## CORE IDEA 2: GENETICS AND INHERITANCE
## TOPIC 2.7: CHROMOSOMAL ABERRATION

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**Learning Outcomes (modified):**

(I) Explain what is meant by the terms *chromosomal aberration*.

For chromosomal aberration, knowledge of numerical aberration (including aneuploidy, as in the case of trisomy 21, i.e. Down syndrome) and structural aberration (including translocation, duplication, inversion and deletion) is required.

***Use the knowledge gained in this section in new situations or to solve related problems.***

**References:**

Reece, J. B. et al. (2018). *Campbell Biology* (11th Ed). Chapter 17: From Gene to Protein, pp407 – 410.

Reece, J. B. et al. (2018). Campbell Biology (11th Ed). Chapter 15: Linkage and Chromosomes, pp356 – 359.

***Note: This textbook is available in our library. You may wish to borrow it to supplement your reading when necessary.***

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## 1. Introduction

Chromosomal aberrations refer to **changes or abnormalities in the structure or number of chromosomes** within a cell.

## 2. Overview of Chromosomal Aberration

There are two main types of chromosomal aberrations:

1. **Numerical aberrations**:

    - **Aneuploidy**: This occurs when a cell has an abnormal number of chromosomes, either too many or too few. It can result from errors during cell division (mitosis or meiosis).

        - Trisomy: Having an extra copy of a particular chromosome, resulting in three copies instead of two (e.g., Down syndrome, which is caused by trisomy of chromosome 21).

        - Monosomy: Missing a copy of a particular chromosome, resulting in only one copy instead of two (e.g., Turner syndrome, caused by monosomy of the X chromosome).

2. **Structural aberrations**:
    - **Deletions**: A portion of a chromosome is missing or deleted.
    - **Duplications**: A part of a chromosome is duplicated or repeated.
    - **Inversions**: A segment of a chromosome is reversed in orientation.
    - **Translocations**: A segment of one chromosome is attached to a different chromosome.

