

Chromosomal Abnormalities

Chromosomal abnormalities are not generally due to mutations in single genes, but are the result of structural alterations that can be seen under the light microscope. These alterations include the rearrangement of genetic material in a chromosome, or numerical abnormalities due to the gain or loss of a chromosome.

I. Standard Cytogenetic Nomenclature

The karyotype is the chromosomal constitution of the individual. It can be visualized by staining metaphase chromosomes.

A. The chromosomal constitution of an individual is described by a **karyotype**. The karyotype includes the total number of chromosomes, the sex chromosome constitution and any abnormalities in number or morphology. A normal human karyotype is 46, XX for human females and 46, XY for human males. Karyotypes are performed when cells are entering mitosis, since the DNA is condensed and can be easily observed when stained.

B. The chromosome can be divided into three regions, the **p**, or **short arm**, the **q**, or **long arm** and the **centromere** (the primary constriction found in each chromosome). During meiosis or mitosis, the centromere is the point at which sister chromatids are held together. Each arm is further subdivided into regions by **landmarks**. Landmarks are consistent features that are useful to identify a given chromosome, such as the ends of the arms, the major bands seen in a stained chromosomal preparation, and the centromere. The area between landmarks is called a region. Regions are numbered consecutively from the centromere and bands, both light and dark, are numbered consecutively within a region.

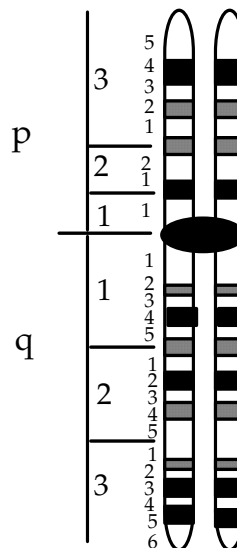


Figure 2-1. Chromosome structure

If Figure 2-1 represents the seventeenth chromosome, then 17q25 refers to the seventeenth chromosome, the long arm, the second region, band 5. Note that a period or similar division is **not** used between the region and the band.

2. Table 2-1 summarizes common symbols used in karyotype nomenclature.

1-22	Autosome number
X, Y	The sex chromosomes
(+) or (-)	When placed before an autosomal number, indicates that chromosome is extra or missing
cen	Centromere
dic	Dicentric
inv	Inversion
p	Short arm of the chromosome
q	Long arm of the chromosome
t	Translocation
del	Deletion
ins	Insertion
dup	Duplication
ter	Terminal or end (pter= end of the short arm; qter = end of the long arm)
:	Break (no reunion, as in a terminal deletion)
::	Break and join
→	From-to
mos	Mosaic

Table 2-1. Symbols Used in Designating Karyotypes

II. Structural Aberrations

There are three categories of structural aberrations caused by breakage of the DNA: deletions, inversions and translocations.

Structural aberrations arise from the incorrect repair of breaks in a chromosome caused by viruses, chemicals, radiation or other events. Although all cells experience chromosome breakage, in terms of human genetics, only aberrations arising within germ cells are important. Enzymes exist that can repair the breaks, but when multiple breaks occur simultaneously, mistakes can occur. The structural aberrations which can arise are grouped into three categories: deletions, inversions or translocations.

A. Deletions

1. A deletion occurs when a chromosome loses a segment due to breakage. This results in partial monosomy for the affected region. If the deletion covers a large area, the affected individual will not be viable. Deletions are classed into two major categories: **terminal deletions** in which the deletion removes one of the ends of a chromosome or **interstitial deletions** in which a central portion of the chromosome is lost (Figure 2-2).

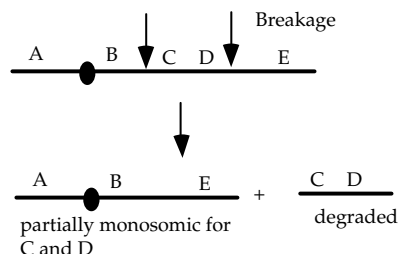


Figure 2-2 An Interstitial Deletion

2. A deletion is indicated by *del* with the chromosome number in parenthesis followed by what is left of the chromosome; e.g., 46, XY, del (15) (pter → q22:) would be a male with 46 chromosomes, of which one of the 15 chromosomes has a deletion from within q22 to the qter.

3. Diseases

Important conditions caused by deletions include: Cri-du-chat syndrome, DiGeorge syndrome, Wilm's tumor, Angelman syndrome and Prader-Willi syndrome

There are two types of inversions: paracentric inversions and pericentric inversions. If a single crossover occurs within the inversion loop, unbalanced gametes result.

