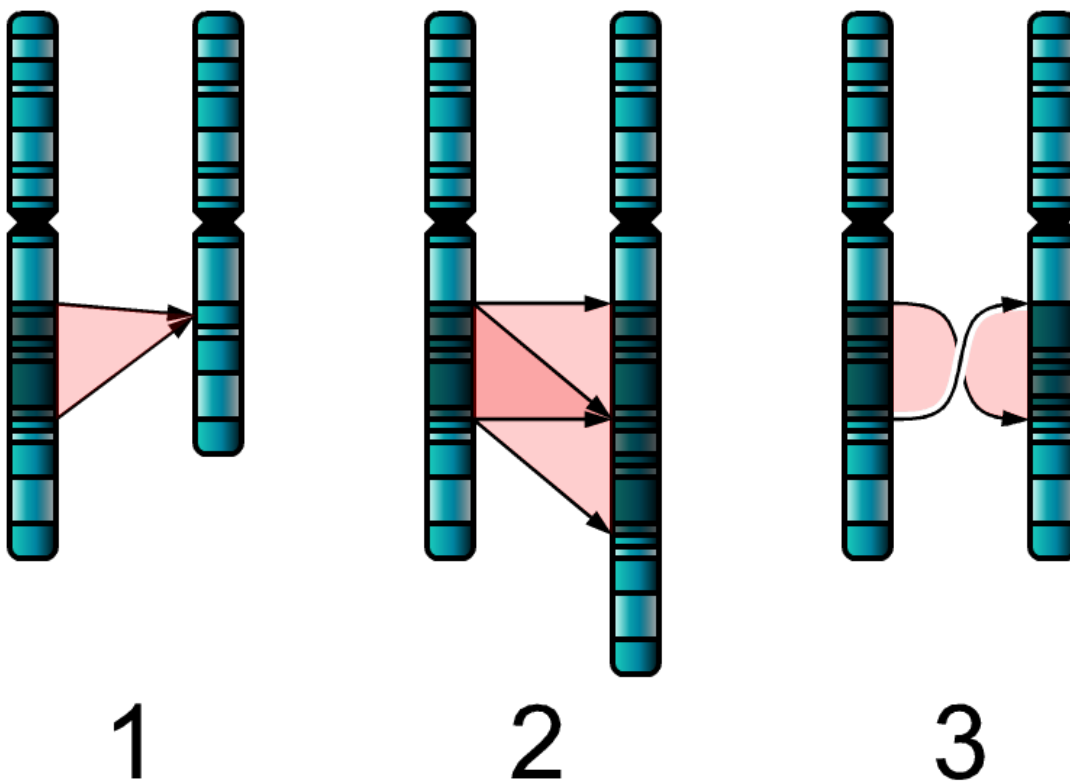


# Human Genetics: Chromosomal Aberrations

[See online here](#)

**Chromosomal aberrations are chromosome mutations that entail changes in the genome. These changes can affect either part of a chromosome or an entire chromosome. The change in genetic material can be due to loss, gain of extra genetic material or rearrangement of the existing genetic material. These aberrations are the source of genetic mutations. Chromosomal aberrations can be even further categorized into numerical and structural chromosomal aberrations.**



## Numerical Chromosomal Aberrations

Numerical chromosomal aberrations are defined as changes in the number of chromosomes or the entire set of chromosomes.

Normally humans carry a diploid set of chromosomes. The diploid chromosome set consists of 22 pairs of **autosomes**, with each pair consisting of individual chromosomes derived from the mother and the father. The 23rd pair consists of 2 sex chromosomes (**gonosomes**) X and Y, resulting in a complete set of 46 chromosomes in a human somatic cell.

Overall, the numerical chromosomal aberrations are **genome mutations**, which are attributed to the faulty distribution of chromosomes among the daughter cells.

