

ADVANCED GENETICS: MECHANISMS OF INHERITANCE AND ANALYSIS



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Advanced Genetics: Mechanisms of Inheritance and Analysis

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CHAPTER OVERVIEW

1: Foundations of Genetic Disorders

Topic hierarchy

[1.1: Defining Disorders](#)

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1.1: Defining Disorders

Defining Disorders

A **disorder** is a disruption to the normal structure or function of the body. Disorders are often distinguished from **diseases**, though the terms are sometimes used interchangeably. A **disease** usually refers to a condition that develops when the body responds to harmful internal or external factors, and it often has a recognizable set of signs and symptoms (for example, *heart disease*). A **disorder**, on the other hand, may simply mean that something in the body is not working properly, even if the exact cause is unclear (for example, an *irregular heartbeat*).

Genetic disorders are a specific class of disorders that arise from abnormalities in an individual's genetic material. These abnormalities can involve a single gene, multiple genes, or entire chromosomes.

"I got excited about genetics as a first-year medical student [when] a pediatric geneticist [brought] a young man with sickle cell disease [to class] who talked about the experience of sickle cell crises and how incredibly painful those are. And yet, it was all because of one single letter in the DNA that is misplaced, a 'T' that should have been an 'A.' And that was profound. You could have all of that happen because of one letter that was misspelled."

— Francis Collins, former Director of the NIH, in a 60 Minutes interview (2019)

Categories of Genetic Disorders

Genetic disorders are typically grouped into three broad categories:

- **Monogenic (single-gene) disorders** — caused by mutations in a single gene.
- **Polygenic or multifactorial disorders** — influenced by the combined effect of multiple genes, often in interaction with environmental factors.
- **Chromosomal disorders** — resulting from structural or numerical abnormalities in chromosomes.

Genetic Anomalies and Mutations

The underlying cause of genetic disorders is variation or damage to DNA. Several types of anomalies can occur:

- **Point mutations** – single nucleotide changes that alter gene function.
- **Deletions** – loss of a section of DNA.
- **Chromosomal abnormalities** – larger scale changes that may include:
 - Duplication (extra copies of a chromosome segment)
 - Translocation (segments exchanged between chromosomes)
 - Inversion (a segment reversed within the chromosome)
 - Insertion (addition of extra DNA into a chromosome)

"There are 7,000 genetic diseases for which we know the precise DNA misspelling. Couldn't this same strategy, this same set of principles [of gene therapy] work for lots of those, maybe someday all of them? ... to see that emerging not just as hoped-for advances, but real data showing cures for people. I believe that this looks like a cure."

— Francis Collins, former Director of the NIH, in a 60 Minutes interview (2019)

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1.2: Examples of Genetic Disorders

Examples of Genetic Disorders

Genetic disorders can be organized not only by their underlying cause but also by the body systems or processes they most affect. Below are representative examples presented in subgroups, each with a short definition followed by specific conditions.

Monogenic Disorders

Metabolic disorders are caused by defects in enzymes or metabolic pathways. These conditions often require strict dietary or metabolic management to prevent toxic buildup of substances in the body.

- **Phenylketonuria (PKU).** An inherited disorder in which phenylalanine accumulates, leading to neurological damage without dietary restriction.
- **Maple syrup urine disease.** Defect in breaking down branched-chain amino acids; urine has a sweet odor.
- **Galactosemia.** Inability to metabolize galactose properly, which can damage the liver and nervous system if untreated.
- **Tay–Sachs disease.** Deficiency of beta-hexosaminidase causes progressive destruction of neurons.

Neurological disorders primarily affect the brain and nervous system. They often present with developmental delay, cognitive decline, or movement disorders.

- **Huntington’s disease.** Progressive degeneration of neurons in the brain, leading to movement, cognitive, and psychiatric symptoms.
- **Fragile X syndrome.** Caused by alterations in the X chromosome; leads to characteristic developmental and behavioral features.

Hematologic (blood) disorders affect red blood cells, hemoglobin, or clotting factors. They often present with anemia, pain crises, or bleeding tendencies.

- **Sickle-cell anemia.** Red blood cells become sickle shaped, causing pain crises, anemia, and organ damage.
- **Beta-thalassemia.** Reduced hemoglobin production results in varying degrees of anemia.
- **Hemophilia.** Blood clotting factors are deficient, leading to prolonged bleeding.

Connective tissue and musculoskeletal disorders affect bone, muscle, and connective tissue. They can alter growth patterns, body structure, or muscular function.

- **Achondroplasia.** Impairs growth of long bones, affecting the spine and skull.
- **Marfan syndrome.** Connective tissue disorder; individuals are often tall and thin with long limbs, and cardiovascular issues are common.
- **Duchenne muscular dystrophy.** Progressive weakening of skeletal and cardiac muscles over time.

Chromosomal Disorders

Trisomies occur when individuals inherit an extra chromosome, leading to characteristic physical and developmental features.

- **Down syndrome (Trisomy 21).** Extra chromosome 21; associated with distinctive features and intellectual disability.
- **Edwards syndrome (Trisomy 18).** Extra chromosome 18; severe congenital anomalies.
- **Patau syndrome (Trisomy 13).** Extra chromosome 13; multiple congenital anomalies, often severe.

Sex chromosome syndromes arise from missing or extra sex chromosomes, affecting sexual development and physical traits.

- **Klinefelter syndrome (47,XXY).** Males with an extra X chromosome; tall stature and infertility are common.
- **Triple X syndrome (47,XXX).** Females with an extra X chromosome; often mild features.
- **Turner syndrome (Monosomy X).** Females missing one X chromosome; short stature and characteristic features such as a webbed neck.

Deletion syndromes occur when parts of a chromosome are missing, often causing distinct developmental and clinical features.

- **Cri du chat syndrome.** Deletion on chromosome 5; infants have a high-pitched “cat-like” cry.

- **Prader–Willi syndrome.** Deletion on chromosome 15 from the paternal copy; associated with hypotonia and obesity.
- **Angelman syndrome.** Disruption of the maternal UBE3A gene on chromosome 15; associated with seizures and developmental delay.
- **DiGeorge syndrome.** Deletion on chromosome 22; linked to congenital heart disease and immune dysfunction.
- **Wolf–Hirschhorn syndrome.** Deletion on chromosome 4; distinctive facial features and intellectual disability.
- **WAGR syndrome.** Deletion on chromosome 11; associated with Wilms tumor, aniridia, and developmental delay.

Translocation disorders result from exchange of material between chromosomes, sometimes creating cancer-causing fusion genes.

- **Philadelphia chromosome.** Reciprocal translocation between chromosomes 9 and 22, producing a shortened chromosome 22. Commonly associated with chronic myelogenous leukemia (CML).

✓ Learning Exercise

Select one disorder from the lists above. In 1–2 paragraphs, summarize:

- Inheritance pattern and causal variant or chromosomal change
- Key clinical features and typical age of onset
- Diagnostic approach
- Prognosis and current treatment or management

Compare your selection with a second disorder that differs in category or mechanism. Highlight at least two similarities and two differences.

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1.3: Summary

Summary and Key Takeaways

Disorders vs. diseases. A *disease* usually refers to a condition with defined signs and symptoms caused by biological or environmental factors. A *disorder* is a broader term describing any disruption of normal body structure or function, even when the cause is not fully understood. Genetic disorders are distinct in that they are rooted in inherited or spontaneous changes in DNA.

Types of genetic mutations. These conditions may result from mutations in a single gene or from large-scale abnormalities of chromosomes. In this chapter, we have focused on the simpler cases most relevant for an introduction to human genetics: **monogenic disorders** and **chromosomal disorders**.

Monogenic disorders result from mutations in a single gene. They can affect many different body systems. Examples include *sickle-cell anemia* and *beta-thalassemia* (blood disorders), *phenylketonuria* and *Tay–Sachs disease* (metabolic disorders), and *Duchenne muscular dystrophy* (muscle disease). These conditions often follow classic Mendelian inheritance patterns such as autosomal dominant, autosomal recessive, or X-linked.

Chromosomal disorders involve changes to whole chromosomes or large sections of them. These may include the presence of extra chromosomes, as in *Down syndrome (trisomy 21)*, *Edwards syndrome (trisomy 18)*, or *Patau syndrome (trisomy 13)*. Others result from missing or rearranged chromosome segments, such as *Cri du chat syndrome* (chromosome 5 deletion) or the *Philadelphia chromosome* (a translocation between chromosomes 9 and 22 associated with leukemia).

Together, these examples illustrate how DNA-level changes manifest in human health. Understanding these foundations prepares us to explore inheritance patterns, diagnostic methods, and emerging genomic therapies in the chapters ahead.

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CHAPTER OVERVIEW

2: DNA Structure and Sequences

2.1: Overview

2.2: DNA is the Genetic Material

2.3: The Structure of DNA

2.4: Genes are the Basic Units of Inheritance

2.5: The Function of Genes

2.6: The Nuclear Genome

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2.1: Overview

Genetics – is the scientific study of heredity and the variation of inherited characteristics. It includes the study of genes, themselves, how they function, interact, and produce the visible and measurable characteristics we see in individuals and populations of species as they change from one generation to the next, over time, and in different environments.

Heredity – Humans have always been aware that the characteristics of an individual plant or animal in a population could be passed down through the generations. Offspring look more like their parents. Humans also knew that some heritable characteristics (such as the size or color of fruit) varied between individuals, and that they could select or breed crops and animals for the most favorable traits. Knowledge of these hereditary properties has been of significant value in the history of human development. In the past, humans could only manipulate and select from naturally existing combinations of genes. More recently, with the discovery of the substance and nature of genetic material, DNA, we can now identify, clone, and create novel, better combinations of genes that will serve our goals. Understanding the mechanisms of genetics is fundamental to using it wisely and for the betterment of all.



Fig.1-1: Parent and offspring. Wolf's Monkey. (Flickr-eclectic echos-CC:AND)

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2.2: DNA is the Genetic Material

By the early 1900's, biochemists had isolated hundreds of different chemicals from living cells. Which of these was the genetic material? Proteins seemed like promising candidates, since they were abundant, diverse, and complex molecules. However, a few key experiments demonstrated that DNA, rather than protein, is the genetic material.

2.2.1: Griffith's Transformation Experiment (1928)

Microbiologists identified two strains of the bacterium *Streptococcus pneumoniae*. The R-strain produced rough colonies on a bacterial plate, while the other S-strain was smooth (Figure 2.2.2). More importantly, the S-strain bacteria caused fatal infections when injected into mice, while the R-strain did not (top, Figure 2.2.3). Neither did "heat-treated" S-strain cells. **Griffith** in 1929 noticed that upon mixing "heat-treated" S-strain cells together with some R-type bacteria (neither should kill the mice), the mice died and there were S-strain, pathogenic cells recoverable. Thus, some non-living component from the S-type strains contained genetic information that could be transferred to and **transform** the living R-type strain cells into S-type cells.

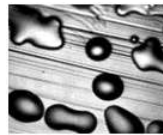


Figure 2.2.2: Colonies of Rough (top) and Smooth (bottom) strains of *S. pneumoniae*. (J. Exp.Med.98:21, 1953-R. Austrian-Pending)

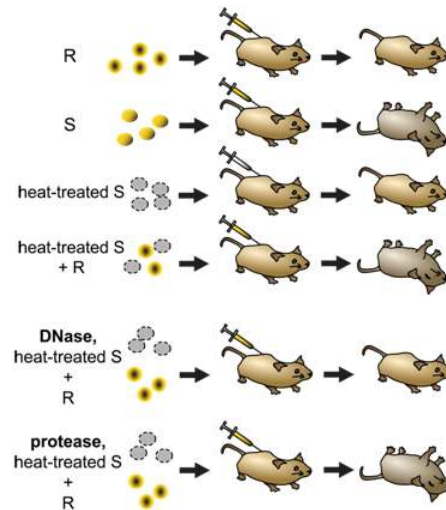


Figure 2.2.3: Experiments of Griffith and of Avery, MacLeod and McCarty. R strains of *S. pneumoniae* do not cause lethality. However, DNA-containing extracts from pathogenic S strains are sufficient to make R strains pathogenic. (Original-Deyholos-CC:AN)

2.2.2: Avery, MacLeod and McCarty's Experiment (1944)

What kind of molecule from within the S-type cells was responsible for the transformation? To answer this, researchers named **Avery, MacLeod and McCarty** separated the S-type cells into various components, such as proteins, polysaccharides, lipids, and nucleic acids. Only the nucleic acids from S-type cells were able to make the R-strains smooth and fatal. Furthermore, when cellular extracts of S-type cells were treated with DNase (an enzyme that digests DNA), the transformation ability was lost. The researchers therefore concluded that DNA was the genetic material, which in this case controlled the appearance (smooth or rough) and pathogenicity of the bacteria.

2.2.3: Hershey and Chase's Experiment (1952)

Further evidence that DNA is the genetic material came from experiments conducted by **Hershey and Chase**. These researchers studied the transmission of genetic information in a virus called the T2 bacteriophage, which used *Escherichia coli* as its host

bacterium (Figure 2.2.4). Like all viruses, T2 hijacks the cellular machinery of its host to manufacture more viruses. The T2 phage itself only contains both protein and DNA, but no other class of potential genetic material.



Figure 2.2.4: Electronmicrograph of T2 bacteriophage on surface of *E. coli*. (Wikipedia-G. Colm-PD)

To determine which of these two types of molecules contained the genetic blueprint for the virus, Hershey and Chase grew viral cultures in the presence of radioactive isotopes of either phosphorus (^{32}P) or sulphur (^{35}S). The phage incorporated these isotopes into their DNA and proteins, respectively (Fig 1.5). The researchers then infected *E. coli* with the radiolabeled viruses, and looked to see whether ^{32}P or ^{35}S entered the bacteria. After ensuring that all viruses had been removed from the surface of the cells, the researchers observed that infection with ^{32}P labeled viruses (but not the ^{35}S labeled viruses) resulted in radioactive bacteria. This demonstrated that DNA was the material that contained genetic instructions.

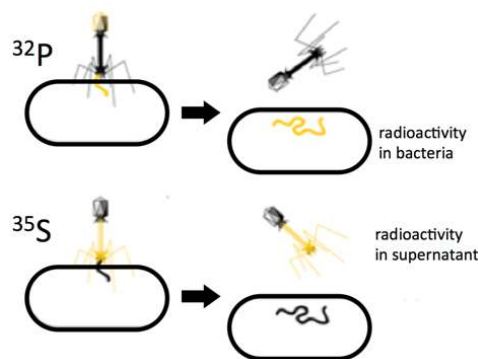


Figure 2.2.5: When ^{32}P -labeled phage infects *E. coli*, radioactivity is found only in the bacteria, after the phage are removed by agitation and centrifugation. In contrast, after infection with ^{35}S -labeled phage, radioactivity is found only in the supernatant that remains after the bacteria are removed. (Original-Deyholos-CC:AN)

2.2.4: Meselson and Stahl experiment (1958)

From the complementary strands model of DNA, proposed by Watson and Crick in 1953, there were three straightforward possible mechanisms for DNA replication: (1) semi-conservative, (2) conservative, and (3) dispersive (Fig 1.6).

1. The **semi-conservative** model proposes the two strands of a DNA molecule separate during replication and then strand acts as a template for synthesis of a new, complementary strand.
2. The **conservative** model proposes that the entire DNA duplex acts as a single template for the synthesis of an entirely new duplex.
3. The **dispersive** model has the two strands of the double helix breaking into units that which are then replicated and reassembled, with the new duplexes containing alternating segments from one strand to the other.

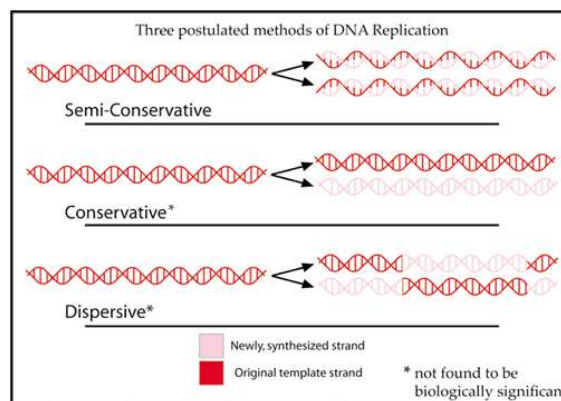


Figure 2.2.6: The three models of DNA replication possible from the double helix model of DNA structure. (Wikipedia-Adenosine-CC:AN)

Each of these three models makes a different prediction about the how DNA strands should be distributed following two rounds of replication. These predictions can be tested in the following experiment by following the nitrogen component in DNA in *E. coli* as it goes through several rounds of replication. Meselson and Stahl used different isotopes of Nitrogen, which is a major component in DNA. **Nitrogen-14** (^{14}N) is the most abundant natural isotope, while **Nitrogen-15** (^{15}N) is rare, but also denser. Neither is radioactive; each can be followed by a difference in density – “light” 14 vs “heavy” 15 atomic weight in a CsCl density gradient ultra-centrifugation of DNA.

The experiment starts with *E. coli* grown for several generations on medium containing only ^{15}N . It will have denser DNA. When extracted and separated in a CsCl density gradient tube, this “heavy” DNA will move to a position nearer the bottom of the tube in the more dense solution of CsCl (left side in Figure 2.2.7). DNA extracted from *E. coli* grown on normal, ^{14}N containing medium will migrate more towards the less dense top of the tube.

If these *E. coli* cells are transferred to a medium containing only ^{14}N , the “light” isotope, and grown for one generation, then their DNA will be composed of one-half ^{15}N and one-half ^{14}N . If the this DNA is extracted and applied to a **CsCl gradient**, the observed result is that one band appears at the point midway between the locations predicted for wholly ^{15}N DNA and wholly ^{14}N DNA (Figure 2.2.7). This “single-band” observation is inconsistent with the predicted outcome from the conservative model of DNA replication (disproves this model), but is consistent with both that expected for the semi-conservative and dispersive models.

If the *E. coli* is permitted to go through another round of replication in the ^{14}N medium, and the DNA extracted and separated on a CsCl gradient tube, then two bands were seen by Meselson and Shahl: one at the ^{14}N - ^{15}N intermediate position and one at the wholly ^{14}N position (Figure 2.2.7). This result is inconsistent with the dispersive model (a single band between the ^{14}N - ^{15}N position and the wholly ^{14}N position) and thus disproves this model. The two band observation is consistent with the semi-conservative model which predicts one wholly ^{14}N duplex and one ^{14}N - ^{15}N duplex. Additional rounds of replication also support the semi-conservative model/hypothesis of DNA replication. Thus, the semi-conservative model is the currently accepted mechanism for DNA replication. Note however, that we now also know from more recent experiments that whole chromosomes, which can be millions of bases in length, are also semi-conservatively replicated.

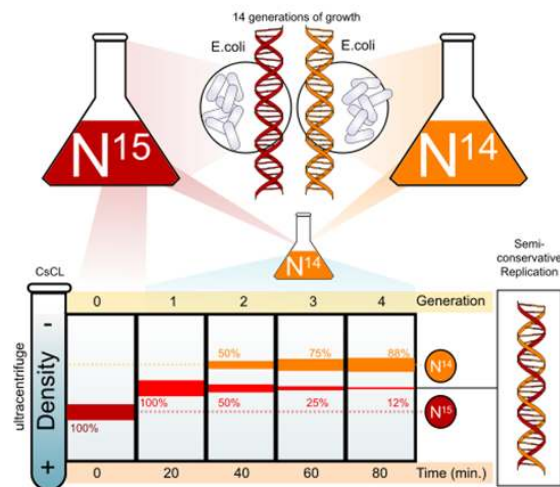


Figure 2.2.7: The positions of the N^{14} and N^{15} containing DNA in the density gradient tube on the left. (Wikipedia-LadyofHats-CC:AN)

These experiments, published in 1958, are a wonderful example of how science works. Researchers start with three clearly defined models (hypotheses). These models were tested, and two (conservative and dispersive) were found to be inconsistent with the observations and thus disproven. The third hypothesis, semi-conservative, was consistent with the observations and thereby supported and accepted as mechanism of DNA replication. Note, however, this is not “proof” of the model, just strong evidence for it; hypotheses are not “proven”, only disproven or supported.

2.2.5: RNA and protein

While DNA is the genetic material for the vast majority of organisms, there are some viruses that use **RNA as their genetic material**. These viruses can be either single or double stranded and include SARS, influenza, hepatitis C and polio, as well as the retroviruses like HIV-AIDS. Typically there is DNA used at some stage in their life cycle to replicate their RNA genome.

Also, the case of **Prion** infections agents transmit characteristics via only a protein (no nucleic acid present). Prions infect by transmitting a misfolded protein state from one aberrant protein molecule to a normally folded molecule. These agents are responsible for bovine spongiform encephalopathy (BSE, also known as "mad cow disease") in cattle and deer and Creutzfeldt–Jakob disease (CJD) in humans. All known prion diseases act by altering the structure of the brain or other neural tissue and all are currently untreatable and ultimately fatal.

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2.3: The Structure of DNA

The experiments outlined in the previous sections proved that DNA was the genetic material, but very little was known about its structure at the time.

2.3.1: Chargaff's Rules

When **Watson and Crick** set out in the 1940's to determine the structure of DNA, it was already known that DNA is made up of a series of four different types of molecules, called bases or nucleotides: adenine (A), cytosine (C), thymine (T), guanine (G). Watson and Crick also knew of **Chargaff's Rules**, which were a set of observations about the relative amount of each nucleotide that was present in almost any extract of DNA. Chargaff had observed that for any given species, the abundance of A was the same as T, and G was the same as C. This was essential to Watson & Crick's model.

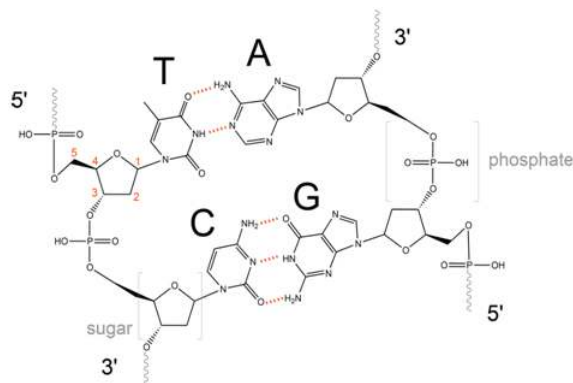


Figure 2.3.8: Chemical structure of two pairs of nucleotides in a fragment of double-stranded DNA. Sugar, phosphate, and bases A,C,G,T are labeled. Hydrogen bonds between bases on opposite strands are shown by dashed lines. Note that the G-C pair has more hydrogen bonds than A-T. The numbering of carbons within sugars is indicated by red numbers. Based on this numbering the polarity of each strand is indicated by the labels 5' and 3'. (Wikipedia-M. Strock-GFDL)

2.3.2: The Double Helix

Using proportional metal models of the individual nucleotides, Watson and Crick deduced a structure for DNA that was consistent with Chargaff's Rules and with x-ray crystallography data that was obtained (with some controversy) from another researcher named Rosalind Franklin. In Watson and Crick's famous **double helix**, each of the two strands contains DNA bases connected through covalent bonds to a sugar-phosphate backbone (Fig 1.8, 1.9). Because one side of each sugar molecule is always connected to the opposite side of the next sugar molecule, each strand of DNA has polarity: these are called the 5' (5-prime) end and the 3' (3-prime) end, in accordance with the nomenclature of the carbons in the sugars. The two strands of the double helix run in **anti-parallel** (i.e. opposite) directions, with the 5' end of one strand adjacent to the 3' end of the other strand. The double helix has a **right-handed** twist, (rather than the left-handed twist that is often represented incorrectly in popular media). The DNA bases extend from the backbone towards the center of the helix, with a pair of bases from each strand forming hydrogen bonds that help to hold the two strands together. Under most conditions, the two strands are slightly offset, which creates a major groove on one face of the double helix, and a minor groove on the other. Because of the structure of the bases, A can only form hydrogen bonds with T, and G can only form hydrogen bonds with C (remember Chargaff's Rules). Each strand is therefore said to be complementary to the other, and so each strand also contains enough information to act as a template for the synthesis of the other. This complementary redundancy is important in DNA replication and repair.

How can this molecule, DNA, contain the genetic material?