B. Inversions are rearrangements of the gene order within a single chromosome due to the incorrect repair of two breaks. The amount of chromosomal material remains the same, but recombination within the inverted region leads to unbalanced gametes. Inversions are classed relative to whether or not the centromere is involved. An inversion in which the centromere is located outside of the inverted region is called a **paracentric inversion**. An inversion in which the centromere is located within the inverted region is called a **pericentric inversion**.

1. Paracentric Inversions

a. In a paracentric inversion, both breaks are on the same side of the centromere, so the overall shape of the chromosome is unchanged. If an individual inherits one normal chromosome and one inverted homologous chromosome, he or she will be phenotypically normal. Problems only arise when the individual produces germ cells.

If a single crossover occurs within a paracentric inversion, a dicentric bridge and an acentric fragment result. This terminates meiosis.

b. During meiosis, recombination or crossing over always occurs between homologues. In an individual heterozygous for a paracentric inversion, if the crossovers occur outside the loop, there will not be any problems. However, a single crossover occurring within the loop leads to the formation of an acentric fragment and an anaphase bridge formed by a dicentric chromatid. Formation of this anaphase bridge leads to the failure of meiosis. The cell does not progress any further in the production of germ cells. This leads to reduced fertility. The severity of the effect is a function of the size of the inversion. The larger the inversion, the greater the risk that a recombination event will occur within the loop.

Paracentric Inversion:

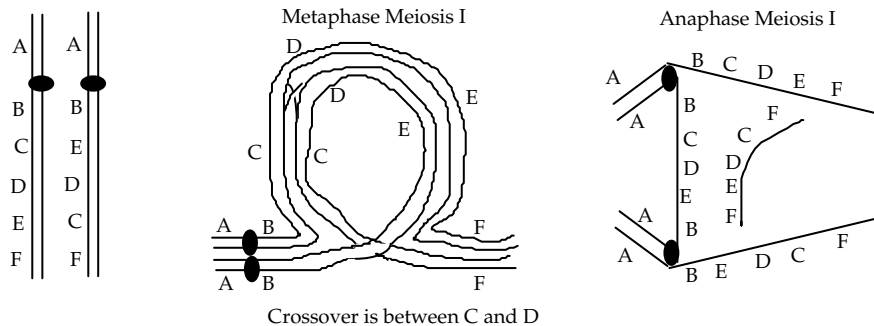


Figure 2-3 Paracentric inversion

2. Pericentric Inversions

a. Pericentric inversions have breakpoints on either side of the centromere. This changes the shape of the chromosome and the position of the centromere. Although heterozygotes for this inversion will usually be phenotypically normal, problems arise during germ cell production.

b. If a crossover event occurs within the inverted segment, the chromatids undergoing the crossover will suffer from the duplication of material from one terminus and the deletion of material from the other. As with paracentric inversions, the larger the inversion, the higher the probability of the crossover occurring within the affected region.

c. Note that in the preceding examples, the crossover event occurs between two strands. It is possible, especially if the inversion is very large, that crossover events involving three or even four strands will occur.

If a single crossover occurs within a pericentric inversion, each chromatid will suffer from the duplication of one terminus and the deletion of another.

Pericentric Inversion:

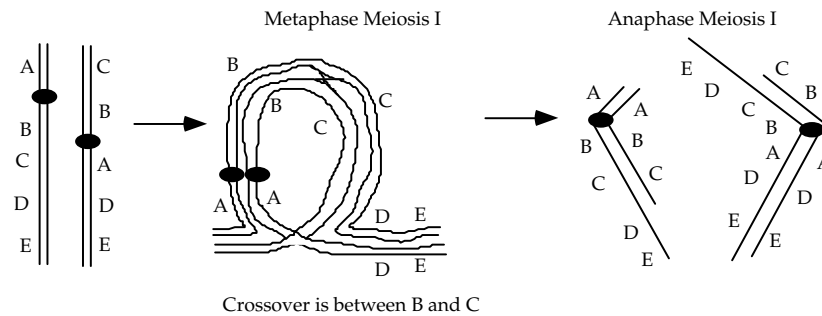


Figure 2-4. Pericentric inversion.

d. An inversion is indicated by the chromosome number in parenthesis followed by the two break points in parenthesis. 46, XX, inv (5) (p12q23) would be a female with a pericentric inversion of chromosome 5 with breakpoints at bands 5p12 and 5q23. The more detailed representation of the karyotype would be 46, XX, inv (5) (pter → p12 :: q23 → p12 :: q23 → qter).

e. The most common inversion in humans is a small pericentric inversion of the ninth chromosome. Although present in up to 1% of individual's karyotypes, it has no known deleterious effects in translocation heterozygotes, and since it is so small, it does not cause a significant impact on fertility.