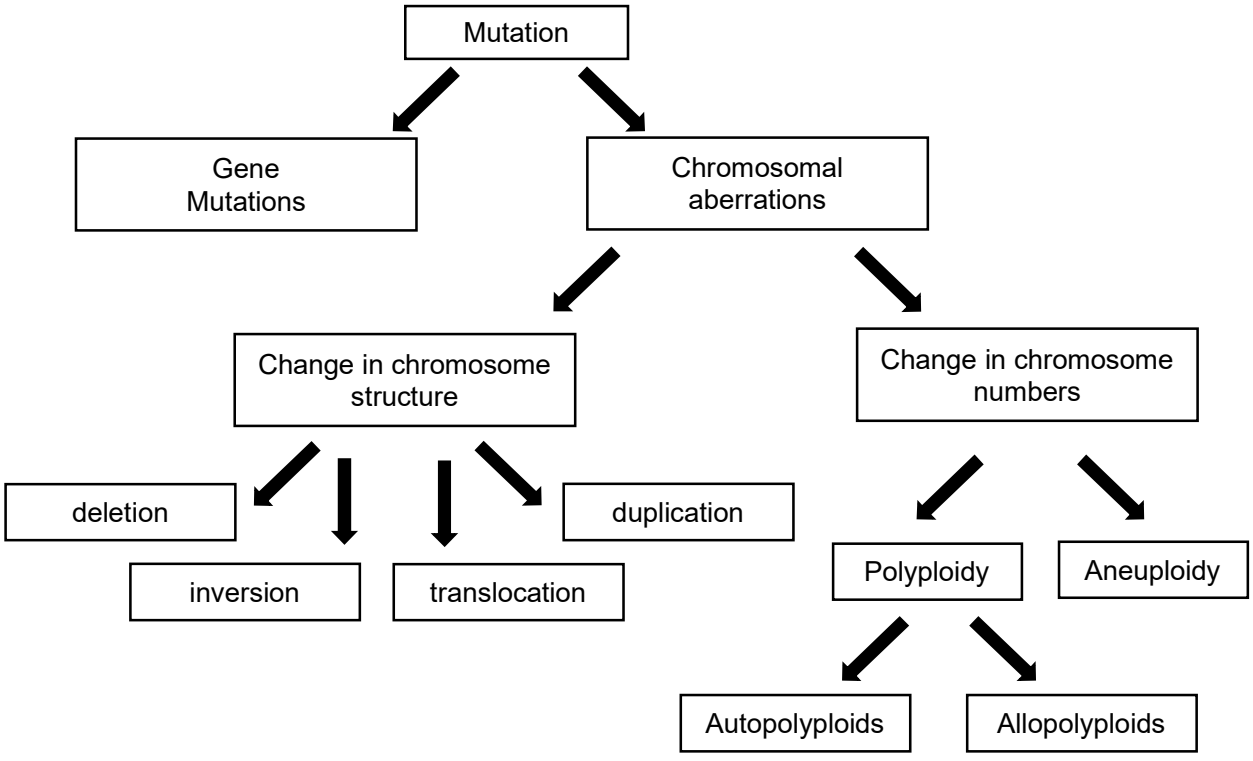



**Fig 2.1: Overview of Chromosomal Aberration**

These chromosomal aberrations can occur spontaneously or be induced by environmental factors like radiation or certain chemicals.

They can lead to genetic disorders, developmental abnormalities, or even cell death, depending on the specific aberration and the genes involved.

## 3. Chromosome Aberration

**Learning Outcome 2(l) modified:**

Explain what is meant by the term ***chromosome aberration***. For chromosomal aberration, knowledge of structural (e.g. translocation, duplication, inversion, deletion) aberration is required.

### 3.1 Structural Aberration

There are different types of structural chromosomal aberrations. Chromosome structural aberrations can arise through physical breakage and rejoining of the DNA that constitutes the chromosome.

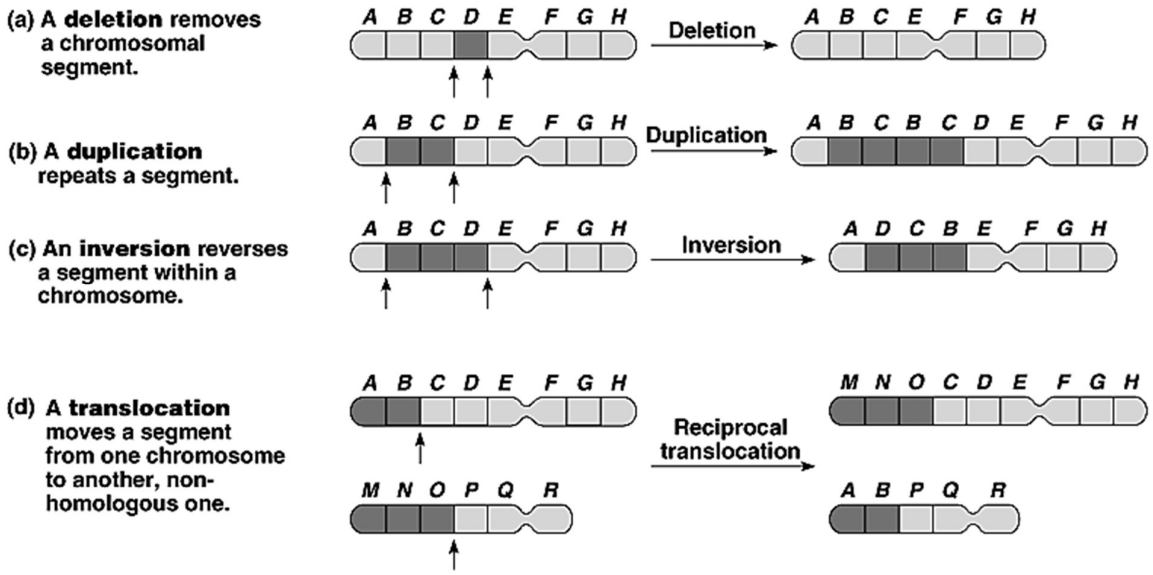



**Fig. 3.1.1: Structural aberration**

**E.g. of diseases caused by structural aberrations:** *(Details of examples of diseases are not required.)*

**a)** Deletions occur when a portion of a chromosome is **missing or deleted**. This can happen due to chromosome or chromatid breaks caused by factors like radiation, chemicals, or viruses during cell division. Deletions can be terminal (occurring near the end of a chromosome) or interstitial (occurring in the middle portion). Deletions lead to loss of genetic material and can result in genetic disorders like *Cri-du-chat* syndrome.

***Extra reading of concrete example:***
*Cri-du-chat* syndrome is due to terminal deletion of the p (short) arm of chromosome 5.

