrying a duplicate gene or genes and the other is deficient in a gene.

This will result in an abnormal fetus with signs and symptoms of abnormality.

Paracentric Inversion



Pericentric Inversion

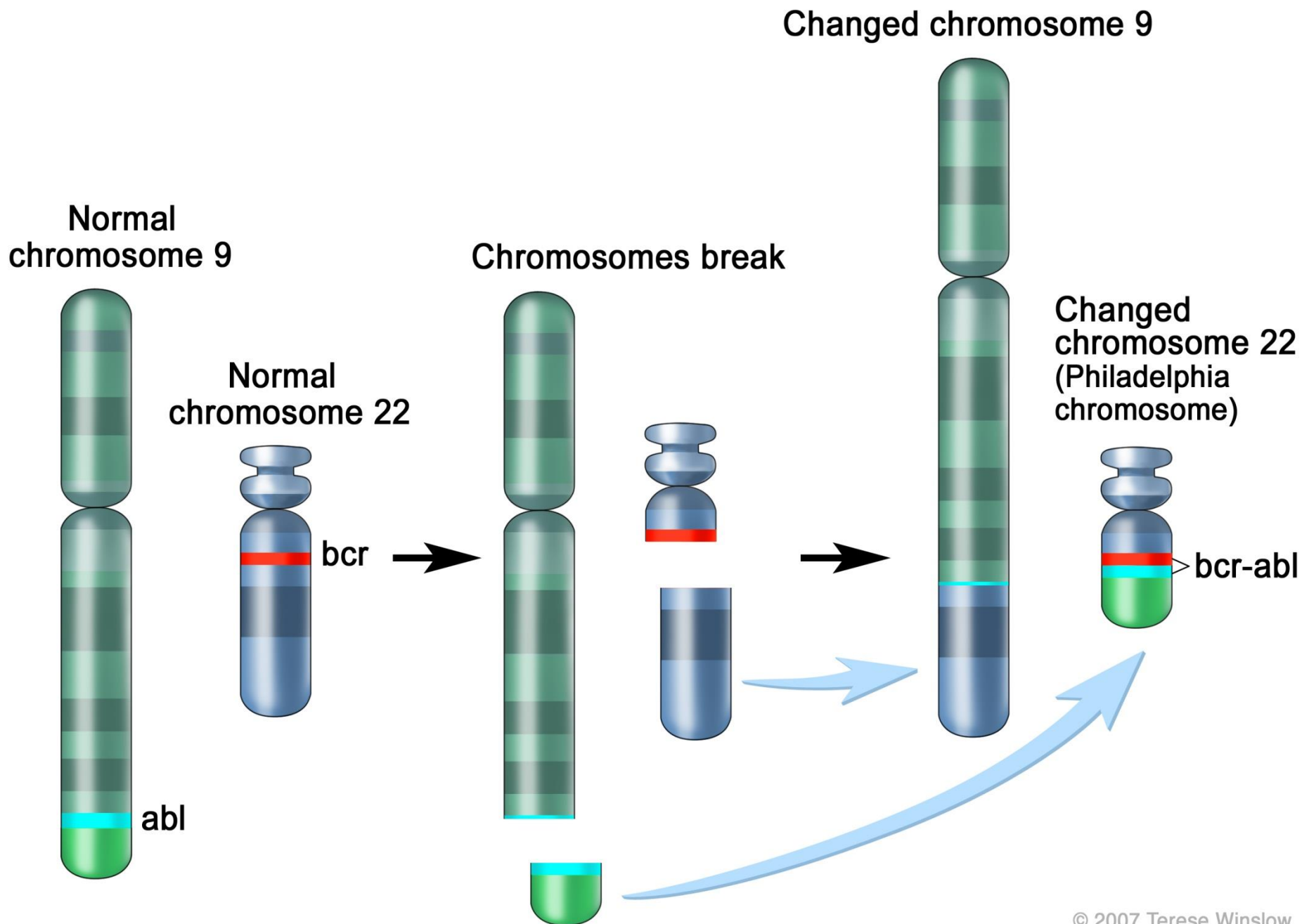


C. Translocation: This is defined as exchanges of segments of chromosome between non-homologous chromosomes. It's of two types:

1. Balanced (Regular) or reciprocal translocation:

Involving exchanges of chromosomal material between two chromosomes with no net gain or loss of genetic material. This is one of pathological changes seen in malignancy.

