

9.2: Changes in Chromosome Structure

If the chromosome is altered, but still retains the three critical features of a chromosome (centromeres, telomeres, and origin of replication), it will continue to be inherited during subsequent cell divisions, however the daughter cell may not retain all the genes. For example, if a segment of the chromosome has been lost, the cell may be missing some genes. The causes of chromosome structural abnormalities and the consequences they have for the cell and the organism is shown below. They all involve breaks in the DNA that makes up the chromosome.

9.2.1 Cause #1: Incorrect Repair of Double Strand DNA Breaks During Interphase

A chromosome is a very long but very thin molecule. In the phosphodiester backbone there are only two covalent bonds holding each base pair to the next. If one of these covalent bonds is broken the chromosome will still remain intact, although a DNA Ligase will be needed to repair the nick (Figure 9.4a). Problems arise when both strands are broken at or near the same location. This **double strand break** will cleave the chromosome into two independent pieces (Figure 9.4b). Because these events do occur in cells there is a repair system called the **non-homologous end joining (NHEJ) system** to fix them. Proteins bind to each broken end of the DNA and reattach them with new covalent bonds. This system is not perfect and sometimes leads to **chromosome rearrangements** (see next section).

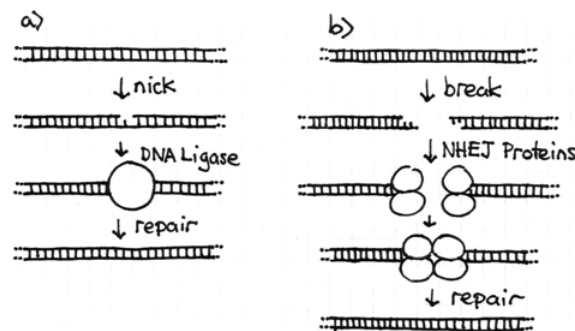


Figure 9.4: Repair of single strand nicks and double strand breaks in DNA. (Original-Harrington-CC:AN)

The NHEJ system proteins only function if required. If the chromosomes within an interphase nucleus are all intact the system is not active. The telomeres at the natural ends of chromosomes prevent the NHEJ system from attempting to join the normal ends of chromosomes together. If there is one double strand break the two broken ends can be recognized and joined. But if there are two double strand breaks at the same time there will be four broken ends in total. The NHEJ system proteins may join the ends together correctly but if they do not the result is a **chromosome rearrangement** (Figure 9.5).

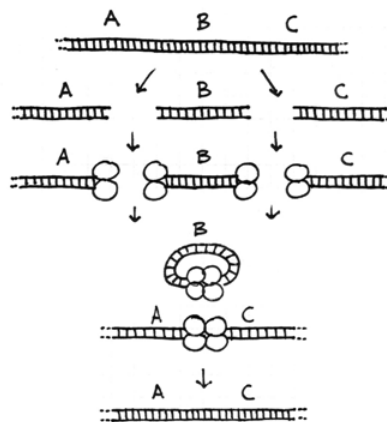
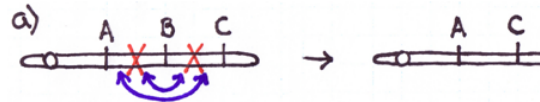


Figure 9.5: Errors during DNA repair can cause a chromosome deletion. In this diagram A, B, and C are genes on the same chromosome. As in Figure 9.4 there has been breaks in the DNA, recruitment of NHEJ proteins, and repair. After the repairs are completed the small piece of DNA with gene B is lost and the chromosome now only has genes A and C. (Original-Harrington-CC:AN)

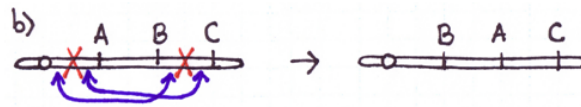
9.2.2 The Four Types of Chromosome rearrangements

Errors during the repair of multiple double strand breaks can cause four types of chromosome rearrangements. The type of chromosome rearrangement is dependent upon where the two breaks were originally and how they are rejoined. Figure 9.5 shows some possibilities but more are shown below. In these there is a double strand DNA break between the B and C genes (shown here as a red X). A second DNA break occurs and the NHEJ proteins mend the damage incorrectly by joining the ends shown with the blue arrows. The chromosomes are drawn unreplicated as they are in G₁ phase but these events can happen anytime during interphase.

