## CELL REPRODUCTION – BASIC INFORMATION

- Cells, the basic units of all living organisms, are surrounded by a plasma membrane.
- Chromosomes (cell structures that carry genes) are made of DNA and proteins, and during transcription, they also contain RNA.
- In eukaryotic cells, chromosomes are located inside a membrane-bound nucleus; in prokaryotic cells, there is no nucleus.
- Haploid eukaryotic cells contain only one copy of each chromosome, while diploid cells contain two copies.
- Prokaryotic cells divide by a process called binary fission, while eukaryotic cells divide by mitosis followed by cytokinesis.
- Eukaryotic chromosomes duplicate through a process called DNA synthesis, which occurs before mitosis in the S-phase of the cell cycle.

## CELL CYCLE

The cell cycle (CC) is the series of events that occur in a cell from the end of one mitosis to the end of the next mitosis. It works as follows: The cell doubles its DNA content and duplicates its cytoplasm, including organelles. Then, the nucleus and its contents divide (mitosis). After mitosis, the cytoplasm is divided between the daughter cells in a process called cytokinesis. Mitosis and cytokinesis together make up the M phase (mitotic phase) of the cell cycle. The remaining part of the cell cycle—the break between each round of cell division—is called **interphase**.

### *Interphase*

Interphase takes up at least 90% of the cell cycle's total time, and the cell is very active during this phase. It has three stages: $G_1$, S, and $G_2$. In the G1 phase ("gap 1"), the cell grows by making proteins, RNA, and organelles, and produces nucleotides and enzymes for DNA replication; this phase has the main control checkpoint for the cycle. In the S phase (synthesis), DNA is duplicated (replication of DNA and histones, doubling chromosomes). In the final stage of the cell cycle, called the **$G_2$ phase** (second gap), the cell's metabolism is active, and it grows in preparation for mitosis, but no DNA replication occurs. During **$G_1$** (in animals and plants) and **$G_2$** (in plants only), cells can temporarily enter a resting phase called **$G_0$**. In multicellular organisms, there are also specialized cells that rarely or never divide after they are formed, like nerve cells.

At the end of interphase, individual chromosomes cannot yet be seen under a microscope because they are still made up of loosely coiled chromatin fibers.

## MITOSIS

When a eukaryotic cell divides, it evenly and accurately distributes its genetic material between the two daughter cells.

Key points:

- Mitosis is divided into 4 (sometimes 6) stages: **prophase**, (sometimes **prometaphase**), **metaphase**, **anaphase**, **telophase**, and **cytokinesis**.
- ***Prophase:*** Duplicated chromosomes condense into rod-like structures that can be seen under a light microscope. Each duplicated chromosome appears as two identical sister chromatids

connected by a centromere. In the cytoplasm, a mitotic spindle starts to form. Toward the end of prophase, the nuclear membrane breaks down, and mitotic spindle fibers attach to the compact chromosomes (maximum chromosome coiling occurs between prophase and metaphase, in a stage called prometaphase).

- ***Metaphase:*** Chromosomes move to the cell's equatorial plane, centromeres align in a row, and they are ready to be split.
- ***Anaphase***: The paired centromeres of each chromosome separate, allowing sister chromatids to move apart. By the end of this phase, both poles of the cell have identical sets of chromosomes.
- ***Telophase:*** Chromosomes start to de-condense, and a new nuclear envelope forms around each set of chromosomes.
- **Cytokinesis**: The cell's cytoplasm divides, and the daughter cells separate. In plants, a new cell wall also forms.