C. Translocations

There are two types of translocations:

Translocations involve the exchange of chromosomal material between two nonhomologous chromosomes. Two types of translocations exist,

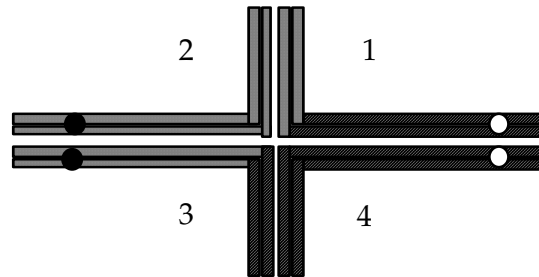
reciprocal translocations and Robertsonian translocations.

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1. Reciprocal Translocations

a. Reciprocal translocations result when two non-homologous chromosomes exchange pieces. The **breakpoint** of a translocation is the region at which the two different chromosomes are joined. Phenotypically, a person who is heterozygous for a reciprocal translocation will appear normal because all the information is present; it is just in a novel order. Problems arise when gametic cells undergo meiosis, because now four chromosomes share homology. Using the light microscope, a configuration called a quadrivalent can be seen (Figure 2-5).

I



Pairing of a Reciprocal Translocation in Meiosis I

Figure 2-5. A quadrivalent.

b. Unlike inversions, crossing over is not as much of an issue with translocations because recombination either produces nonviable gametes or merely switches alleles between homologous regions.

c. During meiosis I, homologous chromosomes separate. However, the centromere is the structure that the cell uses to define a chromosome, so really homologous centromeres are separating. Under normal circumstances if homologous centromeres separate, homologous chromosomes separate. In the case of reciprocal translocation nonhomologous material attached to a centromere confuses the issue. The major problem is how these chromosomes will segregate from each other during meiosis I. There are three possible patterns for segregation named **alternate segregation**, **adjacent I segregation** and **adjacent II segregation**.

4. In alternate segregation, homologous centromeres separate such that one cell contains two normal nonhomologous chromosomes, and the other contains both chromosomes involved in the reciprocal translocation.

5. In adjacent I segregation, homologous centromeres separate such that each cell contains a normal chromosome and a chromosome involved in the translocation.

6. In adjacent II segregation, the breakpoint of the translocation is so close to the centromere that the cell cannot identify the centromere. To our eyes, it seem that two homologous centromeres are placed in the same cell. Figure 2-6 summarizes these segregation patterns.

7. The amount of alternate segregation is always equal to the amount of adjacent I segregation, since to the cell they both involve separating

If a reciprocal translocation undergoes adjacent I or adjacent II segregation, unbalanced gametes result.

homologous centromeres. The amount of adjacent II segregation depends upon how far the breakpoint is located from the centromere. If the breakpoint is very far from the centromere, the cell does not become confused and only alternate and adjacent I segregation will be observed. If the breakpoint of a translocation is located very near the centromere, the cell becomes confused as to which centromere it is sending to which pole, and a significant amount of adjacent II segregation will occur. If the breakpoint involves the centromere, all forms of segregation are equally likely.

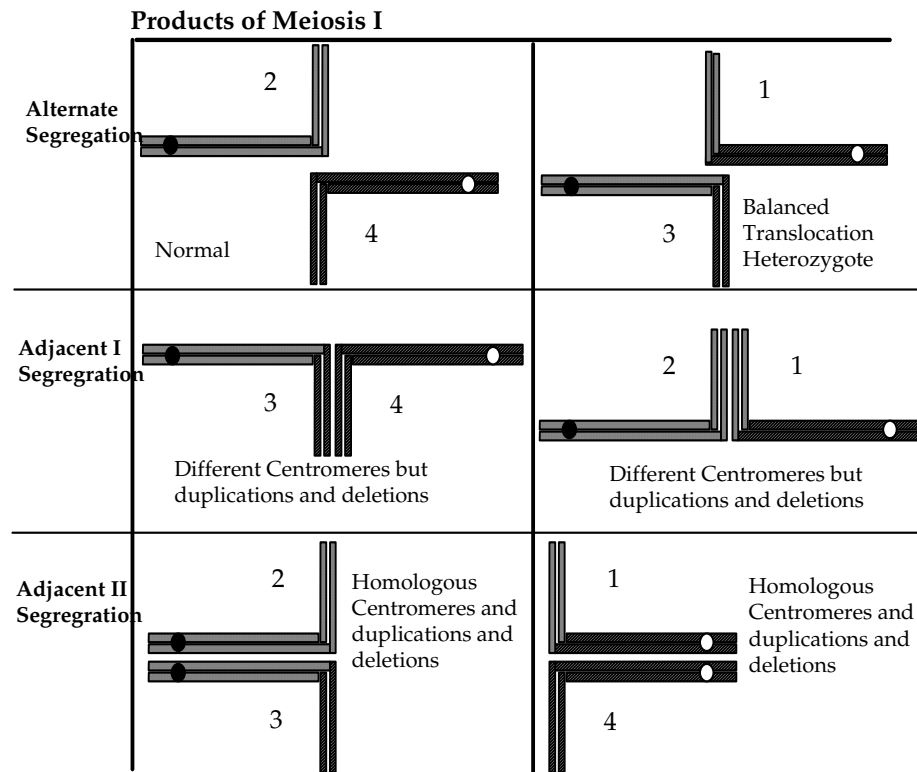


Figure 2-6. Segregation patterns in reciprocal translocations.