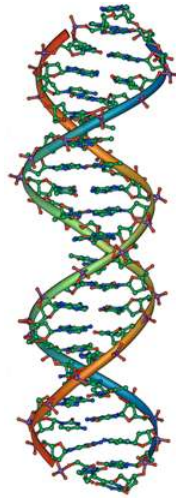


Figure 2.3.9: DNA double helix structure. (Original-unknown-?)

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2.4: Genes are the Basic Units of Inheritance

2.4.1: Blending vs Particulate inheritance

The once prevalent (but now discredited) concept of **blending inheritance** proposed that some undefined essence, in its entirety, contained all of the heritable information for an individual. It was thought that mating combined the essences from each parent, much like the mixing of two colors of paint. Once blended together, the individual characteristics of the parents could not be separated again. However, **Gregor Mendel** (Fig 1.10) was one of the first to take a quantitative, scientific approach to the study of heredity.



Figure 2.4.10: Gregor Mendel. (Original-unknown-PD)

He started with well-characterized strains, repeated his experiments many times, and kept careful records of his observations. Working with peas, Mendel showed that white-flowered plants could be produced by crossing two purple-flowered plants, but only if the purple-flowered plants themselves had at least one white-flowered parent (Fig 1.11). This was evidence that the genetic factor that produced white-flowers had *not* blended irreversibly with the factor for purple-flowers. Mendel's observations disprove blending inheritance and favor an alternative concept, called **particulate inheritance**, in which heredity is the product of discrete factors that control independent traits.

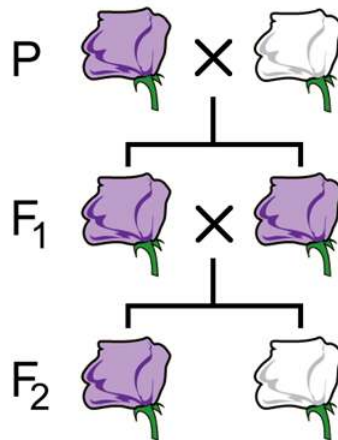


Figure 2.4.11: Inheritance of flower color in peas. Mendel observed that a cross between pure breeding, white and purple peas (generation P) produced only progeny (generation F₁) with purple flowers. However, white flowered plant reappeared among the F₂ generation progeny of a mating between two F₁ plants. The symbols P, F₁ and F₂ are abbreviations for parental, first filial, and second filial generations, respectively. (Original-Deyholos-CC:AN)

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2.5: The Function of Genes

2.5.1: Beadle and Tatum: one gene, one enzyme hypothesis

Life depends on (bio)chemistry to supply energy and to produce the molecules to construct and regulate cells. In 1908, A. Garrod described “in born errors of metabolism” in humans using the congenital disorder, alkaptonuria (black urine disease), as an example of how “genetic defects” led to the lack of an enzyme in a biochemical pathway and caused a disease (phenotype). Over 40 years later, in 1941, **Beadle and Tatum** built on this connection between genes and metabolic pathways. Their research led to the “**one gene, one enzyme (or protein)**” hypothesis, which states that each of the enzymes that act in a biochemical pathway is encoded by a different gene. Although we now know of many exceptions to the “one gene, one enzyme (or protein)” principle, it is generally true that each different gene produces a protein that has a distinct catalytic, regulatory, or structural function.

Beadle and Tatum used the fungus *Neurospora crassa* (a mold) for their studies because it had practical advantages as a laboratory organism. They knew that *Neurospora* was **prototrophic**, meaning that it could synthesize its own amino acids when grown on **minimal medium**, which lacked most nutrients except for a few minerals, simple sugars, and one vitamin (biotin). They also knew that by exposing *Neurospora* spores to X-rays, they could randomly damage its DNA to create mutations in genes. Each different spore exposed to X-rays potentially contained a mutation in a different gene. After genetically screening many, many spores for growth, most appeared to still be prototrophic and still able to grow on minimal medium. However, some spores had mutations that changed them into **auxotrophic** strains that could no longer grow on minimal medium, but did grow on **complete medium** supplemented with nutrients (Figure 2.5.12). In fact, some auxotrophic mutations could grow on minimal medium with only one, single nutrient supplied, such as arginine.

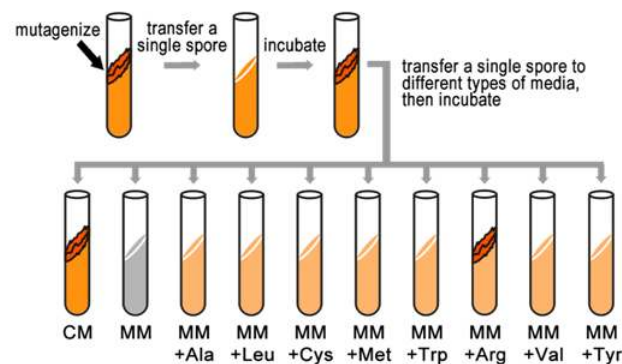


Figure 2.5.12: A single mutagenized spore is used to establish a colony of genetically identical fungi, from which spores are tested for their ability to grow on different types of media. Because spores of this particular colony are able to grown only on complete medium (CM), or on miminal medium supplemented with arginine (MM+Arg), they are considered Arg auxotrophs and we infer that they have a mutation in a gene in the Arg biosynthetic pathway. This type of screen is repeated many times to identify other mutants in the Arg pathway and in other pathways. (Original-Deyholos-CC:AN)

2.5.2: B&T's 1 gene: 1 enzyme hypothesis led to Biochemical Pathway dissection using genetic screens and mutations

Beadle and Tatum’s experiments are important not only for its conceptual advances in understanding genes, but also because they demonstrate the utility of **screening for genetic mutants** to investigate a biological process – **genetic analysis**. Beadle and Tatum’s results were useful to investigate biological processes, specifically the metabolic pathways that produce amino acids. For example, Srb and Horowitz in 1944 tested the ability of the amino acids to **rescue** auxotrophic strains. They added one of each of the amino acids to minimal medium and recorded which of these restored growth to independent mutants. For example, if the progeny of a mutagenized spore could grow on minimal medium only when it was supplemented with arginine (Arg), then the auxotroph must bear a mutation in the Arg biosynthetic pathway and was called an “arginineless” strain (arg-).

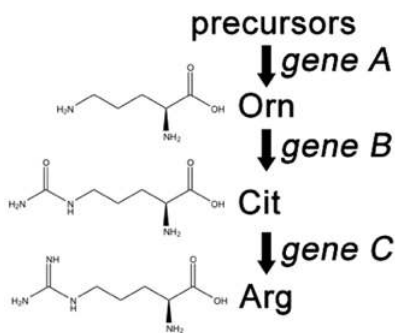


Figure 2.5.13: A simplified version of the Arg biosynthetic pathway, showing citrulline (Cit) and ornithine (Orn) as intermediates in Arg metabolism. These chemical reactions depend on enzymes represented here as the products of three different genes. (Original-Deyholos-CC:AN)

Synthesis of even a relatively simple molecule such as arginine requires many steps, each with a different enzyme. Each enzyme works sequentially on a different intermediate in the pathway (Figure 2.5.13). For arginine (Arg), two of the intermediates are ornithine (Orn) and citrulline (Cit). Thus, mutation of any one of the enzymes in this pathway could turn *Neurospora* into an Arg auxotroph (*arg-*). Srb and Horowitz extended their analysis of Arg auxotrophs by testing the intermediates of amino acid biosynthesis for the ability to restore growth of the mutants (Figure 2.5.14).

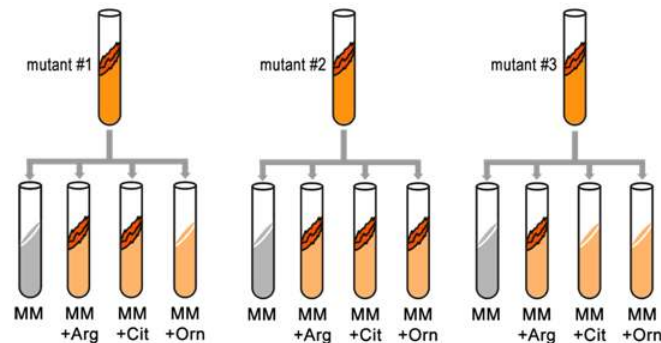


Figure 2.5.14: Testing different Arg auxotrophs for their ability to grow on media supplemented with intermediates in the Arg biosynthetic pathway. (Original-Deyholos-CC:AN)

They found that some of the Arg auxotrophs could be rescued only by Arg, while others could be rescued by either Arg or Cit, and still other mutants could be rescued by Arg, Cit, or Orn (Table 2.5.1). Based on these results, they deduced the location of each mutation in the Arg biochemical pathway, (i.e. which gene was responsible for the metabolism of which intermediate).

Table 2.5.1: Ability of auxotrophic mutants of each of the three enzymes of the Arg biosynthetic pathways to grow on minimal medium (MM) supplemented with Arg or either of its precursors, Orn and Cit. Gene names refer to the labels used in Figure 2.5.14

	MM + Orn	MM + Cit	MM + Arg
<i>gene A</i> mutants	Yes	Yes	Yes
<i>gene B</i> mutants	No	Yes	Yes
<i>gene C</i> mutants	No	No	Yes

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2.6: The Nuclear Genome

2.6.1: The C-value of the nuclear genome

The complete set of DNA within the nucleus of any organism is called its **nuclear genome** and is measured as the **C-value** in units of either the number of base pairs or picograms of DNA. There is a general correlation between the nuclear DNA content of a genome (i.e. the C-value) and the physical size or complexity of an organism. Compare the size of *E. coli* and humans for example in Table 2.6.2.

Table 2.6.2: Measures of genome size in selected organisms. The DNA content (1C) is shown in millions of basepairs (Mb). For eukaryotes, the chromosome number is the chromosomes counted in a gamete (1N) from each organism. The average gene density is the mean number of non-coding bases (in bp) between genes in the genome.

	DNA content (Mb, 1C)	Estimated gene number	Average gene density	Chromosome number (1N)
<i>Homo sapiens</i>	3,200	25,000	100,000	23
<i>Mus musculus</i>	2,600	25,000	100,000	20
<i>Drosophila melanogaster</i>	140	13,000	9,000	4
<i>Arabidopsis thaliana</i>	130	25,000	4,000	5
<i>Caenorhabditis elegans</i>	100	19,000	5,000	6
<i>Saccharomyces cerevisiae</i>	12	6,000	2,000	16
<i>Escherichia coli</i>	5	3,200	1,400	1

There are, however, many exceptions to this generalization, such as the human genome contains only 3.2×10^9 DNA bases, while the wheat genome contains 17×10^9 DNA bases, almost 6 times as much. The Marbled Lungfish (*Protopterus aethiopicus* – Figure 2.6.16) contains $\sim 133 \times 10^9$ DNA bases, (~ 45 times as much as a human) and a fresh water amoeboid, *Polychaos dubium*, which has as much as 670×10^9 bases (200x a human).



Fig 1.16: Marbled Lungfish. (Wikipedia-OpenCage-CC:AS)

2.6.2: The C-value paradox

This apparent paradox (called the **C-value paradox**) can be explained by the fact that not all nuclear DNA encodes genes – much of the DNA in larger genomes is non-gene coding. In fact, in many organisms, genes are separated from each other by long stretches of DNA that do not code for genes or any other genetic information. Much of this “non-gene” DNA consists of transposable elements of various types, which are an interesting class of self-replicating DNA elements discussed in more detail in a subsequent chapter. Other non-gene DNA includes short, highly repetitive sequences of various types.

2.6.3: Other genomes

Organelles such as mitochondria and chloroplasts also have their own genomes. These are, compared to the nuclear genome, relatively small and are also circular, like the prokaryotes from which they originated (Endosymbiont hypothesis).

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CHAPTER OVERVIEW

3: DNA Profiling and Techniques

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3.3: Whole Genome Sequencing

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3.5: DNA Analysis - Gel Electrophoresis

3.6: DNA Analysis- Blotting and Hybridization

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3.1: 'Omics Technologies

The complete set of DNA within an organism is called its **genome**. **Genomics** is therefore the large-scale description, using techniques of molecular biology of many genes or even whole genomes at once. This type of research is facilitated by technologies that increase throughput (i.e. rate of analysis), and decrease cost. The **–omics** suffix has been used to indicate high-throughput analysis of many types of molecules, including transcripts (**transcriptomics**), proteins (**proteomics**), and the products of enzymatic reactions, or metabolites (**metabolomics**; Figure 3.1.1). Interpretation of the large data sets generated by –omics research depends on a combination of computational, biological, and statistical knowledge provided by experts in **bioinformatics**. Attempts to combine information from different types of –‘omics studies is sometimes called **systems biology**.



Figure 3.1.1: A word cloud listing some of the different –omics technologies. Terms that are more widely used are written in the largest characters. There is no significance to the color of each word. (Original-Deyholos-CC:AN)

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3.2: DNA Sequencing

DNA sequencing determines the order of nucleotide bases within a given fragment of DNA. This information can be used to infer the RNA or protein sequence encoded by the gene, from which further inferences may be made about the gene's function and its relationship to other genes and gene products. DNA sequence information is also useful in studying the regulation of gene expression. If DNA sequencing is applied to the study of many genes, or even a whole genome, it is considered an example of genomics.

3.2.1: Dideoxy sequencing

Recall that DNA polymerases incorporate nucleotides (dNTPs) into a growing strand of DNA, based on the sequence of a template strand. DNA polymerases add a new base only to the 3'-OH group of an existing strand of DNA; this is why primers are required in natural DNA synthesis and in techniques such as PCR. Most of the currently used DNA sequencing techniques rely on the random incorporation of modified nucleotides called terminators. Examples of terminators are the **dideoxy nucleotides (ddNTPs)**, which lack a 3'-OH group and therefore cannot serve as an attachment site for the addition of new bases to a growing strand of DNA (Figure 3.2.1). After a ddNTP is incorporated into a strand of DNA, no further elongation can occur. Terminators are labeled with one of four fluorescent dyes, each specific for one of the four nucleotide bases.

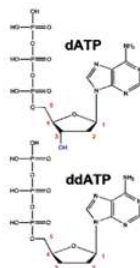


Figure 3.2.1: ddNTPs (Original-Deyholos-CC:AN)

To sequence a DNA fragment, you need many copies of that fragment (Figure 3.2.2). Unlike PCR, DNA sequencing does not amplify the target sequence and only one primer is used. This primer is hybridized to the denatured template DNA, and determines where on the template strand the sequencing reaction will begin. A mixture of dNTPs, fluorescently labeled terminators, and DNA polymerase is added to a tube containing the primer-template hybrid. The DNA polymerase will then synthesize a new strand of DNA until a fluorescently labeled nucleotide is incorporated, at which point extension is terminated. Because the reaction contains millions of template molecules, a corresponding number of shorter molecules is synthesized, each ending in a fluorescent label that corresponds to the last base incorporated.

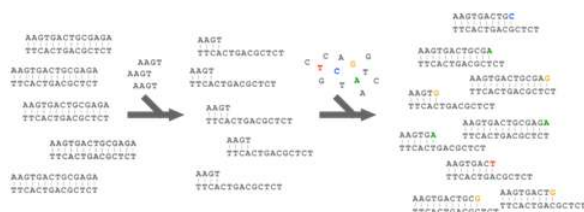


Figure 3.2.2: A sequencing reactions begins with many identical copies of a template DNA fragment. The template is denatured, then primers are annealed to the template. Following the addition of polymerase, regular dNTPS, and fluorescently labeled terminators, extension begins at the primer site. Elongation proceeds until a fluorescently labeled terminator (shown here in color) is incorporated. (Original-Deyholos-CC:AN)

The newly synthesized strands can be denatured from the template, and then separated electrophoretically based on their length (Figure 3.2.3). Since each band differs in length by one nucleotide, and the identity of that nucleotide is known from its fluorescence, the DNA sequence can be read simply from the order of the colors in successive bands. In practice, the maximum length of sequence that can be read from a single sequencing reaction is about 700 bp.

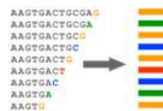


Figure 3.2.3: Fluorescently labeled products can be separated electrophoretically based on their length. (Original-Deyholos-CC:AN)

A particularly sensitive electrophoresis method used in the analysis of DNA sequencing reactions is called **capillary electrophoresis** (Figure 3.2.6). In this method, a current pulls the sequencing products through a gel-like matrix that is encased in a fine tube of clear plastic. As in conventional electrophoresis, the smallest fragments move through the capillary the fastest. As they pass through a point near the end of the capillary, the fluorescent intensity of each dye is read. This produces a graph called a chromatogram. The sequence is determined by identifying the highest peak (i.e. the dye with the most intense fluorescent signal) at each position.

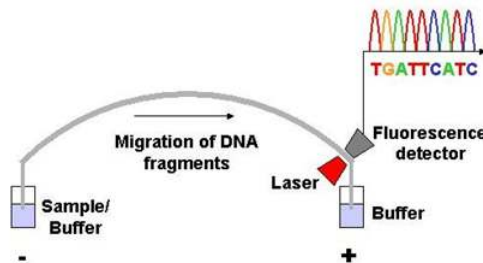


Figure 3.2.4: Fluorescently labeled products can be separated by capillary electrophoresis, generating a chromatogram from which the sequence can be read.(Wikipedia-Abizar Lakdawalla-PD)

3.2.2: Next-generation sequencing

Advances in technology over the past two decades have increased the speed and quality of sequencing, while decreasing the cost. This has become especially true with the most recently developed methods called next-generation sequencing. Not all of these new methods rely on terminators, but one that does is a method used in instruments sold by a company called **Illumina**. Illumina sequencers use a special variant of PCR called bridge PCR to make many thousands of copies of a short (45bp) template fragment. Each of these short template fragments is attached in a cluster in a small spot on a reaction surface. Millions of other clusters, each made by different template fragment, are located at other positions on the reaction surface. DNA synthesis at each template strand then proceeds using dye-labeled terminators that are used are reversible. Synthesis is therefore terminated (temporarily) after the incorporation of each nucleotide. Thus, after the first nucleotide is incorporated in each strand, a camera records the color of fluorescence emitted from each cluster. The terminators are then modified, and a second nucleotide is incorporated in each strand, and again the reaction surface is photographed. This cycle is repeated a total of 45 times. Because millions of 45 bp templates are sequenced in parallel in a single process, Illumina sequencing is very efficient compared to other sequencing techniques. However, the short length of the templates currently limits the application of this technology.

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3.3: Whole Genome Sequencing

3.3.1: The need for assembly

Given that the length of a single, individual sequencing read is somewhere between 45bp and 700bp, we are faced with a problem determining the sequence of longer fragments, such as the chromosomes in an entire genome of humans (3×10^9 bp). Obviously, we need to break the genome into smaller fragments. There are two different strategies for doing this:

1. clone-by-clone sequencing, which relies on the creation of a physical map first then sequencing, and
2. whole genome shotgun sequencing, which sequences first and does not require a physical map.

3.3.2: Physical mapping

A physical map is a representation of a genome, comprised of cloned fragments of DNA. The map is therefore made from physical entities (pieces of DNA) rather than abstract concepts such as the linkage frequencies and genes that make up a genetic map (Figure 3.3.1). It is usually possible to correlate genetic and physical maps, for example by identifying the clone that contains a particular molecular marker. The connection between physical and genetic maps allows the genes underlying particular mutations to be identified through a process call map-based cloning.

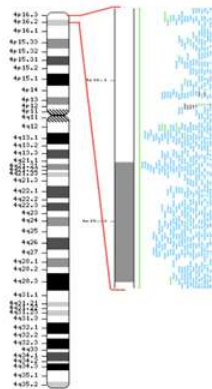


Figure 3.3.1: A portion of the physical map for human chromosome 4. The entire chromosome is shown at left. The physical map is made up of small blue lines, each of which represents a cloned piece of DNA approximately 100kb in length. (NCBI-unknown-PD)

To create a physical map, large fragments of the genome are cloned into plasmid vectors, or into larger vectors called bacterial artificial chromosomes (BACs). BACs can contain approximately 100kb fragments. The set of BACs produced in a cloning reaction will be redundant, meaning that different clones will contain DNA from the same part of the genome. Because of this redundancy, it is useful to select the minimum set of clones that represent the entire genome, and to order these clones relative to the sequence of the original chromosome. Note that this is all to be done without knowing the complete sequence of each BAC. Making a physical map may therefore rely on techniques related to Southern blotting: DNA from the ends of one BAC is used as a probe to find clones that contain the same sequence. These clones are then assumed to overlap each other. A set of overlapping clones is called a **contig**.

3.3.3: Clone-by-clone sequencing

Physical mapping of cloned sequences was once considered a pre-requisite for genome sequencing. The process would begin by breaking the genome into BAC-sized pieces, arranging these BACs into a map, then breaking each BAC up into a series of smaller clones, which were usually then also mapped. Eventually, a minimum set of smaller clones would be identified, each of which was small enough to be sequenced (Figure 3.3.8). Because the order of clones relative to the complete chromosome was known prior to sequencing, the resulting sequence information could be easily assembled into one complete chromosome at the end of the project. Clone-by-clone sequencing therefore minimizes the number of sequencing reactions that must be performed, and makes sequence assembly straightforward and reliable. However, a drawback of this strategy is the tedious process of building physical map prior to any sequencing.

3.3.4: Whole genome shotgun sequencing

This strategy breaks the genome into fragments that are small enough to be sequenced, then reassembles them simply by looking for overlaps in the sequence of each fragment. It avoids the laborious process of making a physical map (Figure 3.3.2). However, it requires many more sequencing reactions than the clone-by-clone method, because, in the shotgun approach, there is no way to avoid sequencing redundant fragments. There is also a question of the feasibility of assembling complete chromosomes based simply on the sequence overlaps of many small fragments. This is particularly a problem when the size of the fragments is smaller than the length of a repetitive region of DNA. Nevertheless, this method has now been successfully demonstrated in the nearly complete sequencing of many large genomes (rice, human, and many others). It is the current standard methodology.

However, shotgun assemblies are rarely able to complete entire genomes. The human genome, for example, relied on a combination of shotgun sequence and physical mapping to produce contiguous sequence for the length of each arm of each chromosome. Note that because of the highly repetitive nature of centromeric and telomeric DNA, sequencing projects rarely include these heterochromatic, gene poor regions.

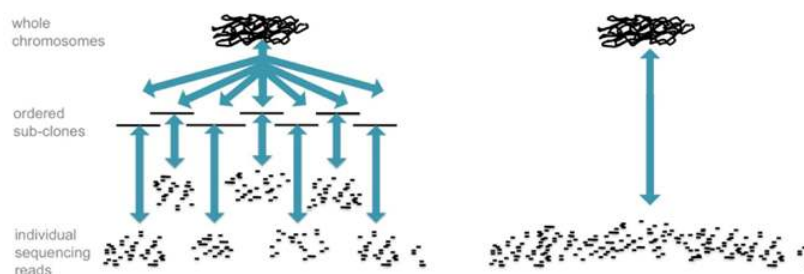


Figure 3.3.2: Genome sequencing strategies. A clone-by-clone strategy (left) in which the genome is divided into progressively smaller units (clones) before sequencing. Whole genome shotgun strategy (right) assembles the sequence from all the smaller reads. (Origianl-Deyholos-CC:AN)

3.3.5: Genome analysis

An assembled genome is a string of millions of A's,C's,G's,T's. Which of these represent nucleotides that encode proteins, and which of these represent other features of genes and their regulatory elements? The process of **genome annotation** relies on computers to define features such a start and stop codons, introns, exons, and splice sites. However, few of the predictions made by these programs is entirely accurate, and most must be verified experimentally for any gene of particular importance or interest.

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3.4: Isolating or Detecting a Specific Sequence by PCR

3.4.1: Components of the PCR Reaction

The **Polymerase Chain Reaction (PCR)** is a method of DNA replication that is performed in a test tube (i.e. *in vitro*). Here “polymerase” refers to a DNA polymerase enzyme extracted and purified from bacteria, and “chain reaction” refers to the ability of this technique produce millions of copies of a DNA molecule, by using each newly replicated double helix as a template to synthesize two new DNA double helices. PCR is therefore a very efficient method of amplifying DNA.

Besides its ability to make large amounts of DNA, there is a second characteristic of PCR that makes it extremely useful. Recall that most DNA polymerases can only add nucleotides to the end of an existing strand of DNA, and therefore require a **primer** to initiate the process of replication. For PCR, chemically synthesized primers of about 20 nucleotides are used. In an ideal PCR, primers only hybridize to their exact complementary sequence on the template strand (Figure 3.4.3).



