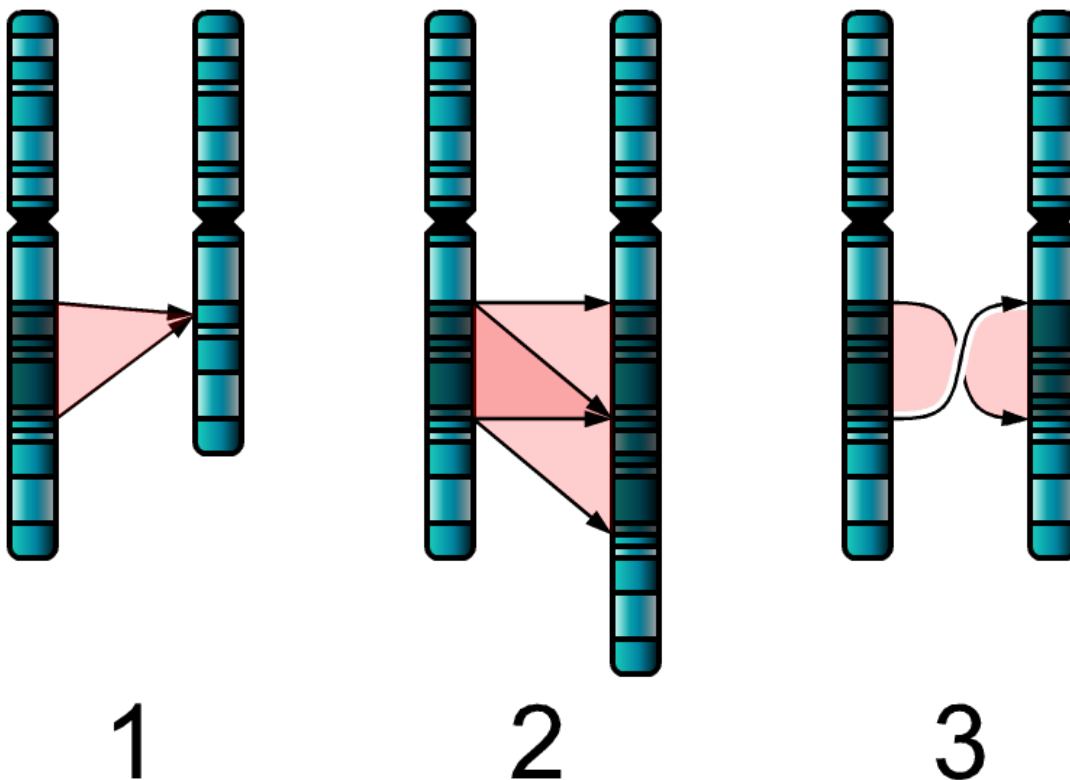


Human Genetics – Chromosomal Aberrations

[See online here](#)

Chromosomal aberrations are chromosome mutations which entail changes in the genome. These changes can affect either parts 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 describe a change in the number of entire chromosomes, or the entire set of chromosomes.

Normally humans have a diploid set of chromosomes. This diploid chromosome set consists of 22 pairs of **autosomes**, whereby in each set one chromosome comes from the mother and the other from the father. Then there are the two **gonosomes** (sex chromosomes) X and Y, resulting in the chromosome set of somatic cells consisting of 46 chromosomes.

Overall the numerical chromosomal aberrations are **genome mutations** and stem from faulty distribution of the chromosomes to the daughter cells.

Maldistribution of the chromosomes

During this maldistribution, e.g. via **nondisjunction** (no separation of a homologous chromosome pair during meiosis), an incorrect quantity of individual chromosomes may form. This is referred to as **aneuploidy**. With aneuploidy the individual chromosome may be present only once (**monosomy**) or more than twice (e.g. **trisomy**).

Note: Contrary to some trisomies, monosomy of autosomes is not compatible with life. In addition to aneuploidy a nondisjunction can also lead to **polyploidy**. This does not just affect an individual chromosome, but rather the entire set of chromosomes is different in quantity, e.g. each chromosome appears thrice (**triploidy**).

