3 - Chromosome Variation

In the first half of Part 3, we will consider deficiencies in chromosome structure. Deficiencies in chromosome structure refer to altering the total amount of genetic information on a chromosome (**deletions, duplications**), rearranging the order of genes on a chromosome (**inversions**), or moving genes from one chromosome to a nonhomologous chromosome (**translocations**).

In the second half of Part 3, we will consider situations in which the number of chromosomes within an individual varies (**variations in euploidy** and **aneuploidy**).

A. Changes in Chromosome Structure

Overview

We learned in Part 1 that most structural genes are unique DNA sequences, found as a single copy on a particular chromosome. However, since we have two copies of each chromosome (one copy of the homologous chromosome pair is inherited from dad; the other member of the pair is inherited from mom), each structural gene is actually present in two copies per genome. Changes to this general rule include the following (see **figure 3.1**):

- **Deletions**. A deletion occurs when a portion of a chromosome is missing. A deletion can be as small as a single base pair or can include the loss of several genes. The portion of the chromosome that is missing is called a **deficiency**. A person who suffers a deletion would have a single copy of one or several structural genes.
- **Duplications**. A duplication occurs when a portion of the chromosome is repeated. In a duplication, a single chromosome can have more than one copy of the same structural gene.

Mutations can also move structural genes from their normal location to a new location in the genome. The mutations that alter the location of a gene include:

- **Inversions**. Inversions involve changing the direction of an internal segment within a single chromosome. Inversions change the location of a structural gene within an individual chromosome.
- **Translocations**. A translocation occurs when a portion of a chromosome becomes attached to a nonhomologous chromosome. For example, a portion of chromosome 1 can be translocated to chromosome 5. There are three types of translocations:
    - **Simple (nonreciprocal) translocation**. A simple translocation occurs when a segment of one chromosome becomes attached to a nonhomologous chromosome. The chromosome receiving the DNA segment remains intact.
    - **Reciprocal translocation**. Reciprocal translocations involve nonhomologous chromosomes exchanging pieces. For example, one copy of chromosome 1 and one copy of chromosome 5 could exchange telomere regions.
    - **Robertsonian translocation**. Robertsonian translocations involve the fusion of the long (*q*) arms of two acrocentric chromosomes. For example, the *q* arm of one copy of chromosome 14 can fuse with the *q* arm of one copy of chromosome 21. The *p* arms of chromosomes 14 and 21 are lost (see below).

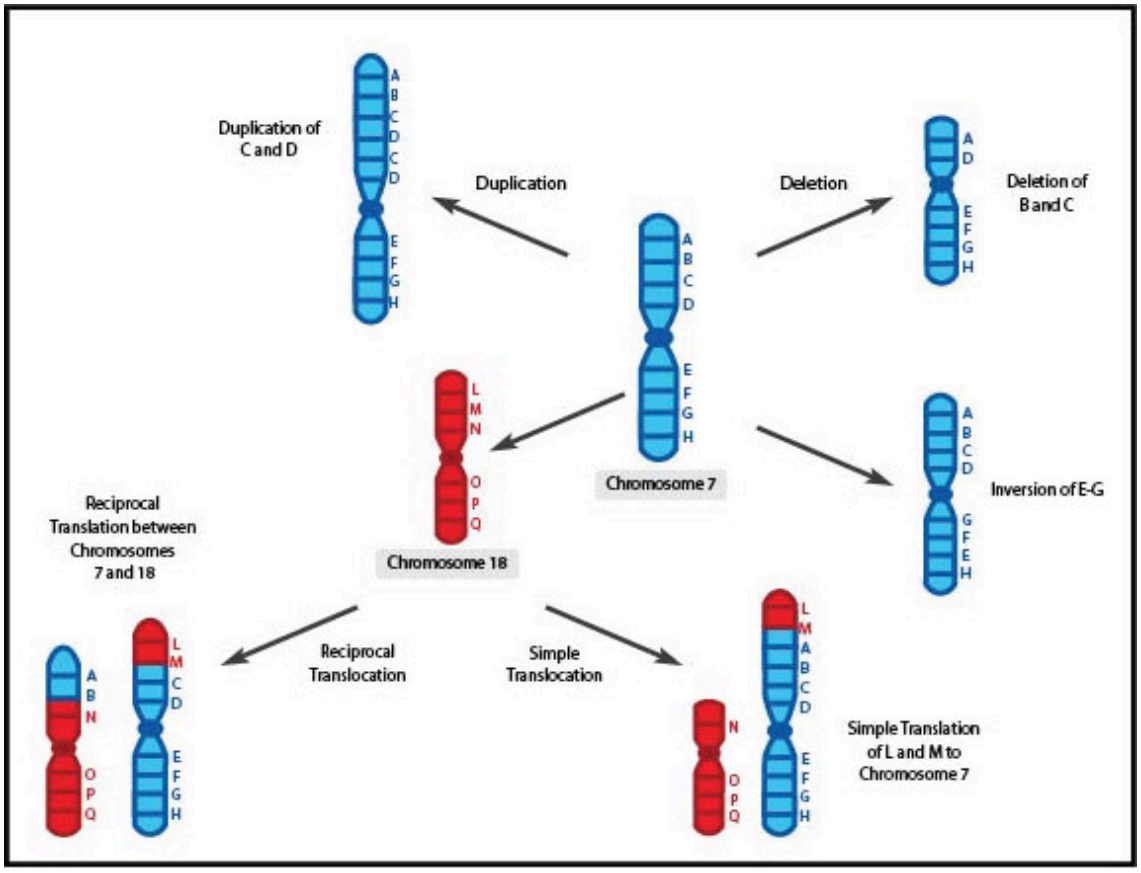


Figure 3.1 Changes in Chromosome Structure (Overview). *The Robertsonian translocation in not shown in the image. Image created by SL.*

Key Questions

- What are the four major types of chromosome structural defects?
- What are the differences between the three types of translocations?

Deletions

One or more DNA breaks can lead to the loss of a portion of the chromosome. This type of chromosomal aberration is called a **deletion** (see **figure 3.2**). A single break in a chromosome can result in a DNA fragment that contains a centromere and a DNA fragment that lacks a centromere. The centromere fragment is retained by the cell, while the DNA fragment that lacks the centromere is lost during cell division. This type of event is a **terminal deletion**. Terminal deletions are usually generated by endonuclease damage or by environmental factors, such as ionizing radiation, that break the DNA backbone. An **interstitial deletion** is a deletion within the interior of the chromosome and does not involve the telomere. Interstitial deletions are generated by defects in synapsis and crossing over during meiosis I (see below).

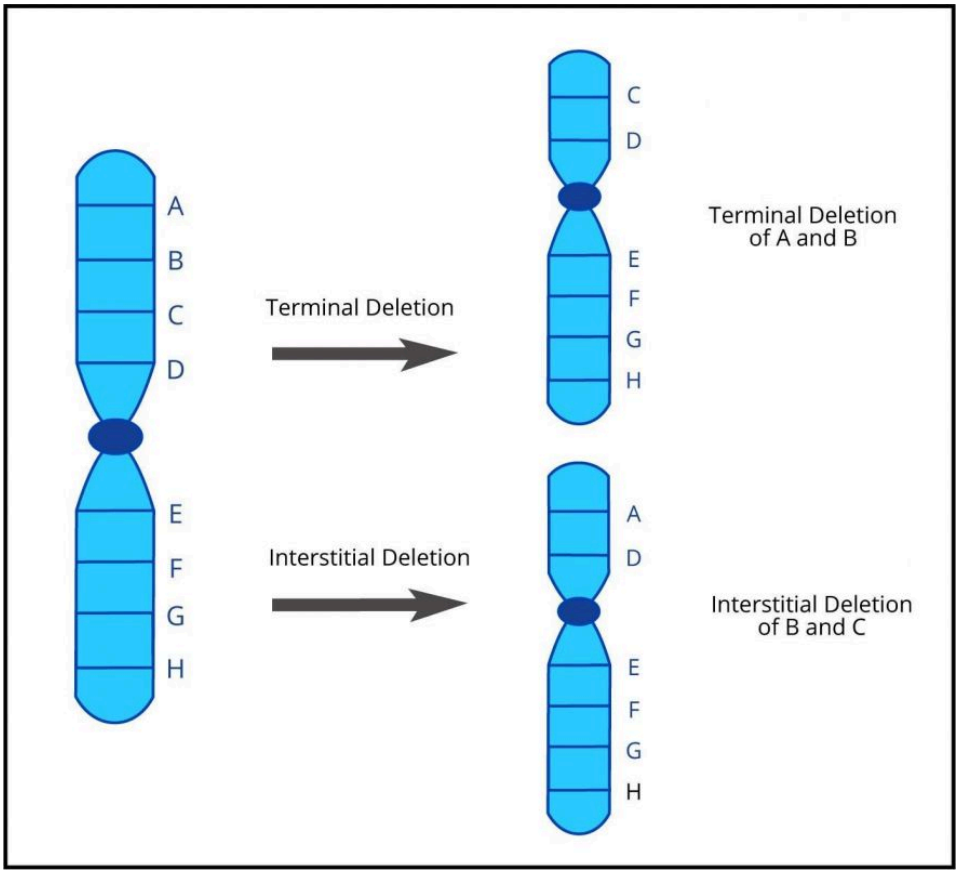


Figure 3.2 Deletions. *A terminal deletion involves the loss of a telomere region. An interstitial deletion involves the loss of genes within the chromosome. --- Image created by SL*

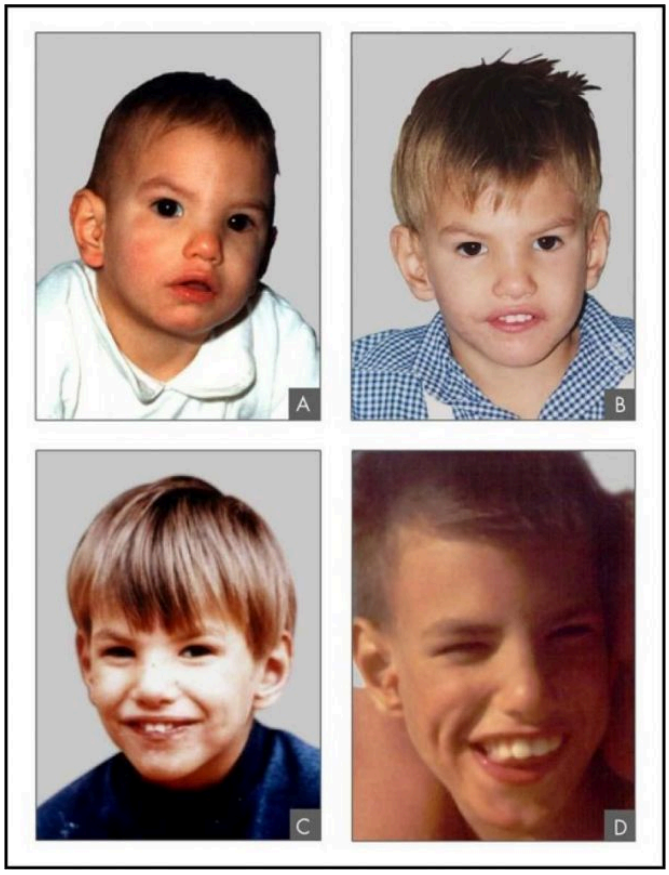
Key Questions

- What is the difference between an interstitial and a terminal deletion?