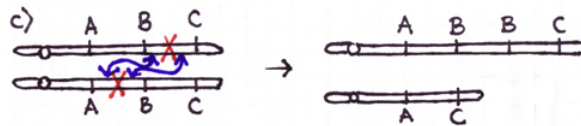
There are four major types of rearrangements:



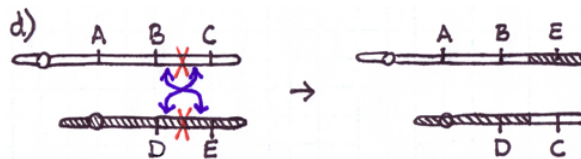
a) Deletions arise when both breaks are on one chromosome. If the ends are joined in this way the piece of DNA with the B gene on it does not have a centromere and will be lost during the next cell division.



b) Inversions also occur when both breaks are on one chromosome. If the ends are joined in this way, part of the chromosome is inverted. This example shows a **paracentric inversion**, named because the inverted section does not include the centromere (para = beside). If the breaks occur on different chromosome arms the inverted section includes the centromere and the result is a **pericentric inversion** (peri = around).



c) Duplications can occur from two DNA breaks at different places in sister chromatids (in a replicated chromosome). The ends are joined together incorrectly to give a chromosome with a duplication (two "B" regions as shown above). Note: the reciprocal product has a deletion.



d) Translocations result from two breaks on different chromosomes (not homologs) and incorrect rejoining. This example shows a **reciprocal translocation** - two chromosomes have 'swapped' arms, the E gene is now part of the white chromosome and the C gene is now part of the shaded chromosome. **Robertsonian translocations** are those rare situations in which all of the genes end up together on one chromosome and the other chromosome is so small that it is typically lost.

9.2.3 Cause #2: Incorrect Crossovers During Meiosis

Meiotic crossovers occur at the beginning of meiosis for two reasons. They help hold the homologous chromosomes together until separation occurs during anaphase I (see Chapter 2). They also allow recombination to occur between linked genes (see Chapter 7). The event itself takes place during prophase I when a double strand break on one piece of DNA is joined with a double strand break on another piece of DNA and the ends are put together (Figure 9.7a). Most of the time the breaks are on non-sister chromatids and most of the time the breaks are at the same relative locations.

Problems occur when the wrong pieces of DNA are matched up along the chromosomes during crossover events. This can happen if the same or similar DNA sequence is found at multiple sites on the chromosomes (Figure 9.7b). For example, if there are two ***Alu* transposable elements** on a chromosome. When the homologous chromosomes pair during prophase I the wrong *Alu* sequences might line up. A crossover may occur in this region. If so, when the chromosomes separate during anaphase I one of the chromatids will have a duplication and one will have a deletion. Ultimately, of the four cells produced by this meiosis, two will be normal, one will have a chromosome with extra genes, and one will have a chromosome missing some genes. Errors of this type can also cause inversions and translocations.

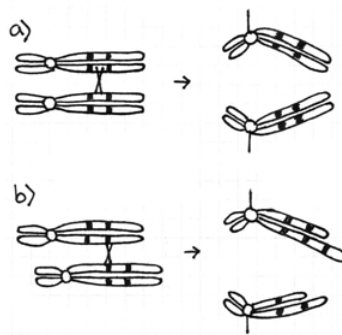


Figure 9.7: Errors during meiotic crossovers can cause duplications and deletions. This diagram shows homologous chromosomes pairing in prophase I and then separating in anaphase I. The shaded boxes are *Alu* transposable elements. a) The homologous chromosomes pair properly, a crossover occurs, and all four chromatids in anaphase I are normal. b) The pairing is incorrect, a crossover occurs in the mispaired region, and in anaphase I one chromatid has a duplication and another has a deletion. (Original-Harrington-CC:AN)

9.2.4 Consequence #1 - Rearrangements Show Abnormal pairing at Meiosis

Homologous regions of chromosomes pair at meiosis I (prophase I). With rearranged chromosomes this can lead to visible abnormalities and segregation abnormalities.

Deletion chromosomes will pair up with a normal homolog along the shared regions and at the missing segment, the normal homolog will loop out (nothing to pair with) to form a **deletion loop**. This can be used to locate the deletion cytologically. The deleted region is also **pseudo-dominant**, in that it permits the mutant expression of recessive alleles on the normal homolog. Deletion mutations don't revert - nothing to replace the missing DNA.

When an **inversion** chromosome is paired up in meiosis there is an **inversion loop** formed. If there is a crossover within the loop then abnormal products will result and abnormal, unbalanced gametes will be produced. For example, a crossover event within the loop of a **paracentric inversion** will lead to a di-centric product that will break into deletion products and produce unbalanced gametes (Figure 9.8n). Similarly, with a **pericentric inversion**, a crossover event leads to duplicate/deletion products that are unbalanced (Figure 9.9n).