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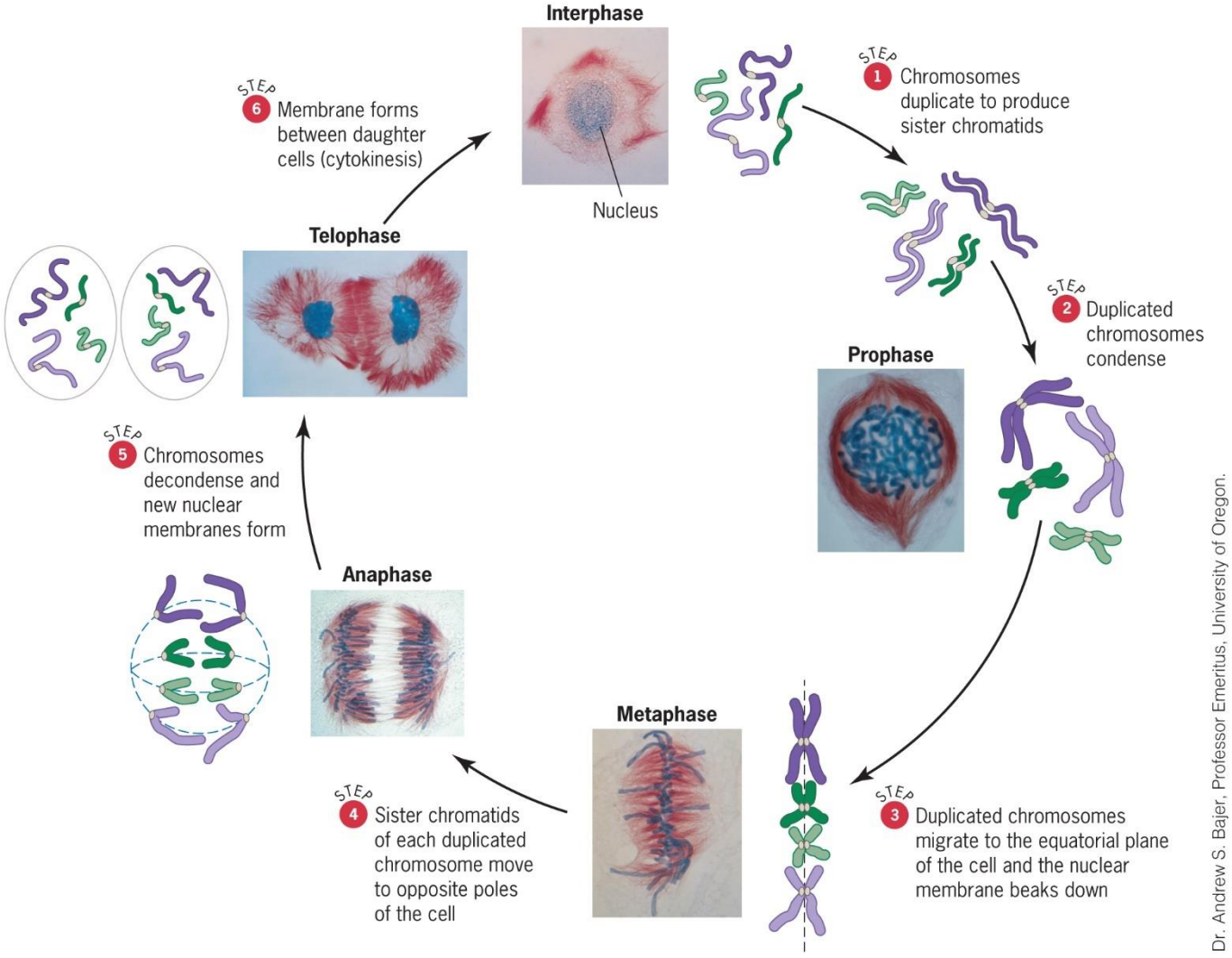



**Figure 2.5** Mitosis in the blood lily *Haemanthus*.

## MEIOSIS

Meiosis is a type of cell division that reduces the chromosome number by half, resulting in haploid cells from diploid eukaryotic cells. This process includes one duplication of chromosomes followed by two cell divisions (meiosis I and meiosis II).

**Key points:**

- Meiosis turns diploid eukaryotic cells into haploid cells. It includes one duplication of chromosomes and two successive cell divisions (meiosis I and meiosis II).
- During **meiosis I**, homologous chromosomes pair up (a process called synapsis), exchange genetic material (crossing-over), and then separate.
- **Chromatids separate** from each other during **meiosis II.**
- In many organisms, the products of meiosis develop directly into gametes.
- In plants, meiosis products divide again by mitosis to form haploid gametophytes. In the plant life cycle, the gametophyte phase alternates with the diploid sporophyte phase, with meiosis occurring in the sporophyte.