Cri-du-chat

In general, the larger the deletion (i.e., the more structural genes involved), the more severe the phenotypic consequences. Moreover, a detrimental phenotype can occur even though the individual may have a normal copy of the homologous chromosome, indicating that most deletions behave as dominant mutations.

Cri-du-chat (*46, 5p-*) is an example genetic disease caused by a deletion in the *p* arm of chromosome 5. Cri-du-chat occurs in 1 in 25,000–50,000 live births (see **figure 3.3**). Cri-du-chat is usually not inherited; instead, the disease is caused by the loss of the *p* arm of chromosome 5 during meiosis. A cri-du-chat individual usually has one normal copy of chromosome 5 and a **terminal deletion** copy of the same chromosome. The deletion in chromosome 5 can be quite small or can encompass much of the *p* arm; however, it is thought that the absence of a specific gene causes cri-du-chat. This missing gene encodes telomerase reverse transcriptase (*TERT*). We will learn about the function of *TERT* in Part 6. The cri-du-chat individual displays mental deficiencies, facial abnormalities, gastrointestinal, and cardiac complications. Those afflicted also tend to vocalize using a catlike cry, due to defects in the formation of the glottis and larynx.


A
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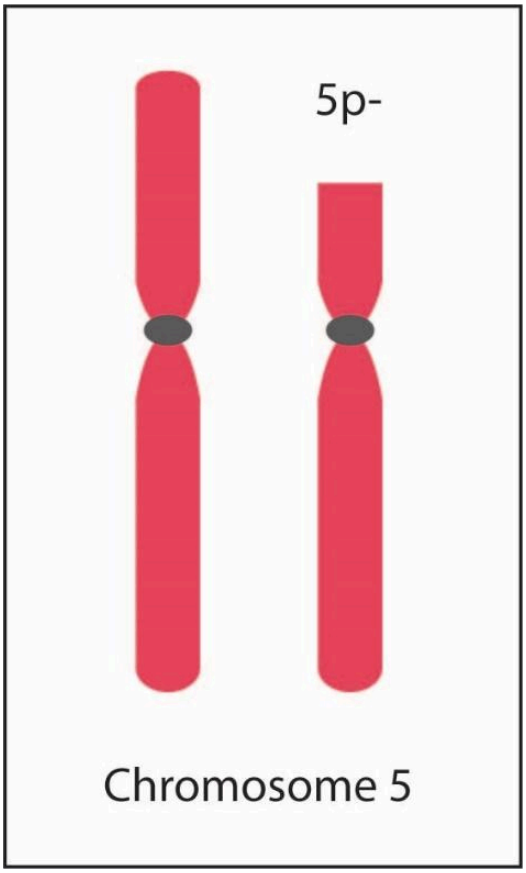


***Figure 3.3 Cri-du-cha**t A) A Cri-du-chat patient--- CriDuChat by Paola Mainardi is licensed under CC BY 2.0 B) Terminal deletion in chromosome 5 --- Image created by SL*

Key Questions

- Which change in chromosome structure produces cri-du-chat?

Duplications

A **duplication** produces two copies of a structural gene on a single chromosome. Since the homologous chromosome contributes another copy of the same structural gene, a person with a duplication has three copies of the structural gene, instead of two copies. As the region of the chromosome that is duplicated gets larger, the phenotypic effect on the individual becomes more severe. One example disease caused by a duplication is the neuropathic disease **Charcot-Marie-Tooth disease type 1A (CMT type 1A)**, produced by a duplication on chromosome 17.

Duplications and interstitial deletions can be produced simultaneously by the misalignment of synapsed homologous chromosomes during meiosis, followed by **unequal crossing over** (see **figure 3.4**). Unequal crossing over produces four gametes. One gamete contains an interstitial deletion chromosome, and a second gamete contains a chromosome with a duplication. The final two gametes contain the normal allele arrangement.

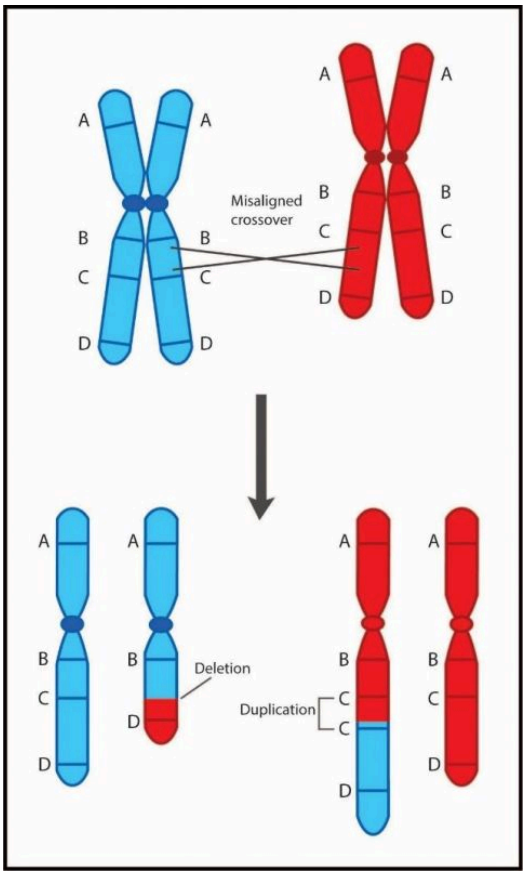


Figure 3.4 Unequal Crossing Over Produces an Interstitial Deletion and a Duplication *--- Image created by SL*

Key Questions

- How can a meiosis defect produce a gamete with a deletion and a gamete with a duplication?
- What human disease is caused by a duplication?

Duplications Can Produce Gene Families

Small duplications can sometimes be beneficial and are important in the formation of **gene families**, closely related genes that have similar but not identical functions. For example, the **globin gene family** in humans is thought to have been formed by multiple duplications from a single ancestral globin gene (see **figure 3.5**). To form the globin gene family, the ancestral globin gene was duplicated to produce two identical genes on the same chromosome. These two

genes then accumulated mutations independently over the course of thousands of generations to become specialized; one gene became a hemoglobin gene, the other became a myoglobin gene. Later, the hemoglobin gene duplicated additional times followed by divergence through the continued accumulation of mutations. The current globin gene family, consisting of fourteen member genes, includes genes that encode the protein subunits of hemoglobin, which is specialized to carry oxygen in the bloodstream, and the protein subunits of myoglobin, which carries oxygen within muscles. The globin gene family is a good example of how gene duplication can produce the genetic variability necessary to drive evolution.

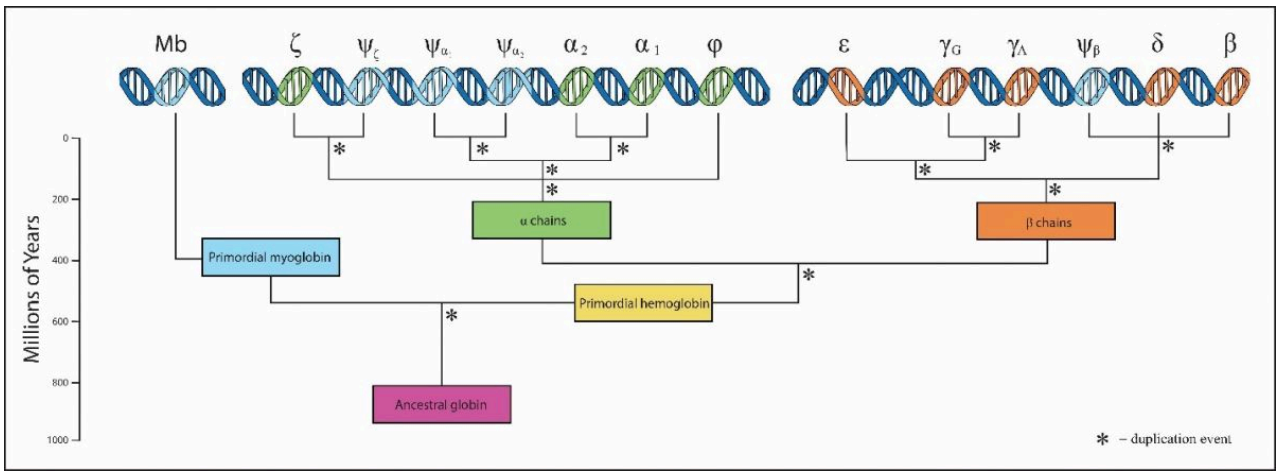


Figure 3.5 The Globin Family. *An ancestral globin gene duplicated to produce a primordial myoglobin and primordial hemoglobin gene. The primordial hemoglobin gene duplicated additional times to produce specialized globin genes.---Image created by SL*

Key Questions

- Describe how gene duplications and mutations can produce a gene family.

Types of Inversions

Inversions involve the rearrangement of genes along a single chromosome. An inversion can be thought of as breaking the chromosome in two places, flipping the DNA between the breaks, and sealing the DNA breaks. The total amount of genetic material (number of structural genes) in the chromosome does not change. Interestingly, inversions are quite common; about 2% of the human population carry a detectable inversion.