## Chromosome maldistribution

Chromosome maldistribution, for e.g., via **nondisjunction** (no separation of a homologous chromosome pair during meiosis) may lead to the formation of abnormal numbers of individual chromosomes. This phenomenon is referred to as **aneuploidy**, in which the individual chromosome may be present only once (**monosomy**) or more than twice (e.g. **trisomy**).

**Note:** Compared with a few trisomies, the monosomy of autosomes is not compatible with life.

In addition to aneuploidy, nondisjunction can also lead to **polyploidy**. Polyploidy does not affect merely an individual chromosome, but rather the entire set of chromosomes, for e.g., each chromosome occurs 3 times (**triploidy**).

Chromosomal nondisjunction is transmitted to the offspring via **gametes**. However, the maldistribution of chromosomes may also affect **somatic cells**, which results in a juxtaposition of changed and unchanged cells. It usually occurs via mitotic losses and the subsequent formation of **somatic mosaics**, for e.g., Turner syndrome with mosaicism.

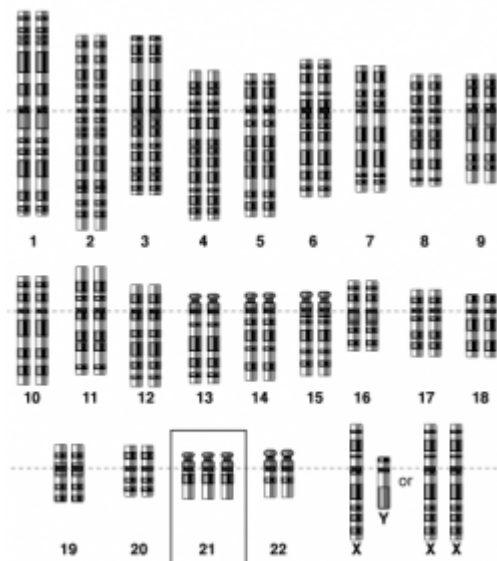
## Aneuploidy of the autosomes

In contrast to the abnormal distribution of gonosomes, the aneuploidy of autosomes results in distinct mental and physical impairment.

The majority of autosomal aberrations thus leads to spontaneous miscarriage before the 12th week of gestation. Trisomies involving chromosomes 21, 18, and 13 are potentially viable.

Trisomy usually occurs during meiosis. In two-thirds of cases, the trisomy is attributed to faulty division during the **1st meiotic division except for trisomy 18**, which usually originates in the **2nd meiotic division**. The risk of abnormal division is increased by the age of the mother at the time of division.

### Definition of trisomy 21 (Down's syndrome)



[Image:](#) Trisomy 21 genome scheme. By Courtesy: National Human Genome Research Institute, License:

**Trisomy 21**, also referred to as Down's syndrome, is a **chromosomal aberration** characterized by the presence of an additional chromosome 21. Trisomy 21 is associated with a rate of incidence of 1:600 among newborns and is one of the most common chromosomal aberrations involving autosomes.

Because the risk of **nondisjunction** correlates with the mother's age, the child's risk of trisomy 21 increases with maternal age at the time of conception.

The symptoms of trisomy 21 usually include impaired intelligence and specific phenotypic characteristics such as the flat face, **brachycephalus**, **epicanthus** (outward and upward slanting eyelids), a small but usually open mouth with a protruding tongue, and small physical stature.

During birth, the children manifest reduced muscle tone (muscular hypotonia) characteristic of a **'floppy infant'**. The reduced muscle tone is clear when the child is lifted in the abdominal position, in which the extremities hang loosely.

A so-called 'sandal' groove appearing on the feet increases the distance between the 1st and 2nd toes. The surface of the palms may also exhibit a 4-finger groove, which manifests as a horizontal line running along the length of the first 4 fingers.

Furthermore, organ systems such as the heart (e.g., in the form of heart defects) and the gastrointestinal tracts (e.g., in the form of **atresia**) are affected. The risk of developing **leukemia**, as well as **Alzheimer's disease**, is greatly increased. Treatment consists of prompt intervention and management of the aforementioned symptoms and malformations.