Figure 3.4.3: The primer-template duplex at the top part of the figure is perfectly matched, and will be stable at a higher temperature than the duplex in the bottom part of the figure, which contains many mismatches and therefore fewer hydrogen bonds. If the annealing temperature is sufficiently high, only the perfectly matched primer will be able to initiate extension (grey arrow) from this site on the template. (Original-Deyholos-CC:AN)

The experimenter can therefore control exactly what region of a DNA template is amplified by controlling the sequence of the primers used in the reaction.

To conduct a PCR amplification, an experimenter combines in a small, thin-walled tube (Figure 3.4.4), all of the necessary components for DNA replication, including DNA polymerase and solutions containing nucleotides (dATP, dCTP, dGTP, dTTP), a DNA template, DNA primers, a pH buffer, and ions (e.g. Mg^{2+}) required by the polymerase. Successful PCR reactions have been conducted using only a single DNA molecule as a template, but in practice, most PCR reactions contain many thousands of template molecules. The template DNA (e.g. total genomic DNA) has usually already been purified from cells or tissues using the techniques described above. However, in some situations it is possible to put whole cells directly in a PCR reaction for use as a template.



Figure 3.4.4: A strip of PCR tubes (Wikipedia-madprime-GFDL)

An essential aspect of PCR is **thermal-cycling**, meaning the exposure of the reaction to a series of precisely defined temperatures (Figure 3.4.5). The reaction mixture is first heated to 95°C. This causes the hydrogen bonds between the strands of the template DNA molecules to melt, or **denature**. This produces two single-stranded DNA molecules from each double helix (Figure 3.4.6). In the next step (**annealing**), the mixture is cooled to 45–65°C. The exact temperature depends on the primer sequence used and the objectives of the experiment. This allows the formation of double stranded helices between complementary DNA molecules, including the annealing of primers to the template. In the final step (**extension**) the mixture is heated to 72°C. This is the temperature at which the particular DNA polymerase used in PCR is most active. During extension, the new DNA strand is synthesized, starting from the 3' end of the primer, along the length of the template strand. The entire PCR process is very quick, with each temperature phase usually lasting 30 seconds or less. Each cycle of three temperatures (denaturation, annealing, extension) is usually repeated about 30 times, amplifying the target region approximately 2^{30} -fold. Notice from the figure that most of the newly synthesized strands in PCR begin and end with sequences either identical to or complementary to the primer sequences; although a few strands are longer than this, they are in such a small minority that they can almost always be ignored.

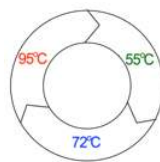


Figure 3.4.5: Example of a thermalcycle, in which the annealing temperature is 55°C. (Original-Deyholos-CC:AN)

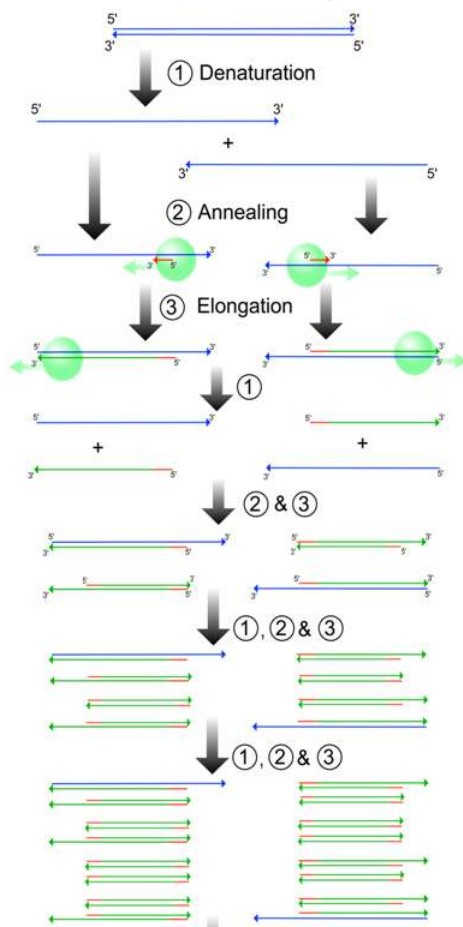


Figure 3.4.6: PCR with the three phases of the thermalcycle numbered. The template strand (blue) is replicated from primers (red), with newly synthesized strands in green. The green strands flanked by two primer binding sites will increase in abundance exponentially through successive PCR cycles. (Wikipedia-madprime-GFDL)

The earliest PCR reactions used a polymerase from *E. coli*. Because the high temperature of the denaturation step destroyed the enzyme, new polymerase had to be added after each cycle. To overcome this, researchers identified **thermostable** DNA polymerases such as **Taq DNA pol**, from *Thermus aquaticus*, a thermophilic bacterium that lives in hot springs. Taq, and similar thermostable polymerases from other hot environments, are able to remain functional in the repeated cycles of amplification. Taq polymerase cannot usually amplify fragments longer than about 3kbp, but under some specialized conditions, PCR can amplify fragments up to approximately 10kbp. Other polymerases, either by themselves or in combination with Taq, are used to increase the length of amplified fragments or to increase the fidelity of the replication.

After completion of the thermalcycling (amplification), an aliquot from the PCR reaction is usually loaded onto an **electrophoretic gel** (described below) to determine whether a DNA fragment of the expected length was successfully amplified or not. Usually, the original template DNA will be so dilute that it will not be visible on the gel, only the amplified PCR product. The presence of a sharp band of the expected length indicates that PCR was able to amplify its target. If the purpose of the PCR was to test for the presence of a particular template sequence, this is the end of the experiment. Otherwise, the remaining PCR product can be used as starting material for a variety of other techniques such as sequencing or cloning.

An Application of PCR: the StarLink Affair

PCR is very sensitive (meaning it can amplify very small starting amounts of DNA), and specific (meaning it can amplify only the target sequence from a mixture of many DNA sequences). This made PCR the perfect tool to test whether genetically modified corn was present in consumer products on supermarket shelves. Although currently (2013) 85% of corn in the United States is genetically modified, and contains genes that government regulators have approved for human consumption, back in 2000, environmental groups showed that a strain of genetically modified corn, which had only been approved for use as animal feed, had been mixed in with corn used in producing human food, like taco shells.

To do this, the groups purchased taco shells from stores in the Washington DC area, extracted DNA from the taco shells and used it as a template in a PCR reaction with primers specific to the unauthorized gene (*Cry9C*). Their suspicions were confirmed when they ran this PCR product on an agarose gel and saw a band of expected size. The PCR test was able to detect one transgenic kernel in a whole bushel of corn (1 per 100,000). The company (Aventis) that sold the transgenic seed to farmers had to pay for the destruction of large amounts of corn, and was the target of a class action law-suit by angry consumers who claimed they had been made sick by the taco shells. While no legitimate cases of harm were ever proven, and the plaintiffs were awarded \$9 million, of which \$3 million went to the legal fees, and the remainder of the judgment went to the consumers in the form of coupons for taco shells. The affair damaged the company, and exposed a weakness in the way the genetically modified crops were handled in the United States at the time.

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3.5: DNA Analysis - Gel Electrophoresis

A solution of DNA is colorless, and except for being viscous at high concentrations, is visually indistinguishable from water. Therefore, techniques such as **gel electrophoresis** have been developed to detect and analyze DNA (Figure 3.5.11).

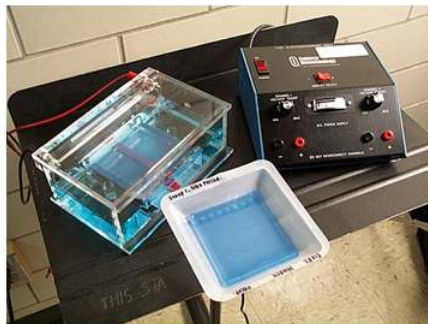


Figure 3.5.11: Apparatus for agarose gel electrophoresis. A waterproof tank is used to pass current through a slab gel, which is submerged in a buffer in the tank. The current is supplied by an adjustable power supply. A gel (stained blue by a dye sometimes used when loading DNA on the gel) sits in a tray, awaiting further analysis, such as photography under a UV light source. (Flickr-457088634_585df11af5_o-pending)

This analysis starts when a solution of DNA is deposited at one end of a gel slab. This gel is made from polymers such as **agarose**, which is a polysaccharide isolated from seaweed. The DNA is then forced through the gel by an electrical current, with DNA molecules moving toward the positive electrode (Figure 3.5.12).

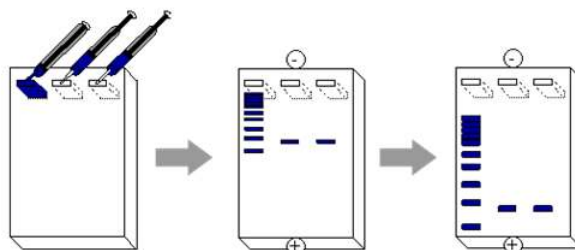


Figure 3.5.12: Agarose gel electrophoresis. DNA is loaded into wells at the top of a gel. A current is passed through the gel, pulling DNA towards the positively charged electrode. The DNA fragments are separated by size, with smaller fragments moving fastest towards the electrode. (Wikipedia-Magnus Manske_PD)

As it migrates, each piece of DNA threads its way through the pores, which form between the polymers in the gel. Because shorter pieces can move through these pores faster than longer pieces, gel electrophoresis separates molecules based on their size (length), with smaller DNA pieces moving faster than long ones. DNA molecules of a similar size migrate to a similar location in each gel, called a **band**. This feature makes it easy to see DNA after staining the DNA with a fluorescent dye such as **ethidium bromide** (Figure 3.5.13). By separating a mixture of DNA molecules of known size (**size markers**) in adjacent lanes on the same gel, the length of an uncharacterized DNA fragment can be estimated. Gel segments containing the DNA bands can also be cut out of the gel, and the size-selected DNA extracted and used in other types of reactions, such as sequencing and cloning.

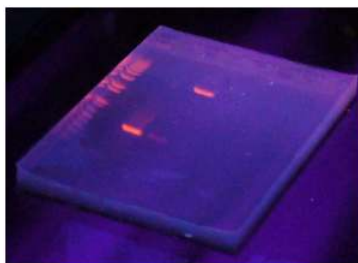


Figure 3.5.13: An agarose gel stained with ethidium bromide and illuminated by UV light. The stain associated with DNA is fluorescent. (Wikipedia-Transcontrol-GFDL)

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3.6: DNA Analysis- Blotting and Hybridization

Bands of DNA in an electrophoretic gel form only if most of the DNA molecules are of the same size, such as following a PCR reaction, or restriction digestion of a plasmid. In other situations, such as after restriction digestion of chromosomal (genomic) DNA, there will be a large number of variable size fragments in the digest and it will appear as a continuous smear of DNA, rather than distinct bands. In this case, it is necessary to use additional techniques to detect the presence of a specific DNA sequence within the smear of DNA separated on an electrophoretic gel. This can be done using a “Southern Blot”.

3.6.1: Southern Blots

A **Southern blot** (also called a **Southern Transfer**) is named after Ed Southern, its inventor. In the first step, DNA is digested with restriction enzymes and separated by gel electrophoresis (as discussed above). Then a sheet or **membrane** of nylon or similar material is laid under the gel and the DNA, in its separated position (bands or smear), is transferred to the membrane by drawing the liquid out of the gel, in a process called **blotting** (Figure 3.6.1). The blotted DNA is usually covalently attached to the nylon membrane by briefly exposing the blot to UV light. Transferring the DNA to the sturdy membrane is necessary because the fragile gel would fall apart during the next two steps in the process. Next, the membrane is bathed in a solution to **denature** (double stranded made single stranded) the attached DNA. Then a **hybridization** solution containing a small amount of single-stranded **probe** DNA that is complementary in sequence to a target molecule on the membrane. This probe DNA is labeled using fluorescent or radioactive molecules, and if the hybridization is performed properly, the probe DNA will form a stable duplex only with those DNA molecules on the membrane that are exactly complementary to it. Then, the unhybridized probe is washed off and remaining radioactive or fluorescent signal will appear in a distinct band when appropriately detected. The band represents the presence of a particular DNA sequence within the mixture of DNA fragments.

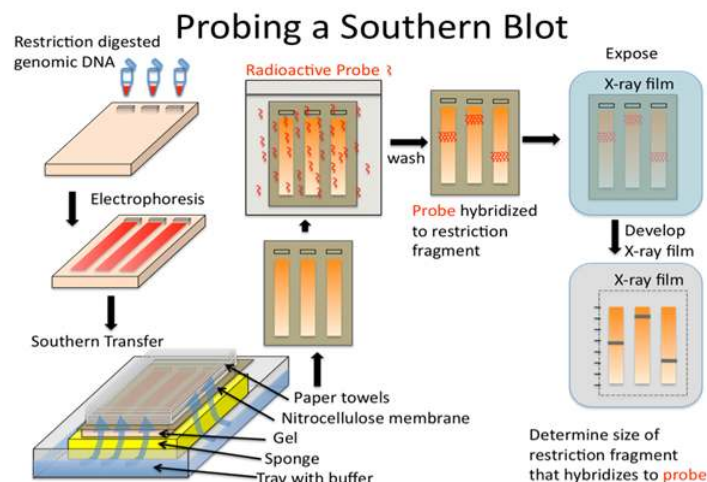


Figure 3.6.1: A diagram of Southern blotting. Genomic DNA that has been digested with a restriction enzyme is separated on an agarose gel, then the DNA is transferred from the gel to a nylon membrane (grey sheet) by blotting. The DNA is immobilized on the membrane, then probed with a **radioactively labeled DNA fragment** that is complementary to a target sequence. After stringent washing, the blot is exposed to X-ray film to detect what size fragment the probe is bound. In this case, the probe bound to different-sized fragments in lanes 1, 2, and 3. In the last image the orange represent the position of the digested DNA, but it is not actually present on the X-ray film. (Original-J. Locke-CC:AN)

The probe is sequence specific (requires complementarity). However, variation in hybridization temperature and washing solutions can alter the **stringency** of the probe. At maximum stringency (higher temperature) hybridization conditions, probes will only hybridize with the exact target sequences that are perfectly complementary (maximum number of hydrogen bonds). At lower temperatures, probes will be able to hybridize to targets to which they do not match exactly, but only are roughly complementary for part of the sequence.

Southern blotting is useful not only for detecting the presence of a DNA sequence within a mixture of DNA molecules, but also for determining the size of a restriction fragment in a DNA sample. Southern blots are useful for detecting fragments larger than those normally amplified by PCR, and when trying to detect fragments that may be only distantly related to a known sequence. Applications of Southern blotting will be discussed further in the context of molecular markers in a subsequent chapter. Southern

blotting was invented before PCR, but PCR has replaced blotting in many applications because of its simplicity, speed, and convenience. Following the development of the Southern blot, other types of blotting techniques were invented.

3.6.2: Northern Blots

The **Northern blot** involves the size separation of RNA in gels like that of DNA. Because we wish to determine the native size of the RNA transcript (and because RNA is single stranded) no restriction enzymes are ever used. Because most RNA is single stranded and can fold into various conformations thorough intra-molecular base pairing, the electrophoresis separation is more haphazard and the bands are often less sharp, compared to that of double stranded DNA.

3.6.3: Western Blots

In a **Western blot**, protein is size separated on a gel (usually an acrylamide gel) before transferring to a membrane, which is then probed with an antibody that specifically binds to an antigenic site on the target protein. This antibody is then detected by other antibodies with some fluorescent or color production marker system. It will also give bands proportional to the amount and size of the target protein (Figure 3.6.2).

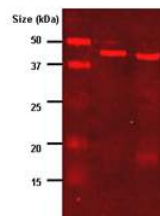


Figure 3.6.2: Western Blot using a anti-lipoic acid primary antibody and an IR-dye labelled secondary antibody in Leishmania major extracts. (Wikipedia-TimVickers-CC:AS)

A comparison of all three blotting methods is shown in Figure 3.6.3.

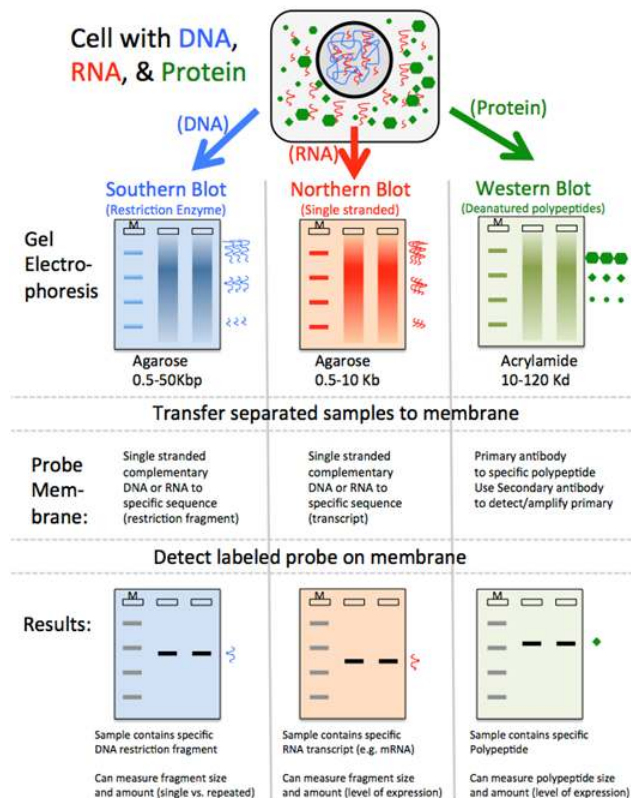


Figure 3.6.3: Comparison of Southern, Northern, and Western blots. Size and amount of DNA, RNA, and polypeptides can be determined using similar blotting methods. DNA is in blue, RNA in red, and polypeptides in green. A marker lane is shown in the left of each gel to determine size. A eukaryote cell is shown, but the same methods can be applied to prokaryotes, too. (Original-Locke-CC:AN)

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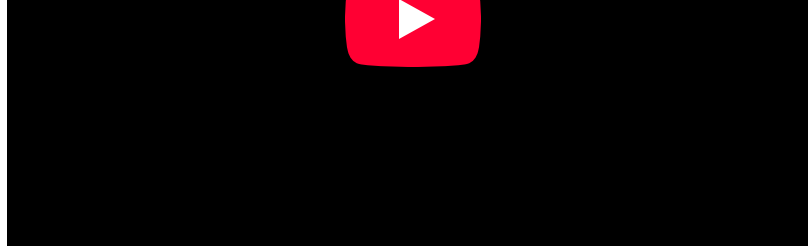
CHAPTER OVERVIEW

4: Mendelian Genetics

- 4.1: Alleles and genes
- 4.2: Mendel's First Law
- 4.3: Mendel and his peas
- 4.4: The law of segregation
- 4.5: The law of independent assortment
- 4.6: Relationships Between Genes, Genotypes and Phenotypes
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- 4.8: Biochemical Basis of Dominance
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4.1: Alleles and genes



A gene as a stretch of DNA on a chromosome. Alleles as versions (sequence variants) of a gene.

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4.2: Mendel's First Law

4.2.1: Character Traits Exist in Pairs that Segregate at Meiosis

Through careful study of patterns of inheritance, Mendel recognized that a single trait could exist in different versions, or **alleles**, even within an individual plant or animal. For example, he found two allelic forms of a gene for seed color: one allele gave green seeds, and the other gave yellow seeds. Mendel also observed that although different alleles could influence a single trait, they remained indivisible and could be inherited separately. This is the basis of **Mendel's First Law**, also called **The Law of Equal Segregation**, which states: during gamete formation, the two alleles at a gene locus segregate from each other; each gamete has an equal probability of containing either allele.

Seed		Flower	Pod		Stem	
Form	Color	Color	Form	Color	Place	Size
						
Round	Yellow	White	Full	Yellow	Axial pods, Flowers along	Long (6-7ft)
						
Wrinkled	Green	Purple	Constricted	Green	Terminal pods, Flowers top	Short $\frac{1}{2}$ -1ft
1	2	3	4	5	6	7

Figure 4.2.2: Seven traits Mendel studied in peas. (Wikipedia-Mariana Ruiz-PD)

4.2.2: Hetero-, Homo-, Hemizygosity

Mendel's First Law is especially remarkable because he made his observations and conclusions (1865) without knowing about the relationships between genes, chromosomes, and DNA. We now know the reason why more than one allele of a gene can be present in an individual: most eukaryotic organisms have at least two sets of homologous chromosomes. For organisms that are predominantly diploid, such as humans or Mendel's peas, chromosomes exist as pairs, with one homolog inherited from each parent. Diploid cells therefore contain two different alleles of each gene, with one allele on each member of a pair of homologous chromosomes. If both alleles of a particular gene are identical, the individual is said to be **homozygous** for that gene. On the other hand, if the alleles are different from each other, the genotype is **heterozygous**. In cases where there is only one copy of a gene present, for example if there is a deletion on the homologous chromosome, we use the term **hemizygous**.

Although a typical diploid individual can have at most two different alleles of a particular gene, many more than two different alleles can exist in a population of individuals. In a natural population the most common allelic form is usually called the **wild-type** allele. However, in many populations there can be multiple **variants** at the DNA sequence level that are visibly indistinguishable as all exhibit a normal, wild type appearance. There can also be various **mutant** alleles (in wild populations and in lab strains) that vary from wild type in their appearance, each with a different change at the DNA sequence level. Such collections of mutations are known as an **allelic series**.

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4.3: Mendel and his peas

4.3.1: How can we study inheritance?

When spending time with your own family, friends, and neighbors, you may have noticed that many traits run in families. For instance, members of a family may share similar facial features, hair color (like the brother and sister below), or a predisposition to health problems such as diabetes. Characteristics that run in families often have a **genetic basis**, meaning that they depend on genetic information a person inherits from his or her parents.



Image credit "[Brother, sister, portrait, russet](#)," by Adina Voicu (CC0, public domain).

What if you wanted to figure out how genetic information is transmitted between generations? For instance, you might be curious how traits can "skip" a generation, or why one child in a family may suffer from a genetic disease while another does not. How could you go about asking these kinds of questions scientifically?

An obvious first idea would be to study human inheritance patterns directly, but that turns out to be a tricky proposition (see the pop-up below for details). In this article, we'll see how a nineteenth-century monk named Gregor Mendel instead uncovered the key principles of inheritance using a simple, familiar system: the pea plant.

[Why didn't Mendel study humans?]

Many of us are curious about genetics because we want to understand human inheritance. If the burning questions of genetics are about humans, why would anyone study inheritance in something like the pea plant?

When it comes to basic principles of inheritance, humans may be the organisms we most want to learn about, but they aren't always the best organisms to study experimentally. For instance, it takes many years for a human being to grow, mature, and have children, making data collection slow. Also, when humans have children, they often have one or two (rather than, say, several thousand), making it harder to see mathematical patterns in the data. Finally, and perhaps most critically, it wouldn't be

possible (or ethical) to set up controlled experiments in human genetics – that is, you couldn't ask a pair of people to have children just because you were curious what those children would look like.

Peas, on the other hand, grow quickly, make many seeds, and can be bred to one another in a simple, controlled way. In other words, they're good organisms to study in many ways that humans aren't. Using pea plants, Mendel was able to uncover fundamental principles of inheritance that apply to many different kinds of organisms. Although these principles would have been nearly impossible to deduce from human family trees alone, they form the core of the modern field of human genetics. Mendel's laws, and later findings building on those laws, allow us to understand and predict the inheritance of many human traits, including genetic disorders.

4.3.2: The monk in the garden: Gregor Mendel

Johann Gregor Mendel (1822–1884), often called the “father of genetics,” was a teacher, lifelong learner, scientist, and man of faith. It would be fair to say that Mendel had a lot of grit: he persevered through difficult circumstances to make some of the most important discoveries in biology.



Image credit: "Mendel's experiments and the laws of probability: Figure 1," by OpenStax College, Biology (CC BY 3.0).

As a young man, Mendel had difficulty paying for his education due to his family's limited means, and he also suffered bouts of physical illness and depression; still, he persevered to graduate from high school and, later, university¹. After finishing university, he joined the Augustinian Abbey of St. Thomas in Brno, in what is now the Czech Republic. At the time, the monastery was the cultural and intellectual hub of the region, and Mendel was immediately exposed to new teachings and ideas¹.