There are two types of inversions (see **figure 3.6**):

- **Pericentric inversion**. In a pericentric inversion, one chromosome break occurs in the *p* arm, while a second break occurs in *q* arm of the same chromosome. The central region of the chromosome, including the centromere, is located within the inverted region. Note that a pericentric inversion has the potential to change the position of the centromere within the chromosome.
- **Paracentric inversion**. In a paracentric inversion, two chromosome breaks occur within the same arm of the chromosome. The chromosome region between the two breaks is inverted, with the centromere of the chromosome lying outside of the inverted region. As a result, a paracentric inversion does not change the position of the centromere within the chromosome.

Most inversions have no phenotypic consequences; however, if one of the chromosome breaks that lead to an inversion occurs within a gene, then a change in phenotype can occur. For example, in **type A hemophilia**, the breakpoint of an inversion on the X chromosome occurs within the **factor VIII** gene. The encoded Factor VIII protein is required for proper blood clotting; this inversion produces a nonfunctional protein, leading to a deficiency in blood clotting (hemophilia). Further, the change in the position of a structural gene on a chromosome can alter the transcription of nearby genes. This alteration of transcription by an inversion is called a **position effect**. In some cases, the position effect can result in the overexpression of genes that regulate the cell cycle, resulting in cancer.

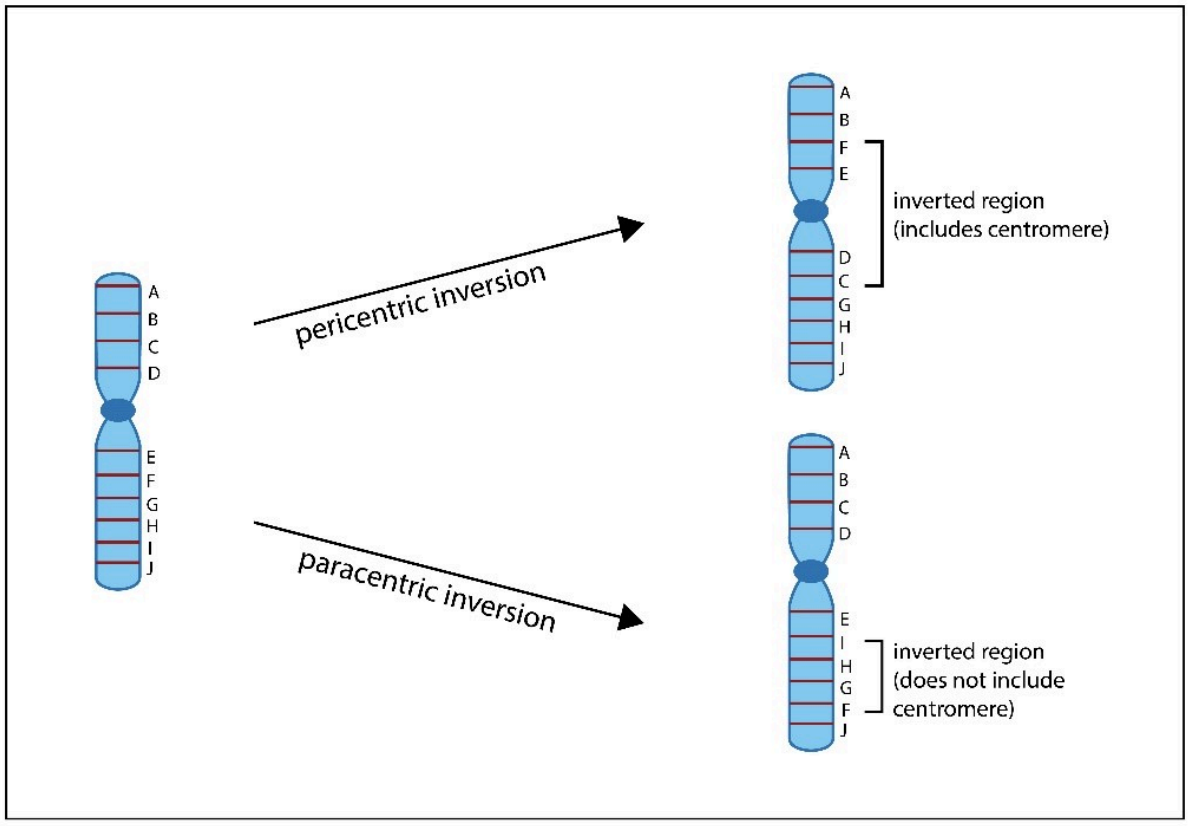


Figure 3.6 Pericentric and Paracentric Inversions. *Pericentric inversions include the centromere in the inverted region, while paracentric inversions do not involve the centromere. --- Image created by SL*

Key Questions

- What is the difference between a pericentric and a paracentric inversion?
- What human disease is caused by an inversion?

Crossing Over in Inversion Heterozygotes

An **inversion heterozygote** is an individual who has a chromosome with a normal gene arrangement, while the homologous chromosome contains an inversion. Even though an inversion heterozygote individual has a normal phenotype, they produce unusual gametes during meiosis. Recall that prior to meiosis, the two chromosomes within a homologous chromosome pair are copied by DNA replication, producing four sister chromatids (see **figure 3.7**). DNA replication is followed by synapsis (alignment) of the homologous chromosome pair during meiosis I. For the normal

chromosome and the inversion chromosome to synapse properly, one of the two chromosomes twists to form an **inversion loop**. After the inversion loop is formed, crossing over occurs between the two chromosomes within the homologous chromosome pair. Once crossing over is concluded, abnormal chromosomes are distributed to gamete cells.

- **Pericentric inversion.** In a pericentric inversion, the centromere lies within the inverted region of the chromosome. When crossing over occurs between the homologous chromosomes and after meiosis is completed, the following gametes are produced:
  - A gamete that contains a chromosome with the normal gene arrangement. This gamete will produce offspring with the normal gene arrangement and phenotype.
  - A gamete that contains an inversion chromosome. Thus, inversion chromosomes are passed from parents to offspring. The resulting offspring will suffer no negative phenotypic effects.
  - Two gametes that contain abnormal chromosomes. Each gamete contains a chromosome with a duplication of some genes and a deletion of other genes. The fertilized egg produced from either of these two gametes is not generally viable.

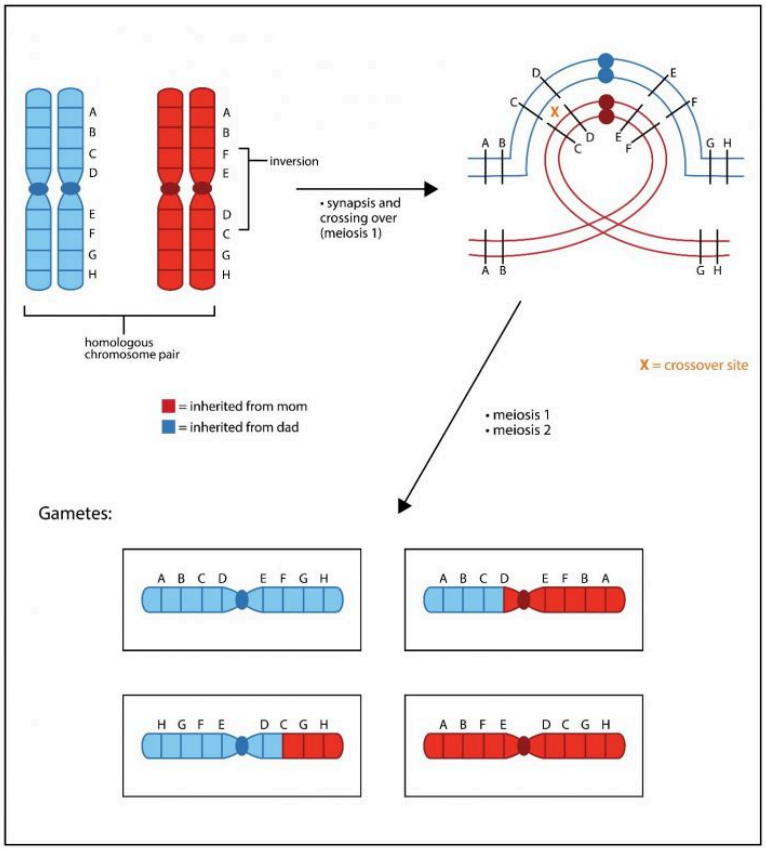


Figure 3.7 Meiosis in an Individual Heterozygous for a Pericentric Inversion. *One of the gametes has the normal allele arrangement, while a second gamete contains the inversion. Two of the gametes (bottom) contain simultaneous duplications and deletions. --- Image created by SL*

- **Paracentric inversion**. In a paracentric inversion, the centromere lies outside of the inverted region of the chromosome. After crossing over between the homologous chromosomes occurs and meiosis is completed, the following gametes are produced (see **figure 3.8**):
    - A gamete that contains a chromosome with the normal gene arrangement. This gamete will produce offspring with the normal gene arrangement and phenotype.
    - A gamete that contains an inversion chromosome. The inversion chromosome is passed from parents to offspring. The resulting offspring will suffer no negative phenotypic effects.
    - Two gametes that contain highly unusual chromosomes. One gamete contains an abnormal chromosome containing duplications and deletions, but more importantly, the chromosome lacks a centromere. This **acentric fragment** will be lost during cell division. The other gamete will contain an abnormal chromosome that has two centromeres (**dicentric chromosome**) along with duplications and deletions. Between the two centromeres of this dicentric chromosome is a region called a **dicentric bridge**. When a dicentric chromosome, attached to opposite spindle poles, tries to separate during anaphase of meiosis, it is torn apart. Breakage produces chromosome fragments that are missing genes.

