

CYTOGENETICS; CHROMOSOMAL ABERRATIONS

PART II: Structural Changes in Chromosomes

There are 4 common types of structural aberrations; duplications, deletions (also called deficiencies), inversions, and translocations.

Along with definitions and descriptions, it is important to understand the consequences of each type of aberration with respect to chromosome pairing at synapsis in meiosis (especially in a cell that is heterozygous for the aberration), on fertility, and their potential roles in evolution.

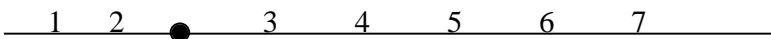
Deletions; loss of chromosomal material

Breaks in chromosomes can result from a variety of factors, including X-rays or stray cosmic radiation. While a single break leading to the loss of the ends of chromosomes should be most common, such 'terminal deletions' are actually rare. Unless telomeres are present to protect and preserve the ends of the chromosome, exonucleases and cell division/DNA replication will lead to the loss of broken chromosomes.

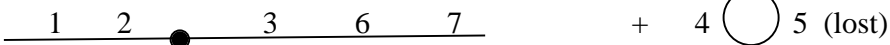
Thus, most deletions that are detected are 'internal' (interstitial) deletions.

If the genes of a normal chromosome fall in the order 1-7, a deletion can be represented as:

Normal:



Deletion:



There are DNA repair mechanisms that recognize broken ends of chromosomes ('sticky ends') and attempt to make repairs. In this example the repair incorrectly attached gene 3 to gene 6 and healed genes 4 and 5 into a small circle, which will be lost during cell division since it does not have a centromere.

Consequences:

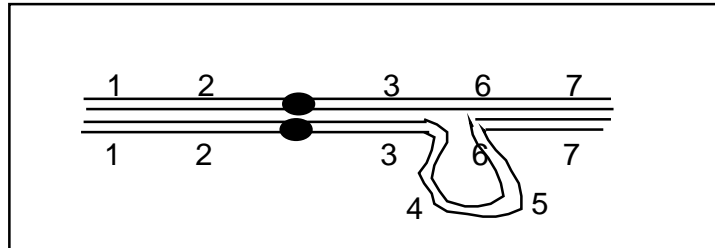
Missing genes generally behave as recessive 'null' alleles meaning no mRNA or protein can be made from the missing gene(s).

Heterozygotes (one normal chromosome and one deleted chromosome are generally OK so long as the deletion is not too large; if it is large, it is liable to overlap with a defective gene on the normal chromosome. The result is a mutant phenotype which may be lethality.

If a gene needed for gamete function is deleted, the individual may have lowered fertility.

Homozygosity for a large deletion is often lethal, since many genes are vital to normal development.

Chromosome pairing in a heterozygote can be detected by the presence of a looped out region on one partner (the normal partner in this case).



Chromosome pairing in an individual homozygous for the deletion will appear normal although the chromosomes are shorter. The map distance for markers flanking the deletion will be reduced.

Examples:

The best known examples of deletions affecting humans are "**cri du chat**", a condition where a deletion in the short arm of chromosome 5 leads to extreme mental retardation (IQ < 20), microcephaly, and a mewing-like cry, even in heterozygous individuals. It occurs in 1 in 20-50,000 births, generally as a result of new mutations. Some cases, about 12% arise from translocations, which will be covered later.

Another rather common example is a deletion on chromosome 22 that leads to a high rate of leukemia. It is called the Philadelphia chromosome based on its discovery in that city.

Deletion of genes involved in regulation of cell division (tumor suppressor genes) leads to an increased risk for cancer in heterozygotes, since loss of function of the one remaining copy in any cell may lead to unchecked cell division. Many pedigrees with high risk of cancer of many types have been associated with inherited deletions.

Duplications; gain of genetic material

Presumably as a result of 'slippage' during DNA replication, extra copies of genes can rarely occur in chromosomes. Once multiple copies of the same sequences are present, pairing and cross-overs between the 'wrong' partners (unequal crossing over) during meiosis can lead to expansion and contraction of the duplicated region.

The most common type of duplication involves tandem repeats:



As with deletions, pairing of a normal chromosome with a chromosome containing a duplication leads to the presence of a loop, this time the loop will occur in the chromosome with the duplicated region.

Since duplications provide extra copies of genes, the consequences are usually not so severe, although over expression of some genes can cause aberrant phenotypes.