His decision to join the order (against the wishes of his father, who expected him to carry on the family farm) appears to have been motivated in part by a desire to continue his education and pursue his scientific interests². Supported by the monastery, he taught physics, botany, and natural science courses at the secondary and university levels.

4.3.2.1: Research on heredity

In 1856, Mendel began a decade-long research project to investigate patterns of inheritance. Although he began his research using mice, he later switched to honeybees and plants, ultimately settling on garden peas as his primary model system². A **model system** is an organism that makes it easy for a researcher to investigate a particular scientific question, such as how traits are inherited. By studying a model system, researchers can learn general principles that apply to other, harder-to-study organisms or biological systems, such as humans.

Mendel studied the inheritance of seven different features in peas, including height, flower color, seed color, and seed shape. To do so, he first established pea lines with two different forms of a feature, such as tall vs. short height. He grew these lines for

generations until they were pure-breeding (always produced offspring identical to the parent), then bred them to each other and observed how the traits were inherited.

In addition to recording how the plants in each generation looked, Mendel counted the exact number of plants that showed each trait. Strikingly, he found very similar patterns of inheritance for all seven features he studied:

- One form of a feature, such as tall, always concealed the other form, such as short, in the first generation after the cross. Mendel called the visible form the **dominant trait** and the hidden form the **recessive trait**.
- In the second generation, after plants were allowed to self-fertilize (pollinate themselves), the hidden form of the trait reappeared in a minority of the plants. Specifically, there were always about 3 plants that showed the dominant trait (e.g., tall) for every 1 plant that showed the recessive trait (e.g., short), making a 3:1 ratio.
- Mendel also found that the features were inherited independently: one feature, such as plant height, did not influence inheritance of other features, such as flower color or seed shape.

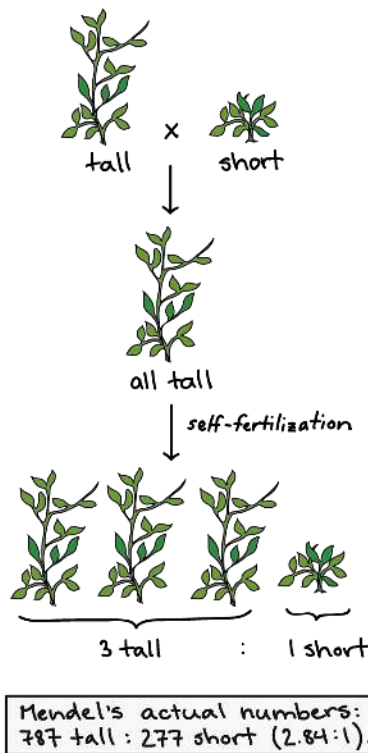


Image modified from "[Mendel seven characters](#)," by Mariana Ruiz Villareal (public domain).

In 1865, Mendel presented the results of his experiments with nearly 30,000 pea plants to the local Natural History Society. Based on the patterns he observed, the counting data he collected, and a mathematical analysis of his results, Mendel proposed a model of inheritance in which:

- Characteristics such as flower color, plant height, and seed shape were controlled by pairs of heritable factors that came in different versions.
- One version of a factor (the dominant form) could mask the presence of another version (the recessive form).
- The two paired factors separated during gamete production, such that each gamete (sperm or egg) randomly received just one factor.
- The factors controlling different characteristics were inherited independently of one another.

We'll take a closer look at how Mendel reached these conclusions in the articles on the [law of segregation](#) and the [law of independent assortment](#). In 1866, Mendel published his observations and his model of inheritance, under the title *Experiments in Plant Hybridization*^{3,4}, in the Proceedings of the Natural History Society of Br $\ddot{u}$ nn.

4.3.2.2: Scientific legacy

Mendel's work went largely unnoticed by the scientific community during his lifetime. How could this have been the case?

In part, Mendel's contemporaries failed to recognize the importance of his work because his findings went against prevailing (popular) ideas about inheritance. In addition, although we now see Mendel's mathematical approach to biology as innovative and pioneering, it was new, unfamiliar, and perhaps confusing or unintuitive to other biologists of the time⁵.

In the mid-1800s, when Mendel was doing his experiments, most biologists subscribed to the idea of **blending inheritance**. Blending inheritance wasn't a formal, scientific hypothesis, but rather, a general model in which inheritance involved the permanent blending of parents' characteristics in their offspring (producing offspring with an intermediate form of a characteristic)⁶. The blending model fit well with some observations of human inheritance: for instance, children often look a bit like both of their parents.

But the blending model could not explain why Mendel crossed a tall and a short pea plant and got only tall plants, or why self-fertilization of one of those tall plants would produce a 3:1 ratio of tall to short plants in the next generation. Instead, if the blending model were correct, a tall plant crossed with a short plant should produce a medium plant, which would go on to produce more medium plants (see below).

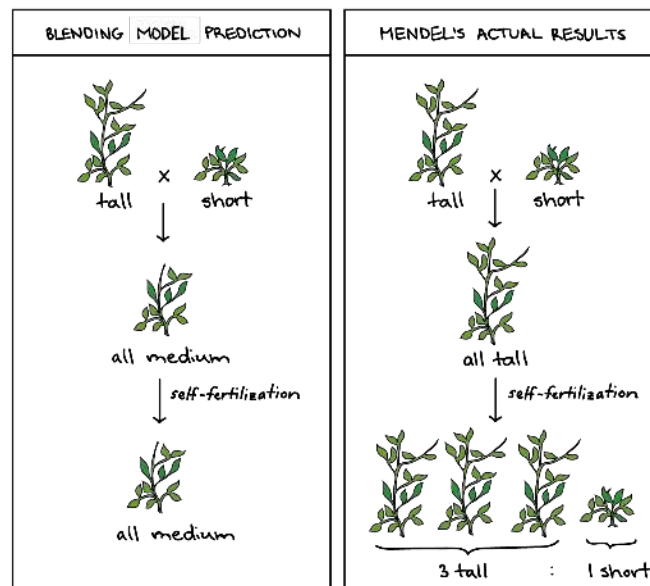


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As it turns out, both pea plant height and human height (along with many other characteristics in a wide range of organisms) are controlled by pairs of heritable factors that come in distinctive versions, just as Mendel proposed. In humans, however, there are many different factors (genes) that contribute fractionally to height and vary among individuals. This makes it difficult to see the contribution of any one factor and produces inheritance patterns that can resemble blending. In Mendel's experiments, in contrast, there was just one factor that differed between the tall and short pea plants, allowing Mendel to clearly see the underlying pattern of inheritance.

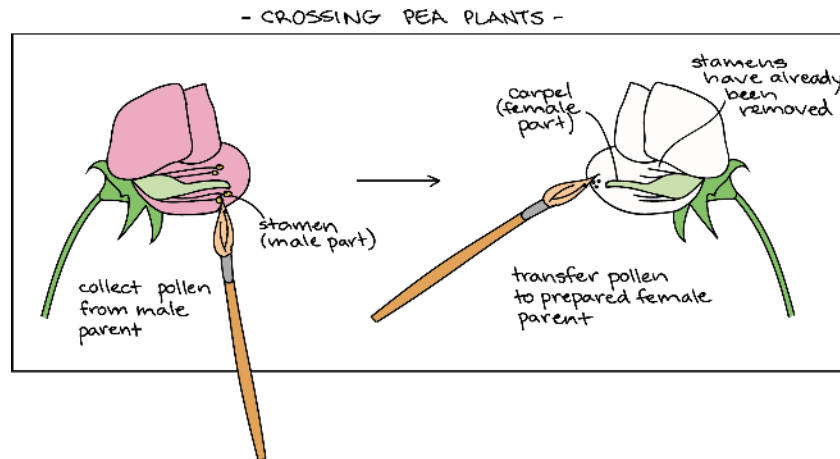
In 1868, Mendel became abbot of his monastery and largely set aside his scientific pursuits in favor of his pastoral duties. He was not recognized for his extraordinary scientific contributions during his lifetime. In fact, it was not until around 1900 that his work was rediscovered, reproduced, and revitalized. Its rediscoverers were biologists on the brink of discovering the chromosomal basis of heredity – that is, about to realize that Mendel's "heritable factors" were carried on chromosomes.

4.3.3: Mendel's model system: The pea plant

Mendel carried out his key experiments using the garden pea, *Pisum sativum*, as a model system. Pea plants make a convenient system for studies of inheritance, and they are still studied by some geneticists today.

Useful features of peas include their rapid life cycle and the production of lots and lots of seeds. Pea plants also typically self-fertilize, meaning that the same plant makes both the sperm and the egg that come together in fertilization. Mendel took advantage of this property to produce **true-breeding** pea lines: he self-fertilized and selected peas for many generations until he got lines that consistently made offspring identical to the parent (e.g., always short).

Pea plants are also easy to cross, or mate in a controlled way. This is done by transferring pollen from the anthers (male parts) of a pea plant of one variety to the carpel (female part) of a mature pea plant of a different variety. To prevent the receiving plant from self-fertilizing, Mendel painstakingly removed all of the immature anthers from the plant's flowers before the cross.



Because peas were so easy to work with and prolific in seed production, Mendel could perform many crosses and examine many individual plants, making sure that his results were consistent (not just a fluke) and accurate (based on many data points).

4.3.4: Mendel's experimental setup

Once Mendel had established true-breeding pea lines with different traits for one or more features of interest (such as tall vs. short height), he began to investigate how the traits were inherited by carrying out a series of crosses.

First, he crossed one true-breeding parent to another. The plants used in this initial cross are called the **P generation**, or parental generation.

Mendel collected the seeds from the P generation cross and grew them up. These offspring were called the **F₁ generation**, short for first filial generation. (*Filius* means "son" in Latin, so this name is slightly less weird than it seems!)

Once Mendel examined the F₁ plants and recorded their traits, he let them self-fertilize naturally, producing lots of seeds. He then collected and grew the seeds from the F₁ plants to produce an **F₂ generation**, or second filial generation. Again, he carefully examined the plants and recorded their traits.

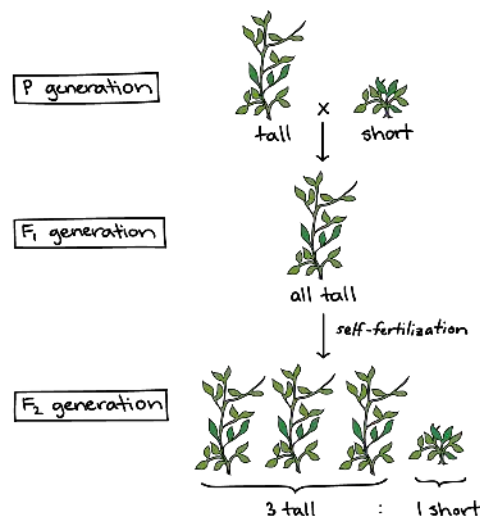


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Mendel's experiments extended beyond the F₂ generation to F₃, F₄, and later generations, but his model of inheritance was based mostly on the first three generations (P, F₁, and F₂).

Mendel didn't just record what his plants looked like in each generation (e.g., tall vs. short). Instead, he counted exactly how many plants with each trait were present. This may sound tedious, but by recording numbers and thinking mathematically, Mendel made discoveries that eluded famous scientists of his time (such as Charles Darwin, who carried out similar experiments but didn't grasp the significance of his results)⁵.

You can use the links below to learn more about Mendel's laws of inheritance:

- The [law of segregation](#), describing how individual traits are inherited.
- The [law of independent assortment](#), describing how two or more traits are inherited relative to one another.

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4.4: The law of segregation

4.4.1: Key points:

- Gregor Mendel studied inheritance of traits in pea plants. He proposed a model where pairs of "heritable elements," or **genes**, specified traits.
- Genes come in different versions, or **alleles**. A **dominant** allele hides a **recessive** allele and determines the organism's appearance.
- When an organism makes gametes, each gamete receives just one gene copy, which is selected randomly. This is known as the **law of segregation**.
- A **Punnett square** can be used to predict **genotypes** (allele combinations) and **phenotypes** (observable traits) of offspring from genetic crosses.
- A **test cross** can be used to determine whether an organism with a dominant phenotype is homozygous or heterozygous.

4.4.2: Introduction

Today, we know that many of people's characteristics, from hair color to height to risk of diabetes, are influenced by genes. We also know that genes are the way parents pass characteristics on to their children (including things like dimples, or—in the case of me and my father—a terrible singing voice). In the last hundred years, we've come to understand that genes are actually pieces of DNA that are found on **chromosomes** and **specify proteins**.

But did we always know those things? Not by a long shot! About 150 years ago, a monk named **Gregor Mendel** published a paper that first proposed the existence of genes and presented a model for how they were inherited. Mendel's work was the first step on a long road, involving many hard-working scientists, that's led to our present understanding of genes and what they do.

In this article, we'll trace the experiments and reasoning that led Mendel to formulate his model for the inheritance of single genes.

4.4.3: Mendel's model: It started with a 3:1 ratio

Mendel studied the genetics of pea plants, and he traced the inheritance of a variety of characteristics, including flower color, flower position, seed color, and seed shape. To do so, he started by crossing **pure-breeding** parent plants with different forms of a characteristic, such as violet and white flowers. Pure-breeding just means that the plant will always make more offspring like itself, when self-fertilized over many generations.

[What is self-fertilization?]

In self-fertilization, sperm and eggs from the same pea plant combine inside a closed flower, producing seeds with a single plant as both mother and father.

What results did Mendel find in his crosses for flower color? In the parental, or P generation, Mendel crossed a pure-breeding violet-flowered plant to a pure-breeding white-flowered plant. When he gathered and planted the seeds produced in this cross, Mendel found that 100 percent of the plants in the next generation, or F₁ generation, had violet flowers.

Conventional wisdom at that time would have predicted that the hybrid flowers should be pale violet—that is, that the parents' traits should blend in the offspring. Instead, Mendel's results showed that the white flower trait had completely disappeared. He called the trait that was visible in the F₁ generation (violet flowers) the **dominant trait**, and the trait that was hidden or lost (white flowers) the **recessive trait**.

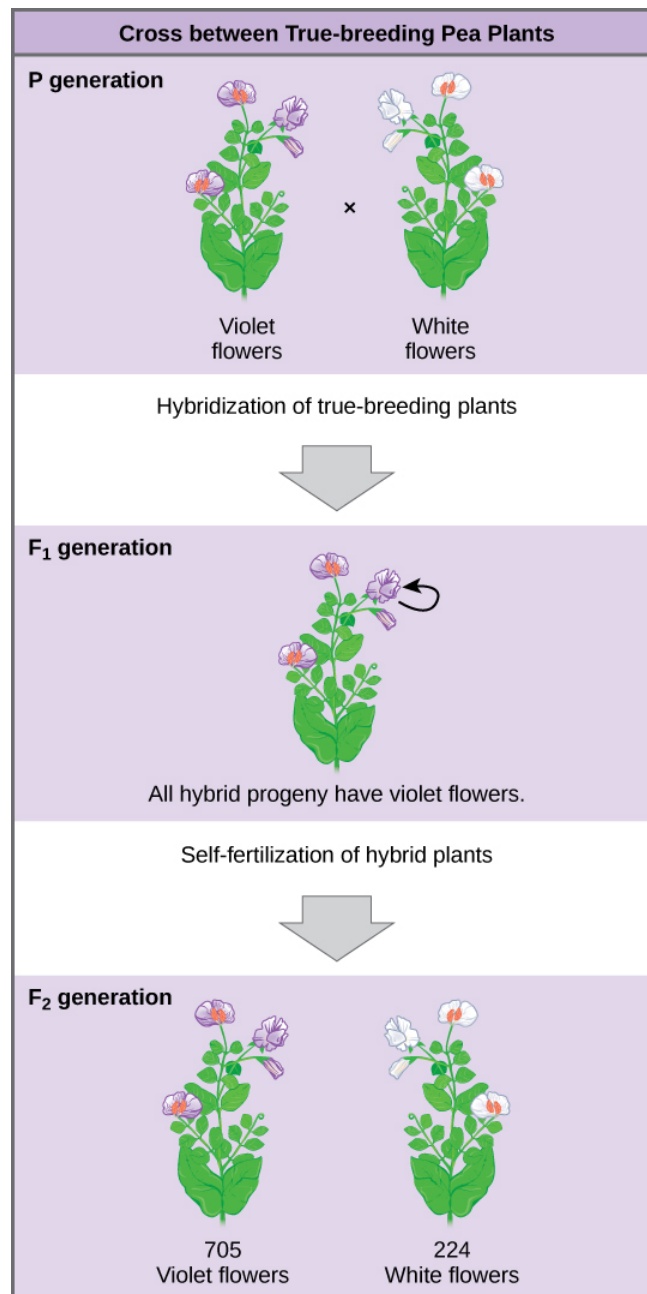


Image credit: "Mendel's experiments: Figure 2," by Robert Bear et al., OpenStax, [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

Importantly, Mendel did not stop his experimentation there. Instead, he let the F₁ plants self-fertilize. Among their offspring, called the F₂ generation, he found that 705 plants had violet flowers and 224 had white flowers. This was a ratio of 3.15 violet flowers to one white flower, or approximately 3:1.

This 3:1 ratio was no fluke. For the other six characteristics that Mendel examined, both the F₁ and F₂ generations behaved in the same way they did for flower color. One of the two traits would disappear completely from the F₁ generation, only to reappear in the F₂ generation in a ratio of roughly 3:1.

[See Mendel's data for all seven characteristics]

Character	Dominant trait	Recessive trait	F ₂ generation	F ₂ ratio
Seed color	Yellow	Green	6022 yellow, 2001 green	3.01:1
Seed shape	Round	Wrinkled	5474 round, 1850 wrinkled	2.96:1
Pod color	Green	Yellow	428 green, 152 yellow	2.82:1
Pod shape	Inflated	Constricted	882 inflated, 299 constricted	2.95:1
Plant height	Tall	Short (dwarf)	787 tall, 277 short	2.84:1
Flower color	Purple	White	705 purple, 224 white	3.15:1
Flower position	Axial (along branch)	Terminal (end of branch)	651 axial, 207 terminal	3.14:1

Adapted from "[The results of Mendel's garden pea hybridizations](#)," by OpenStax College, Biology (CC BY 3.0).

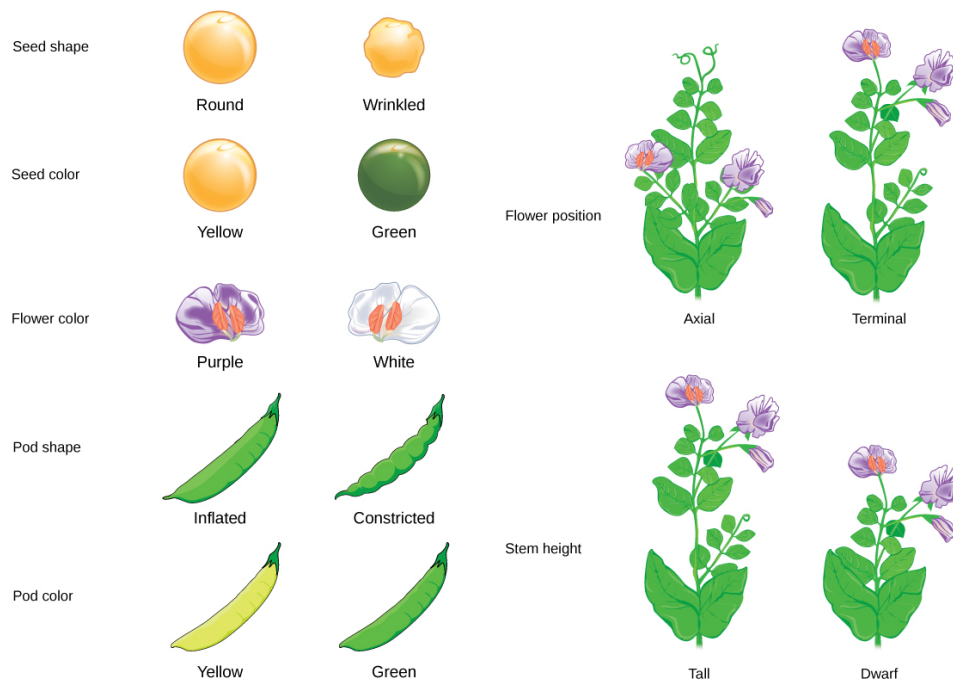


Image credit: "[Mendel's experiments: Figure 3](#)," by Robert Bear et al., OpenStax, CC BY 4.0

As it turned out, the 3:1 ratio was a crucial clue that let Mendel crack the puzzle of inheritance. Let's take a closer look at what Mendel figured out.

4.4.4: Mendel's model of inheritance

Based on his results (including that magic 3:1 ratio), Mendel came up with a model for the inheritance of individual characteristics, such as flower color.

In Mendel's model, parents pass along "heritable factors," which we now call **genes**, that determine the traits of the offspring. Each individual has two copies of a given gene, such as the gene for seed color (Y gene) shown below. If these copies represent different versions, or **alleles**, of the gene, one allele—the **dominant** one—may hide the other allele—the **recessive** one. For seed color, the dominant yellow allele Y hides the recessive green allele y.

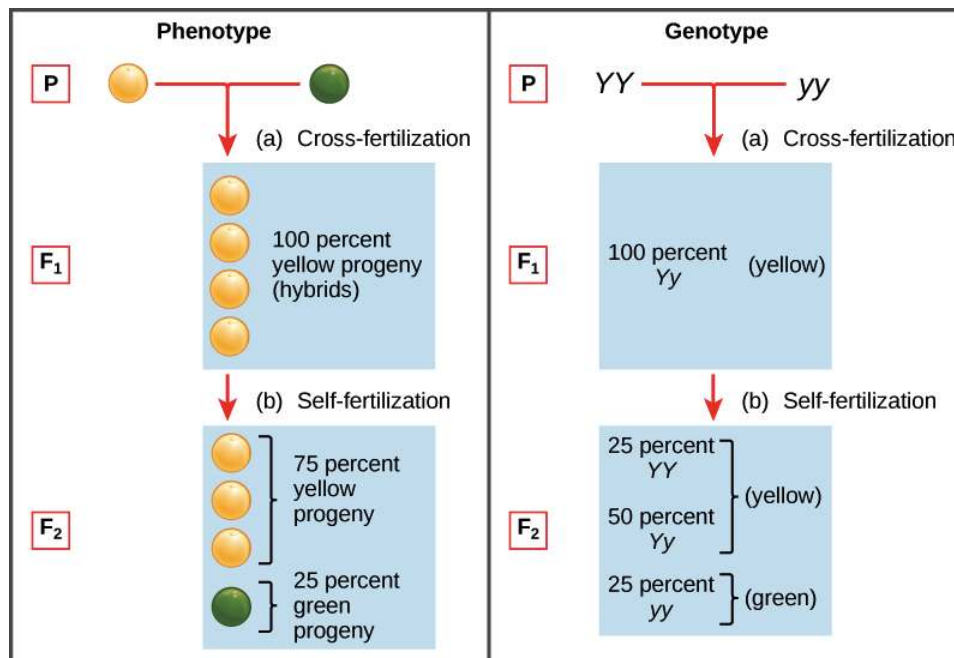


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The set of alleles carried by an organism is known as its **genotype**. Genotype determines **phenotype**, an organism's observable features. When an organism has two copies of the same allele (say, YY or yy), it is said to be **homozygous** for that gene. If, instead, it has two different copies (like Yy), we can say it is **heterozygous**. Phenotype can also be affected by the environment in many real-life cases, though this did not have an impact on Mendel's work.

4.4.4.1: Mendel's model: The law of segregation

So far, so good. But this model alone doesn't explain why Mendel saw the exact patterns of inheritance he did. In particular, it doesn't account for the 3:1 ratio. For that, we need Mendel's law of segregation.