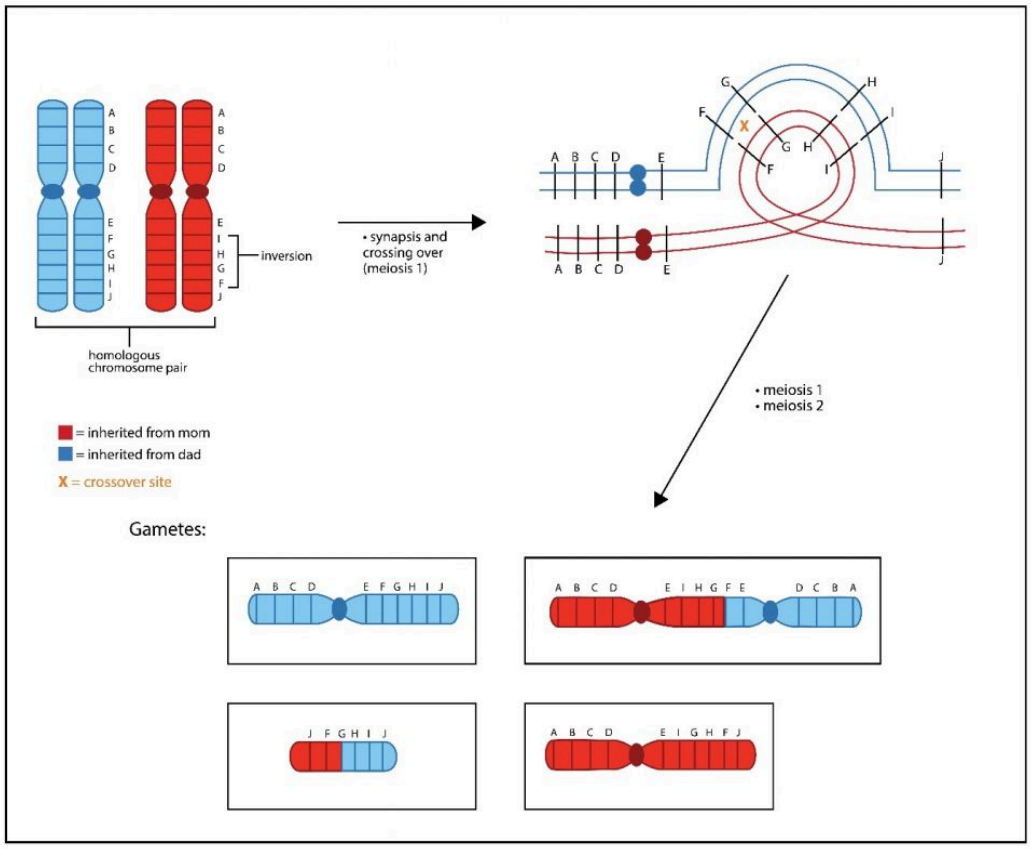


Figure 3.8 Meiosis in an Individual Heterozygous for a Paracentric Inversion. *One of the gametes has the normal allele arrangement, while a second gamete contains the inversion. Two of the gametes (bottom) contain simultaneous duplications and deletions; however, one gamete lacks a centromere (acentric), while the other gamete has two centromeres (dicentric).--- Image created by SL*

Importantly, 50% of the gametes produced by either pericentric or paracentric inversion heterozygotes fail to produce viable offspring. Thus, even though the inversion may not affect the individual's phenotype directly, the inversion causes a 50% reduction in fertility.

Key Questions

- Describe the four gametes produced by an individual who carries a pericentric inversion.
- Describe the four gametes produced by an individual who carries a paracentric inversion.
- What is a dicentric bridge, and why does it produce lethal products?

Reciprocal Translocations

A **translocation** occurs when a piece of a chromosome becomes attached to a nonhomologous chromosome. As mentioned earlier, there are three types of translocations: **simple translocations**, **reciprocal translocations**, and **Robertsonian translocations.** We will focus primarily on reciprocal and Robertsonian translocations.

Reciprocal translocations involve nonhomologous chromosomes exchanging pieces. Reciprocal translocations are formed by two general mechanisms (see **figure 3.9**):

- **Chromosome breakage and defective DNA repair**. Some chemicals or environmental agents can cause chromosomes to break at internal sites, forming reactive ends not protected by **telomeres**. Recall that telomeres are the structures found on the ends of linear eukaryotic chromosomes that are designed to prevent chromosome ends from sticking together (see Part 1). Cells contain repair enzymes to handle these situations, and in most cases, quickly repair these breaks. When nonhomologous chromosomes are broken simultaneously, the repair enzymes can sometimes inadvertently join nonhomologous chromosomes together, resulting in a reciprocal translocation.
- **Nonhomologous chromosomes crossing over**. If two nonhomologous chromosomes accidently synapse and undergo crossing over during meiosis I, a reciprocal translocation occurs.

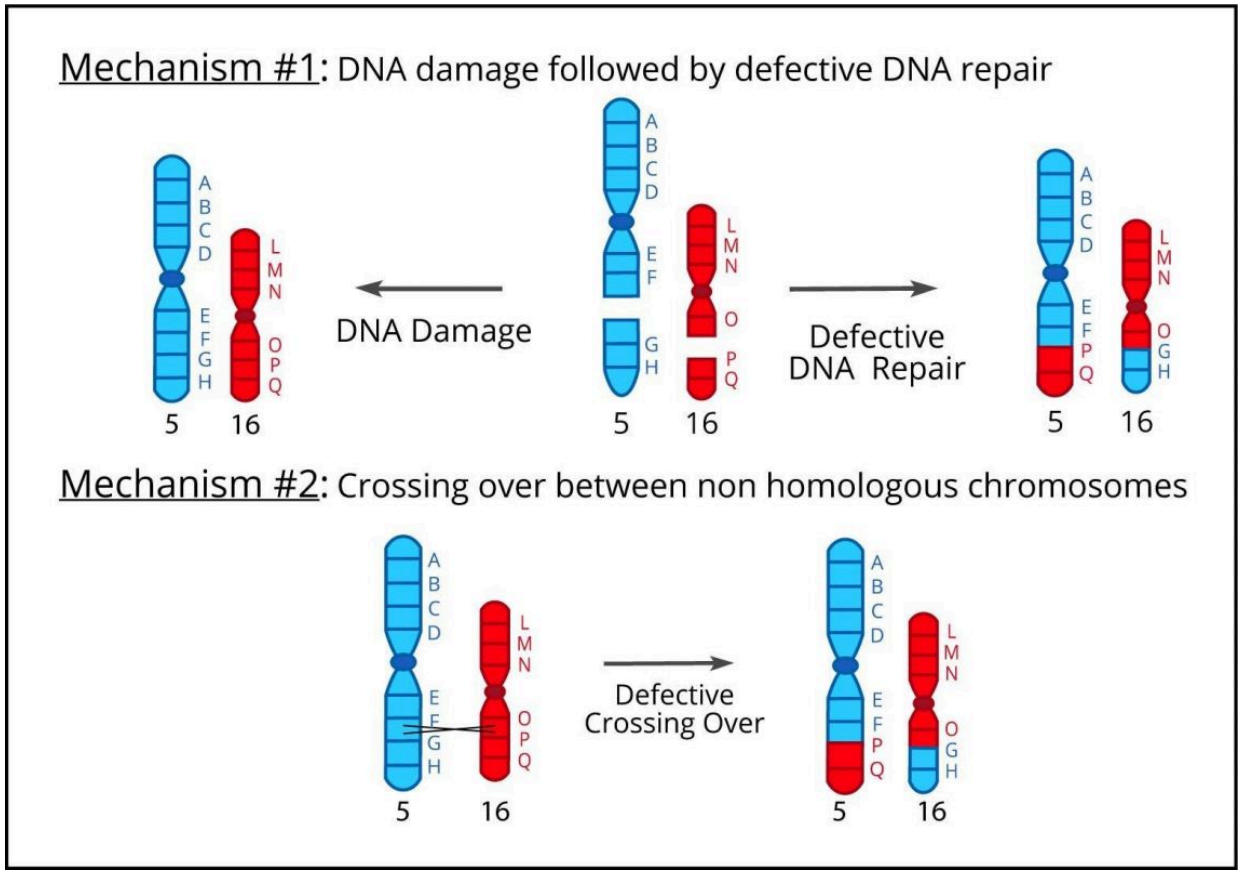


Figure 3.9 Mechanisms for Producing Reciprocal Translocations. *The chromosome number is shown beneath each chromosome. --- Image created by SL*

Key Questions

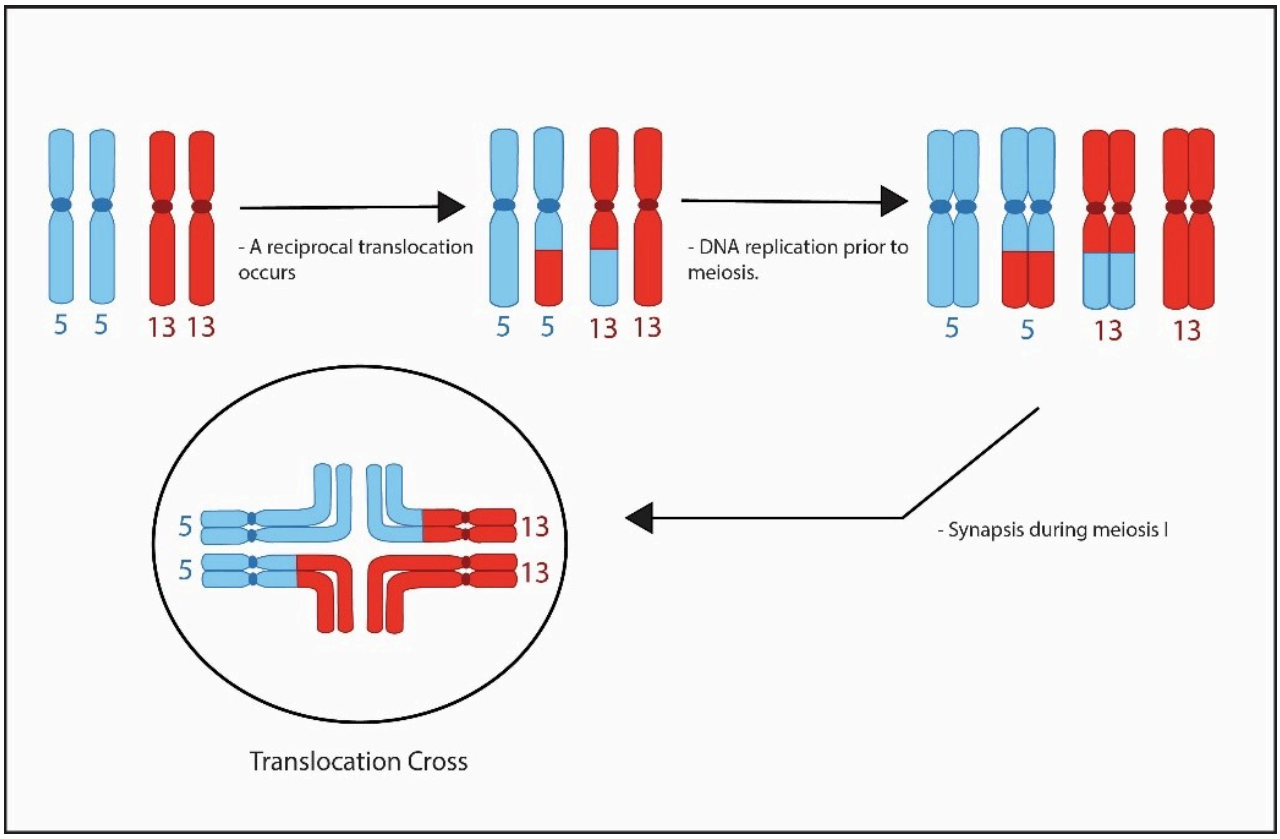
- Describe the two processes that generate reciprocal translocations.