The transfer of nondisjunction occurs via the **gametes** to the respective offspring. However, there is also a maldistribution of chromosomes that affects not the gametes, but rather the **somatic cells**.

This results in a juxtaposition of changed and unchanged cells, usually through losses during mitosis, and subsequently forms a **somatic mosaic**. One example of this would be Turner syndrome with mosaicism.

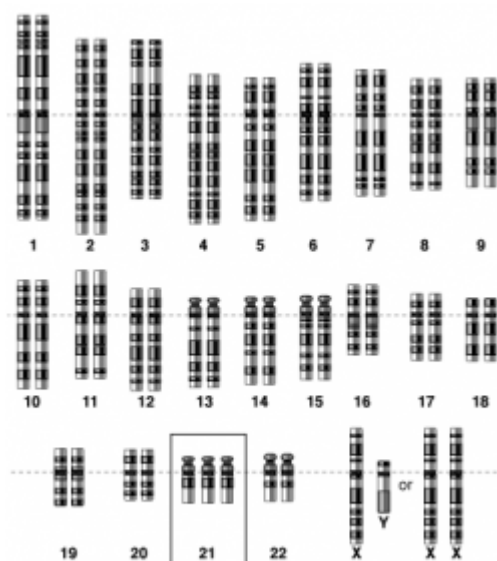
Aneuploidies of the autosomes

Unlike a maldistribution of the gonosomes, a maldistribution of autosomes results in distinct impairment of both mental and physical development.

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

Trisomy usually occurs during meiosis, whereby in two-thirds of cases the cause can be attributed to faulty division during the **first meiotic division**. One exception to this is **trisomy 18**, which usually originates in the **second meiotic division**. The risk of maldistribution corresponds to the age of the mother at the time of division.

Definition of trisomy 21 (Down's syndrome)



Trisomy 21 genome scheme

Trisomy 21, also referred to as Down's syndrome, is one of the **numerical chromosomal aberrations** and indicates an additional chromosome 21. With an incidence rate of 1:600 among living newborns, it is one of the most common autosomal chromosomal aberrations.

Because the risk of **nondisjunction** correlates to the age of the mother, the risk of trisomy 21 occurring in the child increases the older the mother is at the time of conception.

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

During birth the children are partially distinctive for their reduced muscle tone (muscular hypotonia) that can manifest as a **"floppy infant"**. The reduced muscle tone becomes clear when lifting the child in the abdominal position, in which the extremities hang loosely.

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

Furthermore, organ systems like the heart (e.g. in the form of heart defects) or the gastrointestinal tracts (e.g. in the form of **atresia**) are affected. The risk of developing **leukaemia**, as well as **Alzheimer's disease**, is greatly increased.

Treatment consists of treating the aforementioned symptoms and malformations. A targeted early intervention is indicated.

Definition of Trisomy 13 (Patau syndrome)



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Patau syndrome also correlates with the age of the mother, but with an incidence rate of 1:10,000, it is far more uncommon than Down's syndrome.

Another difference from Down's syndrome is the greatly reduced life expectancy. Approximately 95 % of children affected die before 6 months.

Phenotypically, there is a typical triad of symptoms. These include **microcephaly**, cheilognathouranoschisis, and polydactyly, the manifestation of which is usually ulnar and manifests as **hexadactyly**.

A four-finger groove can also appear in the fingers (see Down's syndrome).

Other organ systems like the heart (ventricular septum defect or patent ductus arteriosus botalii, for instance) or the kidneys and urinary tract system may be affected.

Definition of trisomy 18 (Edwards syndrome)

The incidence rate of Edwards syndrome, which means that an additional chromosome 18 is present, is 1:6000. Like the other two **numerical chromosomal aberrations** mentioned above, this correlates with the age of the mother at the time of conception.

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



Overlapping fingers

The affected children's symptoms include a range of characteristic anatomical traits. These may include low-set ears, the auricles of which extend upward (faun ears), a 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 finger are overlapped by the index finger and little finger, respectively.

Aneuploidies of the gonosomes

Unlike with maldistribution of the autosomes, maldistribution of the gonosomes usually only results in relatively minor impairment of mental and physical development.