According to the **law of segregation**, only one of the two gene copies present in an organism is distributed to each gamete (egg or sperm cell) that it makes, and the allocation of the gene copies is random. When an egg and a sperm join in fertilization, they form a new organism, whose genotype consists of the alleles contained in the gametes. The diagram below illustrates this idea:

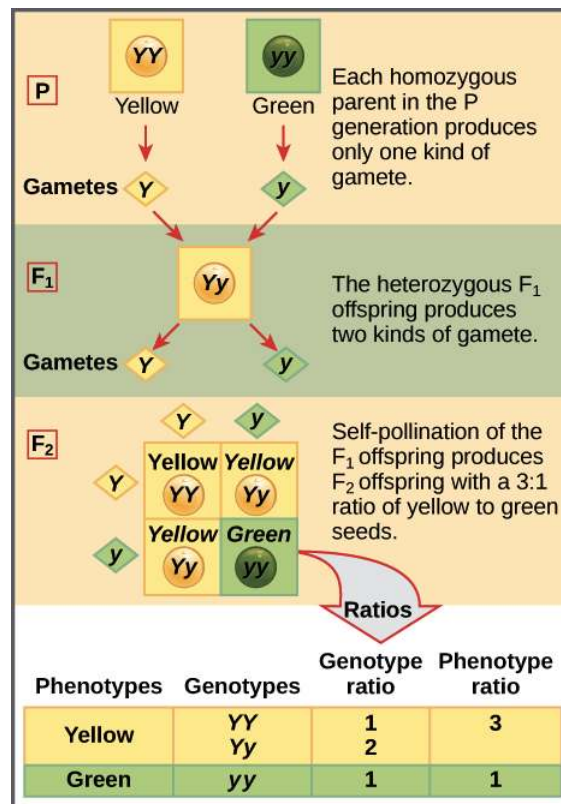


Image modified from "Laws of inheritance: Figure 5," by Robert Bear et al., OpenStax, CC BY 4.0

The four-squared box shown for the F_2 generation is known as a **Punnett square**. To prepare a Punnett square, all possible gametes made by the parents are written along the top (for the father) and side (for the mother) of a grid. Here, since it is self-fertilization, the same plant is both mother and father.

The combinations of egg and sperm are then made in the boxes in the table, representing fertilization to make new individuals. Because each square represents an equally likely event, we can determine genotype and phenotype ratios by counting the squares.

[Why are the boxes all equally likely?]

A key point of the law of segregation is that a parent's two gene copies are randomly distributed to its gametes. Thus, for a Yy heterozygote, Y and y gametes are equally likely to be made: 50% of the sperm and eggs will have a Y allele, 50% will have a y allele, and the same will be true for eggs.

Since each type of gamete is equally common, each fertilization event (meeting of gametes, corresponding to a square of the table) also has an equal chance of happening. Thus, the boxes of the table represent four equal-probability events.

Since the table contains 1 box with a YY genotype, 2 boxes with a Yy genotype, and 1 box with a yy genotype, we'd expect to see YY , Yy , and yy plants in a ratio of 1:2:1 in the F_2 generation. Since both YY and Yy plants are yellow, this genotype ratio translates into a phenotypic ratio of 3:1 yellow-seeded to green-seeded plants, almost exactly what Mendel observed.

YY and yy plants each appear in just one square, while Yy plants are found in two squares. This is because there are two different fertilization events that lead to a Yy plant: the fusion of a Y egg and a y sperm, or the fusion of a y egg and a Y sperm. Either event is equally likely, and has the same likelihood as a YY or yy fertilization event.

4.4.5: The test cross

Mendel also came up with a way to figure out whether an organism with a dominant phenotype (such as a yellow-seeded pea plant) was a heterozygote (Yy) or a homozygote (YY). This technique is called a **test cross** and is still used by plant and animal breeders today.

In a test cross, the organism with the dominant phenotype is crossed with an organism that is homozygous recessive (e.g., green-seeded):

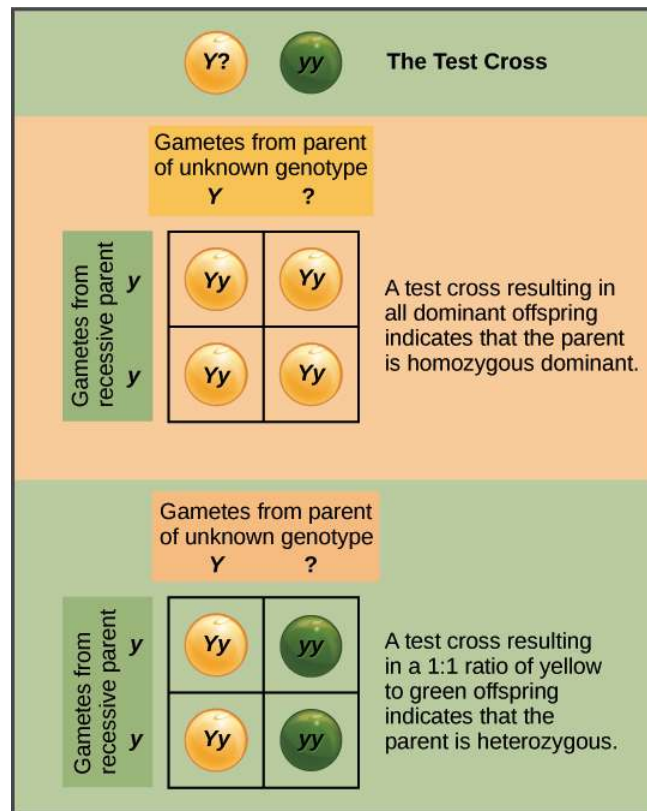


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If the organism with the dominant phenotype is homozygous, then all of the F_1 offspring will get a dominant allele from that parent, be heterozygous, and show the dominant phenotype. If the organism with the dominant phenotype organism is instead a heterozygote, the F_1 offspring will be half heterozygotes (dominant phenotype) and half recessive homozygotes (recessive phenotype).

The fact that we get a 1:1 ratio in this second case is another confirmation of Mendel's law of segregation.

4.4.6: Is that Mendel's complete model of inheritance?

Not quite! We've seen all of Mendel's model for the inheritance of single genes. However, Mendel's complete model also addressed whether genes for different characteristics (such as flower color and seed shape) influence each other's inheritance. You can learn more about Mendel's model for the inheritance of multiple genes in the [law of independent assortment](#) article.

One thing I find pretty amazing is that Mendel was able to figure out his entire model of inheritance simply from his observations of pea plants. This wasn't because he was some kind of crazy super genius, but rather, because he was very careful, persistent, and curious, and also because he thought about his results mathematically (for instance, the 3:1 ratio). These are some of the qualities of a great scientist—ones that anyone, anywhere, can develop!

4.4.6.1: Check your understanding

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4.5: The law of independent assortment

4.5.1: Introduction

The [law of segregation](#) lets us predict how a single feature associated with a single gene is inherited. In some cases, though, we might want to predict the inheritance of two characteristics associated with two different genes. How can we do this?

[Refresher on the law of segregation]

The **law of segregation** states that each gamete (sperm or egg cell) made by an organism will get just one of the two gene copies present in a parent organism, and that the gene copies are randomly allocated to the gametes. For instance, if an organism has a genotype of Aa , half of its gametes will contain an A allele, and the other half will contain an a allele.

You can use the link at the start of the paragraph to learn more about the law of segregation.

To make an accurate prediction, we need to know whether the two genes are inherited independently or not. That is, we need to know whether they "ignore" one another when they're sorted into gametes, or whether they "stick together" and get inherited as a unit.

When [Gregor Mendel](#) asked this question, he found that different genes were inherited independently of one another, following what's called the **law of independent assortment**. In this article, we'll take a closer look at the law of independent assortment and how it is used to make predictions. We'll also see when and why the law of independent assortment does (or doesn't!) hold true.

Note: If you are not yet familiar with how individual genes are inherited, you may want to check out the article on the [law of segregation](#) or the [introduction to heredity](#) video before you dive into this article.

4.5.2: What is the law of independent assortment?

Mendel's **law of independent assortment** states that the alleles of two (or more) different genes get sorted into gametes independently of one another. In other words, the allele a gamete receives for one gene does not influence the allele received for another gene.

4.5.3: Example: Pea color and pea shape genes

Let's look at a concrete example of the law of independent assortment. Imagine that we cross two pure-breeding pea plants: one with yellow, round seeds ($YYRR$) and one with green, wrinkled seeds ($yyrr$). Because each parent is homozygous, the law of segregation tells us that the gametes made by the wrinkled, green plant all are ry , and the gametes made by the round, yellow plant are all RY . That gives us F_1 offspring that are all $RrYy$.

The allele specifying yellow seed color is dominant to the allele specifying green seed color, and the allele specifying round shape is dominant to the allele specifying wrinkled shape, as shown by the capital and lower-case letters. This means that the F_1 plants are all yellow and round. Because they are heterozygous for two genes, the F_1 plants are called **dihybrids** (*di*- = two, *-hybrid* = heterozygous).

A cross between two dihybrids (or, equivalently, self-fertilization of a dihybrid) is known as a **dihybrid cross**. When Mendel did this cross and looked at the offspring, he found that there were four different categories of pea seeds: yellow and round, yellow and wrinkled, green and round, and green and wrinkled. These **phenotypic** categories (categories defined by observable traits) appeared in a ratio of approximately 9:3:3:1.

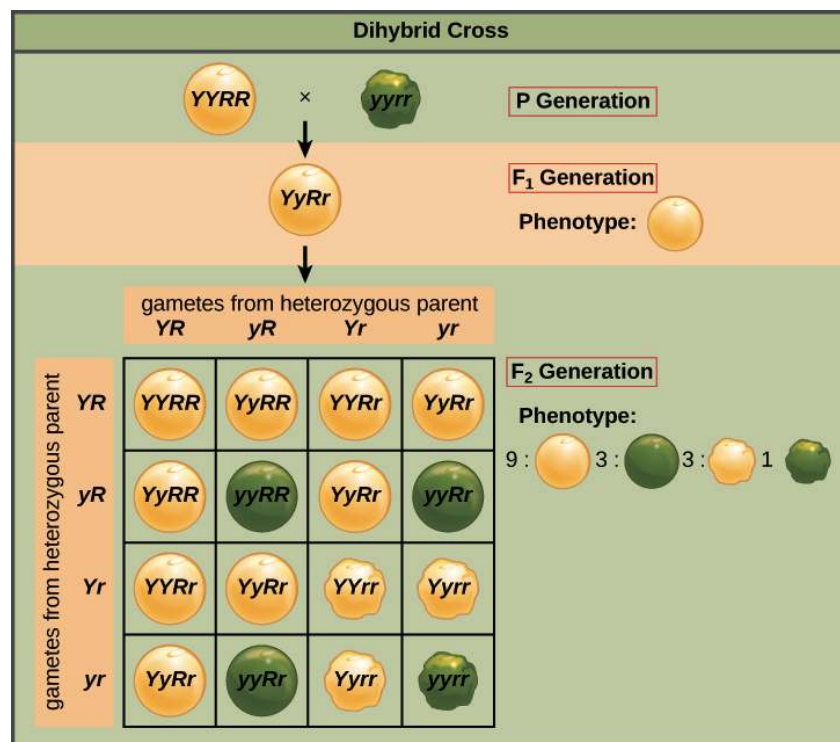


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This ratio was the key clue that led Mendel to the law of independent assortment. That's because a 9:3:3:1 ratio is exactly what we'd expect to see if the F₁ plant made four types of gametes (sperm and eggs) with equal frequency: YR, Yr, yR, and yr. In other words, this is the result we'd predict if each gamete randomly got a Y or y allele, and, in a separate process, also randomly got an R or r allele (making four equally probable combinations).

We can confirm the link between the four types of gametes and the 9:3:3:1 ratio using the Punnett square above. To make the square, we first put the four equally probable gamete types along each axis. Then, we join gametes on the axes in the boxes of the chart, representing fertilization events. The 16 equal-probability fertilization events that can occur among the gametes are shown in the 16 boxes. The offspring genotypes in the boxes correspond to a 9:3:3:1 ratio of phenotypes, just as Mendel observed.

[More about two-gene Punnett squares]

We can draw a Punnett square for a two-gene scenario by following the same basic rules as for a monohybrid cross, placing the gametes along the axes and combining them in the squares to represent fertilization events. However, since there are now more gamete types, there must also be more squares in the table: 4 possible types of maternal gametes x 4 possible types of paternal gametes = 16 squares total.

As with a [single-gene Punnett square](#), we place all the possible types of gametes along the axes, then combine them in the squares where the columns and rows intersect to represent fertilization events (the formation of zygotes, or offspring).

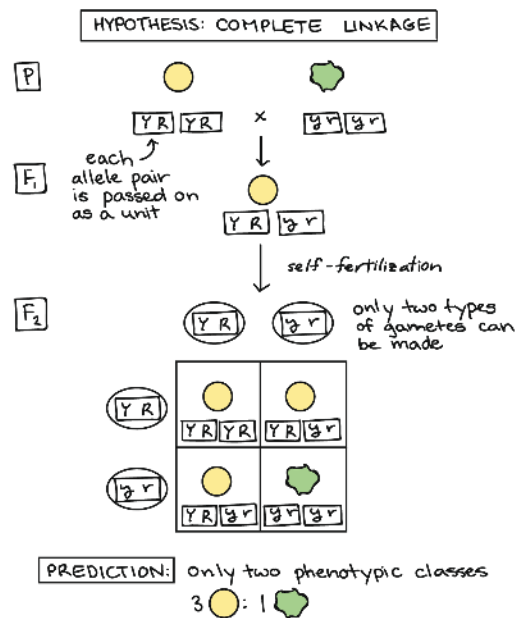
To learn how you can use the rules of probability to predict the outcome of a dihybrid cross, see the [probabilities in genetics](#) article.

4.5.4: Independent assortment vs. linkage

The section above gives us Mendel's law of independent assortment in a nutshell, and lets us see how the law of independent assortment leads to a 9:3:3:1 ratio. But what was the alternative possibility? That is, what would happen if two genes *didn't* follow independent assortment?

In the extreme case, the genes for seed color and seed shape might have always been inherited as a pair. That is, the yellow and round alleles might always have stayed together, and so might the green and wrinkled alleles.

To see how this could work, imagine that the color and shape genes are physically stuck together and cannot be separated, as represented by the boxes around the alleles in the diagram below. For instance, this could happen if the two genes were located very, very close together on a chromosome (an idea we'll explore further at the end of the article).



Rather than giving a color allele and, separately, giving a shape allele to each gamete, the F₁ dihybrid plant would simply give one "combo unit" to each gamete: a YR allele pair or a yr allele pair.

We can use a Punnett square to predict the results of self-fertilization in this case, as shown above. If the seed color and seed shape genes were in fact always inherited as a unit, or **completely linked**, a dihybrid cross should produce just two types of offspring, yellow/round and green/wrinkled, in a 3:1 ratio. Mendel's actual results were quite different from this (the 9:3:3:1 ratio we saw earlier), telling him that the genes assorted independently.

4.5.5: The reason for independent assortment

To see why independent assortment happens, we need to fast-forward half a century and discover that genes are physically located on chromosomes. To be exact, the two copies of a gene carried by an organism (such as a Y and a y allele) are located at the same spot on the two chromosomes of a **homologous pair**. Homologous chromosomes are similar but non-identical, and an organism gets one member of the pair from each of its two parents.

The physical basis for the law of independent assortment lies in meiosis I of gamete formation, when homologous pairs line up in random orientations at the middle of the cell as they prepare to separate. We can get gametes with different combos of "mom" and "dad" homologues (and thus, the alleles on those homologues) because the orientation of each pair is random.

To see what this means, compare chromosome arrangement 1 (top) and chromosome arrangement 2 (bottom) at the stage of metaphase I in the diagram below. In one case, the red "mom" chromosomes go together, while in the other, they split up and mix with the blue "dad" chromosomes. If meiosis happens many times, as it does in a pea plant, we will get both arrangements—and thus RY, Ry, rY, and ry classes of gametes—with equal frequency.

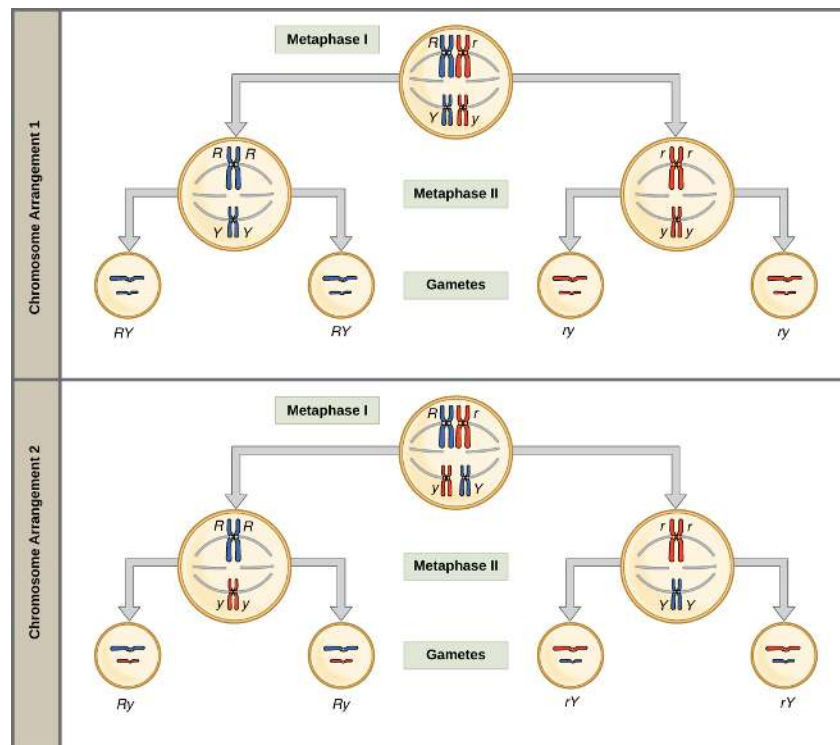
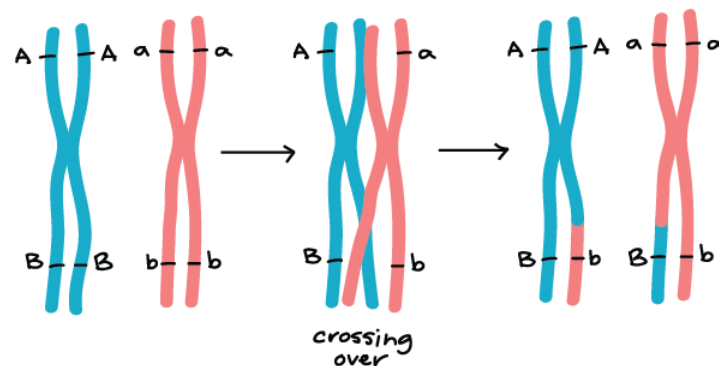


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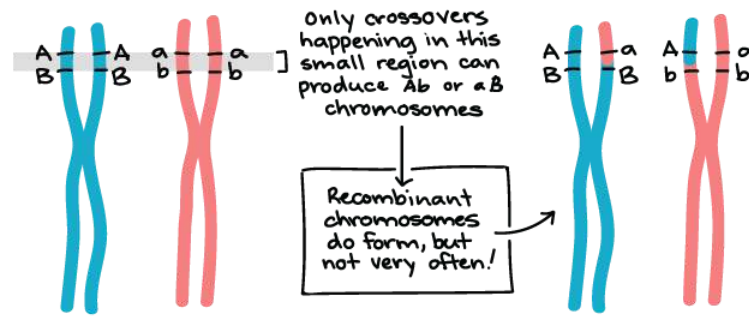
Genes that are on different chromosomes (like the Y and R genes) assort independently. The seed color and seed shape genes are on chromosomes 1 and 7 of the pea genome, respectively, in real life¹. Genes that are far apart on the same chromosome also assort independently thanks to the crossing over, or exchange of homologous chromosome bits, that occurs early in meiosis I.

[See a picture]



There are, however, gene pairs that do not assort independently. When genes are close together on a chromosome, the alleles on the same chromosome tend to be inherited as a unit more frequently than not. Such genes do not display independent assortment and are said to be **linked**. We'll take a closer look at genetic linkage in other articles and videos.

[See a picture]



4.5.5.1: Check your understanding

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4.6: Relationships Between Genes, Genotypes and Phenotypes

4.6.1: Terminology

A specific position along a chromosome is called a **locus**. Each gene occupies a specific locus (so the terms locus and gene are often used interchangeably). Each locus will have an allelic form (allele). The complete set of alleles (at all loci of interest) in an individual is its **genotype**. Typically, when writing out a genotype, only the alleles at the locus (loci) of interest are considered – all the others are present and assumed to be wild type. The visible or detectable effect of these alleles on the structure or function of that individual is called its **phenotype** – what it looks like. The phenotype studied in any particular genetic experiment may range from simple, visible traits such as hair color, to more complex phenotypes including disease susceptibility or behavior. If two alleles are present in an individual, then various interactions between them may influence their expression in the phenotype.

4.6.2: Complete Dominance

Let us return to an example of a simple phenotype: flower color in Mendel's peas. We have already said that one allele as a homozygote produces purple flowers, while the other allele as a homozygote produces white flowers (see Figures 1.8 and 3.3). But what about an individual that has one purple allele and one white allele; what is the phenotype of an individual whose genotype is heterozygous? This can only be determined by experimental observation. We know from observation that individuals heterozygous for the purple and white alleles of the flower color gene have purple flowers. Thus, the allele associated with purple color is therefore said to be **dominant** to the allele that produces the white color. The white allele, whose phenotype is masked by the purple allele in a heterozygote, is **recessive** to the purple allele.

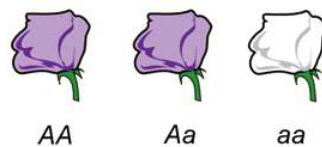


Figure 4.6.3: Relationship between genotype and phenotype for an allele that is completely dominant to another allele. Original-Deholos (Fireworks)-CC:AN

To represent this relationship, often, a dominant allele will be represented by a capital letter (e.g. *A*) while a recessive allele will be represented in lower case (e.g. *a*). However, many different systems of genetic symbols are in use. The most common are shown in Table 4.6.1. Also note that genes and alleles are usually written in *italics* and chromosomes and proteins are not. For example, the *white* gene in *Drosophila melanogaster* on the X chromosome encodes a protein called WHITE.

Table 4.6.1: Examples of symbols used to represent genes and alleles.

Examples	Interpretation
<i>A</i> and <i>a</i>	Uppercase letters represent dominant alleles and lowercase letters indicate recessive alleles. Mendel invented this system but it is not commonly used because not all alleles show complete dominance and many genes have more than two alleles.
<i>a</i> ⁺ and <i>a</i> ¹	Superscripts or subscripts are used to indicate alleles. For wild type alleles the symbol is a superscript +.
<i>AA</i> or <i>A/A</i>	Sometimes a forward slash is used to indicate that the two symbols are alleles of the same gene, but on homologous chromosomes.

4.6.3: Incomplete Dominance

Besides dominance and recessivity, other relationships can exist between alleles. In **incomplete dominance** (also called **semi-dominance**, Figure 4.6.4), both alleles affect the trait additively, and the phenotype of the heterozygote is intermediate between either of the homozygotes. For example, alleles for color in carnation flowers (and many other species) exhibit incomplete dominance. Plants with an allele for red petals (*A*₁) and an allele for white petals (*A*₂) have pink petals. We say that the *A*₁ and the *A*₂ alleles show incomplete dominance because neither allele is completely dominant over the other.

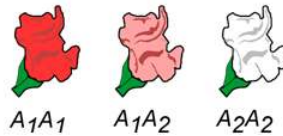


Figure 4.6.4: Relationship between genotype and phenotype for incompletely dominant alleles affecting petal colour in carnations. (Original-Deholos-CC:AN)

4.6.4: Co-Dominance

Co-dominance is another type of allelic relationship, in which a heterozygous individual expresses the phenotype of both alleles simultaneously. An example of co-dominance is found within the **ABO blood group** of humans. The *ABO* gene has three common alleles which were named (for historical reasons) I^A , I^B , and i . People homozygous for I^A or I^B display only A or B type antigens, respectively, on the surface of their blood cells, and therefore have either type A or type B blood (Figure 4.6.5). Heterozygous $I^A I^B$ individuals have both A and B antigens on their cells, and so have type AB blood. Notice that the heterozygote expresses both alleles simultaneously, and is not some kind of novel intermediate between A and B. Co-dominance is therefore distinct from incomplete dominance, although they are sometimes confused.