Meiosis in Cells with Reciprocal Translocations

How do nonhomologous chromosomes that have experienced a reciprocal translocation synapse and then segregate into gametes during meiosis? During synapsis, the two pairs of homologous chromosomes (four chromosomes total) that include two individual chromosomes that have suffered a reciprocal translocation attempt to synapse. Because of the reciprocal translocation, the four chromosomes synapse to form a **translocation cross** (see **figure 3.10**).

For example, suppose a translocation cross is produced from a normal copy of chromosome 5, a normal copy of chromosome 13, and a situation in which the other copies of chromosomes 5 and 13 have undergone a reciprocal translocation. Prior to meiosis, these four chromosomes are copied by DNA replication to produce eight sister chromatids. In order to synapsis properly, the normal copy of chromosomes 5 and 13 end up diagonal from each other in the translocation cross, while the two translocation chromosomes are diagonal from each other (see **figure 3.10**). The chromosomes in the translocation cross can then segregate during anaphase I in three possible ways:

- **Alternate segregation** (common). The chromosomes diagonal from each other segregate into the same cells at the conclusion of meiosis I. For example, the normal copies of chromosomes 5 and 13 segregate with each other into the same daughter cell while the two translocation chromosomes segregate with each other into the same daughter cell. After meiosis II, there are two normal gametes and two gametes that carry translocations. Because none of these gametes are missing genes, all four gametes produced by alternate segregation are capable of producing viable offspring.
- **Adjacent-1 segregation** (common). The two chromosomes on the bottom half of the translocation cross (normal chromosome 13 and translocation chromosome 5) segregate with each other into the same daughter cell. The two chromosomes on the top half of the cross (normal chromosome 5 and translocation chromosome 13) segregate with each other into the same daughter cell at the conclusion of meiosis I. After meiosis II, all four gametes carry duplications and deletions and therefore are not generally viable.
- **Adjacent-2 segregation** (rare). The two chromosomes on the right half of the cross (normal chromosome 5 and translocation chromosome 5) segregate with each other into the same daughter cell, while the two chromosomes on the left half of the cross (normal chromosome 13 and translocation chromosome 13) segregate into the same daughter cell at the conclusion of meiosis I. One daughter cell receives, in essence, both copies of chromosome 5; the other daughter cell receives both copies of chromosome 13. Since both copies of chromosome 5 end up in the same cell and both copies of chromosome 13 end up in the same cell, adjacent-2 segregation can be considered a **nondisjunction** event (see below). After meiosis II, all four gametes carry duplications and deletions and are not generally viable.



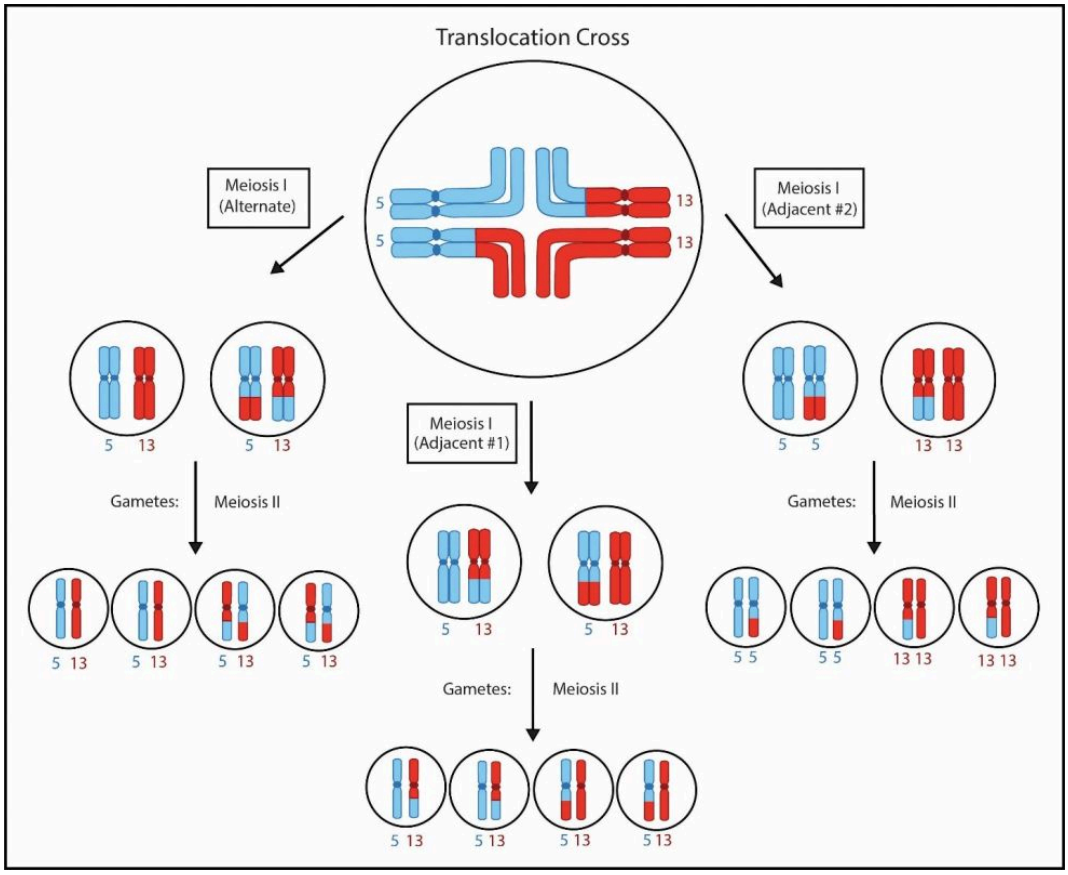


Figure 3.10 Formation of a Translocation Cross and Meiotic Chromosome Segregation – *Top) A reciprocal translocation produces a translocation cross during meiosis. Bottom) Chromosome segregation during meiosis I and II. Only alternate segregation can produce viable offspring.--- Image created by SL.*

Key Questions

- Which segregation pattern produces normal gametes?
- Why does adjacent-2 segregation occur so rarely?

