Chromosomal Abnormalities - Structural

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Introduction

Structural Chromosomal Abnormalities occur due to

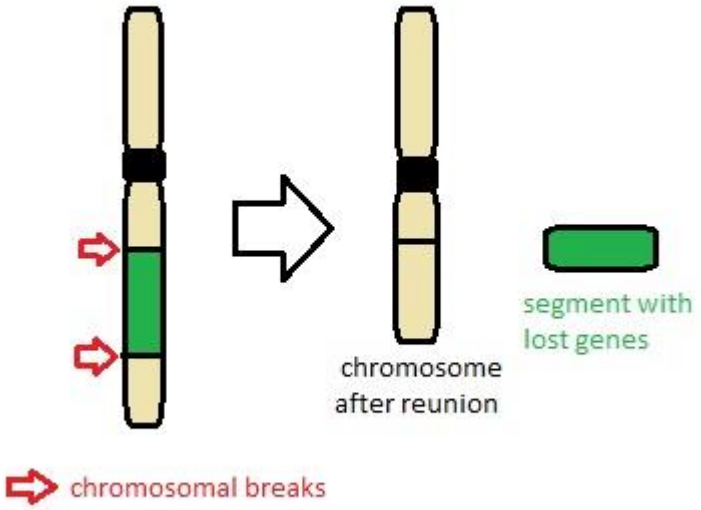
- ✓ a loss or genetic material, or
- ✓ a rearrangement in the location of the genetic material.

They include

1. Deletions
2. Duplications
3. Inversions
4. Translocations and
5. Iso chromosome formations etc.

DELETIONS

- A deletion is characterized by the loss or absence of a piece of a chromosome, resulting in monosomy of the particular chromosomal region.
- Two breaks have to occur for deletion of the interstitial segment. For deletion of terminal segment (telomere) one break is enough.
- Segments which were deleted from the chromosome are not able to "live" on their own and the genes present in those segments are lost.



RING CHROMOSOME

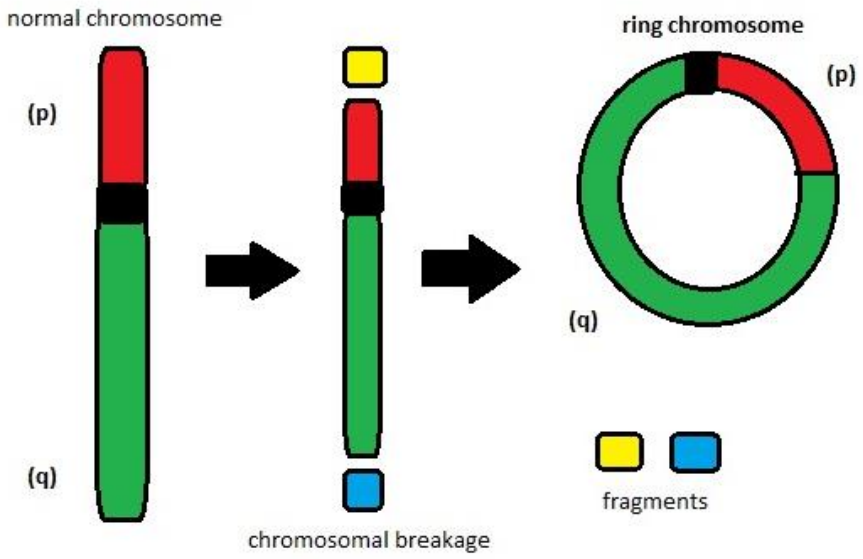
- One special example of deletion exists. It is called "**ring chromosome**". It is a situation when chromosome lost both of its ends. The long and the small arms then connect together and chromosome became a ring shaped.
- Although ring chromosomes are very rare, they have been found in nearly all human chromosomes:

a. r 20 syndrome : associated with epilepsy;

b. r 14 and r 13 syndrome are associated with intellectual disability and dysmorphic facial features;

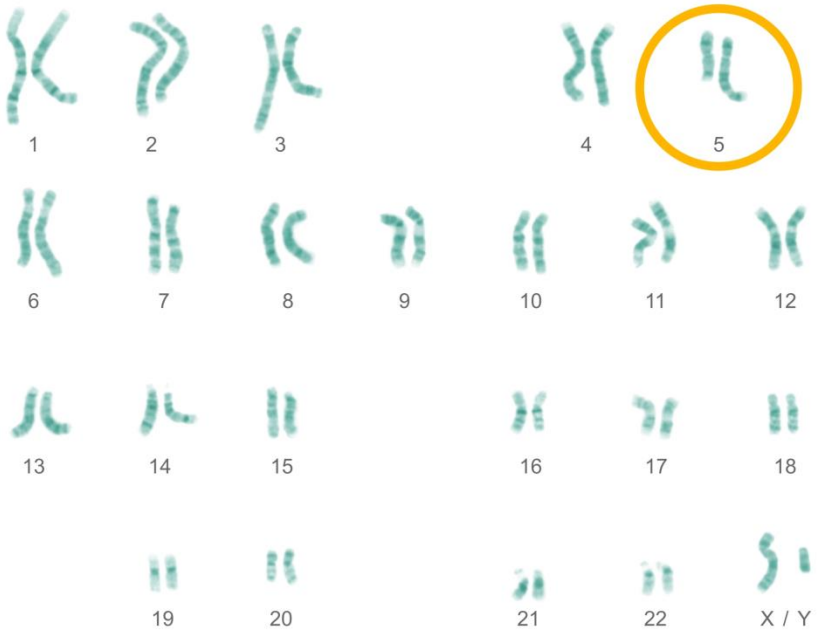
c. r 15 is associated with intellectual disability, dwarfism and microcephaly.