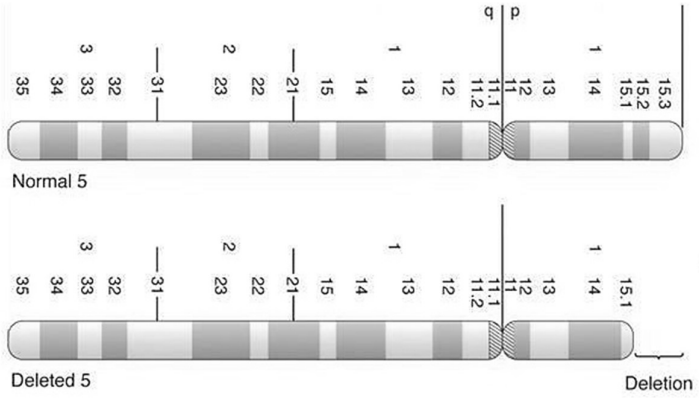



**Fig. 3.1.2: (terminal) Deletion in chromosome 5**

The affected individual cries like the mew of a cat, suffers from severe mental retardation, congenital heart disease and other physical deformities. Such individuals usually die in infancy or early childhood.

**b)** Inversions occur when a chromosome segment excises and reintegrates in the reverse orientation (180° flipped).

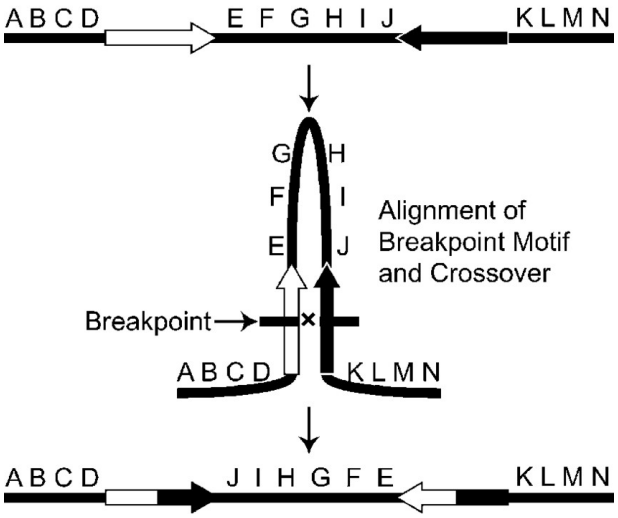



**Fig. 3.1.3: Mechanism for chromosomal inversion.**

***Extra reading of concrete example:***

Chromosomal inversions play a major role in causing severe hemophilia A, an X-linked genetic disorder. Here's how inversions occur in the factor VIII (F8) gene, leading to hemophilia A:

The F8 gene is located on the X chromosome and contains 26 exons. Nearly half of all severe hemophilia A cases are caused by an inversion involving intron 22 of the F8 gene. This inversion occurs due to an intrachromosomal homologous recombination event.

During this recombination process, the region containing exons 1 to 22 of the F8 gene becomes inverted with respect to exons 23 to 26.