8. Diseases:

In 95% of chronic myelogenous leukemia cases, the Philadelphia chromosome, a reciprocal translocation between the long arms of chromosome 22 and chromosome 9, is present.

Robertsonian translocations are caused by the fusion of the long arms of two acrocentric chromosomes. It is most common between chromosome 14 and chromosome 21, or chromosome 21 and chromosome 22.

2. Robertsonian Translocations

a. Robertsonian translocations involve any two acrocentric chromosomes, which experience breaks near the centromeres and rejoin in a way that results in the fusion at the centromeres of the q arms and loss of the p arm. There are three ways that the chromosome involved can segregate during meiosis I, and since both breaks occur at the centromere, all three types of segregation are equally frequent. Individuals who carry the Robertsonian translocations appear phenotypically normal, but experience a large number of spontaneous abortions due to the production of monosomic and trisomic embryos, which are usually nonviable.

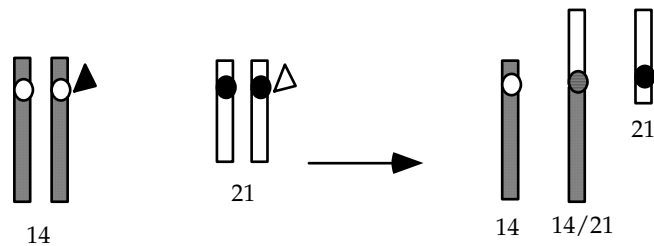


Figure 2-7. Formation of the Robertsonian translocation.

4% of the cases of Down syndrome are due to Robertsonian translocations.

b. Down syndrome, or trisomy 21 is usually the result of a nondisjunction event during meiosis. However approximately 4% of Down individuals actually are affected because of a translocation between chromosome 14 and 21 or between chromosome 22 and 21. The theoretical risk of a translocation heterozygote producing a Down offspring is 1/3, however, since 80% of trisomy 21 fetuses are spontaneously aborted, for every Down child born, 5 normal and 5 balanced translocation heterozygotes are seen. Figure 2-8 shows the consequences of the segregation of a Robertsonian translocation.