This is usually seen in leukemia's and lymphoma i.e. ***Philadelphia chromosome.***

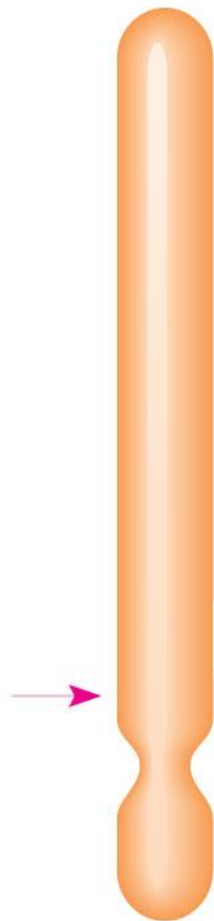


B. Robertsonian (centric) fusion: Being reciprocal translocation between two acrocentric chromosomes involving the short arm of one and the long arm of the other.

Transfer of segments lead to formation of one abnormally large chromosome and one extremely small. The latter is usually lost. This translocation predisposes to the formation of abnormal (unbalanced) gametes.



+



Breakage
and
rejoining



+



Fragment
(usually lost)

Normal, nonhomologous,
acrocentric chromosomes

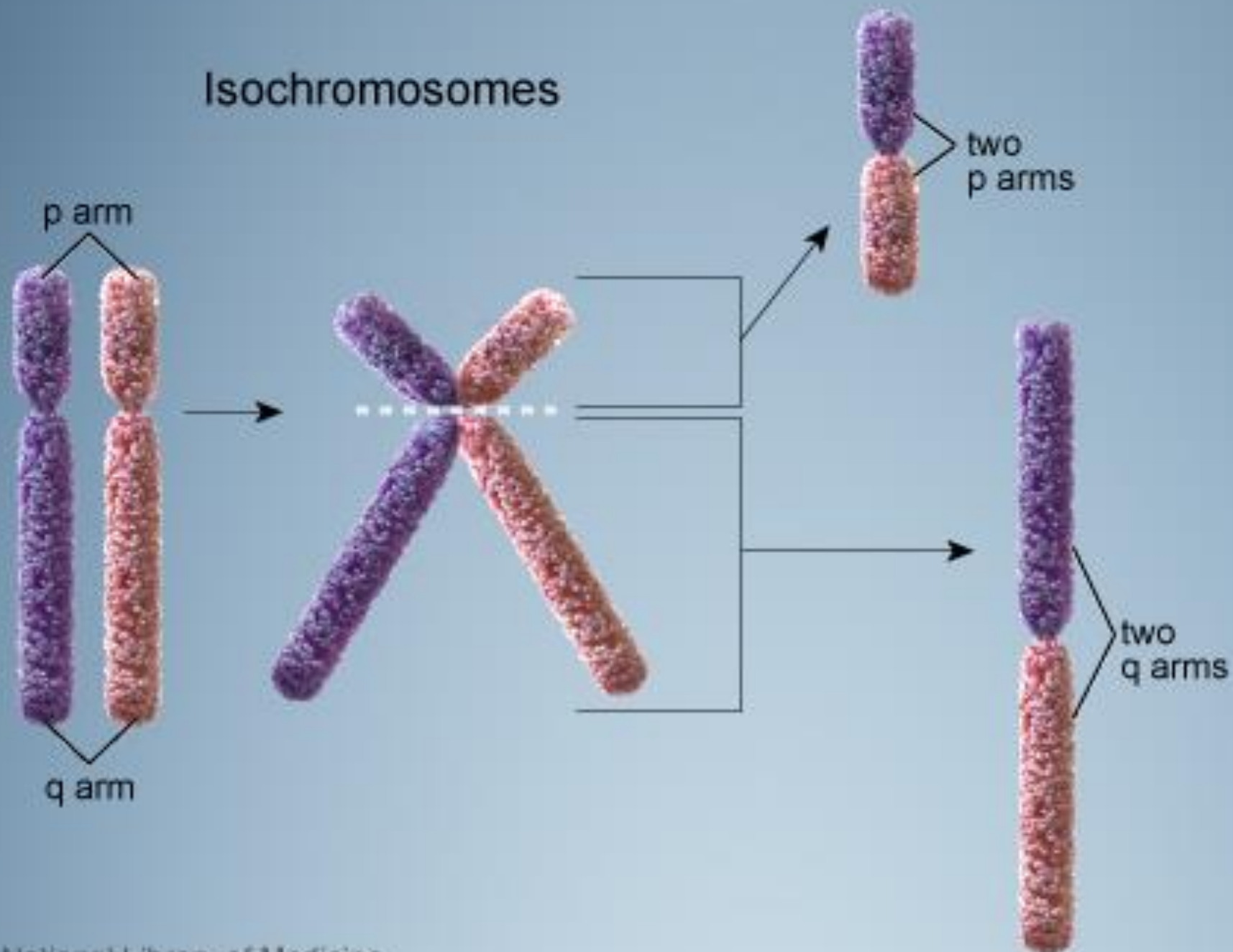
Robertsonian
translocation

D. Isochromosomes: Formed when one arm (short or long) is lost and the remaining arm is duplicated, resulting in chromosome of two short arms only or of two long arms .