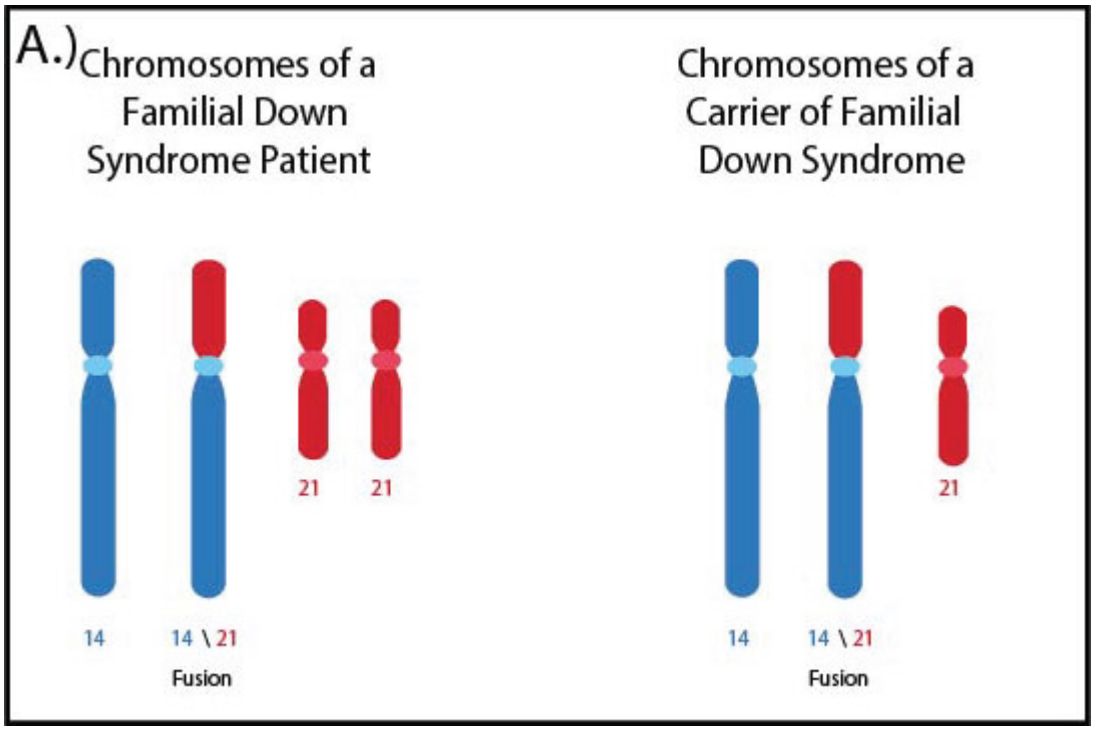
Robertsonian Translocations

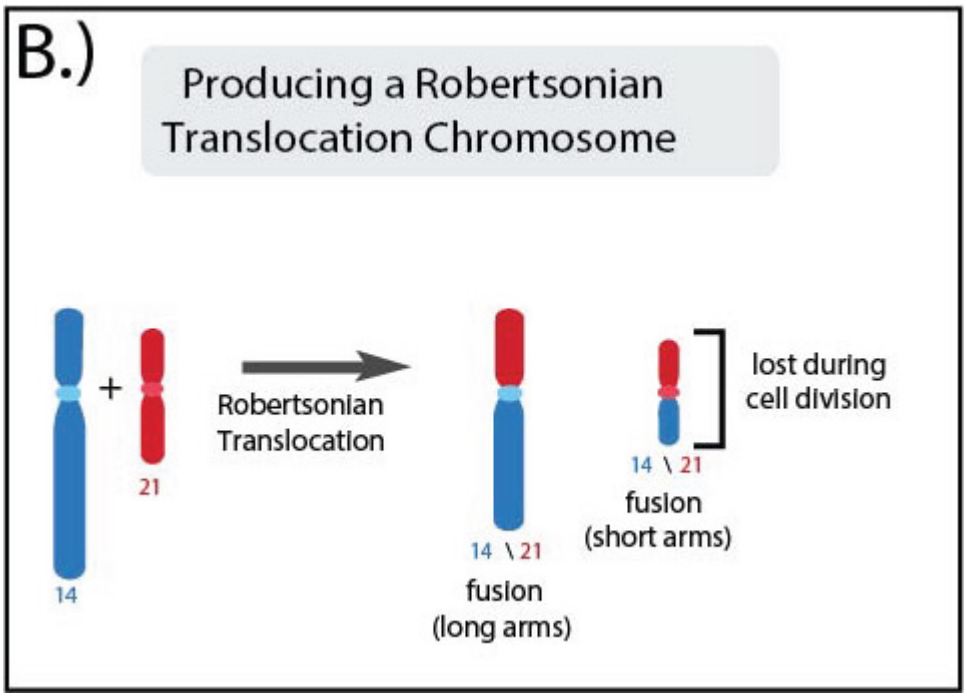
A rare form of Down syndrome called **familial Down syndrome** is inherited (see **figure 3.11**). In familial Down syndrome, a phenotypically normal parent can carry a translocation. This carrier individual has normal copies of chromosomes 14 and 21 and a chromosome that contains a fusion between the long (*q*) arms of chromosome 14 and 21. In this **balanced carrier** person, the short (*p*) arms of chromosome 14 and 21 have been lost, but since these regions carry repetitive DNA sequences that are found on other chromosomes in the genome (see Part 1), the individual can tolerate the loss of the two *p* arms. This type of translocation, involving the fusion of the long arms of two acrocentric chromosomes, is a **Robertsonian translocation**. The Robertsonian translocation, which involves only human chromosomes 13, 14, 15, 21, and 22 (i.e., acrocentric chromosomes), is the most common chromosome abnormality in humans.

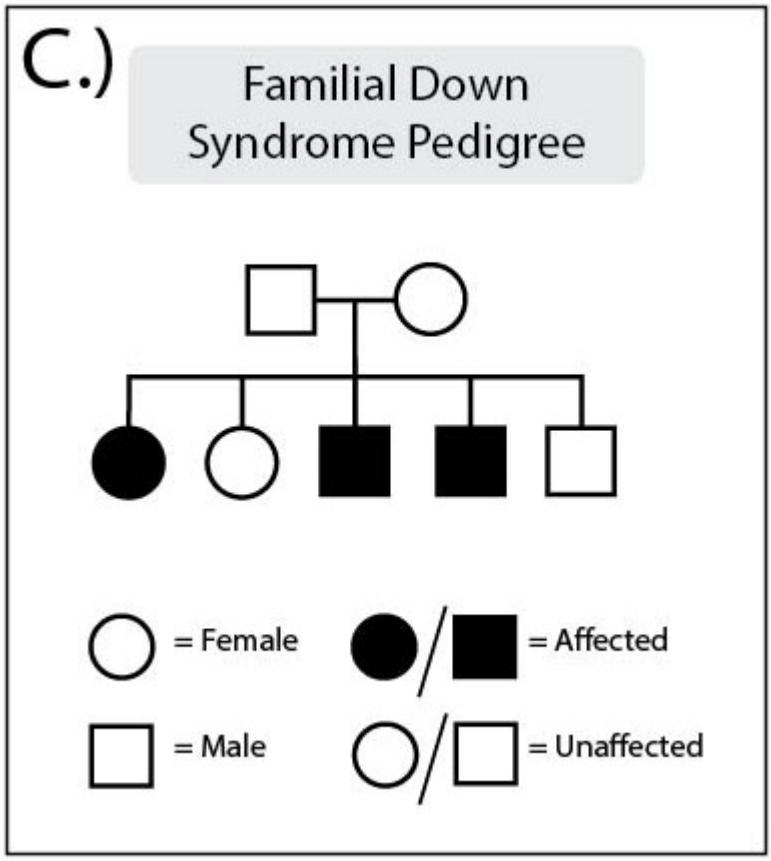
A problem occurs during meiosis in an individual that carries the Robertsonian translocation. In the case of a balanced carrier for familial Down syndrome, the normal chromosome 14, normal chromosome 21, and Robersonian

translocation chromosome replicate, synapse, and attempt to segregate into gametes during meiosis. There are six possible types of offspring that can be produced by the carrier individual:

- **Normal.** When a normal gamete containing chromosomes 14 and 21 produced by the carrier parent fuses with a normal gamete from the other parent during fertilization, an offspring is produced that contains two copies of chromosomes 14 and 21. This offspring is phenotypically normal.
- **Balanced carrier.** When a gamete containing the Robertsonian translocation between chromosomes 14 and 21 fuses with a normal gamete from the other parent during fertilization, a carrier offspring that contains one copy of chromosome 14, one copy of chromosome 21, and a Robertsonian translocation chromosome is produced. The total chromosome number in this person is 45 due to the loss of the short arms of chromosomes 14 and 21. This carrier is phenotypically normal but can produce familial Down syndrome offspring in the next generation.
- **Familial Down syndrome.** A gamete that contains the Robertsonian translocation between chromosomes 14 and 21 and a copy of chromosome 21 can fuse with a normal gamete from the other parent during fertilization. The offspring contains two copies of chromosome 21, one copy of chromosome 14, and the Robertsonian translocation chromosome. Since there are three copies of the long arm of chromosome 21 (trisomy-21), Down syndrome results. A familial Down syndrome patient has 46 total chromosomes. Conversely, conventional Down syndrome patients (see below) have 47 total chromosomes.
- **Unbalanced, lethal (three types of gametes).** Fifty percent of the gametes produced by a balanced carrier individual will not produce viable offspring. The resulting offspring produced from these gametes are either missing chromosome 14 (monosomy 14), missing chromosome 21 (monosomy 21), or have three copies of the long arm of chromosome 14 (trisomy 14).




B.)
Producing a Robertsonian Translocation Chromosome
+
21
14
Robertsonian Translocation
14 \ 21
fusion (long arms)
14 \ 21
fusion (short arms)
lost during cell division


C.)
Familial Down Syndrome Pedigree
= Female
= Affected
= Male
= Unaffected

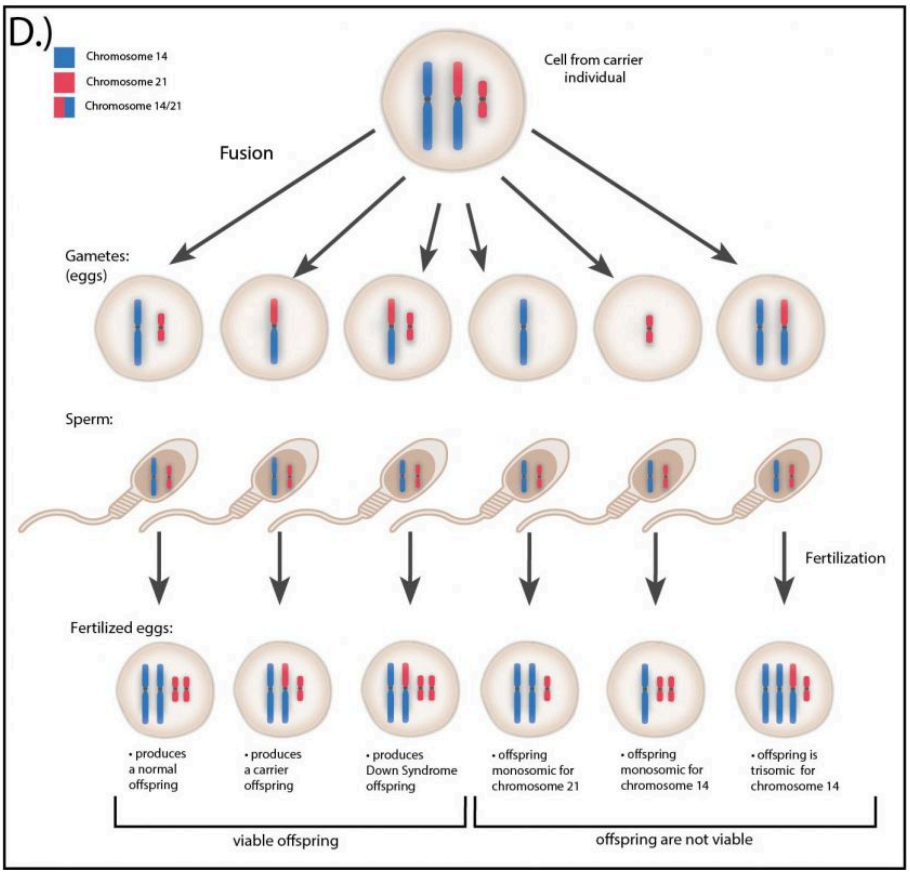


Figure 3.11 Robertsonian Translocation *- A) Chromosomes of a carrier and a familial Down Syndrome patient B) Mechanism of Robertsonian Translocation C) Familial Down Syndrome Pedigree D) Offspring Produced by a Familial Down Syndrome Carrier --- Images created by SL*

Key Questions

- What is a Robertsonian translocation?
- Which chromosomes are involved in familial Down syndrome?
- How many total chromosomes are found per cell in a balanced carrier individual?
- How many total chromosomes are found per cell in a familial Down syndrome patient?
- What repetitive DNA sequences are located on the *p* arms of the five acrocentric human chromosomes (see Part 1). Why would the loss of a few copies of these genes not be lethal to the cell?