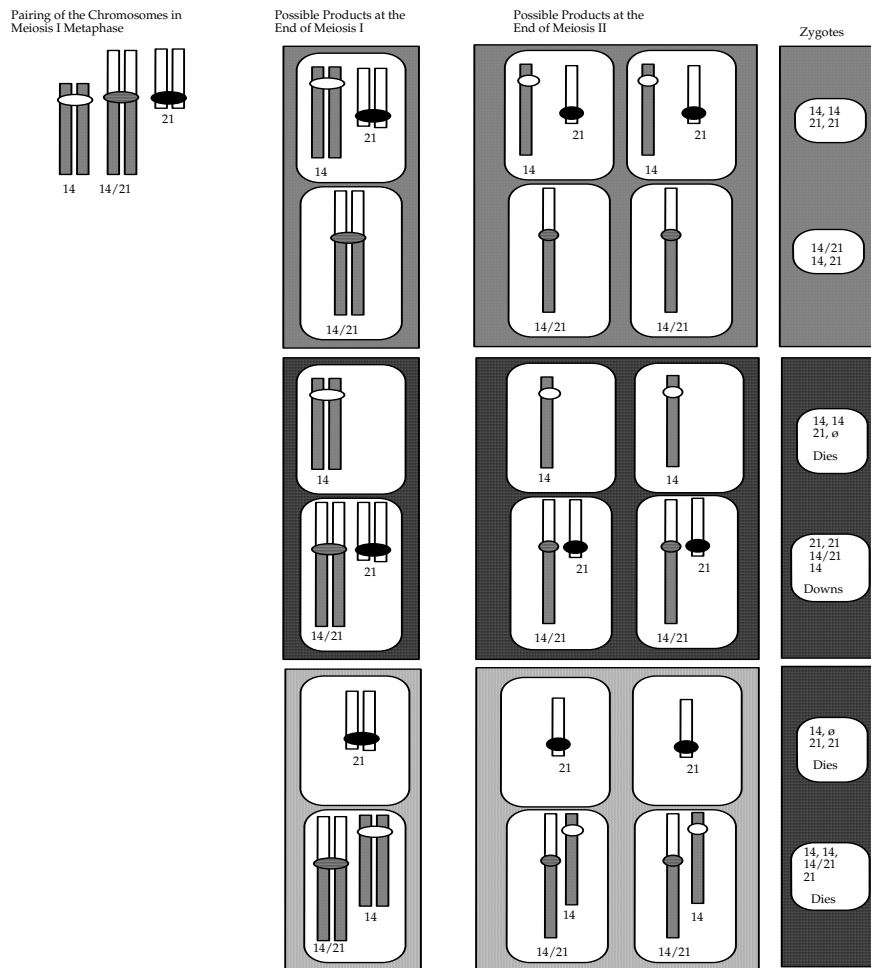


Figure 2-8. Consequences of a Robertsonian translocation.

3. Nomenclature for translocations:

a. When writing the karyotype of a reciprocal translocation, the two chromosome involved are listed in parentheses after t, followed by the breakpoints also in parentheses, e.g., 46, XY, t (7; 9) (q31; q22) would be a male with a balanced translocation involving exchange of the segments distal to 7q31 and 9q22. The more detailed nomenclature would be 46, XY, t (7; 9) (7pter → 7q31 :: 9q22 → 9qter; 9pter → 9q22 :: 7q31 → 7qter).

b. A Robertsonian translocation involves the loss of the short arms of two chromosomes and centromere of one. This results in a reduction in the total number of chromosomes. 45, XX, t(14q; 21q) would be a female with a Robertsonian translocation, with the derivative chromosome having the long arms of 14 and 21. The origin of the centromere is not indicated. A more detailed symbolism would be 45, XX, t(14; 21) (14qter → cen → 21qter). Alternatively, **rob** can be used in place of t to be more specific.

III. A Brief Review of Oogenesis and Spermatogenesis: In males and females, the products of each meiotic division have specific names. Figures 2-9 and 2-10 summarize the key stages of spermatogenesis (males) and oogenesis (females).

A. In females, only one true egg, which contains most of the cytosol, is produced. The unequal division of cytoplasmic material is important since the zygote receives all of the initial cellular organelles, including the mitochondria from the mother. Since the first polar body does not enter the second meiotic division, only three products of meiosis are shown for the female.

B. The sperm fertilizes the ovum during the second meiotic division. While meiosis in the female is being completed, the sperm head rounds up and forms the male pronucleus. A female pronucleus and a polar body are produced at the end of the second meiotic division. When the male and female pronuclei reach each other, they fuse and form a zygote, with the diploid number of chromosomes. DNA synthesis soon commences and the cell undergoes the mitotic divisions of embryogenesis.

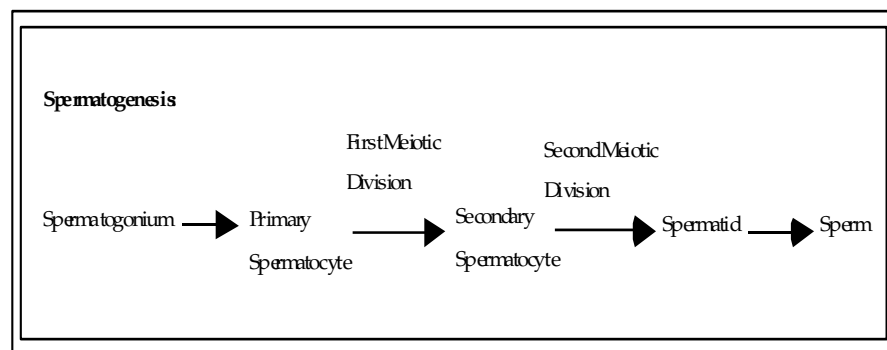


Figure 2-9. Spermatogenesis.

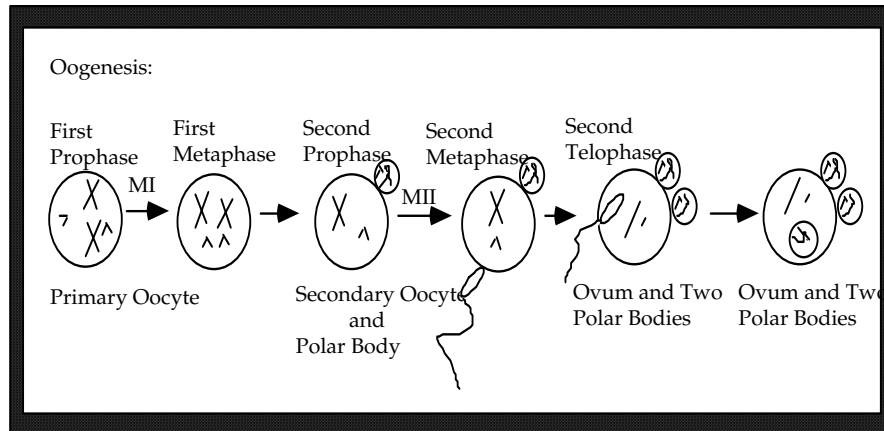


Figure 2-10. Oogenesis.