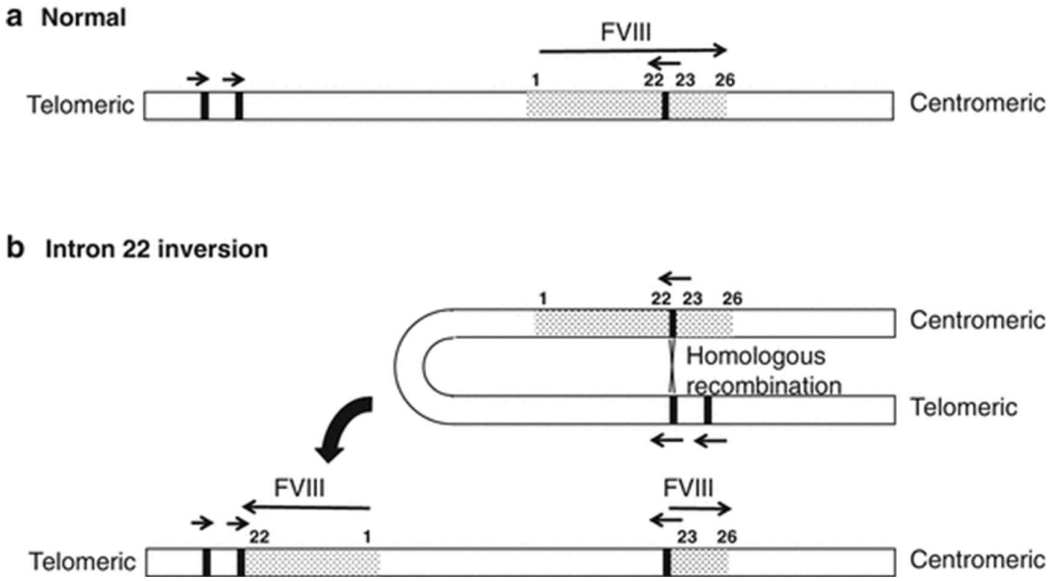



**Fig 3.1.4 Simplified representation of the intron 22 inversion. Recombination between homologous sequences in intron 22 leads to separation of exons 1–22 from exons 23–26.**

This inversion disrupts the normal structure and expression of the F8 gene, leading to a deficiency or absence of the clotting factor VIII protein, which causes hemophilia A.

The inversion event is believed to occur almost exclusively in male germ cells (sperm) during spermatogenesis.

c) **Translocation** may involve a reciprocal exchange between two non-homologous chromosomes or may involve a segment of one chromosome detaching and attaching to a non-homologous chromosome, which is knows as non-reciprocal exchange.

***Extra reading of concrete example:***

***This concrete example is an example of a context that cuts across multiple topics – topic 2.7 chromosomal aberration, topic 2.8 molecular biology of cancer, topic 2.9 transcription and gene regulation (I) and topic 2.10 translation and gene regulation (II).***

A well-known example of how chromosomal translocation can cause overexpression of a gene product leading to cancer is the Philadelphia chromosome in chronic myeloid leukemia (CML).

***Topic 2.7 chromosomal aberration***

In CML, a reciprocal chromosomal translocation occurs between chromosomes 9 and 22. Specifically (Fig, 3.1.5), a portion of the BCR gene from chromosome 22 gets fused with a portion of the ABL gene from chromosome 9. This creates a new fusion gene called BCR-ABL. The BCR-ABL fusion gene produces an abnormal BCR-ABL fusion protein which has increased tyrosine kinase activity compared to the normal ABL protein.

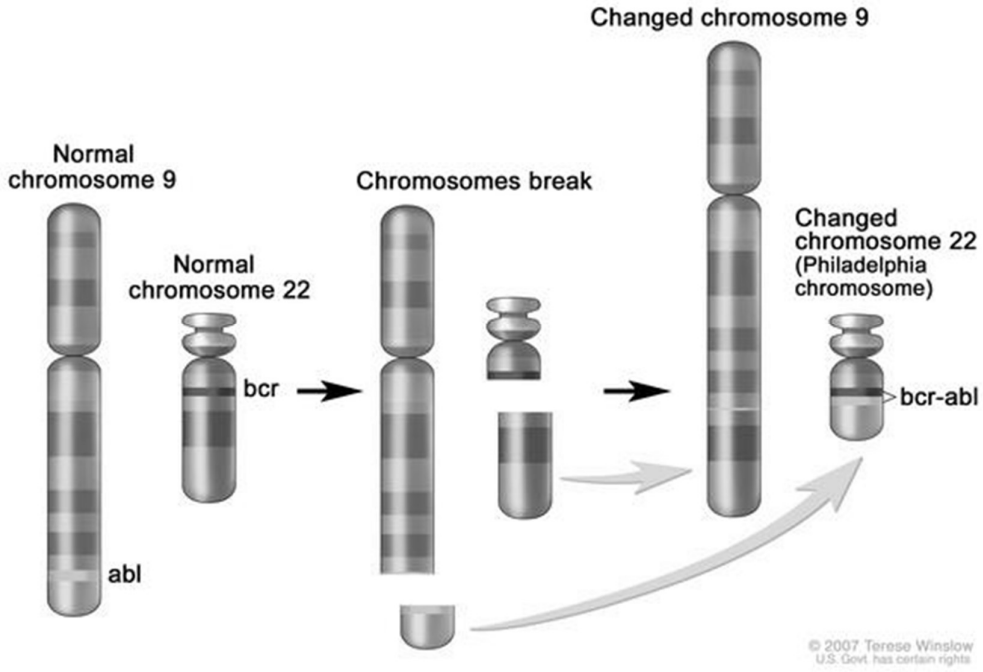



**Fig 3.1.5: Chromosomal translocation**

***Topic 2.8 Molecular biology of Cancer***

This increased tyrosine kinase activity leads to uncontrolled cell division and growth of abnormal myeloid cells in the bone marrow.