B. Changes in Chromosome Number

Euploidy and Aneuploidy

Sometimes the total number of chromosomes within an individual can vary. These variations in chromosome number are placed into two categories (see **figure 3.12**):

- **Variations in euploidy.** Variations in euploidy involve changes in the total number of **chromosome sets** in a cell or individual. Recall that a chromosome set is all of the chromosomes inherited from one parent (i.e. humans contain two chromosome sets; each set contains 23 individual chromosomes). Variations in euploidy involves organisms or cells that are:
    - **Haploid** (n; n = the number of chromosomes within a set). Haploid organisms or cells have one chromosome set (i.e., one copy of every chromosome). Haploid is the normal state for gamete cells and some eukaryotic organisms.
    - **Diploid** (2n). Diploid organisms or cells have two chromosome sets. One chromosome set is inherited from the paternal parent; one chromosome set is inherited from the maternal parent. Diploid is the normal state for many eukaryotic organisms and for most of the cells in the human body.
    - **Triploid** (3n). Triploid organisms or cells have three chromosome sets. Triploid is an abnormal state for most organisms; however, there are examples of triploid plants. For example, seedless watermelon and banana plants are triploid.
    - **Polyploid**. Polyploid organisms or cells have more than two chromosome sets.
- **Aneuploidy.** Aneuploidy involves changes to the number of chromosomes within a chromosome set. For example, aneuploidy occurs when an individual is missing or has an additional chromosome within a set. Interestingly, aneuploidy of the sex chromosomes is usually better tolerated than aneuploidy of the autosomes (non-sex chromosomes) in many organisms. Aneuploid conditions include:
    - **Trisomy** (2n+1). A trisomic organism or cell has one more chromosome than normal. Trisomy is usually better tolerated than monosomy. The conventional form of Down syndrome is an example trisomic human condition (see below).
    - **Monosomy** (2n-1). A monosomic organism or cell is missing a single chromosome. Turner syndrome is an example monosomic human condition (see below).
    - **Disomy** (2n). Disomy is the normal state in which an organism or cell has two copies of a particular chromosome.
    - **Nullisomy** (2n-2). An organism or cell that is nullisomic is missing both copies of the chromosomes that constitute a homologous chromosome pair.

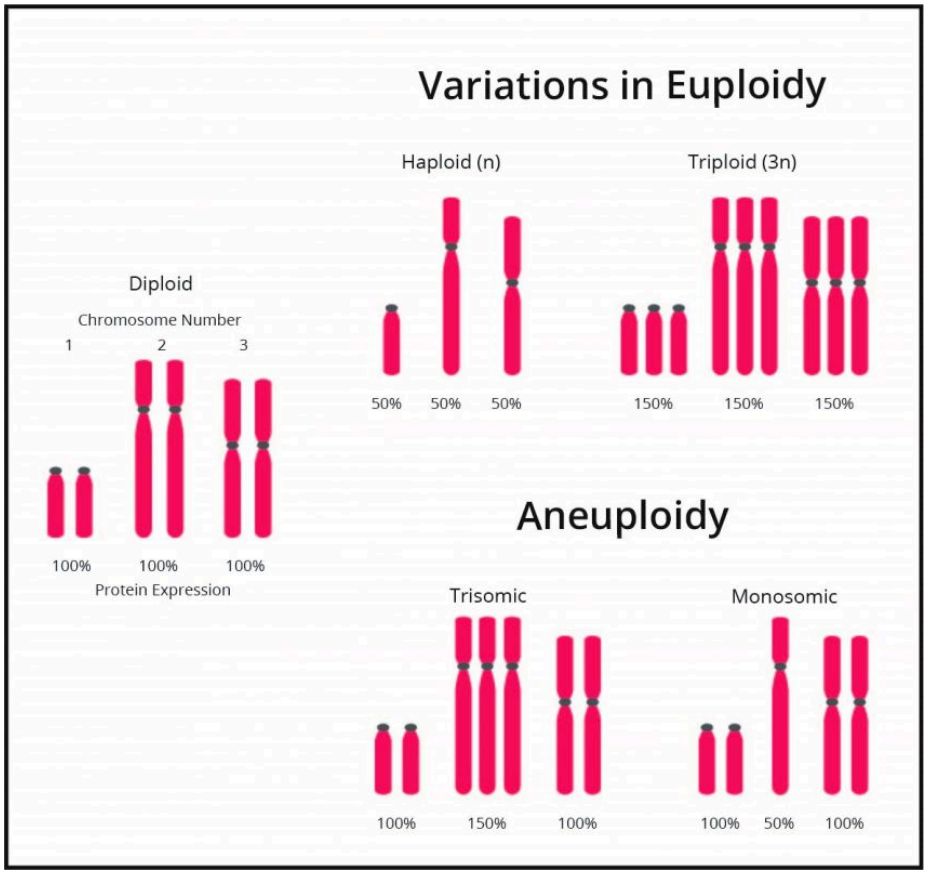


Figure 3.12 Changes in Chromosome Number (Overview). *Suppose an organism contains six total chromosomes organized into three homologous chromosome pairs (i.e., two sets of three chromosomes). Variations in euploidy changes the number of sets. Aneuploidy changes the number of chromosomes within a set. The percentages below each chromosome pair indicates the level of transcription for the structural genes found on particular chromosomes. Variations in euploidy and aneuploidy are often detrimental as each alters transcription levels of structural genes within the cell.--- Image created by SL*

Key Questions

- What is meant by variations in euploidy?
- What does aneuploidy mean?
- How many chromosomes are found in a trisomic human cell? (Note: human somatic cells contain 46 chromosomes.)
- How many chromosomes are found in a monosomic human cell?
- How many chromosomes are found in a triploid human cell?

Aneuploidy and Gene Expression

A phenotypically normal individual has two copies of most structural genes. When the number of structural genes is out of balance, the phenotype is often affected in a negative way. For example, in trisomic individuals with three copies of a particular chromosome, the amount of protein products produced from the three chromosomes are 150% of the normal expression level. These individuals produce too much protein product, so the phenotype is negatively affected (see **figure 3.12**). In the case of monosomy, the single copy of the chromosome can only produce protein products at 50%

of the normal level. Since these individuals produce lower amounts of protein product, the phenotype is negatively affected. Monosomic cells or individuals also have a second problem. In monosomic cells, recessive lethal alleles cannot be “masked” by the normal, dominant allele from the homologous chromosome.

In a trisomic or monosomic animal, the overproduction or underproduction of protein product decreases viability. However, it is worth noting that there are many natural varieties of plants that tolerate higher variations in euploidy. For example, wheat plants are hexaploid, some potato varieties are tetraploid, and wild strawberry plants can be octaploid.

Key Questions

- Why does trisomy have negative phenotypic consequences?
- What are the two reasons that monosomy produces negative phenotypic effects?

Aneuploidy in Humans

About 30% of all fertilization events in humans produces an embryo that is aneuploid. In most cases, the embryo does not survive to birth. That being said, there are some aneuploid human conditions that result in live births. These aneuploid conditions in humans include:

- **Trisomy 13 (*47,13+*)**. Trisomy 13 produces **Patau syndrome**, which occurs in 1 in 19,000 births. Patau syndrome causes mental and motor deficiencies, cleft palate, polydactyly (extra digits), microcephaly (a small head), defects in several organs, and an early death (usually by 3 months of age).
- **Trisomy 18 (*47, 18+*)**. Trisomy 18 produces **Edwards syndrome**, which occurs in 1 in 8,000 births. Edwards syndrome causes skeletal abnormalities such as elongated skulls, deformed hips, and facial deformities. Most infants with this syndrome are females, and death usually occurs within 4 months after birth.
- **Trisomy 21 (*47, 21+*)**. Trisomy 21 causes the conventional form of **Down syndrome**, which occurs in 1 in 800 births. Down syndrome results in mental deficiencies, almond-shaped eyes, flattened faces, round heads, and a short stature. As described earlier, there is another type of Down syndrome called **familial (inherited) Down syndrome**. Familial Down syndrome is caused by a Robertsonian translocation (described above).
- **XXY (*47, XXY*)**. An individual with XXY sex chromosomes has **Klinefelter syndrome**, which occurs in 1 in 1000 male offspring. Klinefelter syndrome results in infertility (no sperm production) and the formation of breast tissue. Klinefelter syndrome patients produce a single Barr body per cell.
- **XYY (*47, XYY*).** An individual with XYY sex chromosomes has **Jacobs syndrome**, which occurs in 1 in 1000 male offspring. Jacobs syndrome produces mild phenotypic effects.
- **XXX (*47, XXX*).** An individual with XXX sex chromosomes has **Triplo-X syndrome**, which occurs in 1 in 1500 female offspring. Triplo-X syndrome produces mild phenotypic effects. Triplo-X syndrome patients have two Barr bodies in each somatic cell.
- **XO (*45, X*)**. An individual with a single X chromosome has **Turner syndrome**, which occurs in 1 in 5000 female offspring. Turner syndrome females are short, have a webbed neck, and have reduced fertility. Turner syndrome patients do not produce Barr bodies.

The aneuploid conditions described above are the result of chromosome **nondisjunction**, a defect in chromosome segregation during meiosis (see below) in one of the two parents.

Key Questions

- The aneuploidies described above are essentially the only ones that result in live human births. Why do you think these aneuploidies are viable while aneuploidies of other chromosomes are not?

Endopolyploidy

Some tissues in an animal can contain cells that have more than two chromosome sets, whereas the somatic cells in the rest of the body are diploid. This situation is called **endopolyploidy**. For example, human liver cells can vary in euploidy (some cells are tetraploid or octaploid). Endopolyploidy allows liver cells to increase the production of protein products to meet the unique metabolic demands placed on liver cells. Moreover, the fruit fly *Drosophila* is a diploid organism containing four pairs of homologous chromosomes. However, the salivary glands of the fruit fly contain higher variations in euploidy. Endopolyploidy occurs when the homologous chromosomes pair with each other and then undergo several rounds of DNA replication without cell division. In fruit flies, DNA replication in this way produces **polytene chromosomes**, a thick bundle of identical DNA molecules, lying parallel to each other.