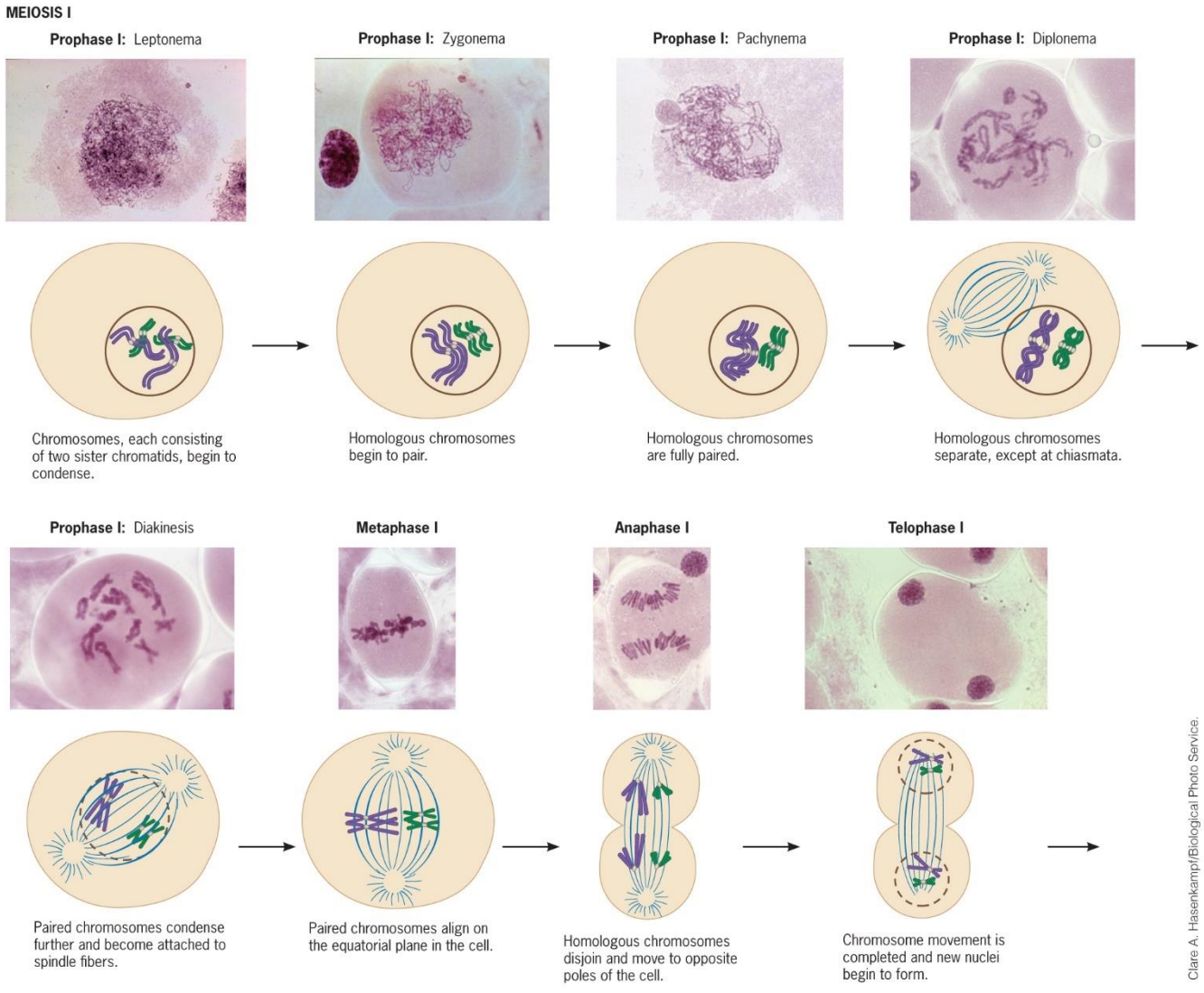



**Figure 2.9** Meiosis in the plant *Lilium longiflorum*.

- Source of images: SNUSTAD, D. Peter and SIMMONS, Michael J. *Principles of Genetics, Seventh Edition*. New York: Wiley, 2015, s.27-29. ISBN 9781119142362