Another difference between these and autosomal aberrations is the fact that monosomy of the gonosomes is compatible with life. One example of this is Ullrich-Turner syndrome, which exhibits the karyotype 45,X.

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

Definition of Ullrich-Turner syndrome

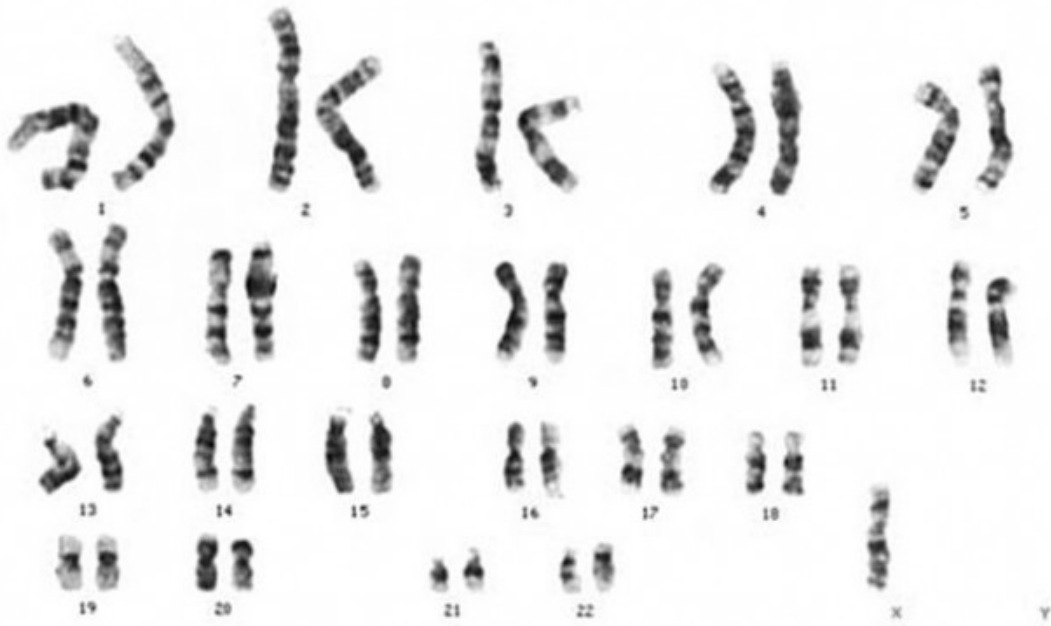


Image: "Karyogram 45,X" by The cat--commonswiki. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

[Ullrich-Turner syndrome](#) constitutes an exception in the group of **numerical chromosomal aberrations**, as it does not correspond to the age of the mother. With Ullrich-Turner syndrome there exists monosomy in the area of the gonosomes. Girls affected possess only one X chromosome, which results in the karyotype **45,XO**.

The missing X chromosome causes misplacement of the female sex organs, e.g. in the form of **ovarian dysgenesis**. These ovaries affected by dysgenesis are also referred to as **streak gonads**, and are interspersed with conjunctive tissue.

Because of these changes in structure the streak gonads do not form hormones, which in turn causes **oestrogen** and **gestagen deficiency**.

This hormone deficiency leads to **primary amenorrhoea** and **infertility**. In addition, patients exhibit partial malformations of internal organs, 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 from the outside. These include changes in the skeletal system, such as decreased length growth or **cubitus valgus**.

Lymphoedema may also appear in the hands and feet at the time of birth.

Another symptomatic trait almost exclusive to Ullrich-Turner syndrome is **pterygium colli**. This describes an additional lateral fold in the neck, located between the processus mastoideus and the acromion.

Ullrich-Turner syndrome has no effect on life expectancy or mental development.

Definition of Klinefelter Syndrome

Klinefelter syndrome is one of the **numerical chromosomal aberrations** with a maldistribution of the **gonosomes**. With Klinefelter syndrome an extra X chromosome is present, which results in the karyotype **47,XXY**. The incidence rate is 1:800.

The clinical symptoms may also stem from the deficiency of testosterone. The **lack of**

testosterone results in delayed sealing of the growth plates, and thus increased length growth with somatomegaly.