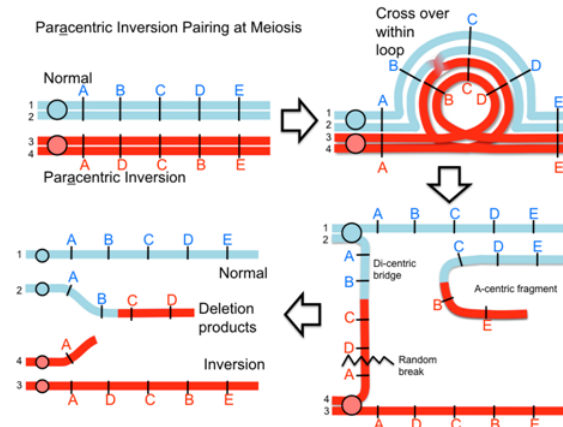


Figure 9.8: A paracentric inversion pairing at meiosis. A crossover within the loop causes the production of an acentric and a dicentric chromatids which leads to deletion product. (Original-Locke-CC:AN)

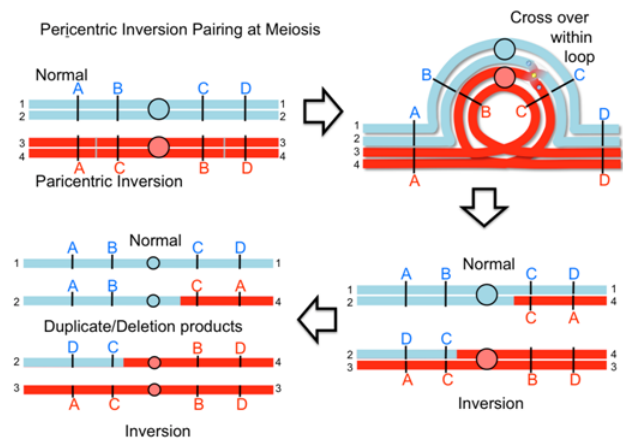


Figure 9.9: A pericentric inversion pairing at meiosis. A crossover within the loop causes the production of duplicate and deletion products. (Original-Locke-CC:AN)

If joined with a normal gamete, they will result in an unbalanced zygote, which are usually lethal. The consequence for this is that crossover products (recombinants) are lost and thus inversions appear to suppress crossovers within the inverted region.

With both types of inversions, crossovers outside the loop are possible and fully viable as they don't alter the gene balance.

Duplications also produce a cytologically visible loop at meiotic pairing. Duplications can revert at a relatively high frequency by unequal crossing over. Duplicated genes offer new possibilities for mutational divergence followed by natural selection in the course of evolution.

For **translocations**, a consequence for the two chromosomes involved is that when they pair at meiosis both replicated chromosome pairs will be together, which can be seen cytologically as a **tetrad**. This tetrad can segregate in three ways. Two of which are shown below. This set of paired, replicated chromosomes can segregate as **Alternate** (balanced) where both normal and both translocated chromosomes go to the same poles. Or the chromosomes can segregate as **Adjacent-1** (unbalanced) where the normal and translocation chromosomes segregate as shown below. Each of these possibilities is approximately equally frequent and thus only about half the time do the gametes end up unbalanced (Figure 10n).

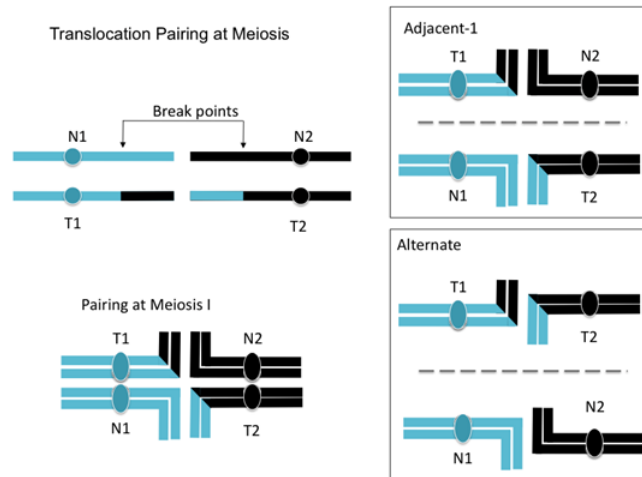


Figure 9.10: A reciprocal translocation pairing at meiosis. There are two main avenues for segregation: Adjacent-1 and Alternate. Adjacent-1 results in duplication and deletion for part of the chromosome segments. Alternate doesn't. (Original-Locke-CC:AN)

9.2.5 Consequence #2: Decreased Viability

All of the chromosome rearrangements shown above produce functional chromosomes. Each has one centromere, two telomeres, and thousands of origins of replication. Because inversions and translocations do not change the number of genes in a cell or organism they are said to be balanced rearrangements. Unless one of the breakpoints occurred in the middle of a gene the cells will not be affected. On the other hand, deletions and duplications are unbalanced rearrangements. The larger they are (more genes involved) the more disruption they cause to the proper functioning of the cell or organism. As explained in Section 9.1.2 above having too much or too little gene action for a large number of genes can disrupt the cellular metabolism to generate a phenotype or reduce viability.