#### **Definition of trisomy 13 (Patau syndrome)**



Image: Trisomy13. By CarloDiDio, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Patau syndrome also correlates with the mother's age. However, its rate of incidence is 1:10,000, suggesting that its relative rarity compared with Down's syndrome. Patau syndrome also differs from Down's syndrome in terms of the substantially diminished life expectancy. Approx. 95% of the affected children die before the age of 6 months.

Phenotypically, it is characterized by a triad of symptoms such as **microcephaly**, cheilognathouranoschisis, and polydactyly. The polydactyly is usually ulnar and manifests as **hexadactyly**.

A 4-finger groove is also visible in the fingers (see Down's syndrome).

Other organ systems such as the heart (defective ventricular septum or patent ductus arteriosus), the kidneys, or the urinary tract may be affected.

### **Definition of trisomy 18 (Edwards syndrome)**

The incidence rate of Edwards syndrome, which is characterized by an additional chromosome 18, is 1:6000. Similar to the other 2 **numerical chromosomal aberrations** discussed above, trisomy 18 correlates with the mother's age at the time of conception.

Life expectancy is also greatly reduced, similar to Patau syndrome. Only approx. 5% of affected children live for longer than 12 months.



[Image](#): Overlapping fingers. By Bobjgalindo, License: [CC BY-SA 4.0](#)

The affected children manifest a range of characteristic anatomical traits, including low-set ears with upward auricles (faun-like and flat pinnae), long and narrow skull, and deformed feet reminiscent of rocker bottoms (rocker-bottom feet).

These children also exhibit a typical hand position of the [fingers](#) in which the middle and ring fingers are overlapped by the index and little fingers, respectively.

## Aneuploidies of the gonosomes

Compared with autosome maldistribution, the abnormal distribution of gonosomes usually results in a relatively minor impairment of mental and physical development.

Aneuploidy of gonosomes also differs from autosomal aberrations in that monosomy of the gonosomes is compatible with life, for e.g., Ullrich-Turner syndrome, which exhibits the karyotype 45,X.

Another example of gonosomal aneuploidy is Klinefelter syndrome, which exhibits karyotype 47, XXY.