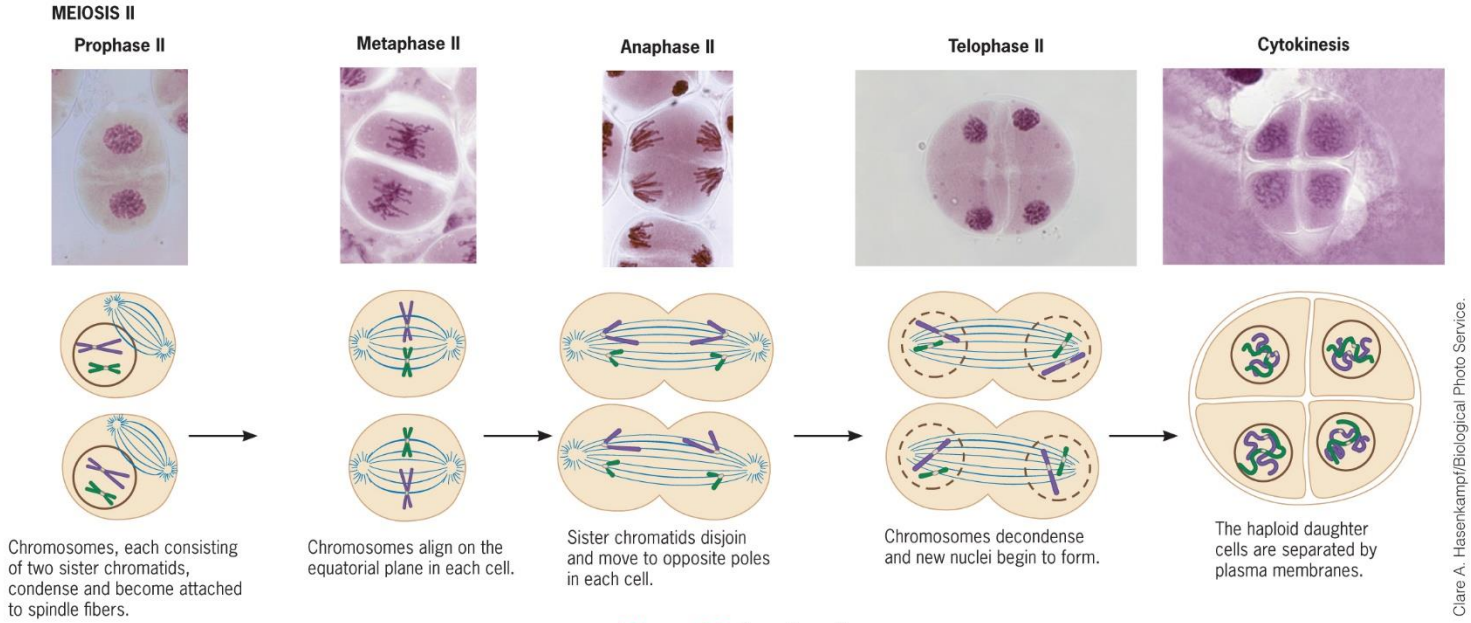



**Figure 2.9** (*continued*)

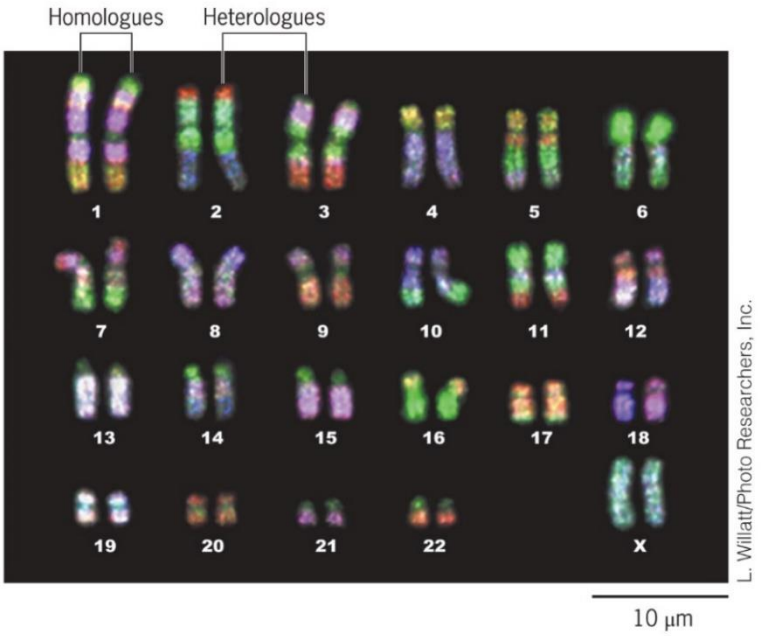



**Figure 2.7** The 23 pairs of homologous chromosomes found in human cells.

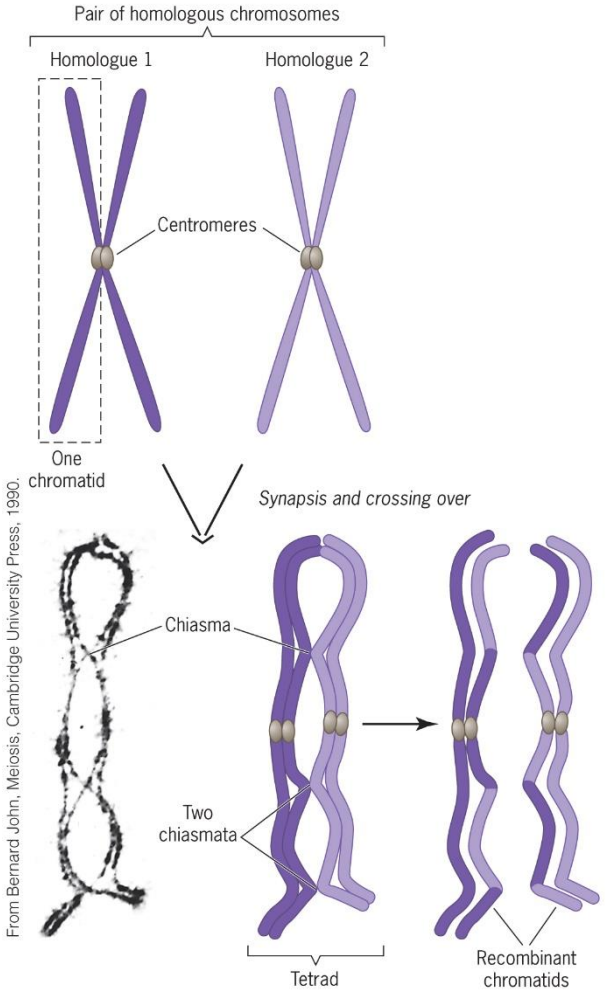



**Figure 2.11** Chiasmata in a bivalent of homologous chromosomes during the diplotene stage of prophase I of meiosis.

Source of images:

SNUSTAD, D. Peter and SIMMONS, Michael J. *Principles of Genetics, Seventh Edition*. New York: Wiley, 2015, s.27-29. ISBN 9781119142362

**HETEROTYPIC DIVISION** (MEIOSIS I)

**PROPHASE I:**

This phase takes the longest time in meiosis, up to 90%. It can last from a few hours to several days, or even years. It can be divided into five stages:

***Leptotene*** (from Greek "leptos" meaning "thin" and "tene" meaning "thread") - During this stage, chromosomes condense, forming two sister chromatids. The chromosomes appear as long, fine threads.

***Zygotene*** (meaning "joined threads") – Homologous chromosomes connect very closely (synapsis). The individual chromomeres[1] (which match in size and shape) lie next to each other. Chromosomes continue to condense.

***Pachytene*** (from Greek "pachys" meaning "thick") – During this phase, chromosomes are visible under a light microscope. Each pair consists of two duplicated chromosomes, each made up of two sister chromatids. When counting homologs, each pair is referred to as a **bivalent**, while if we count the strands, the pair is called a tetrad of chromatids. Once the tetrad stage is formed, repulsive forces develop between the original homologous chromosomes; they tend to move apart, but their complex intertwining keeps them connected. At points where nonsister chromatids cross over, structures called chiasmata (from Greek "chiasma" meaning "cross") form. Due to strong mechanical tension at these chiasma points, chromatids can break, leading to the shifting of break points and their reconnection. This phenomenon is called **crossing-over**, and it results in the exchange (recombination) of genetic material between nonsister chromatids.

***Diplotene*** (meaning "two threads") – In this stage, paired chromosomes start to separate, but they remain in close contact at the crossover points. In humans, the diplotene stage can last for many years. For example, in women, cells can remain in this resting stage for up to 40 years (from the birth of a girl until the induction of follicle maturation in the ovaries, around ages 13-50).

Towards **the end of prophase I**, chromosomes further condense, the n**uclear membrane breaks down, and the spindle apparatus** (spindle fibers) **forms**. The chromosomes (still connected at the chiasmata) move towards the equatorial plane. This movement is characteristic of the last phase of prophase I, called **diakinesis** (meaning "to separate"). The chiasmata move toward the ends of the chromatids, a process known as terminalization of chiasmata.

