Structural chromosomal aberrations

Template:Zkontrolováno **Structural chromosomal aberrations** arise as a result of chromosomal instability (manifested by the formation of breaks), caused by excessive exposition of the individual to **clastogens** or worsened function of reparative mechanisms. The critical lesion leading to chromosomal breakage is DNA double-strand breaks. The consequences of those deviations depend on whether, even after the structural rearrangement, the normal amount of genetic information is preserved. If not, then phenotypic manifestations occur, which depend on how big and which part of the genome is missing or, on the contrary, is extra. Balanced structural aberrations, where the genetic material is quantitatively preserved, are typically without any clinical manifestations, but there is a risk for future generations, which may inherit the rearrangement in an unbalanced form.

Types of structural chromosomal rearrangements

The basic condition for **structural aberrations** to form is the interruption of chromosomal continuity.

Spontaneous

- the impact of inducing mutagenic effects (ionizing radiation, chemical substances)
- **chromosomal** or **chromatid breaks** are created
- exposed ends of DNA have a tendency to **reconnect** to its **original ending** or another free end based on the **terminal end** complementarity – formation of abnormal structures and, with a greater number of breaks, complex **structural rearrengements.**

Stable aberrations

- the altered chromosome contains **cetromeres** and **telomeres**
- it is passed on regularly to the **daughter cells**

Unstable aberrations

- **centromeres** (acentric fragment) or **telomeres** (ring chromosome) are lost
- the segregation into daughter cells is **irregular**, leads to elimination or other changes of those structures

Congenital

- **the phenotypic effect** varies between different types
- we distinguish between balanced and unbalanced changes

Balanced

- there is a **normal amount** of genetic material inside cells
- there was no loss or retention of a part of the **chromosome set**
- the carriers usually **do not have any phenotypic manifestations**, except for rare situations, where the **chromosomal breakage** damages a significant **functional gene**
- poses a risk for their offsprings – gametes with an **unbalanced chromosomal equipment** might form
- translocation, inversion, insertion

Unbalanced

- a change in a genome in the sense of an **absence or additional presence** of a certain section of genetic material
- this condition usually carries **serious clinical manifestations**
- deletion, duplication, ring chromosome, isochromosome

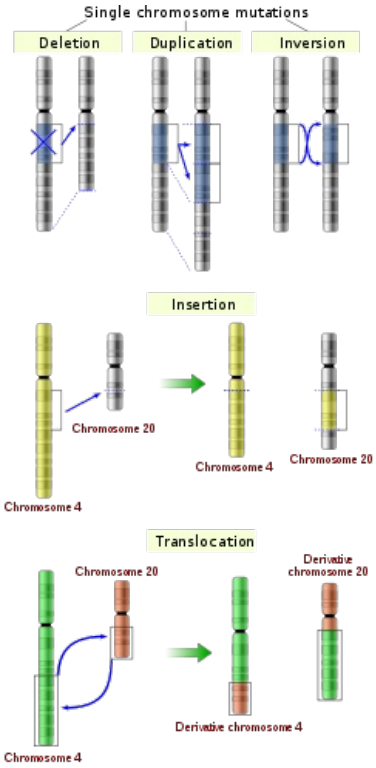
Acquired

- are determined when testing the **mutagenic and genotoxic effects** of chemical substances and the evironment on humans
- to evaluate the **number of chromosomal breaks** and rearrangements, we use classic methods of **cytogenetic analysis**
- in order to do so, we use **specimens** from short-term (48 hours) **cultivated** peripheral blood lymphocytes - we detect structural and numerical **deviations** in 100-200 mitoses
- in practice, we test the exposure of various **harmful substances** at selected workplaces (chemical substances in healthcare, poisons and cytostatics in laboratories and clinical departments) - we evaluate the so-called **group risk** for employees in one workplace as the average value of acquired chromosomal aberrations in a group
- the normal finding of **aberrant mitoses** is up to 2%, higher values are a reason for stricter **safety measures** at a workplace

- **the limiting values** are 2-5% - a reason to repeat the examination with a time gap
- values **above 5%** indicates very high mutagenic exposure or one's increased sensitivity

Examples of structural aberration

BALANCED



Chosen structural chromosomal aberrations

Translocation

Translocation is the exchange of two segments that broke off from two chromosomes. Translocations can be **balanced** (where the same amount of genetic material in a cell is preserved) or **unbalanced** (where the previous amount is not preserved or kept).

- **Reciprocal translocations** are mutual, reciprocal exchanges of segments between two non-homologous chromosomes. The number of chromosomes stays the same. E.g.: translocation t(9;22) in myeloid leukemia - **Philadelphia chromosome**, translocation t(8;14) in **Burkitt's lymphoma**
- **Robertsonian translocation** forms from the break of two acrocentric chromosomes in the area of the centromere and the following **joining of the long arms** - a rearrengement known as **centric fusion**, (after the loss of short arms, satellite stalks, and satellites) – e.g. fusion of 14q and 21q. An individual with such translocation has one less chromosome (45), although the original amount is not completely preserved (the loss of reciprocal product consisting of regions of short arms - they only contain rRNA genes, which occur multiple times on other **acrocenters** as well), the carrier of this translocation does not have any clinical manifestations, thus it is classified as a balanced aberration as well. A carrier of a balanced Robertsonian translocation has a significant risk that their children will be affected by an unbalanced form of the Robertsonian translocation. For example, there is a translocation form of Down syndrome.