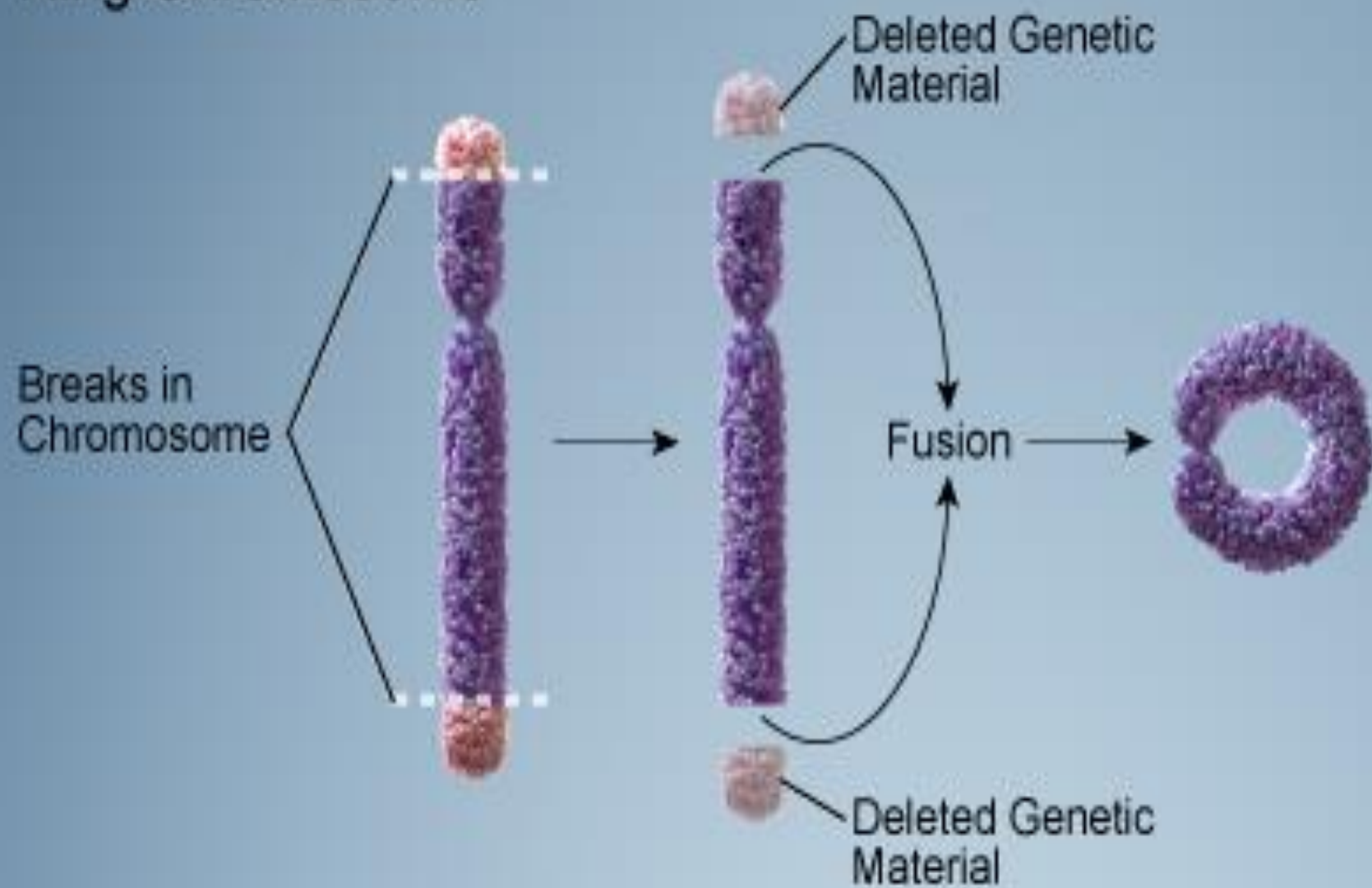
In live births, the most common Isochromosomes is I (Xq) with duplication of long arm and deletion of short arm.

E. Ring chromosome: It result from deletion of both ends of chromosome and then the end become fused.

Isochromosomes



Ring Chromosome



END