d. r X causes Turner syndrome.



Cri du Chat Syndrome

- Also known as chromosome 5p deletion syndrome, 5p− (said minus) syndrome or Lejeune's syndrome
- Rare genetic condition that is caused by the deletion of genetic material on the small arm of chromosome 5.
- Infants with this condition often have a high-pitched cry that sounds like that of a cat, and hence termed as Cri du Chat (French: *cat-cry* or *call of the cat)*.



Symptoms of Cri du Chat

The disorder is characterized by

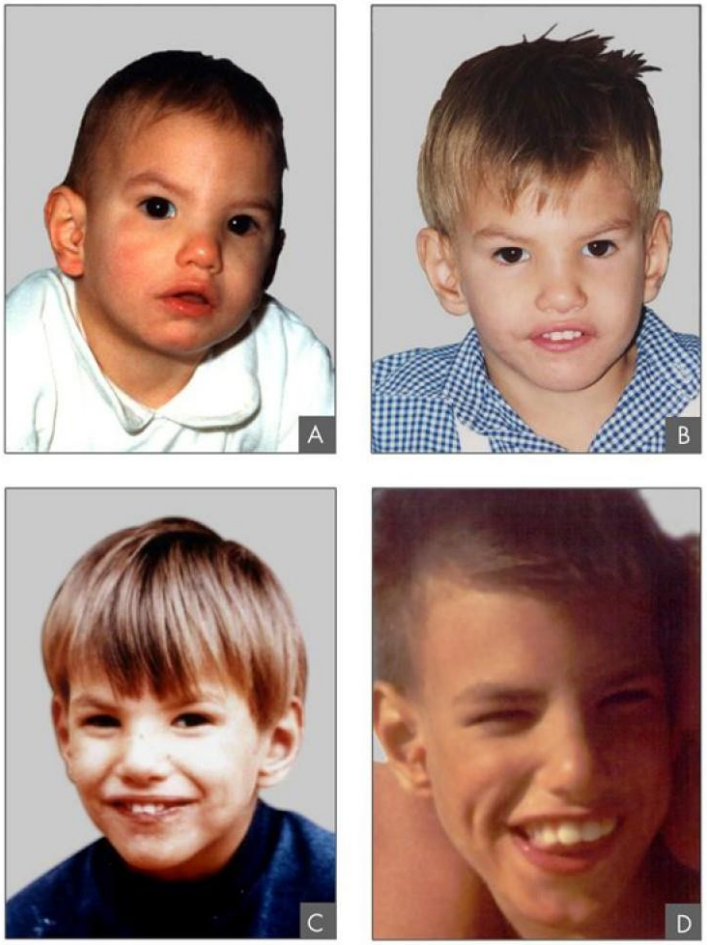
a) intellectual disability and delayed development (cognitive, speech and motor)

b) small head size (microcephaly),

c) low birth weight, and weak muscle tone (hypotonia) in infancy.

d) Affected individuals also have distinctive facial features, including widely set eyes (hypertelorism), low-set ears, a small jaw, and a rounded face.

e) Some children with cri-du-chat syndrome are born with a heart defect.



Frequency and Inheritance of Cri du Chat

- Cri-du-chat syndrome occurs in an estimated 1 in 20,000 to 50,000 newborns.
- This condition is found in people of all ethnic backgrounds.
- The condition is more common in females by a 4:3 ratio.
- Most cases (~90%) are not inherited. The deletion occurs most often as a random event (*de-novo*) during the formation of gametes or in early fetal development.
- The remaining 10-15% are due to unequal segregation of a parental balanced translocation where the 5p monosomy is often accompanied by a trisomic portion of the genome. These individuals may have more severe disease than those with isolated monosomy of 5p.