### **Ullrich-Turner syndrome**

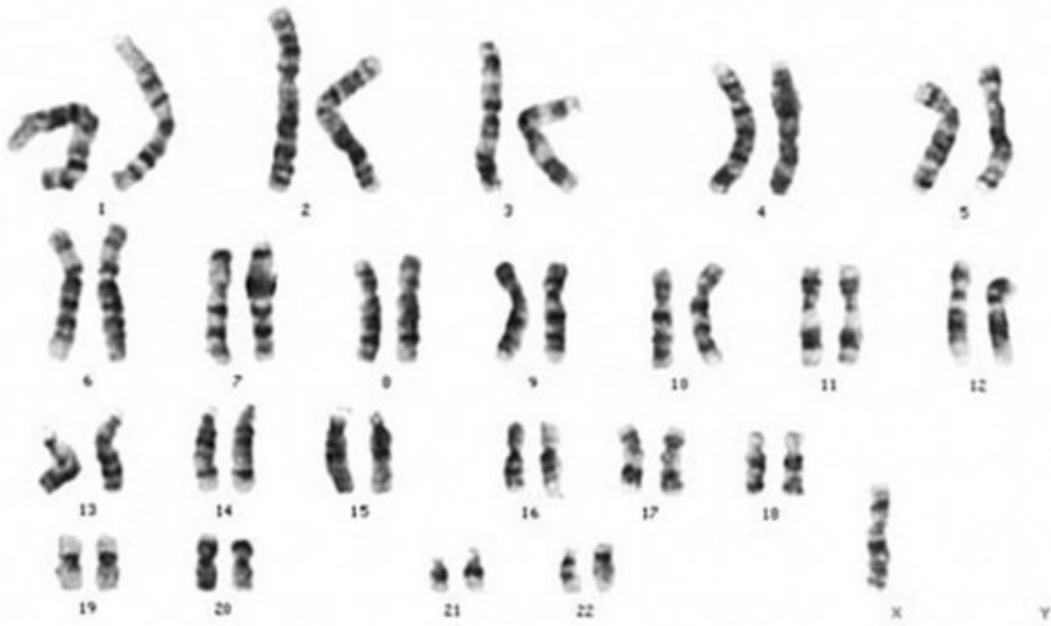


Image: Karyogram 45,X. By The cat--commonswiki, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

[Ullrich-Turner syndrome](#) is an exception in the group of **numerical chromosomal aberrations**, in that it does not correspond to the age of the mother.

Ullrich-Turner syndrome is characterized by monosomy involving gonosomes. The affected girls carry only a single X chromosome, which results in the karyotype **45,XO**.

The loss of X chromosome results in an abnormal location of the female sex organs, for e.g. in the form of **ovarian dysgenesis**. The ovaries affected by dysgenesis are also referred to as **streak gonads**, which are interspersed with conjunctive tissue.

Because of these structural aberrations, the streak gonads do not form hormones, resulting in **estrogen** and **gestagen deficiency**.

This hormone deficiency leads to **primary amenorrhea** and **infertility**. In addition, patients exhibit partial malformations of internal organs, for e.g., the heart (such as **aortic isthmus stenosis**) or the urinary tract, as well as the [kidneys](#) (e.g., horseshoe kidney).

Along with the changes in the internal organs, there is also a series of changes visible externally, including changes involving the skeletal system, such as decreased length or **cubitus valgus**.

**Lymphedema** may also occur in the hands and feet congenitally.

**Pterygium colli** is another symptomatic trait almost exclusive to Ullrich-Turner syndrome, which is characterized by an additional lateral fold in the neck, located between the processus mastoideus and the acromion.

Ullrich-Turner syndrome does not affect life expectancy or mental development.

### **Klinefelter Syndrome**

Klinefelter syndrome is one of the **numerical chromosomal aberrations** involving the maldistribution of the **gonosomes**. It is characterized by the presence of an extra X chromosome, which results in the karyotype **47,XXY**. The incidence rate of Klinefelter

Syndrome is 1:800.

The clinical symptoms may also be attributed to the deficiency of testosterone. The **lack of testosterone** results in delayed closure of the epiphyseal growth plates, leading to abnormally long arms and legs disproportionate to the body size.

In adults, testosterone deficiency also affects bone structure and often leads to **osteoporosis**.

Additional symptoms attributed to testosterone deficiency include testicular hypoplasia with concomitant decrease infertility, as well as **gynecomastia**.

Treatment thus entails lifelong testosterone replacement.