Key Questions

- What is endopolyploidy?
- Provide two examples of endopolyploidy.

Meiotic Nondisjunction

Nondisjunction occurs when chromosomes do not separate properly in either meiosis or mitosis. **Meiotic nondisjunction** produces aneuploid gamete cells that either have an extra chromosome or lack a chromosome (see **figure 3.13**). After fertilization, the resulting offspring will be either trisomic or monosomic. Meiotic nondisjunction can occur during anaphase of either meiosis I or meiosis II.

- **Meiosis I nondisjunction**. During meiosis I nondisjunction, the chromosomes within a homologous pair fail to separate from each other and instead segregate into the same daughter cell. All gamete cells produced from meiosis I nondisjunction are aneuploid. These aneuploid gametes will produce 50% trisomic offspring and 50% monosomic offspring.
- **Meiosis II nondisjunction**. In meiosis II nondisjunction, meiosis I proceeds normally; however, nondisjunction occurs in one of the two daughter cells. During meiosis II nondisjunction, the sister chromatids that constitute one duplicated chromosome fail to separate from each other. Two of the resulting haploid gametes are normal, while two of the gametes are aneuploid. Collectively, the four possible gametes will produce 50% normal offspring, 25% trisomic offspring, and 25% monosomic offspring.

The aneuploid human conditions described above (e.g., conventional Down syndrome, Klinefelter syndrome, Turner syndrome, etc.) are thought to be produced from either meiosis I or meiosis II nondisjunction.

On rare occasions, all chromosomes in a cell fail to separate properly during either meiosis I or II. This event is called **complete nondisjunction** and produces diploid gametes. If a diploid gamete fuses with a normal gamete, a triploid offspring is produced.

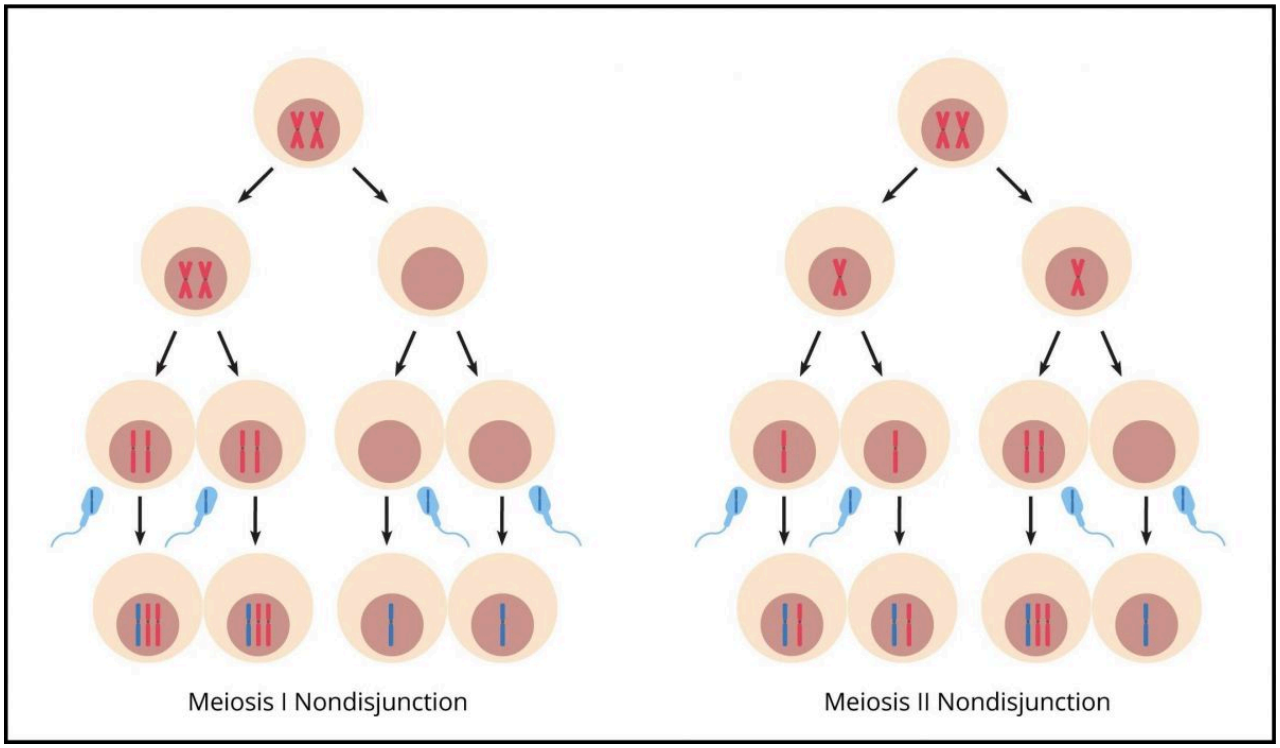


Figure 3.13 ***Meiotic Nondisjunction.*** *A homologous chromosome pair in the maternal parent experiences nondisjunction in meiosis I (left), while the sister chromatids fail to separate in the maternal parent during meiosis II nondisjunction (right). The paternal parent contributes a copy of the same chromosome (in blue). Meiosis I nondisjunction produces 100% aneuploid gametes and offspring. Meiosis II nondisjunction produces 50% aneuploid gametes and offspring.--- Image created by SL*

Key Questions

- What happens during meiosis I nondisjunction?
- Describe the four gametes produced by meiosis I nondisjunction.
- What happens during meiosis II nondisjunction?
- Describe the four gametes **produced** by meiosis II nondisjunction.

Mitotic Nondisjunction

Nondisjunction can also occur during mitosis (**mitotic nondisjunction**). During mitotic nondisjunction, the sister chromatids that constitute one duplicated chromosome fail to separate from each other during anaphase. Mitotic nondisjunction produces one daughter cell with three copies of a particular chromosome (trisomic), while the other daughter cell has one copy of the chromosome (monosomic) (see **figure 3.14; left panel**). All future daughter cells produced from the trisomic cell will also be trisomic, whereas all daughter cells produced from the monosomic cell will be monosomic. As a result, mitotic nondisjunction produces a **mosaic** phenotype with some trisomic tissues in the body, while other tissues are monosomic.

Sometimes chromosomes lose attachment to the mitotic spindle during anaphase (see **figure 3.14; right panel**). A detached chromosome is not retained in the nucleus, and is degraded by nucleases in the cytoplasm. This event produces one daughter cell with two copies of a particular chromosome (disomic), while the other daughter cell has

one copy of the chromosome (monosomic). All future daughter cells produced from the monosomic cell will be monosomic. This failure of a chromosome to attach to the mitotic spindle also results in a mosaic phenotype.

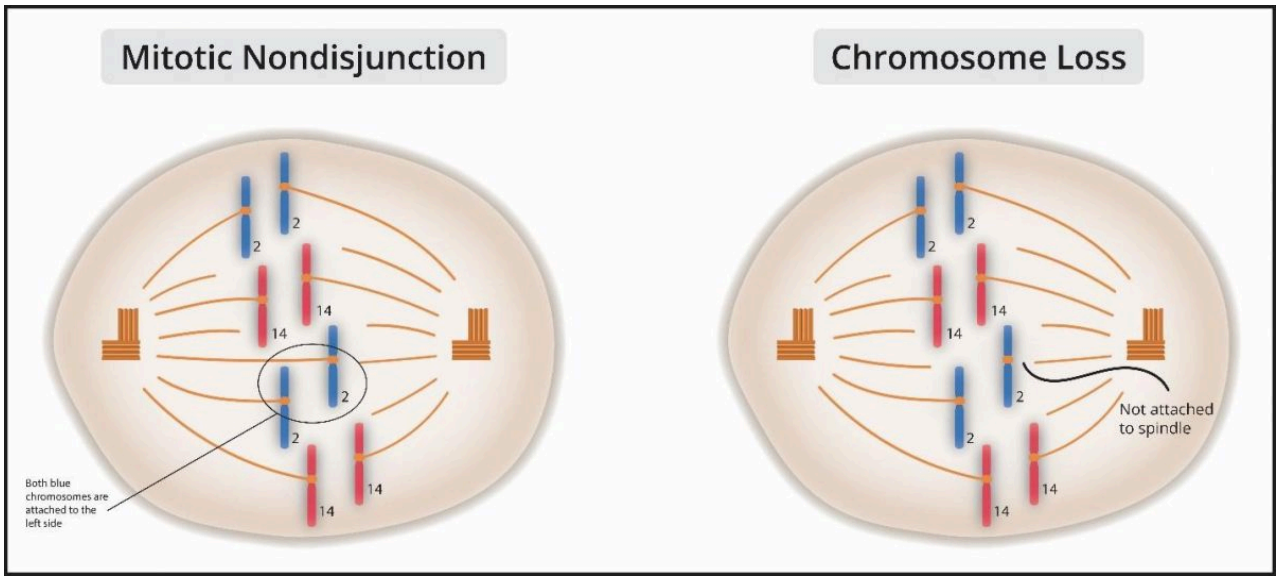


Figure 3.14 ***Mitotic Nondisjunction.*** *This figure highlights the fates of the sister chromatids derived from the two copies of chromosomes 2 and 14. --- Image created by SL*

Key Questions

- Describe the two processes that cause mitotic nondisjunction.

Review Questions

Fill in the Blanks:

1. A _____ is a change in chromosome structure that produces an acentric fragment and a dicentric chromosome during meiosis.
2. The disease _____ is caused by an inversion within the X chromosome.
3. A(n) _____ and a(n) _____ are two changes in chromosome structure that alter the amount of genetic information found on a chromosome.
4. _____ % of the gametes produced by a meiosis II nondisjunction event will result in trisomic offspring.
5. A terminal deletion in chromosome _____ causes _____, a disease that results in a malformation of the glottis and larynx.
6. Nondisjunction in _____ can produce trisomic and monosomic somatic cells.
7. The term _____ can describe a cell with *2n-2* chromosomes.
8. The globin gene family arose due to a _____ (name the chromosome mutation type).
9. A _____ translocation involves only the acrocentric chromosomes.
10. Reciprocal translocations of the _____ segregation type results in two normal gametes and two translocation gametes. All offspring produced from this event are normal.