Consider Trisomy 21 where all genes on chromosome 21 are present in an extra copy. A well-known example of a duplication that has an associated phenotype involves a gene for eye shape in *Drosophila*. While normal eyes are kidney-shaped, the more copies of the gene present, the narrower the eyes become. One extra copy gives eyes in the shape of a wide bar even in a heterozygote, two give bar-shaped eyes, with additional copies eventually going all the way to eyeless. The gene (although it is really the duplication) is called Bar-eyes.

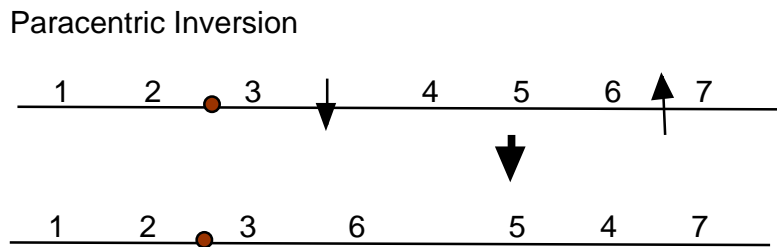
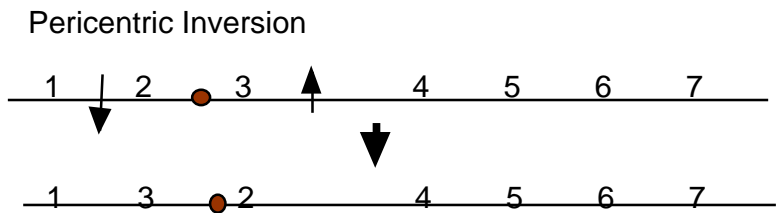
Duplications can account for "**gene families**", that is, copies of genes with very similar sequences that may be differentially expressed. A good example involves the human globin gene families. Along with the alpha and beta forms active in adults there are embryonic globin genes, fetal-expressed globin genes and even promoterless pseudogene versions of globin genes located together on 2 chromosomes. Duplications of an original globin gene such as the myoglobin gene found in whales have served as a source of new genetic material. The extra copies provide a source of genes that can be altered in activity or timing of expression to better suit the utilization of oxygen available under different situations. Mutations in one of the genes can be benign or even helpful since the other copy is still functioning. Overall, duplications play a positive role in evolution by providing the raw material for new genes.

Inversions; an internal segment of a chromosome is inverted.

If a chromosome is broken in two places, the sticky ends can heal such that the internal segment is 'flipped-over' from its normal arrangement.

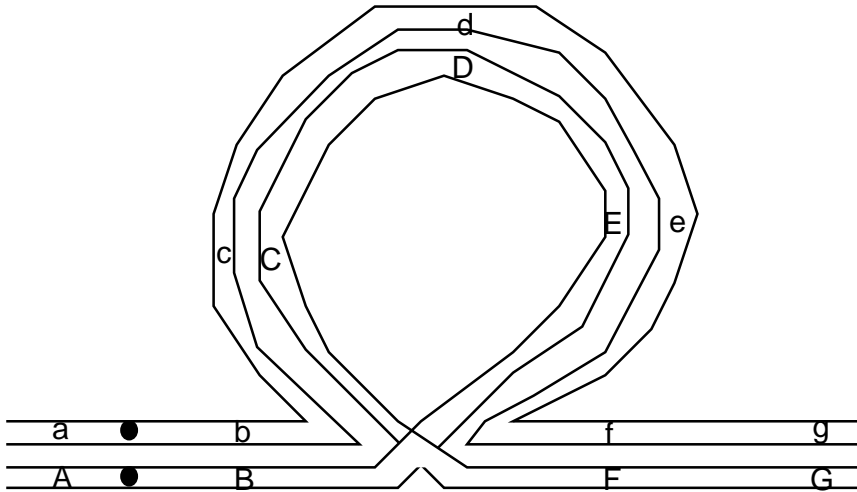
Two types of inversions can be distinguished: those where one break occurs in each arm so the centromere is within the inverted segment are called pericentric inversions.

If both breaks occur in the same chromosome arm so the centromere is not included are called paracentric inversion. Although in the long run the effects of both types of inversions are similar, there are some important differences in consequences.