**METAPHASE I:** Paired chromosomes are oriented toward opposite poles of the spindle apparatus. This spatial orientation ensures that when the cell divides, each pole receives one of the homologous chromosomes from the pair. The terminalization of chiasmata is completed during this stage.

**ANAPHASE I:** The definitive separation (segregation) of chromosomes occurs. The distribution of chromosomes to the spindle poles is entirely random—regardless of which chromosome comes from the father and which comes from the mother. This random combination of chromosomes in the haploid set reflects the law of independent assortment of traits. The number of chromosomes at each pole is haploid.

**TELOPHASE I:** The spindle apparatus breaks down, and the daughter cells are separated by plasma membranes. In some species, new nuclei do not form, and the daughter cells immediately enter meiosis II.

**Note [1]:** Chromomere – well-stained, thickened segments on a chromosome, observable as distinct bands after staining, in contrast to the interchromomeric regions, which are less stainable and narrower. The position of individual chromomeres on a mitotic chromosome is characteristic for a specific tissue type.

**Homeotypic Division** (Meiosis II))

During meiosis II, the chromosomes condense again and attach to a new spindle apparatus **(prophase II)**. Then, they move to the equatorial plane **(metaphase II)**, and their centromeres separate so that sister chromatids can move to opposite poles of the cell **(anaphase II)**. This process is called chromatid separation. During **telophase II**, the separated chromatids (now called chromosomes) gather at the poles, and new daughter nuclei form. Each of these contains a haploid set of chromosomes. Unlike the products of mitosis, the cells resulting from meiosis II are **NOT** genetically identical.

The reason for this is that during meiosis I, the chromatids do not separate; instead, **whole chromosomes** (from each homologous pair) do. One chromosome is inherited from the father, and one from the mother. In the equatorial plane, they orient randomly toward the poles of the spindle apparatus, and then they separate (so one daughter cell receives a maternal homolog, and the other receives a paternal one) → resulting in different genetic products.

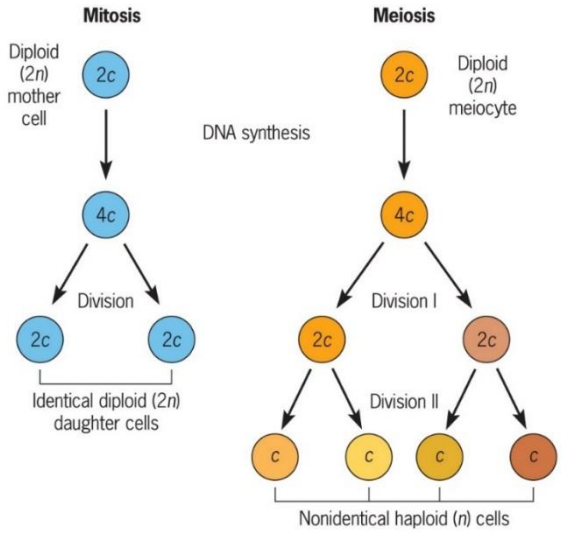



**Figure 2.8** Comparison between mitosis and meiosis; *c* is the haploid amount of DNA in the genome.

Source of image: SNUSTAD, D. Peter and SIMMONS, Michael J. *Principles of Genetics, Seventh Edition*. New York: Wiley, 2015, s.27. ISBN 9781119142362

## SIGNIFICANCE OF MEIOTIC DIVISION

Meiosis involves two rounds of nuclear division but only one division of chromosomes and centromeres.
It realizes fundamental genetic laws, including:

- **Law of Segregation**
- **Law of Independent Assortment of Genes** (which refers to the independent combination of alleles)
- **Law of Recombination of Linked Traits**

The resulting gametes contain different combinations of the original chromosomes, and during fertilization (the fusion of cells – syngamy), various chromosomal combinations are formed in the zygotes. The biological significance of syngamy and meiosis lies in enabling recombination.

***Task No. 1: Counting Chromosomes and Chromatids***

## BASIC PRINCIPLES OF MENDELIAN INHERITANCE, Mendel's Laws

### 1. Law of Uniformity of Hybrids in F1 Generation

When two homozygous individuals are crossed, the offspring are genetically and phenotypically uniform. The offspring of a dominant homozygote and a recessive homozygote are all uniform heterozygotes.

### 2. Law of Segregation (Law of Random Segregation of Genes into Gametes)

When two heterozygous individuals are crossed, the traits of the hybrid parents segregate in the offspring in a characteristic ratio of whole numbers.

*Note: When crossing two heterozygotes, each offspring can inherit either of the two alleles (dominant or recessive) with equal probability. This leads to genotypic and consequently phenotypic segregation. The probabilities for the offspring are as follows: 25% (homozygous dominant individual) : 50% (heterozygous) : 25% (homozygous recessive individual). Thus, the genotypic ratio is 1:2:1, while the phenotypic ratio is 3:1. If there is a relationship of codominance between the alleles, the phenotypic ratio corresponds to the genotypic ratio (1:2:1)*

Notation of Traits: **P** – parental generation
**$F_1$** - first generation of offspring (filial)
**$F_2$** - second generation of offspring (filial)

Typically, female x male (not always strictly followed)

| | | | | | |
|---|---|---|---|---|---|
| **P:** | | AA | x | aa | |
| **F1:** | | | Aa | | |
| **F2:** | AA | : | 2 Aa | : | aa |

### 3. Law of Independent Assortment of Alleles (Genes)

During gamete formation, the alleles of different gene pairs segregate randomly.