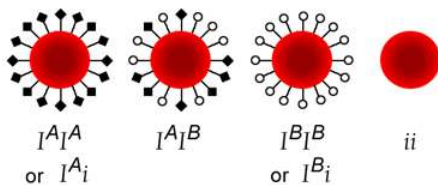


Figure 4.6.5: Relationship between genotype and phenotype for three alleles of the human *ABO* gene. The I^A and I^B alleles show co-dominance. The I^A allele is completely dominant to the i allele. The I^B allele is completely dominant to the i allele. (Original-Deholos-CC:AN)

It is also important to note that the third allele, i , does not make either antigen and is recessive to the other alleles. I^A/i or I^B/i individuals display A or B antigens respectively. People homozygous for the i allele have type O blood. This is a useful reminder that different types of dominance relationships can exist, even for alleles of the same gene. Many types of molecular markers, which we will discuss in a later chapter, display a co-dominant relationship among alleles.

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4.7: Worked example - Punnett squares



Learn how to use Punnett squares to calculate probabilities of different phenotypes. Includes worked examples of dihybrid crosses, independent assortment, incomplete dominance, codominance, and multiple alleles. Created by Sal Khan.

4.7.1: Contributors and Attributions

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4.8: Biochemical Basis of Dominance

Given that a heterozygote's phenotype cannot simply be predicted from the phenotype of homozygotes, what does the type of dominance tell us about the biochemical nature of the gene product? How does dominance work at the biochemical level? There are several different biochemical mechanisms that may make one allele dominant to another.

For the majority of genes studied, the normal (i.e. wild-type) alleles are **haplosufficient**. So in diploids, even with a mutation that causes a complete loss of function in one allele, the other allele, a wild-type allele, will provide sufficient normal biochemical activity to yield a wild type phenotype and thus be dominant and dictate the heterozygote phenotype.

On the other hand, in some biochemical pathways, a single wild-type allele is not enough protein and may be **haploinsufficient** to produce enough biochemical activity to result in a normal phenotype, when heterozygous with a non-functioning mutant allele. In this case, the non-functional mutant allele will be dominant (or semi-dominant) to a wild-type allele.

Mutant alleles may also encode products that have new and/or different biochemical activities instead of, or in addition to, the normal ones. These **novel activities** could cause a new phenotype that would be dominantly expressed.

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4.9: Crossing Techniques Used in Classical Genetics

4.9.1: Classical Genetics

Not only did Mendel solve the mystery of inheritance as units (genes), he also invented several testing and analysis techniques still used today. **Classical genetics** is the science of solving biological questions using controlled matings of model organisms. It began with Mendel in 1865 but did not take off until Thomas Morgan began working with fruit flies in 1908. Later, starting with Watson and Crick's structure of DNA in 1953, classical genetics was joined by **molecular genetics**, the science of solving biological questions using DNA, RNA, and proteins isolated from organisms. The genetics of **DNA cloning** began in 1970 with the discovery of restriction enzymes.

4.9.2: True Breeding Lines

Geneticists make use of **true breeding lines** just as Mendel did (Figure 4.9.6a). These are in-bred populations of plants or animals in which all parents and their offspring (over many generations) have the same phenotypes with respect to a particular trait. True breeding lines are useful, because they are typically assumed to be homozygous for the alleles that affect the trait of interest. When two individuals that are homozygous for the same alleles are crossed, all of their offspring will all also be homozygous. The continuation of such crosses constitutes a true breeding line or strain. A large variety of different strains, each with a different, true breeding character, can be collected and maintained for genetic research.

4.9.3: Monohybrid Crosses

A **monohybrid cross** is one in which both parents are heterozygous (or a hybrid) for a single (mono) trait. The trait might be petal colour in pea plants (Figure 4.9.6b). Recall from chapter 1 that the generations in a cross are named P (parental), F₁ (first filial), F₂ (second filial), and so on.

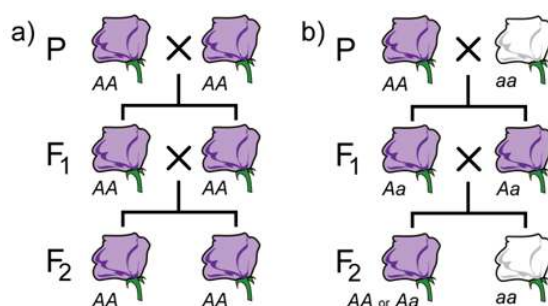


Figure 4.9.6: (a) A true-breeding line (b) A monohybrid cross produced by mating two different pure-breeding lines. (Original-Deholos-CC:AN)

4.9.4: Punnett Squares

Given the genotypes of any two parents, we can predict all of the possible genotypes of the offspring. Furthermore, if we also know the dominance relationships for all of the alleles, we can predict the phenotypes of the offspring. A convenient method for calculating the expected genotypic and phenotypic ratios from a cross was invented by Reginald Punnett. A **Punnett square** is a matrix in which all of the possible gametes produced by one parent are listed along one axis, and the gametes from the other parent are listed along the other axis. Each possible combination of gametes is listed at the intersection of each row and column. The F₁ cross from Figure 4.9.6b would be drawn as in Figure 4.9.7. Punnett squares can also be used to calculate the frequency of offspring. The frequency of each offspring is the frequency of the male gametes multiplied by the frequency of the female gamete.

	A	a
A	AA	Aa
a	Aa	aa

Figure 4.9.7: A Punnett square showing a monohybrid cross. (Original-Deholos (Fireworks)-CC:AN)

4.9.5: Test Crosses

Knowing the genotypes of an individual is usually an important part of a genetic experiment. However, genotypes cannot be observed directly; they must be inferred based on phenotypes. Because of dominance, it is often not possible to distinguish between a heterozygote and a homozygote based on phenotype alone (e.g. see the purple-flowered F_2 plants in Figure 4.9.6b). To determine the genotype of a specific individual, a **test cross** can be performed, in which the individual with an uncertain genotype is crossed with an individual that is homozygous recessive for all of the loci being tested.

For example, if you were given a pea plant with purple flowers it might be a homozygote (AA) or a heterozygote (Aa). You could cross this purple-flowered plant to a white-flowered plant as a **tester**, since you know the genotype of the tester is aa . Depending on the genotype of the purple-flowered parent (Figure 4.9.8), you will observe different phenotypic ratios in the F_1 generation. If the purple-flowered parent was a homozygote, all of the F_1 progeny will be purple. If the purple-flowered parent was a heterozygote, the F_1 progeny should segregate purple-flowered and white-flowered plants in a 1:1 ratio.

	A	A
a	Aa	Aa
a	Aa	Aa

	A	a
a	Aa	aa
a	Aa	aa

Figure 4.9.8: Punnett Squares showing the two possible outcomes of a test cross. (Original-Deholos (Fireworks)-CC:AN)

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4.10: Probabilities in genetics

4.10.1: Introduction

The [Punnett square](#) is a valuable tool, but it's not ideal for every genetics problem. For instance, suppose you were asked to calculate the frequency of the recessive class not for an $Aa \times Aa$ cross, not for an $AaBb \times AaBb$ cross, but for an $AaBbCcDdEe \times AaBbCcDdEe$ cross. If you wanted to solve that question using a Punnett square, you could do it – but you'd need to complete a Punnett square with 1024 boxes. Probably not what you want to draw during an exam, or any other time, if you can help it!

The five-gene problem above becomes less intimidating once you realize that a Punnett square is just a visual way of representing probability calculations. Although it's a great tool when you're working with one or two genes, it can become slow and cumbersome as the number goes up. At some point, it becomes quicker (and less error-prone) to simply do the probability calculations by themselves, without the visual representation of a clunky Punnett square. In all cases, the calculations and the square provide the same information, but by having both tools in your belt, you can be prepared to handle a wider range of problems in a more efficient way.

In this article, we'll review some probability basics, including how to calculate the probability of two independent events both occurring (event X and event Y) or the probability of either of two mutually exclusive events occurring (event X or event Y). We'll then see how these calculations can be applied to genetics problems, and, in particular, how they can help you solve problems involving relatively large numbers of genes.

[Solution to the five-gene cross problem]

In this problem, we're supposed to find the frequency of the recessive class among the offspring of an $AaBbCcDdEe \times AaBbCcDdEe$ cross – that is, the frequency of $aabbccdde$ individuals. How do we get an $aabbccdde$ individual? There's only one way for that to happen: both parents must contribute an $abcde$ gamete.

What, then, is the probability that one of the parents will make an $abcde$ gamete? Both parents are heterozygous for all five genes, so there's a $1/2$ chance of getting the recessive (lowercase) allele for any one gene. To get our desired gamete, we need all five genes in recessive form (a and b and c and d and e). This is a case where we can apply the **product rule**, which states that the probability of event X and event Y happening is the product of their individual probabilities (probability of X times probability of Y), assuming that X and Y are independent events. Thus, the overall probability of one parent producing an $abcde$ gamete is:

Probability of $abcde$ gamete = (probability of a) $\times$ (probability of b) $\times$ (probability of c) $\times$ (probability of d) $\times$ (probability of e)

$$P(abcde) = P(a) \cdot P(b) \cdot P(c) \cdot P(d) \cdot P(e)$$

$$P(abcde) = (1/2) \cdot (1/2) \cdot (1/2) \cdot (1/2) \cdot (1/2) = (1/2)^5 = 1/32$$

If that's the probability of one parent making an $abcde$ gamete, what's the likelihood of both parents doing so? Again, we can apply the "and" rule (product rule), since we need both parent 1 and parent 2 to make an $abcde$ gamete in order to get our target recessive homozygote. Thus, the overall probability is:

Probability of $aabbccdde$ individual = (probability of parent 1 making an $abcde$ gamete) $\times$ (probability of parent 2 making an $abcde$ gamete)

$$P(aabbccdde) = P(abcde_{\text{parent A}}) \cdot P(abcde_{\text{parent B}})$$

$$P(aabbccdde) = (1/32) \cdot (1/32) = 1/1024$$

That's our overall probability for a recessive homozygote for all five genes.

The $1/1024$ probability corresponds to 1 box out of the 1024 boxes of the Punnett square you'd have to draw to represent this cross. The probability calculation is the same calculation we'd implicitly do by drawing the Punnett square, just faster and with fewer chances for mistakes.

4.10.2: Probability basics

Probabilities are mathematical measures of likelihood. In other words, they're a way of quantifying (giving a specific, numerical value to) how likely something is to happen. A probability of 1 for an event means that it is guaranteed to happen, while a probability of 0 for an event means that it is guaranteed not to happen. A simple example of probability is having a $1/2$ chance of getting heads when you flip a coin, as Sal explains in this [intro to probability](#) video.

Probabilities can be either empirical, meaning that they are calculated from real-life observations, or theoretical, meaning that they are predicted using a set of rules or assumptions.

- The **empirical probability** of an event is calculated by counting the number of times that event occurs and dividing it by the total number of times that event could have occurred. For instance, if the event you were looking for was a wrinkled pea seed, and you saw it 1,850 times out of the 7,324 total seeds you examined, the empirical probability of getting a wrinkled seed would be $1,850/7,324 = 0.253$, or very close to 1 in 4 seeds.
- The **theoretical probability** of an event is calculated based on information about the rules and circumstances that produce the event. It reflects the number of times an event is *expected* to occur relative to the number of times it could possibly occur. For instance, if you had a pea plant heterozygous for a seed shape gene (Rr) and let it self-fertilize, you could use the rules of probability and your knowledge of genetics to predict that 1 out of every 4 offspring would get two recessive alleles (rr) and appear wrinkled, corresponding to a 0.25 ($1/4$) probability. We'll talk more below about how to apply the rules of probability in this case.

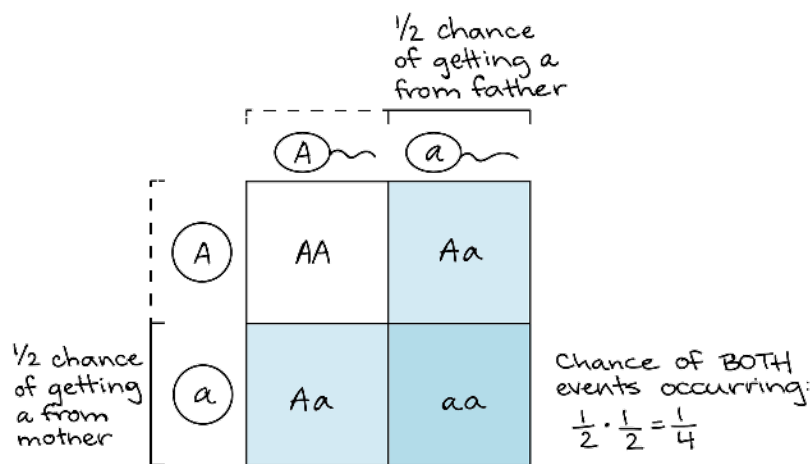
In general, the larger the number of data points that are used to calculate an empirical probability, such as shapes of individual pea seeds, the more closely it will approach the theoretical probability.

4.10.3: The product rule

One probability rule that's very useful in genetics is the **product rule**, which states that the probability of two (or more) independent events occurring together can be calculated by multiplying the individual probabilities of the events. For example, if you roll a six-sided die once, you have a $1/6$ chance of getting a six. If you roll two dice at once, your chance of getting two sixes is: (probability of a six on die 1) $\times$ (probability of a six on die 2) = $(1/6) \cdot (1/6) = 1/36$.

In general, you can think of the product rule as the "and" rule: if both event X *and* event Y must happen in order for a certain outcome to occur, and if X and Y are independent of each other (don't affect each other's likelihood), then you can use the product rule to calculate the probability of the outcome by multiplying the probabilities of X and Y.

We can use the product rule to predict frequencies of fertilization events. For instance, consider a cross between two heterozygous (Aa) individuals. What are the odds of getting an aa individual in the next generation? The only way to get an aa individual is if the mother contributes an a gamete and the father contributes an a gamete. Each parent has a $1/2$ chance of making an a gamete. Thus, the chance of an aa offspring is: (probability of mother contributing a) $\times$ (probability of father contributing a) = $(1/2) \cdot (1/2) = 1/4$.



This is the same result you'd get with a Punnett square, and actually the same logical process as well—something that took me years to realize! The only difference is that, in the Punnett square, we'd do the calculation visually: we'd represent the $1/2$ probability of an a gamete from each parent as one out of two columns (for the father) and one out of two rows (for the mother). The 1-square intersect of the column and row (out of the 4 total squares of the table) represents the $1/4$ chance of getting an a from both parents.

4.10.4: The sum rule of probability

In some genetics problems, you may need to calculate the probability that any one of several events will occur. In this case, you'll need to apply another rule of probability, the sum rule. According to the **sum rule**, the probability that any of several mutually exclusive events will occur is equal to the sum of the events' individual probabilities.

For example, if you roll a six-sided die, you have a $1/6$ chance of getting any given number, but you can only get one number per roll. You could never get both a one and a six at the same time; these outcomes are mutually exclusive. Thus, the chances of getting either a one or a six are: (probability of getting a 1) + (probability of getting a 6) = $(1/6) + (1/6) = 1/3$.

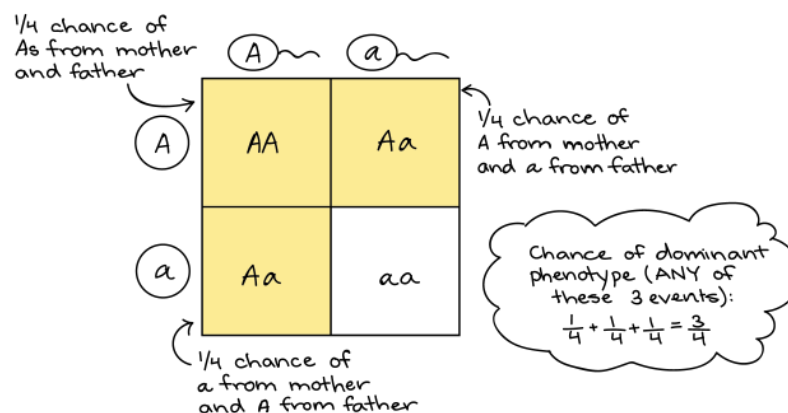
You can think of the sum rule as the “or” rule: if an outcome requires that either event X or event Y occur, and if X and Y are mutually exclusive (if only one or the other can occur in a given case), then the probability of the outcome can be calculated by adding the probabilities of X and Y.

As an example, let's use the sum rule to predict the fraction of offspring from an $Aa \times Aa$ cross that will have the dominant phenotype (AA or Aa genotype). In this cross, there are three events that can lead to a dominant phenotype:

- Two A gametes meet (giving AA genotype), or
- A gamete from Mom meets a gamete from Dad (giving Aa genotype), or
- a gamete from Mom meets A gamete from Dad (giving Aa genotype)

In any one fertilization event, only one of these three possibilities can occur (they are mutually exclusive).

Since this is an “or” situation where the events are mutually exclusive, we can apply the sum rule. Using the product rule as we did above, we can find that each individual event has a probability of $1/4$. So, the probability of offspring with a dominant phenotype is: (probability of A from Mom and A from Dad) + (probability of A from Mom and a from Dad) + (probability of a from Mom and A from Dad) = $(1/4) + (1/4) + (1/4) = 3/4$.



Once again, this is the same result we'd get with a Punnett square. One out of the four boxes of the Punnett square holds the dominant homozygote, AA. Two more boxes represent heterozygotes, one with a maternal A and a paternal a , the other with the opposite combination. Each box is 1 out of the 4 boxes in the whole Punnett square, and since the boxes don't overlap (they're mutually exclusive), we can add them up ($1/4 + 1/4 + 1/4 = 3/4$) to get the probability of offspring with the dominant phenotype.

4.10.4.1: The product rule and the sum rule

Product rule	Sum rule
For independent events X and Y , the probability (P) of them both occurring (X and Y) is $P(X) \cdot P(Y)$.	For mutually exclusive events X and Y , the probability (P) that one will occur (X or Y) is $P(X) + P(Y)$.

4.10.5: Applying probability rules to dihybrid crosses

Direct calculation of probabilities doesn't have much advantage over Punnett squares for single-gene inheritance scenarios. (In fact, if you prefer to learn visually, you may find direct calculation trickier rather than easier.) Where probabilities shine, though, is when you're looking at the behavior of two, or even more, genes.

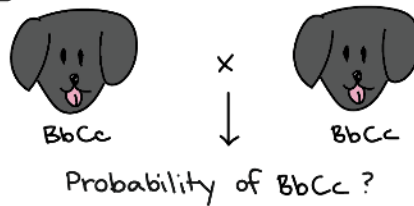
For instance, let's imagine that we breed two dogs with the genotype $BbCc$, where dominant allele B specifies black coat color (versus b , yellow coat color) and dominant allele C specifies straight fur (versus c , curly fur). Assuming that the two genes assort independently and are not sex-linked, how can we predict the number of $BbCc$ puppies among the offspring?

One approach is to draw a 16-square Punnett square. For a cross involving two genes, a Punnett square is still a good strategy. Alternatively, we can use a shortcut technique involving four-square Punnett squares and a little application of the product rule. In this technique, we break the overall question down into two smaller questions, each relating to a different genetic event:

1. What's the probability of getting a Bb genotype?
2. What's the probability of getting an Cc genotype?

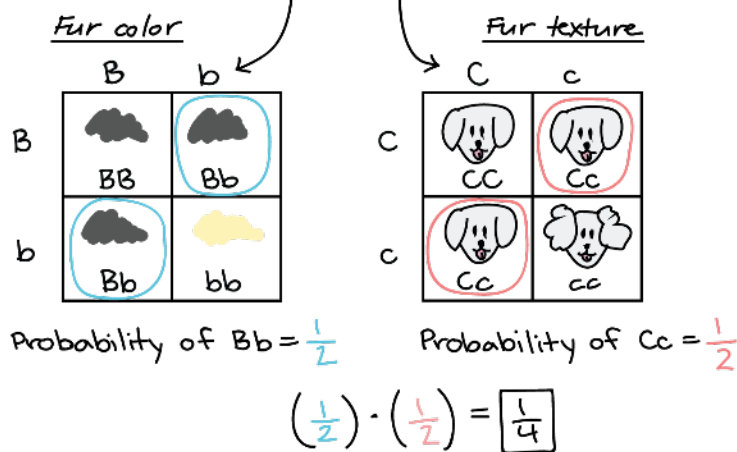
In order for a puppy to have a $BbCc$ genotype, both of these events must take place: the puppy must receive Bb alleles, *and* it must receive Cc alleles. The two events are independent because the genes assort independently (don't affect one another's inheritance). So, once we calculate the probability of each genetic event, we can multiply these probabilities using the product rule to get the probability of the genotype of interest ($BbCc$).

QUESTION:



SOLUTION:

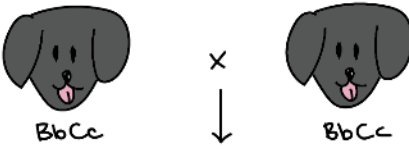
$$\text{Probability of } BbCc = (\text{probability of } Bb) \cdot (\text{probability of } Cc)$$



To calculate the probability of getting a Bb genotype, we can draw a 4-square Punnett square using the parents' alleles for the coat color gene only, as shown above. Using the Punnett square, you can see that the probability of the Bb genotype is $1/2$. (Alternatively, we could have calculated the probability of Bb using the product rule for gamete contributions from the two parents and the sum rule for the two gamete combinations that give Bb .) Using a similar Punnett square for the parents' fur texture alleles, the probability of getting an Cc genotype is also $1/2$. To get the overall probability of the $BbCc$ genotype, we can simply multiply the two probabilities, giving an overall probability of $1/4$.

[Let's check that with a Punnett square]

QUESTION:



$BbCc \times BbCc$

Probability of $BbCc$?

SOLUTION:



$BbCc$

	BC	Bc	bC	bc
BC	$BBCC$	$BBCc$	$BbCC$	$BbCc$
Bc	$BBCc$	$BBcc$	$BbCc$	$Bbcc$
bC	$BbCC$	$BbCc$	$bbCC$	$bbCc$
bc	$BbCc$	$Bbcc$	$bbCc$	$bbcc$



$\frac{4}{16} = \frac{1}{4} BbCc$

You can also use this technique to predict phenotype frequencies. Give it a try in the practice question below!

4.10.5.1: Check your understanding

4.10.6: Beyond dihybrid crosses

The probability method is most powerful (and helpful) in cases involving a large number of genes.

For instance, imagine a cross between two individuals with various alleles of four unlinked genes: $AaBbCCdd \times AabbCcDd$. Suppose you wanted to figure out the probability of getting offspring with the dominant phenotype for all four traits. Fortunately, you can apply the exact same logic as in the case of the dihybrid crosses above. To have the dominant phenotype for all four traits, and organism must have: one or more copies of the dominant allele *A* and one or more copies of dominant allele *B* and one or more copies of the dominant allele *C* and one or more copies of the dominant allele *D*.

Since the genes are unlinked, these are four independent events, so we can calculate a probability for each and then multiply the probabilities to get the probability of the overall outcome.

- The probability of getting one or more copies of the dominant *A* allele is $3/4$. (Draw a Punnett square for $Aa \times Aa$ to confirm for yourself that 3 out of the 4 squares are either AA or Aa .)
- The probability of getting one or more copies of the dominant *B* allele is $1/2$. (Draw a Punnett square for $Bb \times bb$: you'll find that half the offspring are Bb , and the other half bb .)
- The probability of getting one or more copies of the dominant *C* allele is 1. (If one of the parents is homozygous CC , there's no way to get offspring without a *C* allele!)

- The probability of getting one or more copies of the dominant D allele is $1/2$, as for B . (Half the offspring will be Dd , and the other half will be dd .)

To get the overall probability of offspring with the dominant phenotype for all four genes, we can multiply the probabilities of the four independent events: $(3/4) \cdot (1/2) \cdot (1) \cdot (1/2) = 3/16$.