***Topic 2.9 Transcription and Gene Regulation (I), Topic 2.10 Translation and Gene regulation (II)***

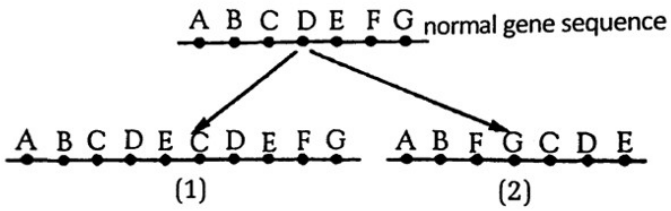
The reason for the overexpression of the BCR-ABL fusion protein is that the BCR-ABL gene gets placed under the control of the strong BCR promoter/enhancer on chromosome 22. This strong promoter drives high levels of expression of the BCR-ABL fusion protein, leading to the development of CML. ***(You will learn more about the idea of how regulatory genes such as promoter and enhancer influence gene expression in topic 2.9 and topic 2.10)***

This example highlights how chromosomal translocations can deregulate gene expression by fusing a proto-oncogene to a strong promoter, resulting in overexpression of an oncogenic fusion protein that drives cancer development.

So in summary, the chromosomal translocation in CML creates a new fusion gene (BCR-ABL) that gets overexpressed due to its fusion with a strong promoter. The overexpressed fusion protein (BCR-ABL) has abnormally high tyrosine kinase activity, causing uncontrolled cell growth and leading to chronic myeloid leukemia.

***Checkpoint 1:***

The diagrams below show two types of chromosomal mutation producing changes from the normal gene sequence.




What are the two forms of chromosome mutation shown above? Explain your answer.

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## 3.2 Numerical Aberration

Numerical chromosomal aberrations refer to changes in the number of chromosomes present in a cell, deviating from the normal diploid number.

### 3.2.1 Polyploidy

Polyploidy is a condition where a cell has more than two complete sets of chromosomes. It is relatively rare in humans but can occur during early embryonic development.

Triploidy is a form of polyploidy where cells have three complete sets of chromosomes (69 chromosomes) instead of the normal two sets (46 chromosomes). Triploidy is not compatible with life and typically results in miscarriage or stillbirth.

Polyploidy can arise from errors during meiosis or fertilization, such as the fusion of two diploid gametes or the failure of a zygote to undergo subsequent cell divisions.

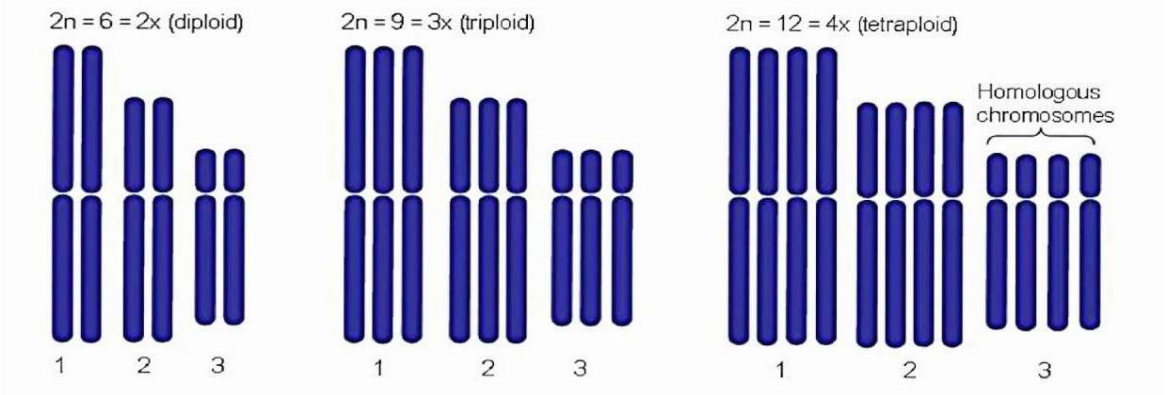


**Fig. 3.2.1.1 Visual representation of diploid, triploid and tetraploid.**

***Checkpoint 2:***

Which combination of chromosomes would result in a zygote showing polyploidy, if the parental chromosome number is 36?

| | sperm | ovum |
|---|---|---|
| **A** | 9 | 9 |
| **B** | 18 | 18 |
| **C** | 18 | 19 |
| *D* | *18* | *36* |

### 3.2.2 Aneuploidy

Aneuploidy occurs when a cell has an abnormal number of chromosomes that is not an exact multiple of the haploid set. Aneuploidy often results from an error called **nondisjunction** during meiosis.