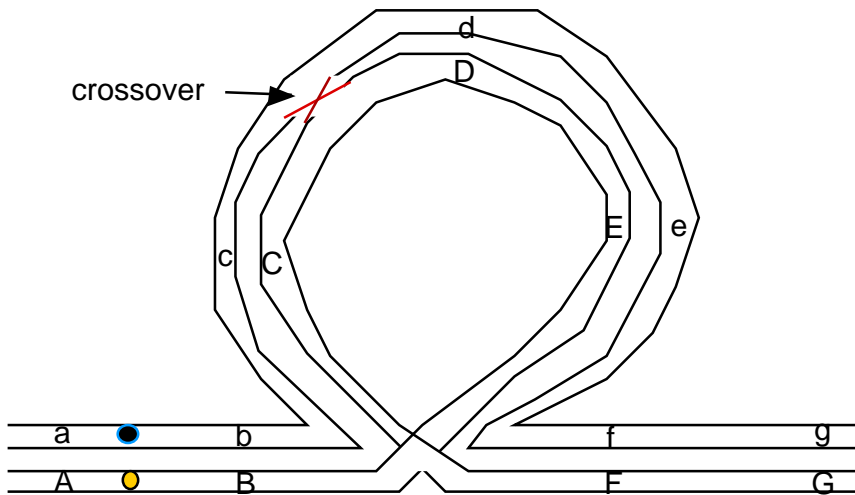
Unless one of the breaks disrupts a functional gene there is not likely to be any "mutant" phenotype associated with an inversion. Individuals homozygous or heterozygous for the inversion still have two copies of all genes.

Problems arise during meiosis only in individuals heterozygous for the translocation. Since pairing of homologs occurs in a gene for gene fashion all along the chromosome, heterozygotes must form an inverted loop within another loop during synapsis.



**Inversion heterozygote in synapsis
(Paracentric)**

If there is a crossover between paired strands problems arise when the centromeres are pulled to opposite poles. Try to pull the centromeres in the figure below to opposite poles:



As you can see, one crossover strand will have the gene arrangement:

a ● b c D E B ● A

Another chromosome fragment G F C d e f has no centromere so will not move to either pole and will be lost.

The part with two centromeres will form a bridge between the poles and must break somewhere before the nuclei can reform. As a result, all gametes resulting from meiosis where a crossover occurs within the inversion loop will have gene duplications and deficiencies; these

are almost always nonfunctional. Individuals heterozygous for one inversion are 'semisterile'. In plants, it is easy to see that half the pollen is collapsed and inviable. In females, the daughter cells from the bridge often end up in polar bodies, so the normal non-crossover chromosomes end up in the egg with little loss in fertility.

Crossovers within the loop of a pericentric inversion heterozygote still cause duplications and deletions, but do not cause a bridge. (Draw this out so that you can convince yourself it is true!) As a result, pericentric inversions cause semisterility in both males and females.

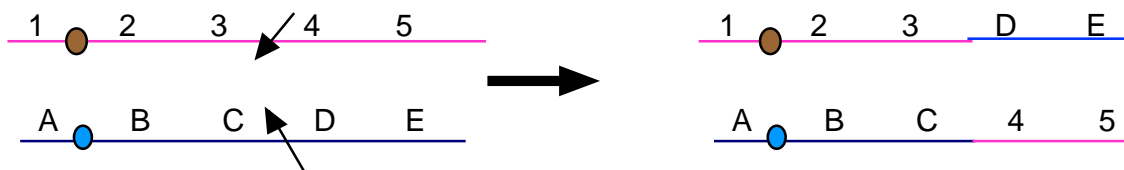
If two different populations of the same species differ in chromosomal arrangements for 2 or more chromosomes, hybrids may still be formed, but will likely be sterile. The two populations may thus be on the way to evolving into separate species.

Translocations; aberrations involving 2 different chromosomes

If the ends of two different broken chromosomes heal by attaching to the wrong partner, a translocation has occurred.