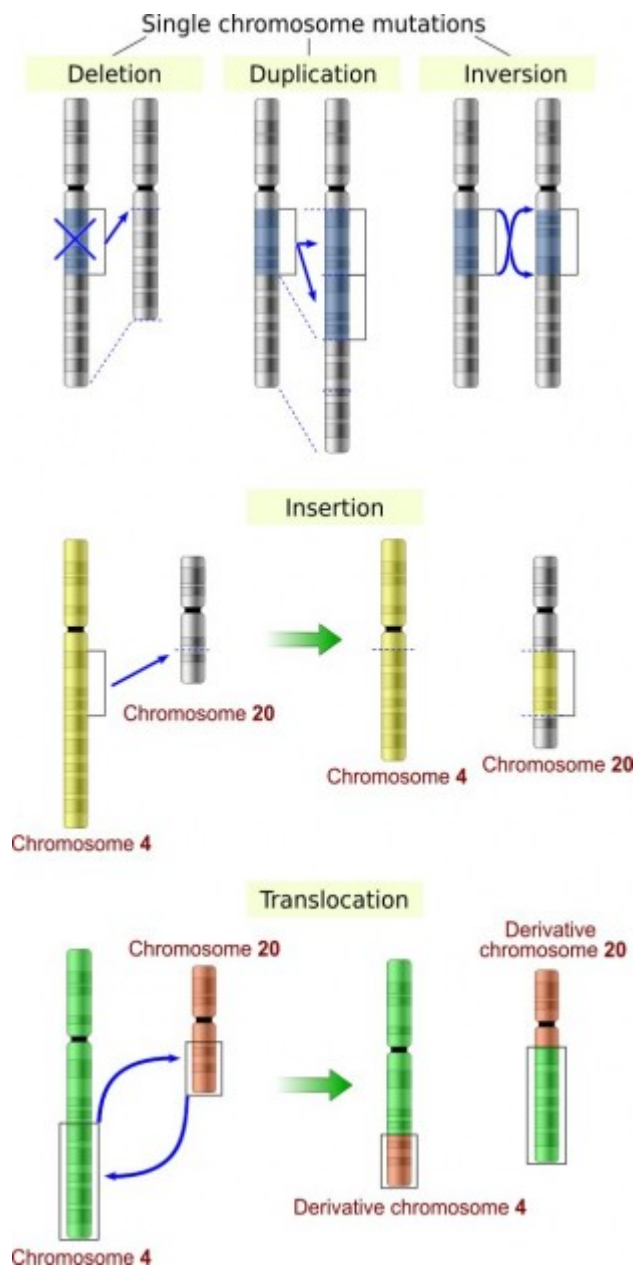
## Polyploidies

In addition to the chromosomal aneuploidies mentioned above, in which none of the autosomal monosomies and few autosomal trisomies are compatible with life, polyploidies of the chromosomes affect entire sets of chromosomes (see above).

However, polyploidies rarely result in live birth and are the most common cause of early **spontaneous abortion**. In this regard, karyotypes 69,XXX and 69,XXY are the most frequent.

The majority of polyploidies are attributed to malformation of the **spindle apparatus** during meiosis I or II.

## Structural Chromosomal Aberrations



[Image:](#) Chromosomes mutations. By YassineMrabet, License: Public domain

The group of structural chromosomal aberrations is also referred to as **chromosome rearrangement**, as it entails the repositioning of chromosomal sections resulting in an altered sequence of gene segments.

Chromosomal rearrangements include **deletions, duplications, inversions, and translocations**. Deletions and duplications suggest a loss or duplication of individual gene sequences within a chromosome, whereas translocation refers to an exchange between non-homologous chromosomes. During an inversion, similar changes occur within a chromosome.

Ionizing radiation (e.g., X-rays) is a possible cause of chromosomal aberrations. This energy-rich radiation induces breaks within the chromosomes, some of which are then improperly repaired, resulting in chromosomal deletions or duplications.

Structural chromosomal aberrations in routine clinical practice are primarily encountered in bone marrow cells, fibroblasts, and lymphocytes. However, these changes can be found in all bodily tissues essentially.



## Deletions

A deletion entails the loss of a specific segment of the chromosome, with multiple genes located within a specific area. The loss of a chromosome segment may be accompanied by:

- Reunification or reconstitution with the same chromosome
- Subsequent rejoining of the individual sections after the loss of a segment-leading to truncated chromosome
- Segregation of the broken segment, albeit without a centromere

Depending on the number of fragments and their location, a **terminal** or **interstitial deletion** may occur. Terminal deletion involves loss of one of the 2 end pieces of a chromosome, whereas interstitial deletion refers to a loss between the 2 ends.

**Homozygous** and **homologous** deletions: Homozygous deletion refers to the deletion occurring in both homologous chromosomes. The complete loss of the chromosome segment affected by the deletion results in lethal outcomes generally.