IV. Nondisjunction

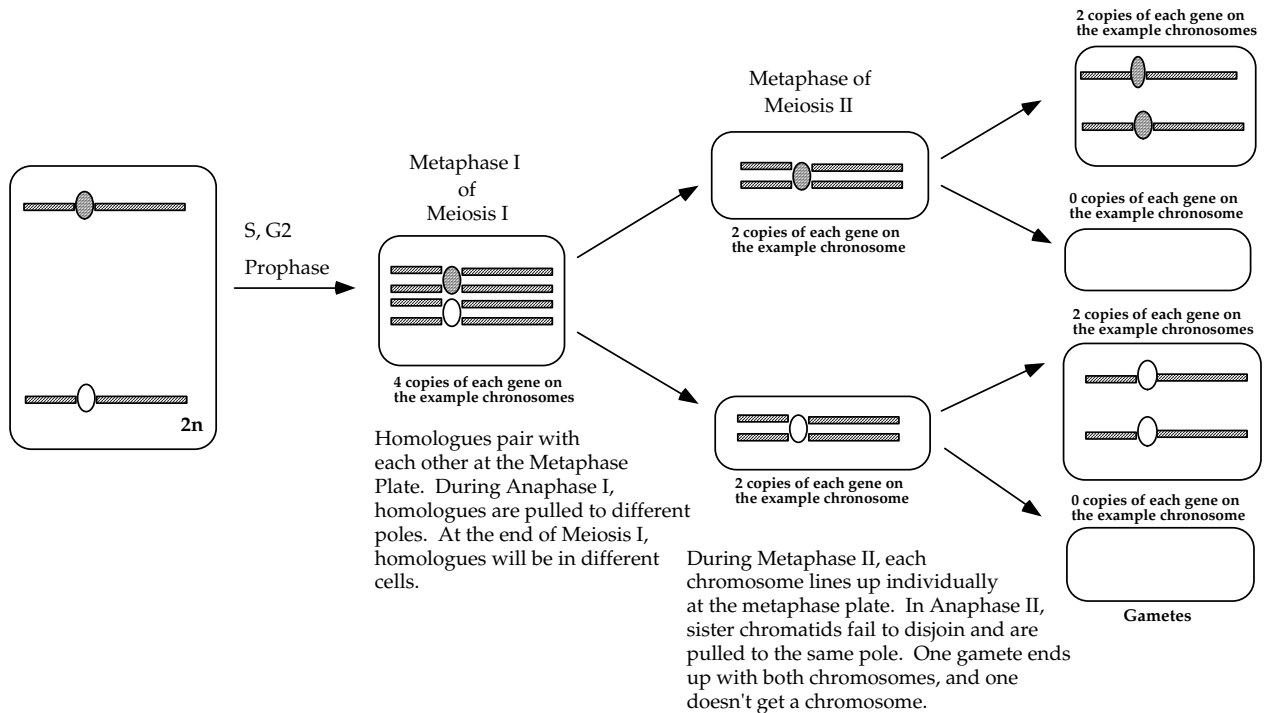
A. Definitions

1. The normal gametic constitution contains the **haploid** or **n** number of chromosomes. This refers to the fact that every normal gamete contains one copy of each chromosome, and hence one copy of every gene in the genome.
2. The normal somatic constitution of the cell is referred to as the **diploid** or $2n$ number. This refers to the fact that every somatic cell contains two copies of each chromosome and hence two copies of every gene in the human genome.
3. **Nondisjunction** is the failure of chromosomes to disjoin from each other during cell division. It can happen during either the division steps of meiosis or during mitosis.

Nondisjunction is the failure of chromosomes to disjoin during meiosis.

B. Timing of nondisjunction

1. The most common time for nondisjunction to occur is during meiosis I. The mechanisms of failure are not well understood, however, there is a strong correlation between increasing nondisjunction with increasing maternal age.
2. If nondisjunction occurs during mitosis in the developing embryo, some of the cells will have the normal number of chromosomes, some will lack a chromosome, and some will have an extra chromosome. The cells which lost a copy of the chromosome usually die because monosomy is not well tolerated. The cells that gained a chromosome may live, producing a situation in which individual cells in the person's body will have two different karyotypes. This condition is called **mosaicism**, and the person is said to be a mosaic for that chromosome.
3. Nondisjunction during meiosis I is characterized by the failure of homologous chromosomes to separate. Figure 2-11 illustrates a failure



during meiosis I.
Figure 2-11. Nondisjunction during meiosis I.