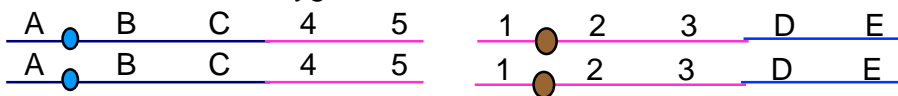
Normal chromosomes

Translocation chromosomes

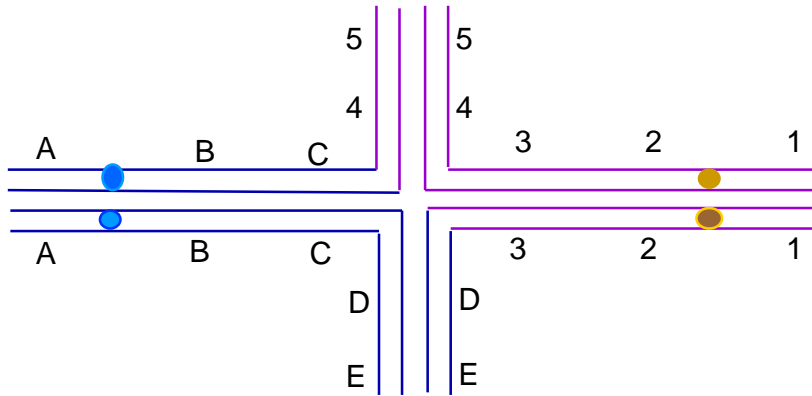


Again, unless the break disrupts a gene or attaches it to the wrong promoter, there is seldom a phenotype associated with translocations. Homozygous individuals have no problems in mitosis or meiosis. The change may show up as differences in genetic maps depending on which parents are being examined.

Translocation homozygote



As for inversions, problems arise in gametogenesis of a translocation heterozygote.



Translocation heterozygote in Metaphase of Meiosis

Imagine your eyes form one of the poles for meiosis I. If the top blue and top gold centromeres both move to that pole (adjacent segregation), the gametes that result will be defective since they have duplications and deficiencies.

If the top blue and bottom gold happen to go that pole (alternate segregation) then the gametes will have either normal or translocation chromosomes, both of which are functional.

These two types of segregation are expected to occur in equal frequency, so again translocation heterozygotes lead to semisterility.

Translocations are involved in cases of trisomy that appear to run in families (about 5% of the cases of trisomy 21). For example, in some individuals the long arm, which is essentially all of chromosome 21 is attached to the short arm of chromosome 14. These individuals have the karyotype (45 T14:21) but are normal since they have 2 copies of all genes. When gametes are made, since there is no centromere on the translocated arm of 21, the free 21 can go to either pole. Thus, the gametes often end up with both the 14:21 and 21 chromosomes, leading to the potential for trisomy 21. If the mother is the translocation-carrier, the actual risk is 11% if the mother is a carrier and 5% if the father is the carrier, so there is some selection against the aneuploid gametes. (The relative fraction of Edwards' and Patau's syndromes that occur in this fashion is higher.)

Roles of aberrations in speciation:

As explained previously, both inversions and translocations seem to be involved in the evolution of new species. Individual translocations and inversions that occur in one population may become established as the norm, especially in small inbreeding populations. If two populations differ by several rearrangements, hybrids between the two may be sterile. Thus

the two populations can become reproductively isolated from one another and eventually evolve to what are considered to be different species. Be aware, though, that chromosomal rearrangements are not the only cause of sterility in a hybrid. For example mules that result from crossing a mare and a male ass are sterile due to abnormal sexual development so chromosomal pairing in meiosis never has a chance to occur.

In some cases, two short one-armed chromosomes can fuse at the centromere to form one bi-armed chromosome (or *vice versa*). This is called a **Robertsonian Translocation**. For example, the same banding patterns seen on the two long arms of chromosome 2 in humans appear on two telocentric chromosomes in the other primates, which have 24 rather than 23 chromosomes per genome.

Chromosomal changes and cancer

Both inversions and translocations can occur in somatic cells as well as in germline tissues. Many recurring cancers have been associated with specific chromosomal rearrangements. For example, in Burkitts Lymphoma a piece at the end of chromosome 8 is exchanged with the tip of chromosome 14. This moves an oncogene called *c-myc* next to a promoter for an immunoglobulin gene resulting in overexpression of the oncogene and the disease. A similar event involving a translocation between chromosomes 22 and 9 moves another onc gene (*c-abl*) to an area where overexpression leads to chronic myelogenous leukemia. Many other inversions, deletions and translocations can typically be found in cancer cells.

Overall frequencies of chromosomal aberrations

About 2-3% of newborns carry some sort of chromosomal abnormality. Most involve extra or missing sex chromosomes, followed by trisomy, especially trisomy 21. However, at least 50% of spontaneously aborted fetuses have visible chromosomal abnormalities, so most of the abnormal conceptions are eliminated by nature. Recent improvements in technology permitting better detection reveal aberrations in up to 80% of fetuses that abort spontaneously during the first trimester.