When alleles are segregated into gametes, the alleles of different genes (on different loci) combine independently. In the cross of multiple heterozygous hybrids, the number of combinations among the alleles of the observed traits (genes) corresponds to the theoretically possible mathematical combinations of mutually independent variables.

**Conditions for Validity**

- It concerns genomic inheritance.
- The genes are located on autosomes and are not linked (they are on different chromosomes).
- The genes work independently (there is no gene interaction).

**Note**: If we have **two polyhybrids, AaBb**, each can produce 4 different gametes (AB, Ab, aB, ab). When these two gametes cross, they create 16 different zygotic combinations. However, some combinations repeat, resulting in only 9 different genotypes (ratio 1:2:1:2:4:2:1:2:1).

There are only 4 possible phenotypes (*dominant in both traits, dominant in the first trait and recessive in the second, recessive in the first trait and dominant in the second, and recessive in both*). **The phenotypic ratio is 9:3:3:1.** This law applies only if the genes being studied are on different chromosomes.

**Notation of Traits:**

| | Alela | | | | Dominance |
|---|---|---|---|---|---|
| Standardní | dominantní | A | recesivní | a | A nad a |
| Mutační genetika | standardní | + | mutantní | y | + nad y |
| | | $y^+$ | | y | $y^+$ nad y |
| | | $B^+$ | | B | B nad $B^+$ |

**OVERVIEW OF BASIC TYPES OF CROSSES**

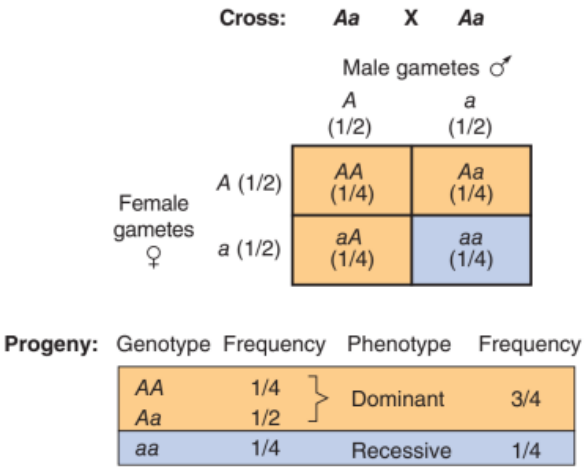
| Type of crossing | Genotypic levels | Phenotypic levels |
|---|---|---|
| **AA x aa** | Aa (neštěpí) | A (neštěpí) |
| **Aa x Aa** | AA : 2Aa : aa | 3A : 1a |
| **Aa x aa** | 1Aa : 1aa | 1A : 1a |
| **Aa x AA** | 1Aa : 1AA | A (neštěpí) |

In human genetics, dominant traits are described (for example, achondroplasia, brachydactyly, congenital night blindness, Huntington's disease, Marfan syndrome, neurofibromatosis, widow's peak hairline, wavy hair) along with the resulting dominant hereditary diseases. There are also diseases with recessive inheritance caused by recessive traits (for example, albinism, alkaptonuria, cystic fibrosis, Duchenne muscular dystrophy, galactosemia, glycogen storage disease, phenylketonuria, sickle cell anemia, Tay-Sachs disease).

## APPLICATION OF MENDELIAN PRINCIPLES:

### A. PUNNETT SQUARE METHOD

In situations where we consider one or two genes, we can write down all the gametes, combine them systematically, and create a set of all the genotypes of the zygotes. In more complicated situations, where we consider more than two genes, the Punnett square is impractical




Crossing with an example of the probability method in the Punnett square. The frequency of each genotype is obtained from the frequencies in the Punnett square, which are gradually obtained by multiplying the frequencies of the two types of gametes from heterozygous parents.

B. **METHOD OF PROBABILITY**

An alternative and quicker method compared to the Punnett square is based on the principle of probability. Probability theory explains the frequency of events. There are two types of questions related to probability:

1. What is the probability that **two events**, A and B, will occur **together**? The **multiplication rule** applies here: **If events A and B are independent, then the probability of both occurring, written as P(A and B), is P(A) x P(B).**

*For example, if we draw one card from a deck and it's an ace, this doesn't tell us anything about the card's color. Drawing the ace of hearts is an example of two independent events happening together. The card is an ace (A) and it's a heart (H). According to the multiplication rule, P(A and H) = P(A) x P(H). Since P(A) = 4/52 and P(H) = 1/4, then P(A and H) = (4/52) x (1/4) = 1/52.*

*Similarly, when crossing Aa x Aa → the probability that the zygote will be AA is the probability that each participating gamete contains allele A, or (1/2) x (1/2) = 1/4.*

2. What is the probability that at least **one of two events**, A or B, will occur? The **addition rule** applies here: **If events A and B are independent, then the probability that at least one of them will happen, written as P(A or B), is P(A) + P(B) - [P(A) x P(B)].**

Here, P(A) x P(B) (the probability of both events happening together) is subtracted from the sum of probabilities because, otherwise, this value would be counted twice.

Note: If the two events do not overlap (cannot happen at the same time), then the addition rule simplifies to **P(A or B) = P(A) + P(B)**.