Molecular Genetics of Cri du Chat

- The size of the deletion varies among affected individuals - larger deletions tend to result in more severe intellectual disability and developmental delay than smaller deletions.
- The signs and symptoms of cri-du-chat syndrome are probably related to the loss of multiple genes on the 5p. Candidate genes are:

1. CTNND2 gene (5p15.2 - **cri du chat critical region**) - implicated in the mental retardation phenotype.
2. TERT gene (5p15.33) - is essential for telomere length maintenance; haploinsufficiency for telomere maintenance may be one genetic element contributing to the phenotypic changes in cri-du-chat syndrome.

- Loss of 5p15.3 (catlike critical region) correlates with the catlike cry.

DUPLICATIONS

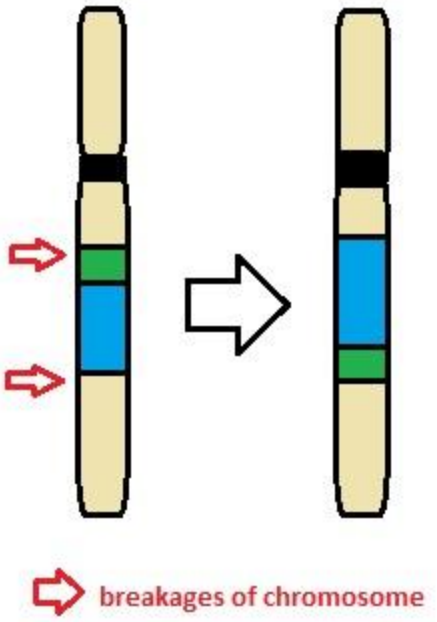
- A portion of the chromosome is duplicated, resulting in extra genetic material.
- Known disorders include **Charcot-Marie-Tooth** disease type 1A which may be caused by duplication of the gene encoding peripheral myelin protein 22 (PMP22) on chromosome 17 (1.5-Mb Duplication of 17p12-p11).
- Typically, the earliest symptoms of Charcot-Marie-Tooth disease involve balance difficulties, clumsiness, and muscle weakness in the feet.

INVERSIONS

- A portion of the chromosome has broken off, turned upside down and reattached, therefore the genetic material is inverted.
- Although we still don´t know why inversion exists, we know that it is the most important mechanism of reorganizing of the genome.
- Types:

  pericentric – causing deletions, insertions or abnormal centromeres;

  paracentric – more common type, it is less harmful for its carrier.
- Inversion suppresses the recombination process.

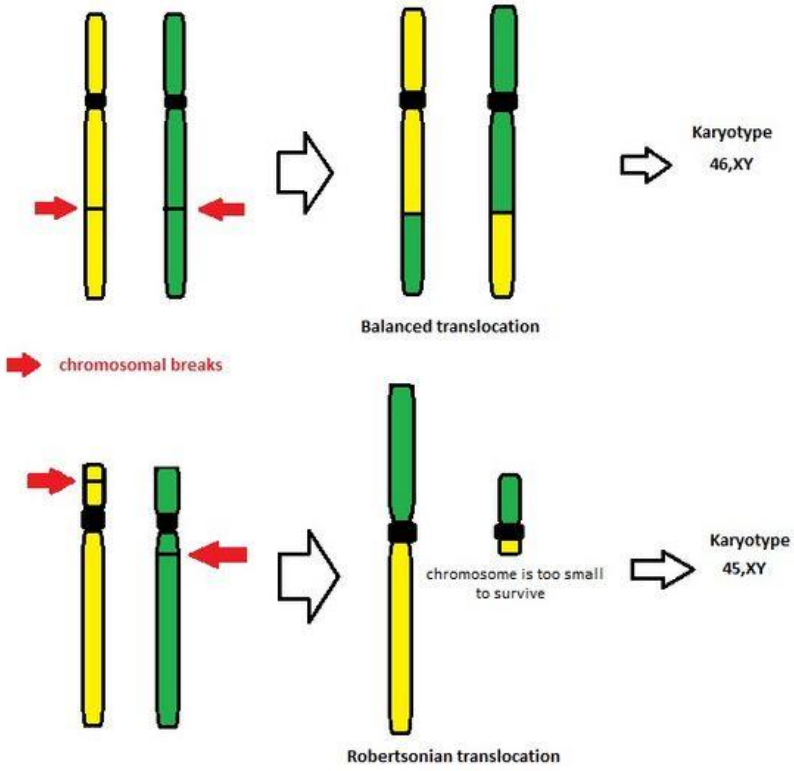


TRANSLOCATIONS

- When a portion of one chromosome is transferred to another chromosome.
- There are two main types of translocations:

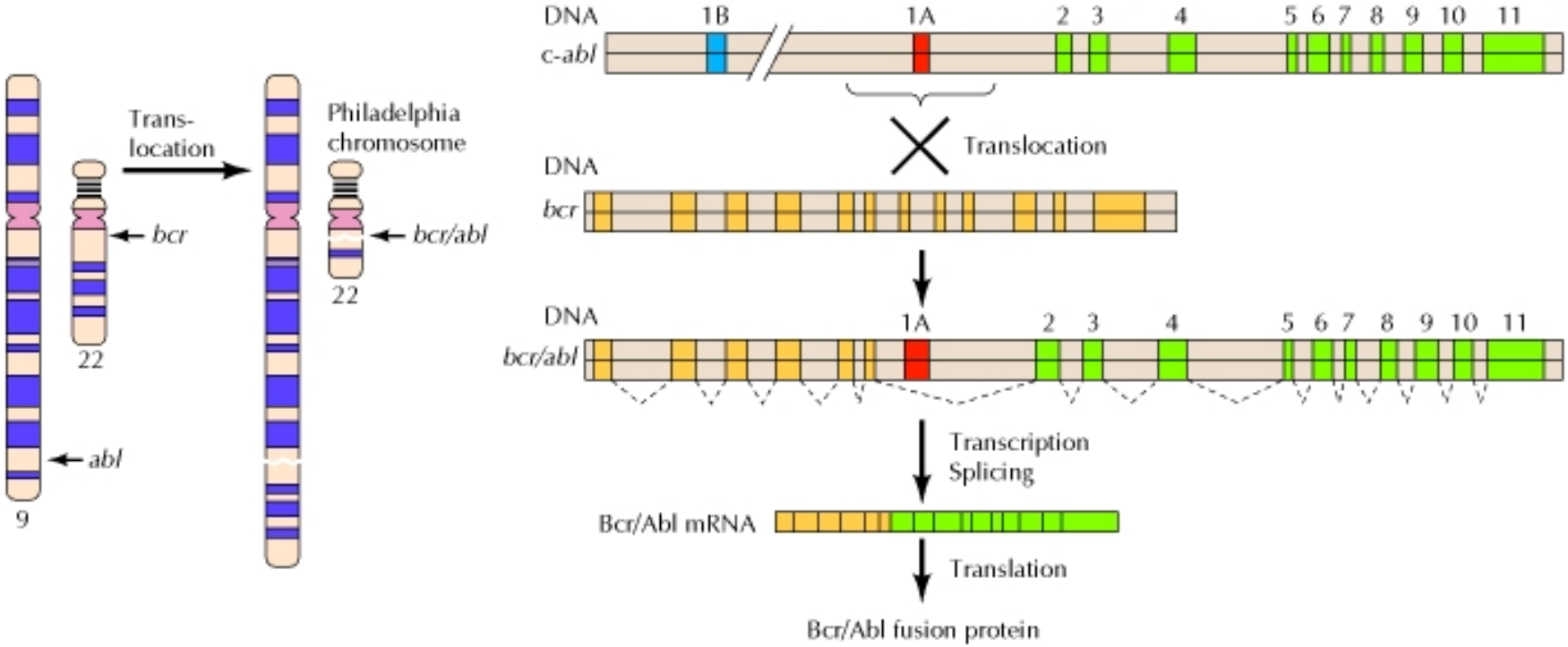
➢ In a **reciprocal translocation**, segments from two different chromosomes have been exchanged. translocation between two chromosomes ("A segment" goes to "B chromosome" and "B segment" goes to "A chromosome"). This is also known as **Balanced Transloaction**, i.e., two chromosomes just exchange their parts but the number of chromosomes(46 chromosomes) as well as no loss of genetic material stays the same.

➢ In a **Robertsonian translocation**, an entire chromosome has attached to another at the centromere; these only occur with chromosomes 13, 14, 15, 21 and 22 (fusion of two acrocentric chromosomes).



Philadelphia Chromosome

- The chromosomal defect in the Philadelphia chromosome [Ph (or Ph')] is a reciprocal translocation, in which parts of two chromosomes, 9 and 22, swap places. The translocation is termed t(9;22)(q34.1;q11.2).
- Ph contains a fusion gene called BCR-ABL1. This gene is the ABL1 gene of chromosome 9 juxtaposed onto the BCR gene of chromosome 22, coding for a hybrid (fusion) protein: a tyrosine kinase signaling protein that is "always on", causing the cell to divide uncontrollably.



ISOCHROMOSOMES

- Isochromosomes are created by the *incorrect division of centromere*. Normally centromere divides vertically. In this case it divides **horizontally**.
- The result is usually the loss of one arm. It means that newly created chromosome has just two long arms or two short arms which are normally connected by centromere.
- It occurs relatively frequently in X chromosome.
- It is a huge problem during the fertilization. Because fetus then becomes trisomic for one arm and monosomic for the second arm.
- An isochromosome can be abbreviated as i(chromosome number and arm). For example, an isochromosome of chromosome 17 containing two q arms can be identified as i(17q).
- In 15% of Turner syndrome patients, the structural abnormality is isochromosome X, which is composed of two copies of the q arm (i(Xq)).