In adult age the testosterone deficiency also affects bone structure and often leads to **osteoporosis**.

Additional symptoms attributed to the testosterone deficiency include testicular hypoplasia with simultaneously reduced fertility, as well as **gynecomastia**.

Treatment thus entails lifelong substitution of testosterone.

Polyploidies

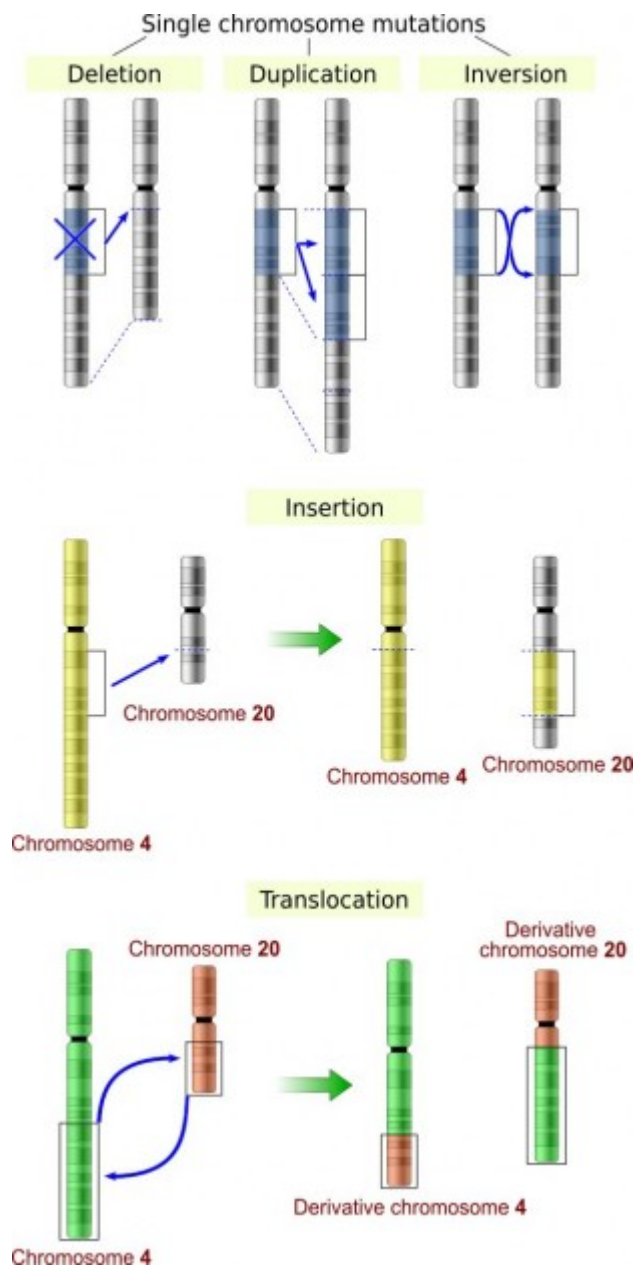
Along with the above aneuploidies of the chromosomes, regarding which no autosomal monosomies and the minority of autosomal trisomy's are compatible with life, there also exist polyploidies of the chromosomes (see above).

Note: A polyploidy affects the entire set of chromosomes.

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

The majority of polyploidies form as a result of malformation of the **spindle apparatus**, which originates in meiosis I or II.

Structural Chromosomal Aberrations



Chromosomes mutations

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

This group includes **deletions, duplications, inversions** and **translocations**. Deletion and duplication describe a loss or duplication of individual gene sequences within a chromosome, whereas translocation describes an exchange between non-homologous chromosomes. During an inversion, the changes likewise occur within a chromosome.

Ionising radiation is one possible cause of chromosomal aberrations, e.g. from X-rays. This energy-rich radiation causes breaks within the chromosomes, some of which are then improperly put back together, which can, in turn, cause deletions or duplications.

The verification of structural chromosomal aberrations in daily hospital work primarily occurs in bone marrow cells, fibroblasts, and lymphocytes. However, essentially these changes can be found in all bodily tissues.