*For example, we can calculate the probability that a card drawn from a deck is either an ace (A) or a heart (H). According to the addition rule, P(A or H) is P(A) + P(H) - [P(A) x P(H)] = (4/52) + (1/4) - [(4/52) x (1/4)] = **16/52.***

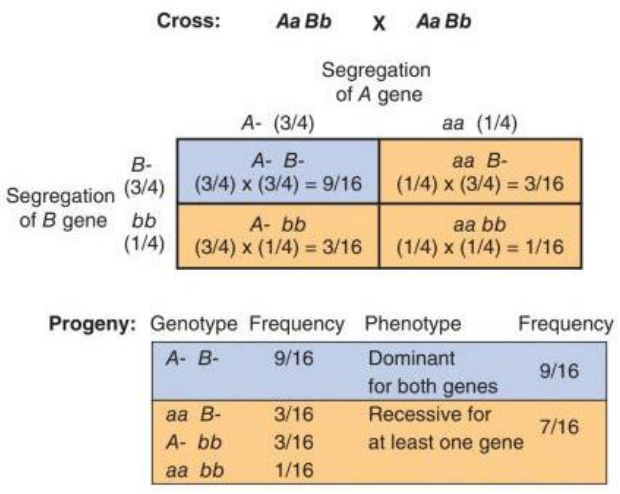



Fig.: Using the Probability Method in Crosses Considering Two Genes

Let's consider a cross of **Aa Bb x Aa Bb**. We want to find out the proportion of offspring that will show a recessive phenotype in at least one gene. In this cross, each gene independently produces dominant and recessive phenotypes with probabilities of 3/4 and 1/4, respectively.

Since independent segregation applies here, we calculate the frequencies of combined phenotypes in the table using the multiplication rule. To determine the frequency of offspring with a recessive phenotype in at least one gene, we use the addition rule by adding the frequencies in the relevant cells of the table (highlighted in pink). The final answer is therefore **7/16**.

***Practical Tasks:***

***Task No. 2:***

Consider parents who are both heterozygous (Cc) for a recessive allele that causes cystic fibrosis in the homozygous form (cc). What is the probability in their family with four children for the following combinations:

**(a)** all 4 children are healthy

**(b)** three are healthy and one has cystic fibrosis

**(c)** one is healthy and three have cystic fibrosis

C. **BINOMIAL DISTRIBUTION**

In offspring from a cross, two different groups often occur – for example, males or females, healthy or sick, normal or mutant, etc. These two groups can generally be labeled as **P** and **Q**, where the probability that an offspring will belong to group **P** is **p**, and the probability that it will belong to group **Q** is **q**. We have two groups, and it holds that q=1−p. Let's assume the number of offspring is ***n*** (births are independent events).

Then, we can calculate the probability that exactly ***x*** offspring will fall into one group and ***y*** into the other using the binomial distribution (probability of x in group P and y in group Q):

$$\left[\frac{n!}{x!\,y!}\right] p^x q^y$$

Let's assume a family with six children. What is the probability that exactly four of them will be girls? To answer this question, we need to remember that for each child, the probability of being a girl (p) is ½, and the probability of being a boy (q) is also ½. The probability that exactly four children in the family will be girls (and two will be boys) is therefore $[(6!)/(4!\,2!)] \times (1/2)^4 \times (1/2)^2 = 720/48 \times 1/16 \times 1/4 =$ **15/64**.

Similarly, we can apply this to Task 2. The probability that a child will be sick is p = 1/4, and the probability that the child will be healthy is q = 3/4. The total number of children is n = 4, the number of sick children is x = 1, and the number of healthy children is y = 3. The probability that exactly one child in a family of four will have cystic fibrosis is: $[(4!)/(1!\,3!)] \times (1/4)^1 \times (3/4)^3 = 4 \times (1/4) \times (27/64)=$ **108/256.**

***Task No. 3.***

Albinism in humans is caused by a recessive allele a. What proportion of children with albinism is expected from a marriage where one partner is a carrier (Aa) and the other partner is albino (aa)? What is the probability that in a family with three children, one will be healthy (without albinism) and two will have albinism?

***Task No. 4:***

What is the probability that in a family with six children, at least three will be girls?

# CHROMOSOMAL BASIS OF MENDELIAN INHERITANCE

The chromosome theory of inheritance says that genes are always arranged linearly on chromosomes, and the genes on one chromosome form a linkage group. The number of linkage groups in an organism is the same as the number of pairs of homologous chromosomes in that organism. Genes on homologous chromosome pairs can exchange during crossing over. The frequency of crossing over is directly related to the distance between genes.

Mendel's principles of inheritance (1) states that paired alleles of genes separate into gametes, and (2) alleles of different genes combine independently in gametes, which can be explained by the meiotic behavior of chromosomes.

1) **Mendel's Law of Segregation** (2nd Law) is based on the separation of homologous chromosomes during anaphase I.
2) **Mendel's Law of Independent Assortment** (3rd Law) also has its foundation in the anaphase separation of chromosomes and refers to the random arrangement of chromosome pairs in metaphase. As mentioned earlier, for genes that are located on the same chromosome pair, the principle of independent assortment does not apply. Instead, because they are physically close to each other, they tend to be inherited together during meiosis.

Key points:

- Genes are located on chromosomes.
- The separation of chromosomes during meiosis is responsible for the segregation and independent combination of genes.
- Nondisjunction during meiosis leads to abnormal chromosome numbers in gametes, and consequently in zygotes.