Nondisjunction (Fig. 3.2.2.1) occurs when **chromosome pairs fail to separate properly** during meiosis, leading to gametes (egg or sperm) with an abnormal number of chromosomes. If one of these abnormal gametes is fertilized, the resulting embryo will have aneuploidy.

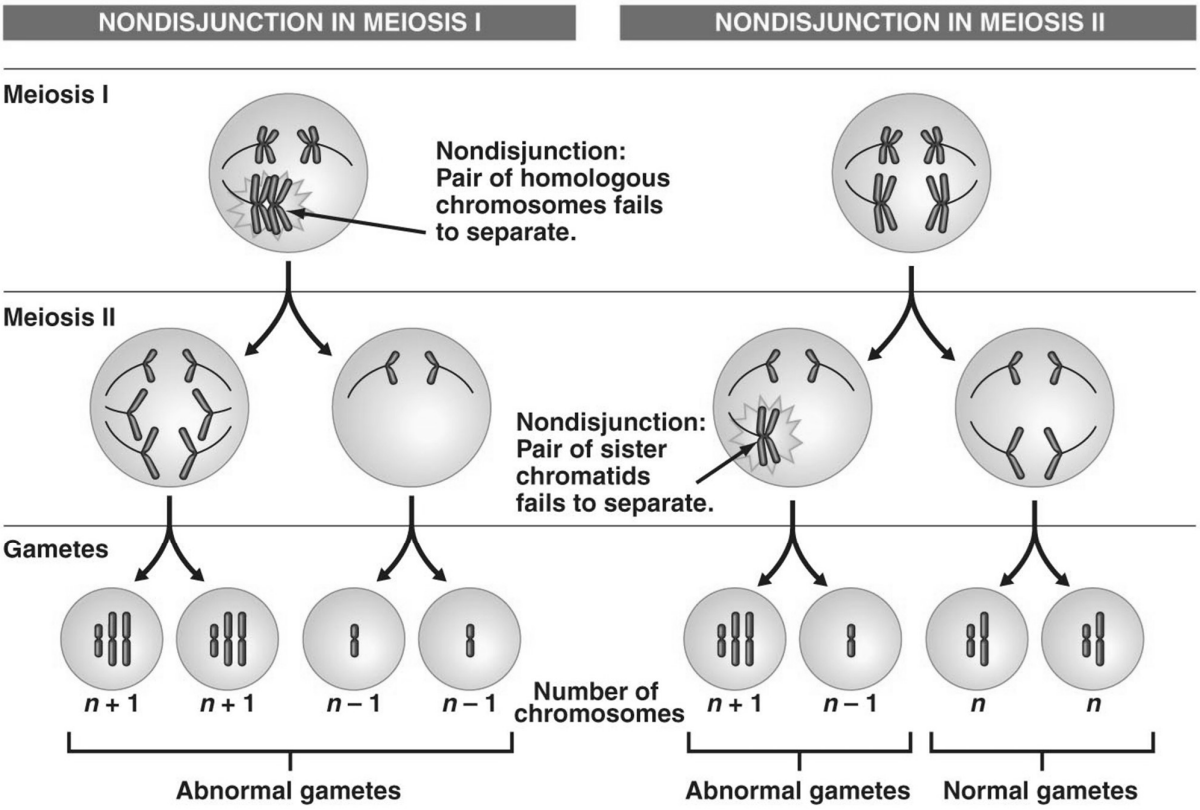


**Fig. 3.2.2.1 Meiotic nondisjunction**

The most common type of aneuploidy is trisomy, where there are three copies of a particular chromosome instead of the usual pair. For example, trisomy 21 causes Down syndrome, where cells have three copies of chromosome 21.

Monosomy is another form of aneuploidy, where a cell is missing one chromosome from a pair. An example is Turner syndrome, caused by monosomy of the X chromosome, where cells have only one X chromosome instead of the typical XX or XY.

It's important to note that numerical chromosomal aberrations can have severe consequences for an individual's development and health, as they disrupt the normal genetic balance and can lead to

## 4. Disease caused by Chromosomal Aberration

**Learning Outcome 2(l) modified:**

Explain what is meant by the term ***chromosome aberration*** in the case of trisomy 21, i.e. Down syndrome).