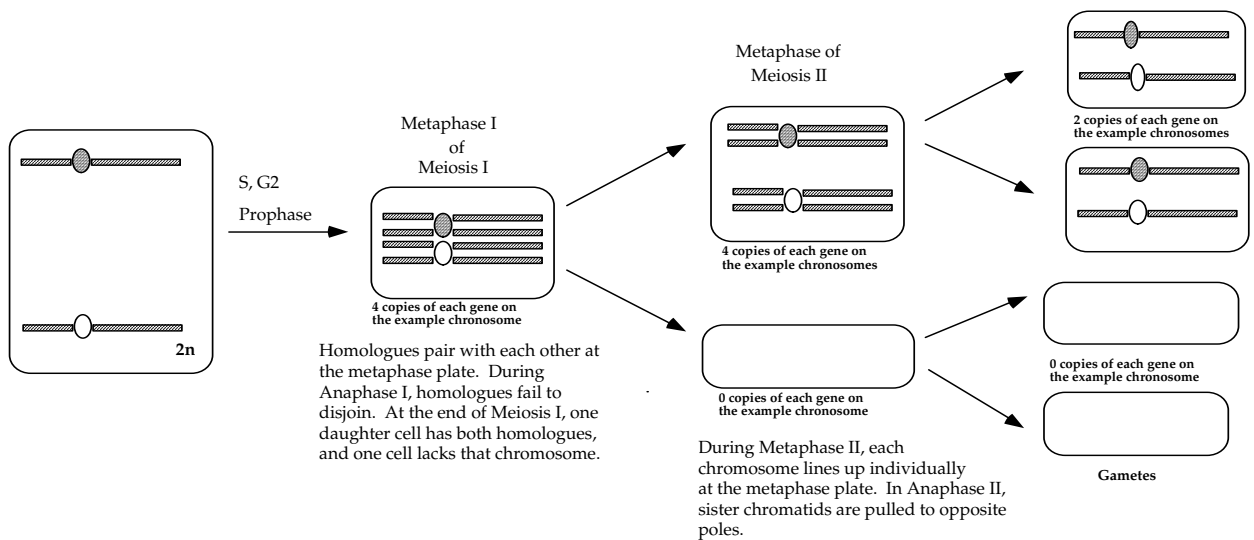


Figure 2-12. Nondisjunction during meiosis II.

4. Nondisjunction during meiosis II is characterized by the failure of sister chromatids to separate. Figure 2-12 illustrates failures during meiosis II.

5. If certain conditions are met, it can be reliably determined in which meiotic division and in which parent the failure occurred. For an unambiguous determination, there must be a way to determine which

Potential chromosomal abnormalities in a fetus can be identified by two techniques: amniocentesis and chorionic villus sampling (CVS).

Amniocentesis is usually performed around the 16 week of gestation. A small amount of amniotic fluid is removed and the cells are analyzed by standard cytogenetic techniques, fluorescence in situ hybridization (FISH), biochemical and DNA analysis. The risk of complications due to amniocentesis is approximately 0.5%.

Chorionic villus sampling has diagnostic similar accuracy to amniocentesis. However, it can be carried out at 9 to 12 weeks of gestation. This allows the results to be available much earlier, however, the risk of inducing a spontaneous abortion is approximately 3%.

chromosomes came from which parent and to distinguish between a parent's homologues. This can be accomplished if a restriction fragment length polymorphism (RFLP) or a staining polymorphism exists on the chromosome of interest very near the centromere. Centromeres exercise crossover suppression, so the RFLP or staining polymorphism will be a reliable marker for that chromosome. Assume each parent has two different forms of the polymorphism, and they do not share forms with each other. If an AB mother and a CD father produce an ABC child, then nondisjunction occurred in meiosis I of the mother. She has two different forms of the polymorphism, and since the child has both of her forms, her homologues failed to disjoin. If the child born from the cross was BCC, the failure must have occurred in meiosis II of the male. The child has two forms from the male parent and they are both of the same form, so it can be concluded that sister chromatids failed to disjoin during meiosis II.

C. Results

1. The term **polyploidy** is used to refer to the state in which there are extra sets of chromosomes in the cell (e.g., a triploid = $3n$, a tetraploid = $4n$). **Euploidy** refers to the condition in which the number of chromosomes is equal to some multiple of n . Hence, diploidy and triploidy are both euploid states.

2. Rarely, both triploid and tetraploid fetuses have been reported. Several triploid live births have also been recorded, but the infants do not survive very long.

3. **Aneuploidy** is the condition in which there is either an extra chromosome or a missing chromosome [e.g., trisomy or 47 chromosomes ($2n+1$) chromosomes, or monosomy]. Aneuploidy is the most common type of chromosomal disorder, occurring in approximately 4% of live births. The incidence of autosomal aneuploidies is directly related to increasing maternal age.