## SEX-LINKED GENES IN HUMANS

Recessive mutations (RM) on gonosomes (sex chromosomes) are easier to detect in most organisms (including humans) than recessive mutations on autosomes. RM on autosomes are expressed only when both mutant alleles are in a homozygous state, whereas on gonosomes, the mutation is expressed in hemizygotes (mutation on one sex chromosome).

### X-LINKED INHERITANCE:

Among the most well-known diseases caused by recessive mutations on the X chromosome are hemophilia (both hemophilia A and B) and color blindness (the X-linked inheritance is related to green and red light perception, while the gene for blue color perception is on the autosomes).

### GENES ON THE HUMAN Y CHROMOSOME:

The Human Genome Project identified 307 genes on the Y chromosome, and more than 1000 genes on the X chromosome. However, very few Y-linked traits have been detected, even though they should be easily recognized in the transmission from father to son. One possible explanation is that some genes on the Y chromosome are crucial for male fertility. It is clear that mutations in such genes affect male reproductive ability and thus have little or no chance of being passed on to the next generation.

**GENES ON THE X AND Y CHROMOSOMES:**

Some genes are found on both the X and Y chromosomes, typically near the ends of the short arms. The alleles of these genes do not show clear X- or Y-linked inheritance and are passed from fathers and mothers to both sons and daughters equally. These genes are known as pseudoautosomal genes.

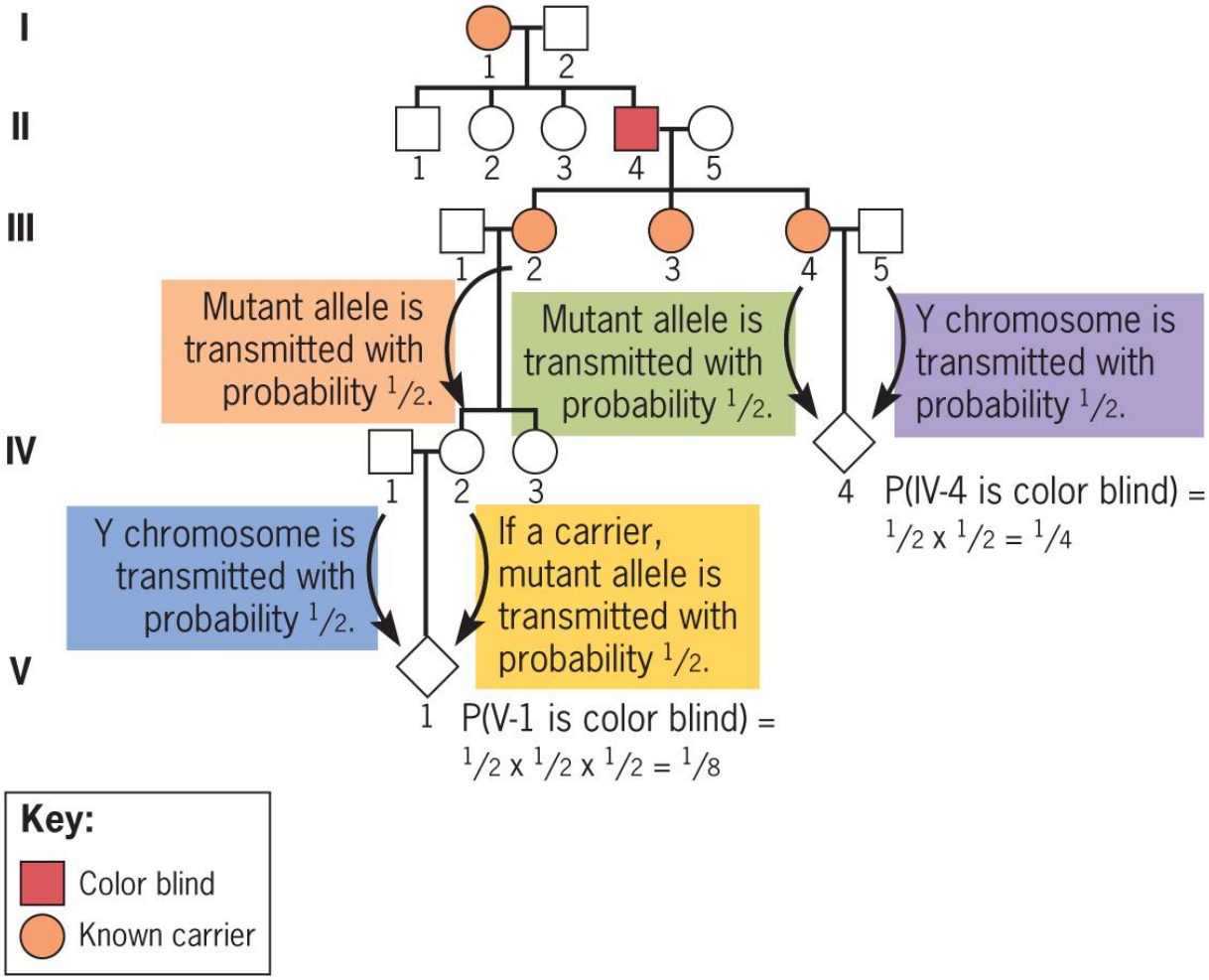



**Fig.: Analysis of a pedigree illustrating the segregation of X-linked color blindness.**
Source: SNUSTAD, D. Peter and SIMMONS, Michael J. *Principles of Genetics, Seventh Edition*. New York: Wiley, 2015, s.27. ISBN 9781119142362