4.10.6.1: Check your understanding

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CHAPTER OVERVIEW

5: Allele and Gene Interactions

- 5.1: Phenotypes May Not Be As Expected from the Genotype
- 5.2: Co-dominance and Incomplete Dominance
- 5.3: Phenotypic Ratios May Not Be As Expected
- 5.4: Multiple alleles, incomplete dominance, and codominance
- 5.5: Pleiotropy and lethal alleles
- 5.6: Polygenic inheritance and environmental effects
- 5.7: Non-Mendelian inheritance review

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5.1: Phenotypes May Not Be As Expected from the Genotype

5.1.1: Environmental Factors

The phenotypes described thus far have a nearly perfect correlation with their associated genotypes; in other words an individual with a particular genotype always has the expected phenotype. However, many phenotypes are not determined entirely by genotype alone. They are instead determined by an interaction between genotype and non-genetic, environmental factors and can be conceptualized in the following relationship:

$$\text{Genotype} + \text{Environment} \Rightarrow \text{Phenotype} \quad (G + E \Rightarrow P) \quad (5.1.1)$$

Or:

$$\text{Genotype} + \text{Environment} + \overset{\text{Genetics and Environment}}{\text{Interaction}_{GE}} \Rightarrow \text{Phenotype} \quad (G + E + I_{GE} \Rightarrow P) \quad (5.1.2)$$

This interaction is especially relevant in the study of economically important phenotypes, such as human diseases or agricultural productivity. For example, a particular genotype may pre-dispose an individual to cancer, but cancer may only develop if the individual is exposed to certain DNA-damaging chemicals. Therefore, not all individuals with the particular genotype will develop the cancer phenotype.

5.1.2: Penetrance and Expressivity

The terms penetrance and expressivity are also useful to describe the relationship between certain genotypes and their phenotypes.

- **Penetrance** is the proportion of individuals (usually expressed as a percentage) with a particular genotype that display a corresponding phenotype (Figure 5.1.16). Because all pea plants that are homozygous for the allele for white flowers (e.g. *aa* in Figure 5.1.3) actually have white flowers, this genotype is completely penetrant. In contrast, many human genetic diseases are incompletely penetrant, since not all individuals with the disease genotype actually develop symptoms associated with the disease.
- **Expressivity** describes the variability in mutant phenotypes observed in individuals with a particular phenotype (Figure 5.1.16). Many human genetic diseases provide examples of broad expressivity, since individuals with the same genotypes may vary greatly in the severity of their symptoms. Incomplete penetrance and broad expressivity are due to random chance, non-genetic (environmental), and genetic factors (mutations in other genes).

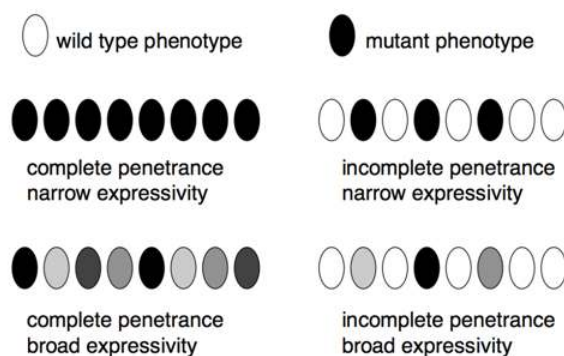


Figure 5.1.16: Relationship between penetrance and expressivity in eight individuals that all have a mutant genotype. Penetrance can be complete (all eight have the mutant phenotype) or incomplete (only some have the mutant phenotype). Amongst those individuals with the mutant phenotype the expressivity can be narrow (very little variation) to broad (lots of variation). (Original-Locke-CC:AN)

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5.2: Co-dominance and Incomplete Dominance



In complete dominance, only one allele in the genotype is seen in the phenotype. In codominance, both alleles in the genotype are seen in the phenotype. In incomplete dominance, a mixture of the alleles in the genotype is seen in the phenotype. Created by Ross Firestone.

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5.3: Phenotypic Ratios May Not Be As Expected

5.3.1: Explanation

For a variety of reasons, the phenotypic ratios observed from real crosses rarely match the exact ratios expected based on a Punnett Square or other prediction techniques. There are many possible explanations for deviations from expected ratios. Sometimes these deviations are due to **sampling effects**, in other words, the random selection of a non-representative subset of individuals for observation. On the other hand, it may be because certain genotypes have a less than 100% survival rate. For example, *Drosophila* crosses sometimes give unexpected results because the more mutant alleles a zygote has the less likely it is to survive to become an adult. Genotypes that cause death for embryos or larvae are underrepresented when adult flies are counted.

5.3.2: The χ^2 Test For Goodness-of-fit

A statistical procedure called the **chi-square** (χ^2) test can be used to help a geneticist decide whether the deviation between observed and expected ratios is due to sampling effects, or whether the difference is so large that some other explanation must be sought by re-examining the assumptions used to calculate the expected ratio. The procedure for performing a chi-square test is covered in the labs.

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5.4: Multiple alleles, incomplete dominance, and codominance

5.4.1: Introduction

Gregor Mendel knew how to keep things simple. In Mendel's work on pea plants, each gene came in just two different versions, or **alleles**, and these alleles had a nice, clear-cut dominance relationship (with the dominant allele fully overriding the recessive allele to determine the plant's appearance).

Today, we know that not all alleles behave quite as straightforwardly as in Mendel's experiments. For example, in real life:

- Allele pairs may have a variety of dominance relationships (that is, one allele of the pair may not completely “hide” the other in the heterozygote).
- There are often many different alleles of a gene in a population.

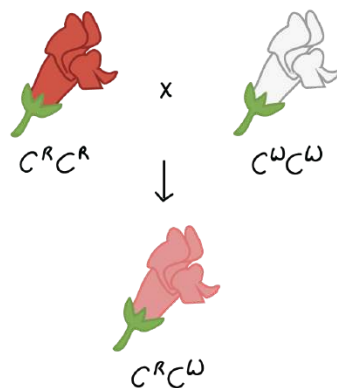
In these cases, an organism's **genotype**, or set of alleles, still determines its **phenotype**, or observable features. However, a variety of alleles may interact with one another in different ways to specify phenotype.

As a side note, we're probably lucky that Mendel's pea genes didn't show these complexities. If they had, it's possible that Mendel would not have understood his results, and wouldn't have figured out the core principles of inheritance—which are key in helping us understand the special cases!

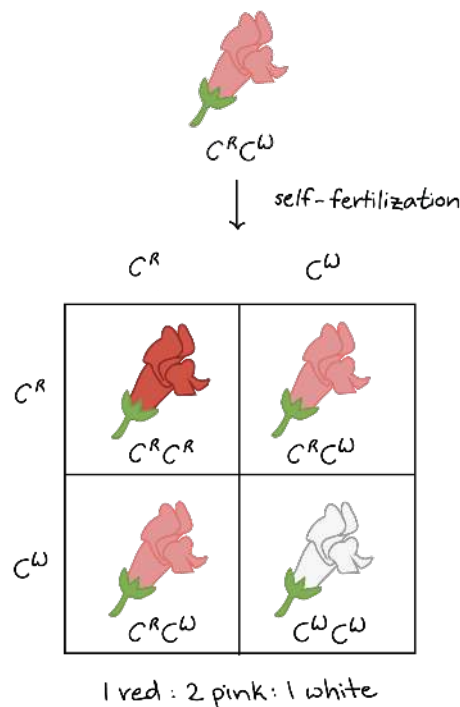
5.4.2: Incomplete dominance

Mendel's results were groundbreaking partly because they contradicted the (then-popular) idea that parents' traits were permanently blended in their offspring. In some cases, however, the phenotype of a heterozygous organism *can* actually be a blend between the phenotypes of its homozygous parents.

For example, in the snapdragon, *Antirrhinum majus*, a cross between a homozygous white-flowered plant ($C^W C^W$) and a homozygous red-flowered plant ($C^R C^R$) will produce offspring with pink flowers ($C^R C^W$). This type of relationship between alleles, with a heterozygote phenotype intermediate between the two homozygote phenotypes, is called **incomplete dominance**.



We can still use Mendel's model to predict the results of crosses for alleles that show incomplete dominance. For example, self-fertilization of a pink plant would produce a genotype ratio of $1 C^R C^R : 2 C^R C^W : 1 C^W C^W$ and a phenotype ratio of $1 : 2 : 1$ red: pink: white. Alleles are still inherited according to Mendel's basic rules, even when they show incomplete dominance.



5.4.3: Codominance

Closely related to incomplete dominance is **codominance**, in which both alleles are simultaneously expressed in the heterozygote.

We can see an example of codominance in the MN blood groups of humans (less famous than the ABO blood groups, but still important!). A person's MN blood type is determined by his or her alleles of a certain gene. An L^M allele specifies production of an M marker displayed on the surface of red blood cells, while an L^N allele specifies production of a slightly different N marker.

Homozygotes ($L^M L^M$ and $L^N L^N$) have only M or N markers, respectively, on the surface of their red blood cells. However, heterozygotes ($L^M L^N$) have both types of markers in equal numbers on the cell surface.

As for incomplete dominance, we can still use Mendel's rules to predict inheritance of codominant alleles. For example, if two people with $L^M L^N$ genotypes had children, we would expect to see M, MN, and N blood types and $L^M L^M$, $L^M L^N$, and $L^N L^N$ genotypes in their children in a **1 : 2 : 1** ratio (if they had enough children for us to determine ratios accurately!)

5.4.4: Multiple alleles

Mendel's work suggested that just two alleles existed for each gene. Today, we know that's not always, or even usually, the case! Although individual humans (and all diploid organisms) can only have two alleles for a given gene, multiple alleles may exist in a population level, and different individuals in the population may have different pairs of these alleles.

As an example, let's consider a gene that specifies coat color in rabbits, called the C gene. The C gene comes in four common alleles: C , c^{ch} , c^h , and c :

- A CC rabbit has black or brown fur.
- A $c^{ch}c^{ch}$ rabbit has chinchilla coloration (grayish fur).
- A $c^h c^h$ rabbit has Himalayan (color-point) patterning, with a white body and dark ears, face, feet, and tail.
- A cc rabbit is albino, with a pure white coat.

Genotype			
CC	$c^{ch}c^{ch}$	$c^h c^h$	cc
Phenotype			
BLACK	CHINCHILLA	HIMALAYAN	ALBINO
			

Image credit: "Characteristics and traits: Figure 5," by OpenStax College, Biology (CC BY 3.0).

Multiple alleles makes for many possible dominance relationships. In this case, the black C allele is completely dominant to all the others; the chinchilla c^{ch} allele is incompletely dominant to the Himalayan c^h and albino c alleles; and the Himalayan c^h allele is completely dominant to the albino c allele.

Rabbit breeders figured out these relationships by crossing different rabbits of different genotypes and observing the phenotypes of the heterozygous kits (baby bunnies).

[How do these alleles change the rabbit's color?]

The C gene in rabbits encodes an enzyme that's needed to make a type of pigment called melanin in hairs^{1,2}.

- The C allele of this gene encodes a fully functional enzyme that makes lots of pigment and results in black fur.
- The c^{ch} allele encodes an enzyme that is less effective at making pigment, resulting in lighter, more grayish fur.
- The c^h allele encodes a defective enzyme, where the defect makes the enzyme very sensitive to temperature: it works fine at low temperatures, but doesn't work at all at higher temperatures. The rabbit's extremities (paws, ears, etc.) are cooler, so the enzyme functions there and makes pigment. The rabbit's main body is warmer, so the enzyme does not function and no pigment is made.
- The c allele encodes a completely nonfunctional enzyme, leading to an albino rabbit (one that does not produce any pigment in its hairs).

Note to rabbit fanciers: Rabbit coat color is determined by a number of genes, not just by the C gene. The allelic series described here for C assumes a certain genetic background for the other genes, one in which a CC genotype results in a black rabbit.

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5.5: Pleiotropy and lethal alleles

5.5.1: Introduction

From Mendel's experiments, you might imagine that all genes control a single characteristic and affect some harmless aspect of an organism's appearance (such as color, height, or shape). Those predictions are true for some genes, but definitely not all of them! For example:

- A human genetic disorder called Marfan syndrome is caused by a mutation in one gene, yet it affects many aspects of growth and development, including height, vision, and heart function. This is an example of **pleiotropy**, or one gene affecting multiple characteristics.
- A cross between two heterozygous yellow mice produces yellow and brown mice in a ratio of 2:1, not 3:1. This is an example of **lethality**, in which a particular genotype makes an organism unable to survive.

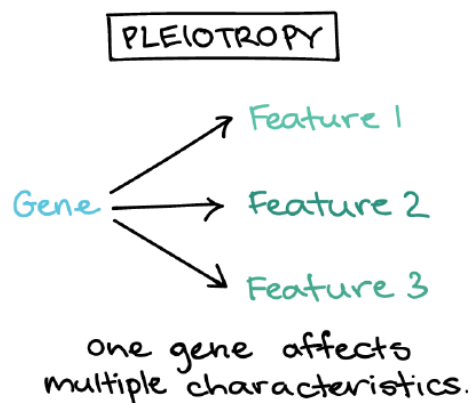
In this article, we'll take a closer look at pleiotropic genes and lethal alleles, seeing how these variations on Mendel's rules fit into our modern understanding of inheritance.

5.5.2: Pleiotropy

When we mentioned Mendel's [experiments](#) with purple-flowered and white-flowered plants, we didn't discuss any other phenotypes associated with the two flower colors. However, Mendel noticed that the flower colors were always correlated with two other features: the color of the seed coat (covering of the seed) and the color of the axils (junctions where the leaves met the stem)^{1,2}.

In plants with white flowers, the seed coats and axils were colorless. In plants with purple flowers, on the other hand, the seed coats were brown-gray and the axils were reddish. Thus, rather than affecting just one characteristic, the flower color gene actually affected three.

Genes like this, which control multiple, seemingly unrelated features, are said to be **pleiotropic** (*pleio-* = many, *-tropic* = effects)¹. We now know that Mendel's flower color gene specifies a protein that causes colored particles, or pigments, to be made². This protein works in several different parts of the pea plant (flowers, seed coat, and leaf axils). In this way, the seemingly unrelated phenotypes can be traced back to a defect in one gene with several jobs.



Based on similar diagram by Ingrid Lobo¹.

Importantly, alleles of pleiotropic genes are transmitted in the same way as alleles of genes that affect single traits. Although the phenotype has multiple elements, these elements are specified as a package, and the dominant and recessive versions of the package would appear in the offspring of two heterozygotes in a ratio of 3:1.

5.5.2.1: Pleiotropy in human genetic disorders

Genes affected in human genetic disorders are often pleiotropic. For example, people with a hereditary disorder called Marfan syndrome may have a set of seemingly unrelated symptoms, including the following^{1,3}:

• Tall stature

- Unusually tall height
- Thin fingers and toes
- Dislocation of the lens of the eye
- Heart problems (in which the aorta, the large blood vessel carrying blood away from the heart, bulges or ruptures).

These symptoms don't seem directly related, but as it turns out, they can all be traced back to the mutation of a single gene. This gene encodes a protein that assembles into chains, making elastic fibrils that give strength and flexibility to the body's connective tissues⁴. Mutations that cause Marfan syndrome reduce the amount of functional protein made by the body, resulting in fewer fibrils.

How does the identity of this gene explain the range of symptoms? Our eyes and the aortas normally contain many fibrils that help maintain structure, which is why these two organs are affected in Marfan syndrome⁵. In addition, the fibrils serve as “storage shelves” for growth factors. When there are fewer of them in Marfan syndrome, the growth factors cannot be shelved and thus cause excess growth (leading to the characteristic tall, thin Marfan build)⁴.

5.5.3: Lethality

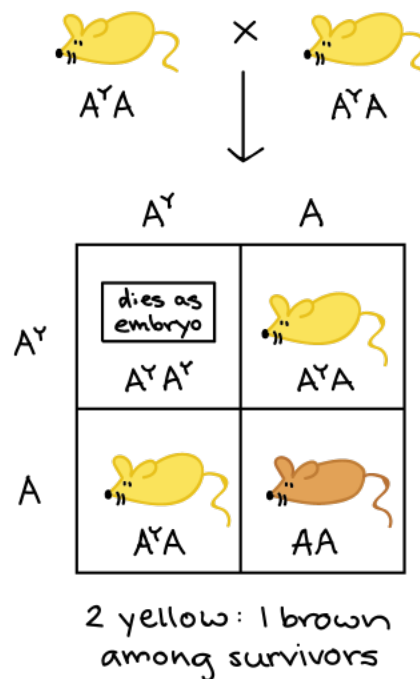
For the alleles that Mendel studied, it was equally possible to get homozygous dominant, homozygous recessive, and heterozygous genotypes. That is, none of these genotypes affected the survival of the pea plants. However, this is not the case for all genes and all alleles.

Many genes in an organism's genome are needed for survival. If an allele makes one of these genes nonfunctional, or causes it to take on an abnormal, harmful activity, it may be impossible to get a living organism with a homozygous (or, in some cases, even a heterozygous) genotype.

5.5.3.1: Example: The yellow mouse

A classic example of an allele that affects survival is the lethal yellow allele, a spontaneous mutation in mice that makes their coats yellow. This allele was discovered around the turn of the 20th century by the French geneticist Lucien Cuenót, who noticed that it was inherited in an unusual pattern^{6,7}.

When yellow mice were crossed with normal agouti (brown) mice, they produced half yellow and half brown offspring. This suggested that the yellow mice were heterozygous, and that the yellow allele, A^Y , was dominant to the agouti allele, A . But when two yellow mice were crossed with each other, they produced yellow and brown offspring in a ratio of 2:1, and the yellow offspring did not breed true (were heterozygous). Why was this the case?



As it turned out, this unusual ratio reflected that some of the mouse embryos (homozygous $A^Y A^Y$ genotype) died very early in development, long before birth. In other words, at the level of eggs, sperm, and fertilization, the color gene segregated normally, resulting in embryos with a 1:2:1 ratio of $A^Y A^Y$, $A^Y A$, and AA genotypes. However, the $A^Y A^Y$ mice died as tiny embryos, leaving a 2:1 genotype and phenotype ratio among the surviving mice^{7,8}.

Alleles like A^Y , which are lethal when they're homozygous but not when they're heterozygous, are called **recessive lethal alleles**.

[Wait, isn't yellow color dominant?]

The lethal recessive A^Y allele also happens to give a dominant, non-lethal phenotype in the heterozygote (yellow coloration, along with health problems such as obesity, diabetes, and tumor formation). The trick is that the *lethality* is recessive, even though the color phenotype is dominant.

The color of the yellow mouse heterozygote is helpful because it lets us keep track of genotypes, but in many other cases, recessive lethal genes don't have a dominant phenotype in the heterozygote. Instead, they are purely recessive to the normal allele, resulting in a normal phenotype for the heterozygote and an embryonic lethal phenotype for the homozygote.

5.5.3.2: Lethal alleles and human genetic disorders

Some alleles associated with human genetic disorders are recessive lethal. For example, this is true of the allele that causes achondroplasia, a form of dwarfism. A person heterozygous for this allele will have shortened limbs and short stature (achondroplasia), a condition that is not lethal. However, homozygosity for the same allele causes death during embryonic development or the first months of life, an example of recessive lethality^{7,9}.

Some human disorders are also caused by **dominant lethal alleles**. These are alleles that cause death when they are present in just a single copy. If an allele leads to death of heterozygotes before birth, we'll never see that allele in the living human population (but rather, as an implantation failure or miscarriage). However, if a dominant lethal allele allows heterozygotes to survive past birth, it can be seen in the population as a genetic disorder.

In fact, if a dominant lethal allele lets a person survive to reproductive age, it may even be passed on to children. This is the case in Huntington's disease, a fatal genetic disorder affecting the nervous system. People with a Huntington allele inevitably develop the disease, but they may not show any symptoms until age 40 and can unknowingly pass the allele on to their children.

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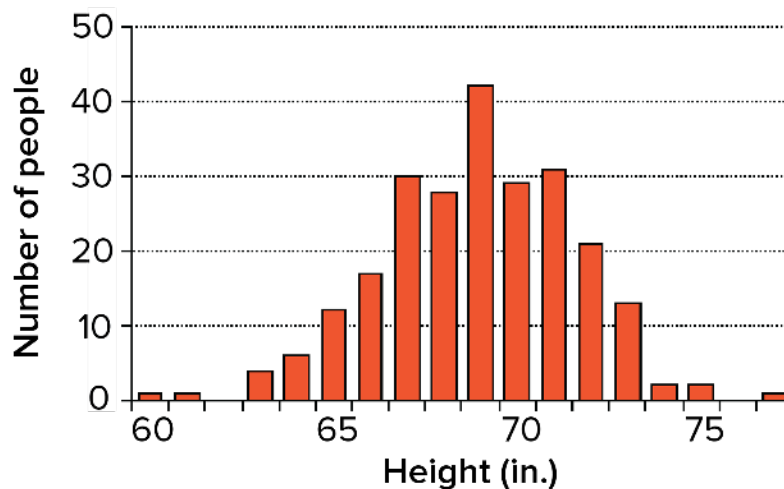
5.6: Polygenic inheritance and environmental effects

5.6.1: How is height inherited?

If what you're really interested in is human genetics, learning about Mendelian genetics can sometimes be frustrating. You'll often hear a teacher use a human trait as an example in a genetics problem, but then say, "that's an oversimplification" or "it's much more complicated than that." So, what's actually going on with those interesting human traits, such as eye color, hair and skin color, height, and disease risk?

As an example, let's consider human height. Unlike a simple Mendelian characteristic, human height displays:

- **Continuous variation.** Unlike Mendel's [pea plants](#), humans don't come in two clear-cut "tall" and "short" varieties. In fact, they don't even come in four heights, or eight, or sixteen. Instead, it's possible to get humans of many different heights, and height can vary in increments of inches or fractions of inches¹.



The heights of a group of male high school seniors. Image modified from "[Continuous variation: Quantitative traits](#)," by J. W. Kimball ([CC BY 3.0](#))

- **A complex inheritance pattern.** You may have noticed that tall parents can have a short child, short parents can have a tall child, and two parents of different heights may or may not have a child in the middle. Also, siblings with the same two parents may have a range of heights, ones that don't fall into distinct categories.

Simple models involving one or two genes can't accurately predict all of these inheritance patterns. How, then, is height inherited?

Height and other similar features are controlled not just by one gene, but rather, by multiple (often many) genes that each make a small contribution to the overall outcome. This inheritance pattern is sometimes called **polygenic inheritance** (*poly-* = many). For instance, a recent study found over 400 genes linked to variation in height².

When there are large numbers of genes involved, it becomes hard to distinguish the effect of each individual gene, and even harder to see that gene variants (alleles) are inherited according to Mendelian rules. In an additional complication, height doesn't just depend on genetics: it also depends on environmental factors, such as a child's overall health and the type of nutrition he or she gets while growing up.

In this article, we'll examine how complex traits such as height are inherited. We'll also see how factors like genetic background and environment can affect the **phenotype** (observable features) produced by a particular **genotype** (set of gene variants, or alleles).

5.6.2: Polygenic inheritance

Human features like height, eye color, and hair color come in lots of slightly different forms because they are controlled by many genes, each of which contributes some amount to the overall phenotype. For example, there are two major eye color genes, but at least 14 other genes that play roles in determining a person's exact eye color³.

Looking at a real example of a human polygenic trait would get complicated, largely because we'd have to keep track of tens, or even hundreds, of different allele pairs (like the 400 involved in height!). However, we can use an example involving wheat kernels to see how several genes whose alleles "add up" to influence the same trait can produce a spectrum of phenotypes^{1,4}.

In this example, there are three genes that make reddish pigment in wheat kernels, which we'll call *A*, *B*, and *C*. Each comes in two alleles, one of which makes pigment (the capital-letter allele) and one of which does not (the lowercase allele). These alleles have additive effects: the *aa* genotype would contribute no pigment, the *Aa* genotype would contribute some amount of pigment, and the *AA* genotype would contribute more pigment (twice as much as *Aa*). The same would hold true for the *B* and *C* genes^{1,4}.