Deletions

A deletion entails the loss of a specific chromosome section, with multiple genes being located within a section. After loss of a section of the chromosome section several occurrences may happen which include :

- They segment may be reunited back to reconstitute the same chromosome.
- The subsequent reconnection of the individual sections after loss of a segment causes a truncated chromosome section.
- The broken part may be separated but lacks a centromere.

Depending on how many fragments there are and which position these are located in, there may be a **terminal** or **interstitial deletion**. Terminal deletion means that one of the two end pieces of a chromosome is missing, whereas interstitial deletion describes a loss between the two ends.

There are also **homozygous** and **homologous** deletions. Homozygous deletion describes the deletion occurring in both homologous chromosomes. The complete loss of the chromosome section affected by the deletion means that this form of deletion is generally lethal.

One clinical example of deletion is cri-du-chat syndrome (French for “cat’s cry”), which means that a deletion has occurred in the short arm of chromosome 5 (5p). The name of this disease stems from the cat-like cries made by children affected, they have a small head and an intellectual disability.

Duplications

Duplication means that there has been a multiplication of individual chromosome sections. It is thus the opposite of deletion. Depending on the way in which the duplicated sections are located next to one another, there are several types of duplications which include:

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

Developmentally, duplications play a special role in that new or additional genetic material is created from them. This additional material may result in new functions, for instance.

Inversions

An inversion results in the 180°-rotation of a chromosome section and the subsequent reintegration into the original chromosome. This reintegration of the chromosome

ultimately results in no loss of chromosome sections, and an inversion is generally not lethal.

Depending on whether the inverted section contains the centromere of the chromosome or not, distinctions are made between a

- **Paracentric inversion** that does not contain the centromere.
- **Pericentric inversion** means that the **centromere** is located within the inversion.

Translocations

Translocation describes an exchange of fragments between **non-homologous chromosomes**. The most common form of translocation is **reciprocal translocation**, in which one 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 move which may result in morphological changes of the respective chromosome, e.g. the centromere may be in a different position after the exchange, or the size of the chromosome may be altered.

Distinctions are also made between balanced and unbalanced translocations :

Balanced translocation means that the entire amount of genetic material has gone unchanged, and remains symptomatically inconspicuous. One clinical example in which a balanced translocation is initially present is heterozygous translocation of chromosome 21. This entails 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". In families in which this translocation is present, a common result is Down's syndrome, in which chromosome 21 is tripled.

Unbalanced translocation, on the other hand, describes an altered set of chromosomes or an altered amount of genetic material.

Types of translocations:

1. Simple translocation happens when the end of one chromosome breaks off to join the end of another.
2. Shift/ Intercalary translocation involves three breaks where a two-break section of one 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 in two homologous chromosomes and the exchange of their genetic content between them.
4. Alternate segregation where alternate or opposite centromeres lie in a zigzag fashion for translocation of genetic material.
5. Adjacent-1 segregation
6. Adjacent-2 segregation

Review Questions

The answers are below the references.

1. Which of the following statements on numerical chromosomal aberrations is not true?

- A. The numerical chromosomal aberrations entail a maldistribution of the chromosomes to the daughter cells.
- B. A nondisjunction may result in aneuploidy.
- C. Monosomy of the autosomes is compatible with life.
- D. The majority of autosomal aberrations lead to spontaneous miscarriage.
- E. Polyploidy means that the entire chromosome set has been altered.

2. Which of the following statements on trisomy is true?

- A. The most common form of trisomy is trisomy 18.
- B. The life expectancy for trisomy 13 is greater than that for trisomy 21.
- C. Hexadactyly is typical of trisomy 18.
- D. Reduced muscle tone at the time of birth is typical of Edwards syndrome.
- E. The risk of newborns suffering from trisomy increases with the age of the mother at the time of conception.

3. Which of the following statements on structural chromosomal aberrations is not true?

- A. Deletion means that there is a loss of a genetic sequence of a chromosome.
- B. Duplication means that there is double the amount of individual gene sections in a chromosome.
- C. Inversion refers to a 180°-rotation of a chromosome section.
- D. Translocation refers to an exchange between two homologous chromosomes.
- E. Balanced translocation indicates an unaltered amount of genetic material.

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Correct answers: 1C, 2E, 3D

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