Inversion

When an **inversion** occurs, there are two breaks on one chromosome, the segment in between the breaks turns over and then joins with the distal segments. For example, an inversion on the chromosome with the original sequence A-B-**C-D-E-F**-G-H would be a sequence A-B-**F-E-D-C**-G-H. Based on whether the breaks are both on the short and the long arm of the chromosome or two breaks on one arm, we distinguish:

- **pericentric inversion** – the inverted segment of the chromosome **contains** a centromere;
- **paracentric inversion** – the inverted segment of the chromosome **does not contain** a centromere.

Inversion belongs to balanced aberrations, it won't usually manifest itself in the phenotype, but the inversion carrier does hold a risk for an unbalanced aberration in their offsprings if a meiotic recombination (crossing-over) between a normal and an inverted chromosome occurs.

Insertion

- **insertion of a chromosomal segment** into any place of a different or the same chromosome
- requires a **minimum of 3 breaks** and affects one or two chromosomes
- **the inserted segment** can be in a normal or inverted position in its new place (direct or inverted insertion)
- **the insertion is a balanced** rearrangement without affecting the phenotype
- if **two different chromosomes are affected,** it represents a 50% chance for its carrier of creating **unbalanced gametes** carrying either a deleted or an inserted chromosome

UNBALANCED

Duplication (partial trisomy)

Duplication of a chromosomal segment. It can be caused, among other things, by uneven crossing-over, as a result of which the monitored segment duplicates on one chromosome, while the same segment is deleted on the other one (see below).

Deletion (partial monosomy)

A part of a chromosome is **missing**. The termial end of an arm can be deleted (then it is a **terminal deletion**) or a middle part of one of the arms (**interstitial deletion**). Deletions happen as a result of a chromosomal break (terminal deletion), two breaks (interstitial deletion), or an uneven crossing-over (see above).

Dicentric chromosome

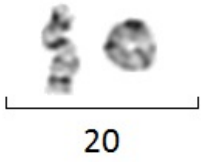
A dicentric chromosome occurs as a result of breakage on two chromosomes and fusion of the chromosomes with their broken ends, so the formed abnormal chromosome has two centromeres. If it occurs as a congenital chromosomal aberration, one of the centromeres is inactive, then the chromosome looks and acts monocentric and can survive repeated cell divisions.

Isochromosome

An isochromosome is a chromosome that has one arm duplicated, while the second one is deleted. It arises from a faulty (transverse) splitting of the centromere (instead of longitudinal) in the second meiotic division or during mitosis. The most frequent case of isochorosome in live births is the isochromosome for long arms of the X chromosome, present in some patients with Turner syndrome. Patients with this chromosomal finding may be fertile (the critical region of genes on the long arms of the X is preserved). Isochromosomes are often present in **tumor cells karyotypes**.

Ring chromosome

If both ends of the arms of a chromosome are deleted, this chromosome can twist, the broken ends join and a **circular chromosome** (ring chromosome) is formed. This unbalanced aberration is linked with the loss of the distal ends of both arms. One of the most frequent findings of this aberration is the **ring chromosome X,** usually present in a **mosaic form,** another line may be, for example, 46,XX, 45,X or 46,XY as well.



Ring chromozom

Marker chromosome

Marker chromosome is a small, supernumerary chromosome, whose origin cannot be determined by standard cytogenetic techniques. Its origin varies, it may be a reciprocal product of Robertsonian translocation, formed by regions of short arms of acrocenters, or an isochromosome for short arms of, e.g. the 18th chromosome, or pericentromeric region of a chromosome, etc. Depending on whether it does or does not contain euchromatin, it may or may not be associated with clinical symptoms. The origin of the marker can be determined by FISH methods with centromeric probes. The occurence of a marker chromosome in a **mosaic** is relatively frequent, the most common finding tends to be a **marker chromosome** from a part of the **15th chromosome.** A classic example is the **Philadelphia chromosome** - a marker of chronic myeloid leukemia.

Fragile sites

During examination, we find areas on **some chromosomes**, in which the chromatin in not fully **spiralized** and both chromatides look like they are almost **broken**. Those non-staining spaces (gaps) are **fragile sites** – individual chromatides **break** more often at those spots. The occurence of fragile sites is distinguishable after **cell cultivation** in a medium with a reduced amount of **folic acid or thymidine**, techniques of **molecular diagnostics** are used more often for its **detection**. Fragile sites occur relatively **rarely**, the fragile site on the **long arm of the X chromosome** has a special position.