9.2.6 Consequence #3: Decreased Fertility

Recall that during meiosis I homologous chromosomes pair up. If a cell has a chromosome with a rearrangement this chromosome will have to pair with its normal homolog.

Cells heterozygous for balanced rearrangements actually have more difficulties in prophase I. Consider the chromosomes shown in Figure 9.11n. There are different ways they might pair during prophase I - one is shown in Figure 9.12n. But if a crossover occurs in the inverted region the result will be unbalanced gametes. Embryos made with unbalanced gametes rarely survive. The consequence is that the heterozygous organism will have **reduced fertility**.

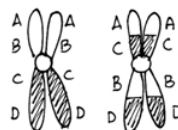


Figure 9.11: An unrearranged chromosome (left) and a homolog with a pericentric inversion (right). (Original-Harrington-CC:AN)

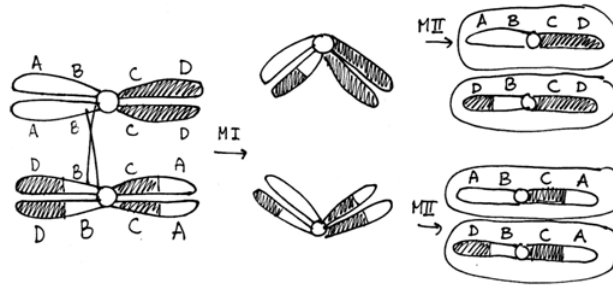


Figure 9.12: Meiosis in a cell heterozygous for the chromosomes shown in Figure 9.11. Note that of the four gametes one has a deletion of the A gene and a duplication of the D gene while another gamete has a duplication of A and a deletion of D. (Original-Harrington-CC:AN)

Note that an organism homozygous for this inversion chromosome will not be affected in this way because no loops are formed. The chromosomes can pair along their entire length and crossovers will not produce any unbalanced gametes. This is a general property of inversions and translocations. In heterozygotes there are problems during meiosis resulting in a lot of the gametes being unbalanced and an overall reduction in fertility. In homozygotes the rearranged chromosomes pair with one another just fine and there is no effect on fertility.

9.2.7 Consequence #4: Cancer

Some chromosome rearrangements have breakpoints within genes leading to the creation of hybrid genes – the first part of one gene with the last part of another. If the hybrid gene inappropriately promotes cell replication, the cell can become cancerous. An example of this is shown in Figure 9.1 where the chromosomes are from a patient with leukemia caused by a translocation between chromosomes 9 and 22 (the red and green spots side-by-side).

9.2.8 Consequence #5: Evolution

Those chromosome changes that duplicate genes are important for evolution. If an organism has an extra copy of important genes, one gene can be retained for their original function while others can mutate and potentially acquire new functions (Figure 9.13n). An example of this is the multiple copies of the globin genes found in mammals (see Figure 12.13).

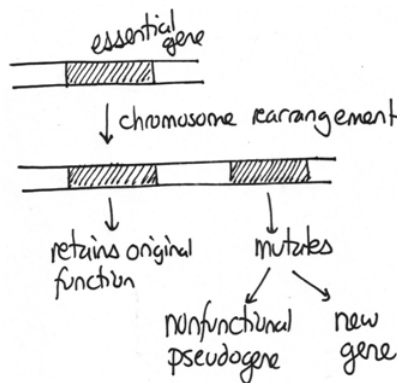


Figure 9.13: Duplicated genes can mutate without compromising the viability of the organism. Occasionally the result is a new gene. (Original-Harrington-CC:AN)

Chromosome rearrangements that decrease fertility are also important for the origin of new species. If a rearrangement, such as the inversion shown in Figure 9.11n, becomes common in a small isolated population, that population has 100% fertility if they mate within their group, but a reduced fertility if they mate with members of the larger population. As rearrangements accumulate the small population will become more and more reproductively isolated. When members are incapable of forming viable, fertile offspring with the original population the group will have become a new species.

Contributors



- [Dr. Todd Nickle and Isabelle Barrette-Ng](#) (Mount Royal University) The content on this page is licensed under CC SA 3.0 licensing guidelines.