### 4.1 Down Syndrome (*Trisomy 21)*

There are two main types of Down syndrome – regular Down syndrome and mosaic Down syndrome.

#### 4.1.1 Regular Down Syndrome

In regular Down syndrome, every cell in the body has an extra copy of chromosome 21 (three copies instead of the usual two). This can happen due to two reasons:

1. **Trisomy 21**: The extra copy of chromosome 21 is present in every cell from conception. This means that all the cells in these individuals will have 47 chromosomes instead of the typical 46 chromosomes (Fig. 4.1.1.1).

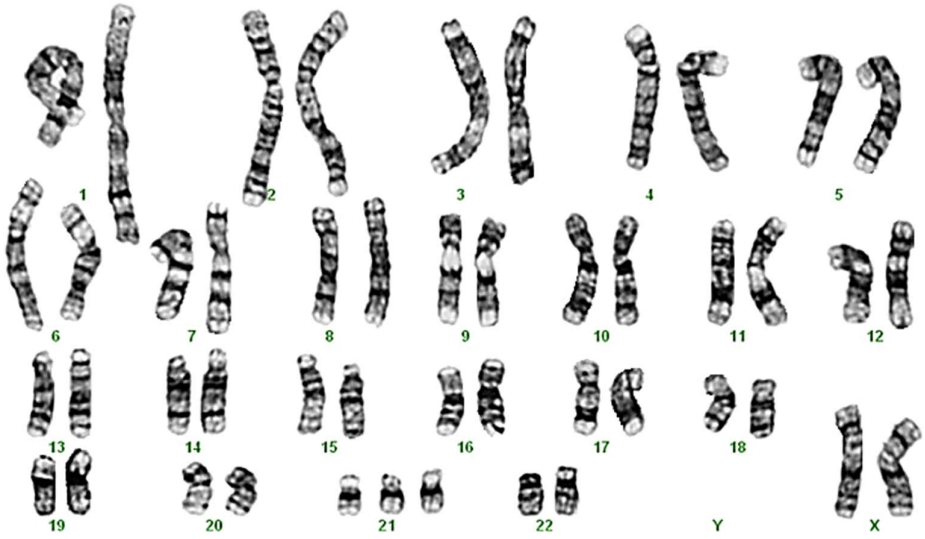


**Fig. 4.1.1.1 Karyotype of a female with Trisomy 21 (47, XX, 3 copies of 21)**

Trisomy 21 is a type of aneuploidy. The extra copy of chromosome 21 is due to nondisjunction during nuclear division. Nondisjunction happens when the chromosome 21 pairs fail to separate properly during meiosis (the process of forming eggs or sperm) (Fig. 3.2.2.1).

2. **Translocation Down syndrome**: During the formation of egg or sperm cells, or in early fetal development, a part of chromosome 21 breaks off. Instead of being lost, this broken piece of chromosome 21 attaches itself to another chromosome. This is typically chromosome 14. Hence, the extra genetic material is still present in every cell.