4. Polyploid and aneuploid states most commonly arise from a nondisjunction event during meiosis I or meiosis II.

5. Autosomal Trisomies

a. Although trisomy for any chromosome is possible, only three autosomal trisomies are compatible with postnatal survival, barring mosaicism. These are Down's syndrome (trisomy 21), Edwards' syndrome (trisomy 18) and Patau syndrome (Trisomy 13).

(1) **Trisomy 21** ($47, XX, +21$ or $47, XY, +21$) is the most common of the chromosomal disorders and is a major cause of mental retardation. Of the individuals affected with Trisomy 21, 95% are caused by nondisjunction during gametogenesis, 4% have a Robertsonian translocation that usually involves chromosome 14 or chromosome 22, and 1% are mosaics due to Mitotic nondisjunction during embryogenesis.

(2) The phenotype of a Down's child is recognizable at birth because of their dysmorphic features including epicanthal folds, brachycephaly, flat nasal bridge, low set ears, and short, broad hands with a single transverse

palmar crease. Mental retardation is a prominent feature with 80% having IQs between 25 and 50. Approximately 40% have congenital heart disease, most of which is due to septal defects. Down's children also have an 18-20 fold increased risk of developing acute leukemia, and in patients over 35 pathological changes in the brain are seen which are similar to those seen in Alzheimer disease.

(3) The incidence of live born Trisomy 21 is approximately 1/800. In 80% of cases, the extra chromosome is of maternal origin, and is associated with increasing maternal age. When the maternal age is greater than 45 years, the occurrence is 1 in 25 births.

b. **Trisomy 18** (47, XX, +18 or 47, XY, +18) occurs in approximately 1/8000 births. It is estimated that the rate of conception is much higher, but that 95% of these fetuses spontaneously abort. 90% of the cases are due to nondisjunction and 10 % are due to mosaicism. Individuals with Edwards' syndrome suffer from intrauterine growth retardation, mental retardation, severe failure to thrive, short sternum, small pelvis, cardiac, renal and intestinal defects, and rocker bottom feet. Most die before 1 year of age.

c. **Trisomy 13** (47, XX, +13 or 47, XY, +13) occurs in approximately 1/25,000 births. 90% of the cases are due to nondisjunction and 20 % are due to an unbalanced translocation. Individuals with Patau syndrome suffer from mental retardation, microcephaly, abnormal brain development (arhinencephaly, holoprosencephaly), cleft lip and palate, ocular colobomas, postaxial polydactyly, cardiac dextroposition and ventricular septal defect. The defects are so severe that survival past 6 months is very rare.

6. Sex Chromosome Aneuploidy:

a. In mammals, the presence of the Y chromosome determines maleness. Males are the heterogametic sex having two different types of sex chromosomes, an X chromosome and a Y chromosome, in their normal state.

b. Females are the homogametic sex since they have two copies of the X chromosome. If levels of an enzyme produced by a gene located on the X chromosome are measured in males and females, they are found to be the same. This phenomenon is explained by the **Lyon Hypothesis**. It states that during early embryogenesis in the female, a decision is made in each somatic cell to turn off most of one of the X chromosomes. In fact, if the embryo contains more than 2 X chromosomes, the extra ones will be inactivated until only one X chromosome remains active in a given cell line. This X inactivation equalizes the expression of X-linked genes between males and females. The inactive X is visible under a light microscope as a chromatin mass called a **Barr body**. Since X inactivation is a random event in mammals, if a female is heterozygous for an X-linked recessive trait, she will usually have a normal phenotype because approximately one half of her cells will express the normal allele.

Females are mosaics for genes on the X chromosome, since in each of their cells, one X chromosome is randomly inactivated while the genes on the other X chromosome are expressed.

c. Examples of sex chromosome aneuploidy:

(1) Turner **Syndrome** (45, X and variants) is due to the complete or partial monosomy of the X chromosome. It is characterized by short stature, primary amenorrhea, infertility, webbed neck, shield chest and often, coarctation of aorta. The incidence is approximately 1/6000 female births.

(2) Klinefelter **Syndrome** (47, XXY and variants) was the first human sex chromosome abnormality reported. It is characterized by hypogonadism, testicular atrophy, azoospermia, and a eunuchoid body with a lack of male secondary sexual characteristics. It occurs in approximately 1/2000 male births.

(3) XYY **Syndrome** (47, XYY and variants) is not associated with an obviously abnormal phenotype. Individuals with this syndrome may be excessively tall and have severe acne. In newborn screening programs without ascertainment bias, XYY individuals were found to have normal intelligence, but had an increased risk of behavioral problems. Fertility of these individuals is normal. XYY syndrome occurs in approximately 1/1000 live male births.