Selected syndromes

Cri du chat syndrome

File:Syndrom Cri du chat.jpg
Caryotype 46,XX,del(5p)

The Cri du chat syndrome (or the cat's cry syndrome - or meowing syndrome, OMIM 123450 (https://www.omim.org/entry/123450)) is caused by a **deletion** on the short arm of the 5th chromosome. The extent of this deletion is variable, it can even be a deletion of the entire short arm, but then the extent of the disability is more severe. The most typical symptom is a characteristic sound, caused by an anomaly of the larynx, made by the affected individuals and after which the syndrome is named. Other symptoms include severe mental retardation, microcephaly, motor disorders, growth retardation, congenital heart defects, etc.

Wolf-Hirschhorn syndrome

The Wolf-Hirschhorn syndrome (OMIM 194190 (https://www.omim.org/entry/194190)) is caused by a **deletion** of the short arms of the 4th chromosome. The patients are retarded, have dimorphic features, clift lip and palate, microcephaly, heart defects, hypospadias.

Turner syndrome - deletion form

a) deletion on the short arm Xp

- **signs of Turner syndrome** are present, especially the short stature and skeletal abnormalities
- the changes are related to the absence of the distal part of Xp, where the **SHOX gene** (Short stature HomeoboX-containing gene) is located, which is not subject to **inactivation**
- this gene has a key role in **skeletal development**
- the presence of abnormalities in the development of the **secondary sexual characteristics** and sterility is variable, based on the **extent** of the missing part of Xp

b) deletion on the long arm Xq

- relatively **rare cases**
- from the signs of Turner syndrome, it is mainly **ovarian dysgenesis** with primary amenorrhea and **sterility**
- **a growth defect** does not have to be present

Prader-Willy syndrome and Angelman syndrome

- **the critical site** associated with Prader-Willy and Angelman syndrome is located on the long arm of the 15th chromosome (15q11-13)
- in 70% of cases, there is an interstitial deletion of varying extent in this region and if the deletion affects the 15th chromosome **originating from the father**, the clinical picture of Prader-Willy syndrome develops
- **deletion of maternal** origin leads to **Angelman syndrome**
- **the influence of the origin of the deletion** on the development of the syndrome is explained by the existence of **genomic imprinting** in the critical region of 15q
  - there are **two gene sections** in this region, the first (PWCR – Prader-Willy critical region) is active on the **paternal chromosome** 15 only and the analogous section on the **maternal** is **silenced** due to the imprinting
  - **the second region** is only active on the **maternal chromosome** 15 (ACR – Angelman critical region) and **inactive** on the **paternal** chromosome
  - under normal circumstances, one paternal and one maternal chromosome is present – the individual has one **active copy of both** of the critical gene sections and their phenotype is not **affected**
  - however, in case of a deletion, **one critical section** is missing and a **specific syndrome** arises depending on the origin of the deleted section

- however, both syndromes can be caused by **another cause** without deletion
- the most common is **uniparental disomy** – the origin of both chromosomes or their critical regions from only **one parent**
- if both **originate fron the father** = Angelman syndrome (the active ACR is missing and both analogous section of the paternal chromosome are inactive by imprinting)
- if both **originate from the mother** = Prader-Willi syndrome (the active PWCR is missing)
- **Angelman syndrome** can also be cause by a mutation in the UBE3A gene in the ACR section and in 10% the cause is unknown
- in **rare cases** of both of the syndromes, there may be a defect in the imprinting itself (imprinting center mutation, IC) and the activation/inactivation of critical regions is faulty
- **both syndromes** are clinically classified as behavioral syndromes with typical behavior
- the phenotype of both units is **significantly** different

Prader-Willy syndrome

- 1 : 10 000 – 15 000 children
- noticeable severe **hypotonia** in newborns
- infants have a problem with breastfeeding, swallowing – **they do not thrive**
- from the age of two, **pathological overeating** even gluttony starts occuring - extreme obesity
- mental retardation tends to be mild
- noticeable **mood swings**, behavioral disorders in the sense of aggression
- intolerance when changing **routine situations** and sleep disorders
- the prognosis depends on the occurence of **obesity complications** (diabetes, cardiovascular complications, metabolic disorders)
- can be influenced by **limiting food intake** and adjusting the exercise regime

Angelman syndrome

- 1 : 12 000 children
- severe **psychomotor retardation**, the children do not usually learn to speak
- in a third, a pathological EEG and **epileptic seizures**
- typical **clumsy gait**, stereotypical ataxic limb movements
- unmotivated **fits of laughter**
- kids with this syndrome love water, plastc objects, sound toys, and balloons
- **their fascination with water** can be life-threatening and so they require constant supervision
- because of their peculiar gait and cheerful expression, this syndrome was formerly call the **happy puppet**

References

Related articles

- Chromosomal abnormalities
  - Numerical chromosome abnormalities
  - Acquired chromosomal aberrations
- Microdeletion syndrome
- Structure of the metaphase chromosome
- Identification of chromosomes
- Causes of chromosmal aberrations
- Tumor cytogenetics
- Chromosomal mosaicism

Used literature

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