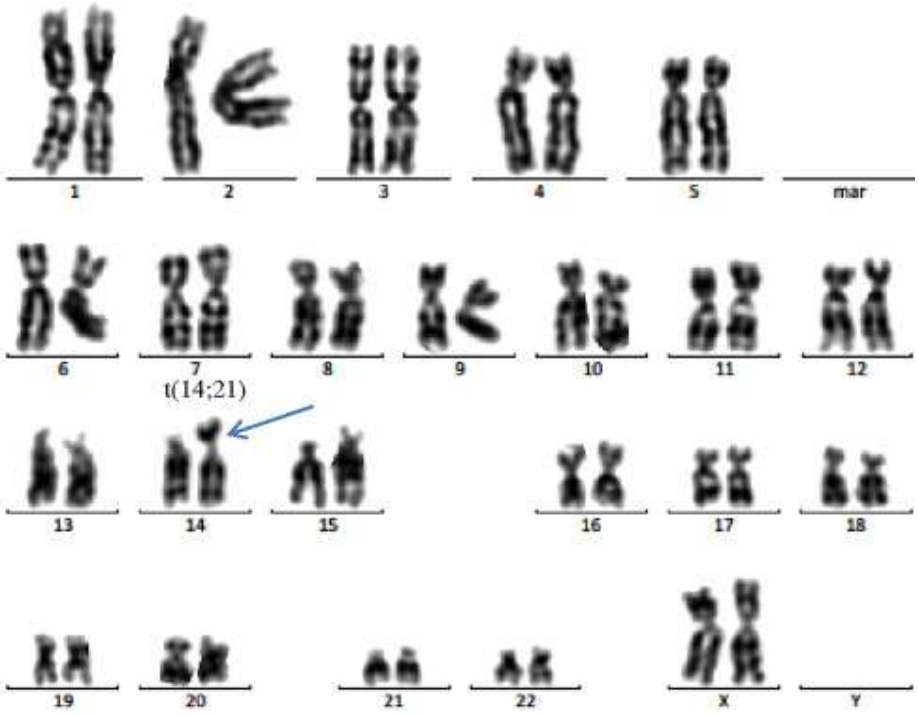


**Fig. 4.1.1.2 Karyotype of a female with translocation down syndrome (46, XX, extra 21 on chromosome 14)**

### 4.1.2 Mosaic Down Syndrome

In mosaic Down syndrome, the extra copy of chromosome 21 is not present in every cell of the body. Instead, there is a mixture of cells - some cells have the typical two copies of chromosome 21, while others have three copies (Fig 4.1.2.1).

This mosaicism occurs due to a random nondisjunction during nuclear division after fertilization. The initial cell division results in some cells with the extra chromosome 21 and others without it. As these cells continue to divide and develop into different tissues and organs, the proportion of cells with the extra chromosome can vary.

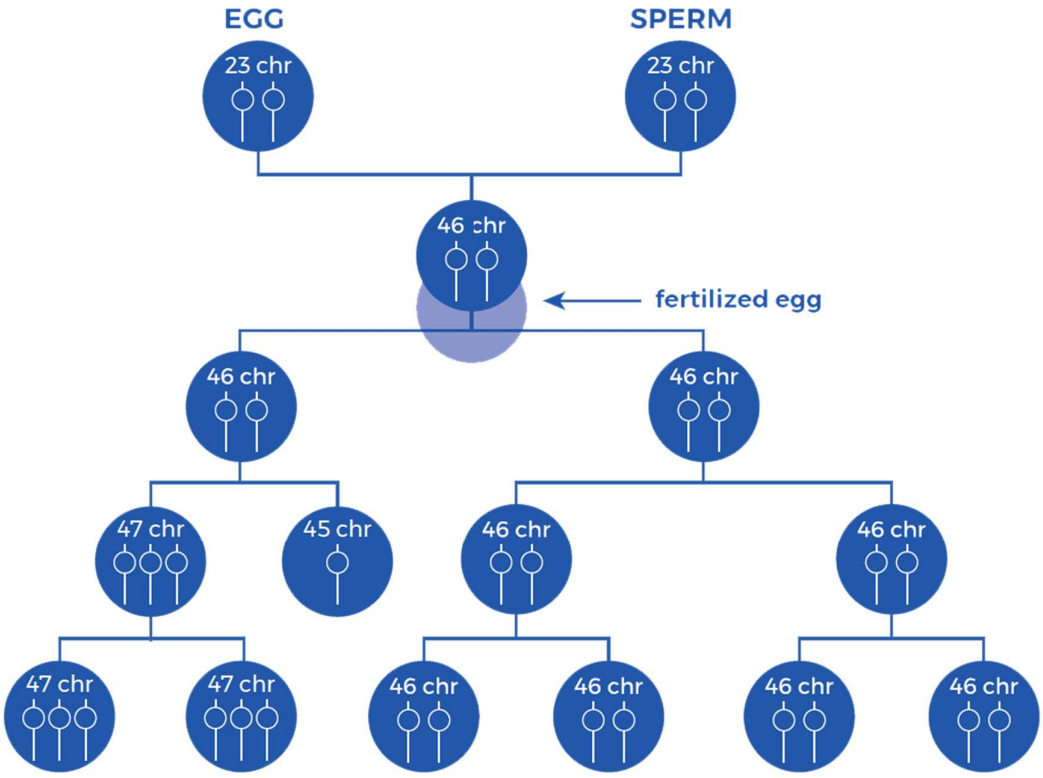


**Fig. 4.1.2.1: Mixture of two types of cells, some containing the usual 46 chromosomes and some containing 47. Those cells with 47 chromosomes contain an extra chromosome 21.**