A clinical condition known as cri-du-chat syndrome (French for 'cat's cry') is characterized by a deletion in the short arm of chromosome 5 (5p). Children diagnosed with this disease manifest cat-like cries. They carry a small head and exhibit intellectual disability.

## Duplications

Duplication is the opposite of deletion and is characterized by a multiplication of individual chromosome sections. Depending on the location of the duplicate chromosomal segments adjacent to one another, this chromosomal aberration is classified into several types:

- **Tandem arrangement** (a **bc bc** d) occurs when the repeated segment is near the centromere as shown with **bc** above, and the centromere is in position **d**.
- **Reverse tandem duplication** (a **bc cb** d) occurs when the duplicate chromosome segment is located in the reverse direction compared to the normal pattern of the original chromosome, i.e., the repeated segment is **cb** instead of **bc**.
- **Displaced tandem duplication** occurs when the segment is repeated elsewhere, and away from its original location. It may be located on the same arm (homobrachial displacement) or on the other arm (heterobrachial displacement).
- **Transposition duplication** occurs when a segment is duplicated on a non-homologous chromosome.

Developmentally, duplications play a significant role in the formation of new or additional genetic material with possibly novel functions.

## Inversions

An inversion results in a 180° rotation of a chromosome section and its subsequent reintegration into the original chromosome. The reintegration of the chromosome does not ultimately result in any chromosomal loss, and inversion is generally not lethal.

Depending on whether or not the centromere is present, inversions are divided into:

- **Paracentric inversion** that does not contain the centromere.
- **Pericentric inversion**, in which the **centromere** is located within the inversion.

## Translocations

Translocation involves an exchange of fragments between **non-homologous chromosomes**. The most common form of translocation is **reciprocal translocation**, in which a section of a chromosome is exchanged for another section of a non-homologous chromosome.

The segment is neither lost nor added; it is just exchanged. A translocation may result in morphological changes of the respective chromosome, for e.g., the centromere may be located in a different position after the exchange, or the size of the chromosome may be altered.

### Balanced and unbalanced translocations

**Balanced translocation** in which the total genetic material remains unchanged, is associated with inconspicuous symptom manifestations. For e.g., the heterozygous translocation of chromosome 21 is balanced by the fusion of chromosome 21 with another chromosome, usually resulting in the loss of the short arms. Carriers of this balanced translocation are phenotypically normal and are referred to as 'carriers'. Families carrying this translocation eventually result in Down's syndrome, characterized by trisomy 21.

**Unbalanced translocation**, however, refers to an altered set of chromosomes or an altered amount of genetic material.

### Types of translocations:

1. Simple translocation occurs when the end of 1 chromosome breaks off to join the end of another
2. Shift/intercalary translocation involves 3 breaks, and a 2-break section of 1 of the chromosomes is inserted within the break created at the end of another non-homologous chromosome.
3. Reciprocal/interchange translocation refers to a single break involving 2 homologous chromosomes and the exchange of their genetic content.
4. Alternate segregation occurs when the translocation of genetic material involves alternate or opposite centromeres lying in a zigzag fashion.
5. Adjacent-1 segregation
6. Adjacent-2 segregation

## References

The Frequency and Types of Chromosomal Aberrations in the Patients with Hypogonadism. (2015). *Human Genetics & Embryology*, 05(01). doi:10.4172/2161-0436.1000124

Heim, S. (2015). *Cancer cytogenetics: Chromosomal and molecular genetic aberrations of tumor cells*. Chichester: Wiley.

Kirsch, I. R. (1993). *The Causes and consequences of chromosomal aberrations*. Boca Raton: CRC Press.

Obe, G., & Vijayalaxmi. (2007). *Chromosomal alterations: Methods, results, and importance in human health*. Berlin: Springer.

Thompson, J. S., & Thompson, M. W. (1980). *Genetics in medicine*. Philadelphia: Saunders.

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