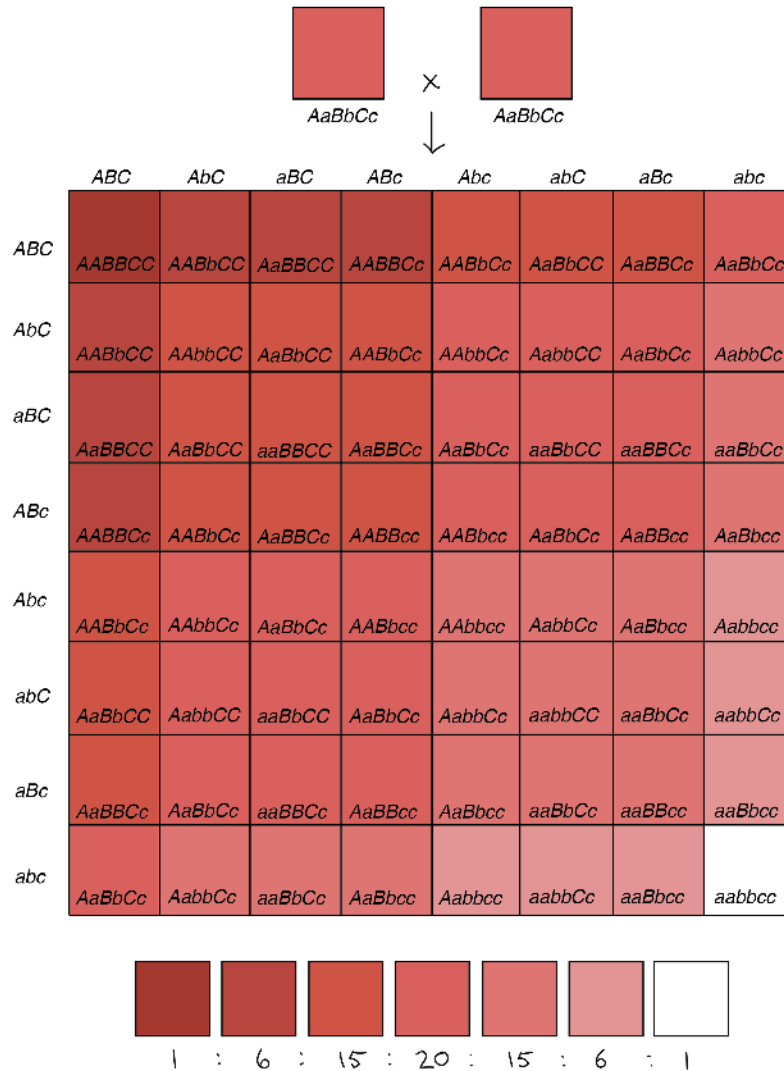


Diagram based on similar diagram by W. P. Armstrong⁵.

Now, let's imagine that two plants heterozygous for all three genes (*AaBbCc*) were crossed to one another. Each of the parent plants would have three alleles that made pigment, leading to pinkish kernels. Their offspring, however, would fall into seven color groups, ranging from no pigment whatsoever (*aabbcc*) and white kernels to lots of pigment (*AABBCC*) and dark red kernels. This is in fact what researchers have seen when crossing certain varieties of wheat^{1,4}.

This example shows how we can get a spectrum of slightly different phenotypes (something close to continuous variation) with just three genes. It's not hard to imagine that, as we increased the number of genes involved, we'd be able to get even finer variations in color, or in another trait such as height.

5.6.3: Environmental effects

Human phenotypes—and phenotypes of other organisms—also vary because they are affected by the environment. For instance, a person may have a genetic tendency to be underweight or obese, but his or her actual weight will depend on diet and exercise (with these factors often playing a greater role than genes). In another example, your hair color may depend on your genes—until you dye your hair purple!

One striking example of how environment can affect phenotype comes from the hereditary disorder **phenylketonuria (PKU)**⁶. People who are homozygous for disease alleles of the PKU gene lack activity of an enzyme that breaks down the amino acid phenylalanine. Because people with this disorder cannot get rid of excess phenylalanine, it rapidly builds up to toxic levels in their bodies⁷.

If PKU is not treated, the extra phenylalanine can keep the brain from developing normally, leading to intellectual disability, seizures, and mood disorders. However, because PKU is caused by the buildup of too much phenylalanine, it can also be treated in a very simple way: by giving affected babies and children a diet low in phenylalanine⁸.

If people with phenylketonuria follow this diet strictly from a very young age, they can have few, or even no, symptoms of the disorder. In many countries, all newborns are screened for PKU and similar genetic diseases shortly after birth through a simple blood test, as shown in the image below.



Image credit: "Phenylketonuria testing," by Eric T. Sheler, USAF Photographic Archives (public domain).

5.6.4: Variable expressivity, incomplete penetrance

Even for characteristics that are controlled by a single gene, it's possible for individuals with the same genotype to have different phenotypes. For example, in the case of a genetic disorder, people with the same disease genotype may have stronger or weaker forms of the disorder, and some may never develop the disorder at all.

In **variable expressivity**, a phenotype may be stronger or weaker in different people with the same genotype. For instance, in a group of people with a disease-causing genotype, some might develop a severe form of the disorder, while others might have a milder form. The idea of expressivity is illustrated in the diagram below, with the shade of green representing the strength of the phenotype.

[Example]

The genetic disorder retinoblastoma causes cancerous tumors of the eyes, but the disease varies in severity and speed of onset. Children with retinoblastoma may develop tumors in just one eye or in both eyes, and the tumors may appear more quickly or slowly after birth⁹.

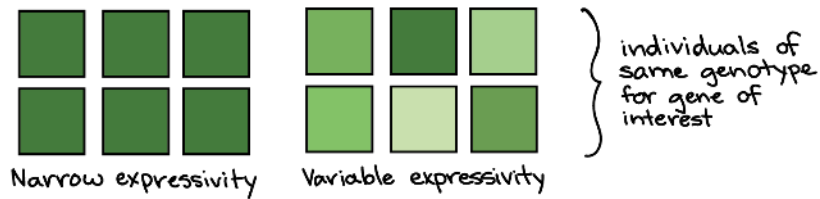


Illustration modeled after similar image by Steven M. Carr¹⁰.

In **incomplete penetrance**, individuals with a certain genotype may or may not develop a phenotype associated with the genotype. For example, among people with the same disease-causing genotype for a hereditary disorder, some might never actually develop the disorder. The idea of penetrance is illustrated in the diagram below, with green or white color representing the presence or absence of a phenotype.

[Example]

Some mutations in the retinoblastoma gene have high penetrance, but others have lower (incomplete) penetrance. For mutations in this latter category, some family members with the mutation are normal, while others develop retinoblastoma tumors^{6,11}.

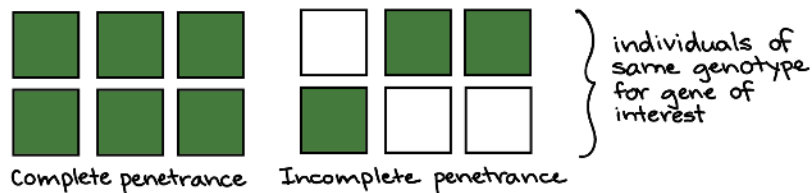


Illustration modeled after similar image by Steven M. Carr¹⁰.

What causes variable expressivity and incomplete penetrance? Other genes and environmental effects are often part of the explanation. For example, disease-causing alleles of one gene may be suppressed by alleles of another gene elsewhere in the genome, or a person's overall health may influence the strength of a disease phenotype¹¹.

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5.7: Non-Mendelian inheritance review

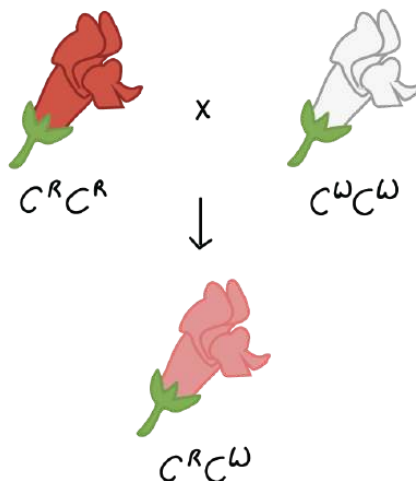
5.7.1: Key terms

Term	Meaning
Incomplete dominance	Pattern of heredity in which one allele is not completely dominant over another
Codominance	Pattern of heredity in which both alleles are simultaneously expressed in the heterozygote
Multiple alleles	A gene that is controlled by more than two alleles
Pleiotropy	When one gene affects multiple characteristics
Lethal allele	Allele that results in the death of an individual
Polygenic trait	Traits that are controlled by multiple genes

5.7.2: Variations involving single genes

Some of the variations on Mendel's rules involve single genes.

- **Incomplete dominance.** Two alleles may produce an intermediate phenotype when both are present, rather than one fully determining the phenotype.



An example of this is the snapdragon plant. A cross between a homozygous white-flowered plant ($C^W C^W$) and a homozygous red-flowered plant ($C^R C^R$) will produce offspring with pink flowers ($C^R C^W$).

- **Codominance.** Two alleles may be simultaneously expressed when both are present, rather than one fully determining the phenotype.



Codominance in erminette chicken. Image from [Wikimedia](#), CC BY 2.0.

In some varieties of chickens, the allele for black feathers is codominant with the allele for white feathers. A cross between a black chicken and a white chicken will result in a chicken with both black and white feathers.

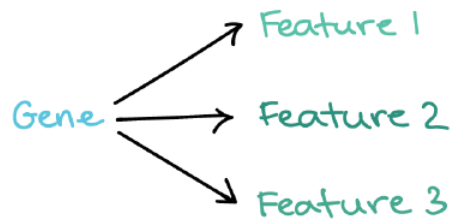
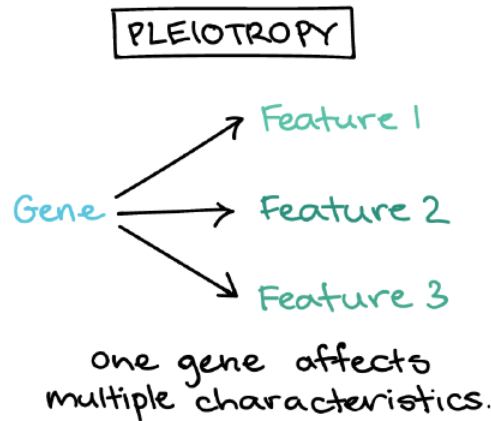
- **Multiple alleles.** Mendel studied just two alleles of his pea genes, but real populations often have multiple alleles of a given gene.

Genotype			
CC	$c^{ch}c^{ch}$	$c^h c^h$	cc
Phenotype			
BLACK	CHINCHILLA	HIMALAYAN	ALBINO
			

Image from [OpenStax](#), CC BY 3.0

An example of this is the gene for coat color in rabbits (the C gene) which comes in four common alleles: C , c^{ch} , c^h , and c .

- **Pleiotropy.** Some genes affect many different characteristics, not just a single characteristic.

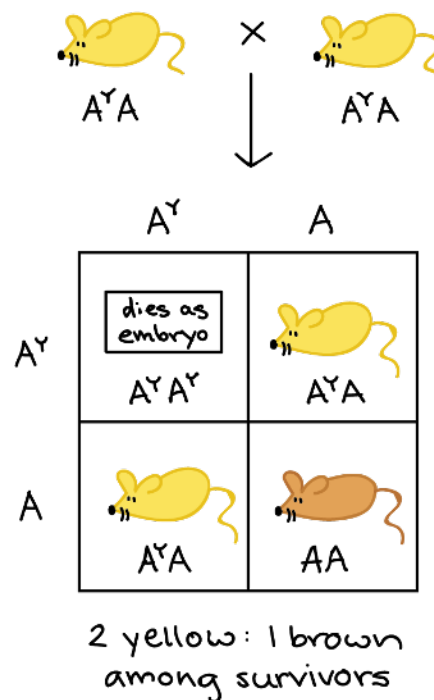


one gene affects multiple characteristics.

Based on similar diagram by Ingrid Lobo¹.

An example of this is Marfan syndrome, which results in several symptoms (unusually tall height, thin fingers and toes, lens dislocation, and heart problems). These symptoms don't seem directly related, but as it turns out, they can all be traced back to the mutation of a single gene.

- **Lethal alleles.** Some genes have alleles that prevent survival when homozygous or heterozygous.

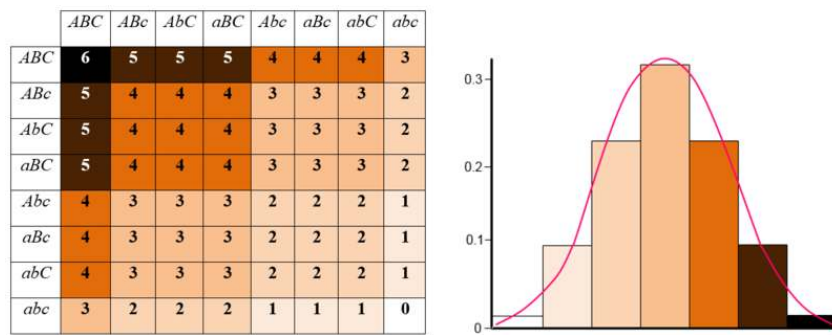


A classic example of an allele that affects survival is the lethal yellow allele, a spontaneous mutation in mice that makes their coats yellow. Mice that are homozygous ($A^Y A^Y$) genotype die early in development. Although this particular allele is dominant, lethal alleles can be dominant or recessive, and can be expressed in homozygous or heterozygous conditions.

5.7.3: Polygenic inheritance and environmental effects

Many characteristics, such as height, skin color, eye color, and risk of diseases, are controlled by many factors. These factors may be genetic, environmental, or both.

- **Polygenic inheritance.** Some characteristics are **polygenic**, meaning that they're controlled by a number of different genes. In polygenic inheritance, traits often form a phenotypic spectrum rather than falling into clear-cut categories.



Human skin color chart. Image from [Wikimedia](#), CC BY-SA 4.0.

An example of this is skin pigmentation in humans, which is controlled by several different genes.

- **Environmental effects.** Most real-world characteristics are determined not just by genotype, but also by environmental factors that influence how genotype is translated into phenotype.



Blue and pink hydrangea due to variance in soil pH. Image by [Lynn Greyling](#), Public domain

An example of this is the hydrangea flower. Hydrangea of the same genetic variety may vary in color from blue to pink depending on the pH of the soil they are in.

5.7.4: Common mistakes and misconceptions

- **Some people confuse pleiotropy and polygenic inheritance.** The major difference between the two is that pleiotropy is when *one gene* affects multiple characteristics (e.g. Marfan syndrome) and polygenic inheritance is when *one trait* is controlled by multiple genes (e.g. skin pigmentation).
- **Codominance and incomplete dominance are not the same.** In codominance, neither allele is dominant over the other, so both will be expressed equally in the heterozygote. In incomplete dominance, there is an intermediate heterozygote (such as a pink flower when the parents' phenotypes are red and white).

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CHAPTER OVERVIEW

6: Chromosomal Inheritance

6.1: DNA is Packaged into Chromatin

6.2: Mitosis

6.3: Meiosis

6.4: Karyotypes Describe Chromosome Number and Structure

6.5: Polyploidy Arises from Changes in Whole Sets of Chromosomes

6.6: Sex-Linkage- An Exception to Mendel's First Law

6.7: Example punnet square for sex-linked recessive trait

6.8: X-linked inheritance

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6.1: DNA is Packaged into Chromatin

6.1.1: DNA can be highly compacted

If stretched to its full length, the DNA molecule of the largest human chromosome would be 85mm. Yet during mitosis and meiosis, this DNA molecule is compacted into a chromosome approximately 5µm long. Although this compaction makes it easier to transport DNA within a dividing cell, it also makes DNA less accessible for other cellular functions such as DNA synthesis and transcription. Thus, chromosomes vary in how tightly DNA is packaged, depending on the stage of the cell cycle and also depending on the level of gene activity required in any particular region of the chromosome.

6.1.2: Levels of compaction

There are several different levels of structural organization in eukaryotic chromosomes, with each successive level contributing to the further compaction of DNA (Figure 6.1.2). For more loosely compacted DNA, only the first few levels of organization may apply. Each level involves a specific set of proteins that associate with the DNA to compact it. First, proteins called the **core histones** act as spool around which DNA is coiled twice to form a structure called the **nucleosome**. Nucleosomes are formed at regular intervals along the DNA strand, giving the molecule the appearance of “beads on a string”. At the next level of organization, **histone H1** helps to compact the DNA strand and its nucleosomes into a **30nm fibre**. Subsequent levels of organization involve the addition of **scaffold proteins** that wind the 30nm fibre into coils, which are in turn wound around other scaffold proteins.

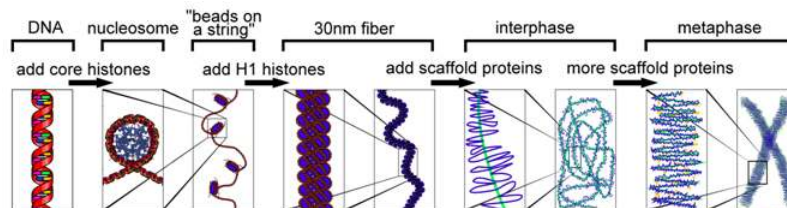


Figure 6.1.2: Successive stages of chromosome compaction depend on the introduction of additional proteins. (Wikipedia-R. Wheeler-GFDL)

6.1.3: Chromatin Packaging Varies inside the Nucleus: Euchromatin & Heterochromatin

Chromosomes stain with some types of dyes, which is how they got their name (chromosome means “colored body”). Certain dyes stain some regions along a chromosome more intensely than others, giving some chromosomes a banded appearance. The material that makes up chromosomes, which we now know to be proteins and DNA, is called **chromatin**. Classically, there are two major types of chromatin, but these are more the ends of a continuous and varied spectrum. **Euchromatin** is more loosely packed, and tends to contain genes that are being transcribed, when compared to the more densely compacted **heterochromatin**, which is rich in repetitive sequences and tends not to be transcribed. Heterochromatin sequences include short, highly-repetitive sequences called **satellite DNA**, which acquired their name because their buoyant density is distinctly different from the main band of DNA following ultracentrifugation.

6.1.4: Morphological features of Chromosomes

Chromosomes also contain other distinctive features such as centromeres and telomeres. Both of these are usually heterochromatin. In most cases, each chromosome contains one **centromere**. These sequences are bound by centromeric proteins that link the centromere to microtubules that transport chromosomes during cell division. Under the microscope, centromeres of metaphase chromosomes can sometimes appear as constrictions in the body of the chromosome (Figure 6.1.3) and are called primary (1°) constrictions. If a centromere is located near the middle of a chromosome, it is said to be **metacentric**, while an **acrocentric** centromere is closer to one end of a chromosome, and a **telocentric** chromosome is at, or near, the very end. In contrast, some species have a **holocentric** centromere, where no single centromere can be defined and the entire chromosome acts as the centromere. **Telomeres** are repetitive sequences near the ends of linear chromosomes, and are important in maintaining the length of the chromosomes during replication, and protecting the ends of the chromosomes from alterations.



Figure 6.1.3: A pair of metacentric chromosomes. The arrow shows a centromeric region (primary constriction). (Unknown-Unknown-pending)

It is essential to describe the similarity between chromosomes using appropriate terminology (Fig 2.4). **Homologous chromosomes** are typically pairs of similar, but non-identical, chromosomes in which one member of the pair comes from the male parent, and the other comes from the female parent. Homologs contain the same gene loci but not necessarily the same alleles. **Non-homologous chromosomes** contain different gene loci, and are usually distinguishable based on cytological features such as length, centromere position, and banding patterns.

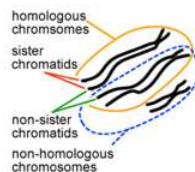


Figure 6.1.4: Relationships between chromosomes and chromatids. (Original-Deyholos-CC:AN)

An **unreplicated chromosome** can undergo replication, to produce a **replicated chromosome** that has two **sister chromatids**, which are physically connected to each other at the centromere and remain joined until cell division. Because a pair of sister chromatids is produced by the replication of a single DNA molecule, their sequences are essentially identical (same alleles), differing only because of DNA replication errors. On the other hand, **non-sister chromatids** come from two separate, but homologous chromosomes, and therefore usually contain the same gene loci in the same order, but do not necessarily have identical DNA sequences (allelic differences).

The decondensed chromosomes are not randomly arranged in within the interphase nucleus. They often have specific locations within the nucleus and relative to one another (Figure 6.1.5)

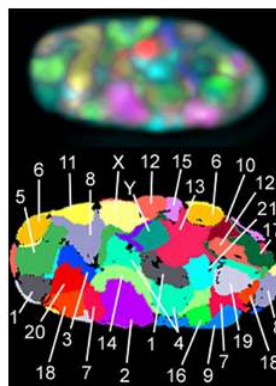


Figure 6.1.5: Top: FISH (Fluorescence in situ hybridization) labeling of all 24 different human chromosomes (1 - 22, X, and Y) in a fibroblast nucleus, each with a different combination of in total seven fluorochromes. **Bottom:** False color representation of all chromosome territories visible in this mid-section after computer classification. (BMC-Unknown-pending)

6.1.5: Chromosome and DNA Replication

When the cell enters *S-phase* in the cell cycle (G1-S-G2-M) all the chromosomal DNA is replicated. This is done by enzymes called **DNA polymerases**. All DNA polymerases synthesize new strands by adding nucleotides to the 3'OH group present on the previous nucleotide. For this reason they are said to work in a 5' to 3' direction. DNA polymerases use a single strand of DNA as a template upon which it will synthesize the complementary sequence. This works fine for the middle of chromosomes - DNA-directed DNA polymerases travel along the original DNA strands making complementary strands (Figure 6.1.6a).

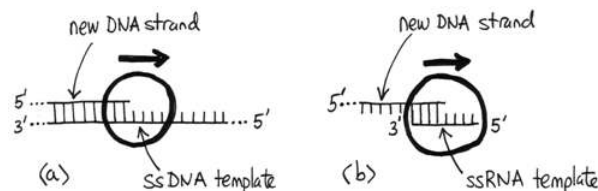


Figure 6.1.6: DNA polymerases make new strands in a 5' to 3' direction. (a) Regular DNA polymerases are proteins or protein complexes that use a single strand of DNA as a template. For example, the main human DNA polymerase, Pol α , is large protein complex made of four polypeptides. (b) Telomerases use their own RNA as a template. The human telomerase is a complex made of one polypeptide and one RNA molecule. (Original-Harrington-CC:AN)

DNA replication in both prokaryotes and eukaryotes begins at an **Origin of Replication (Ori)**. Origins are specific sequences on specific positions on the chromosome. In *E. coli*, the *OriC* origin is ~245 bp in size. Chromosome replication begins with the binding of the DnaA initiator protein to an AT-rich 9-mer in *OriC* and melts the two strands. Then DnaC loader protein helps DnaB helicase protein extend the single stranded regions such that the DnaG primase can initiate the synthesis of an RNA primer, from which the DNA polymerases can begin DNA synthesis at the two replication forks. The forks continue in opposite directions until they meet another fork or the end of the chromosome (Figure 6.1.7).

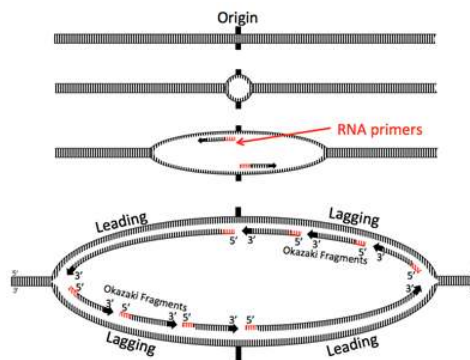


Figure 6.1.7: An origin of replication. The sequence specific DNA duplex is melted then the primase synthesizes RNA primers from which bidirectional DNA replication begins as the two replication forks head off in opposite directions. The leading and lagging strands are shown along with Okazaki fragments. Note the 5' and 3' orientation of all strands. (Original-Locke-CC:AN)

The ends of linear chromosomes present a problem – at each end one strand cannot be completely replicated because there is no primer to extend. Although the loss of such a small sequence would not be a problem, the continued rounds of replication would result in the continued loss of sequence from the chromosome end to a point where it would begin to lose essential gene sequences. Thus, this DNA must be replicated. Most eukaryotes solve the problem of synthesizing this unreplicated DNA with a specialized DNA polymerase called **telomerase**, in combination with a regular polymerase. Telomerases are RNA-directed DNA polymerases. They are a **riboprotein**, as they are composed of both protein and RNA. As Figure 6.1.6b shows, these enzymes contain a small piece of RNA that serves as a portable and reusable template from which the complementary DNA is synthesized. The RNA in human telomerases uses the sequence 3-AAUCCC-5' as the template, and thus our telomere DNA has the complementary sequence 5'-TTAGGG-3' repeated over and over 1000's of times. After the telomerase has made the first strand a primase synthesizes an RNA primer and a regular DNA polymerase can then make a complementary strand so that the telomere DNA will ultimately be double stranded to the original length (Figure 6.1.8). Note: the number of repeats, and thus the size of the telomere, is not set. It fluctuates after each round of the cell cycle. Because there are many repeats at the end, this fluctuation maintains a length buffer – sometimes it's longer, sometimes it's shorter – but the average length will be maintained over the generations of cell replication.

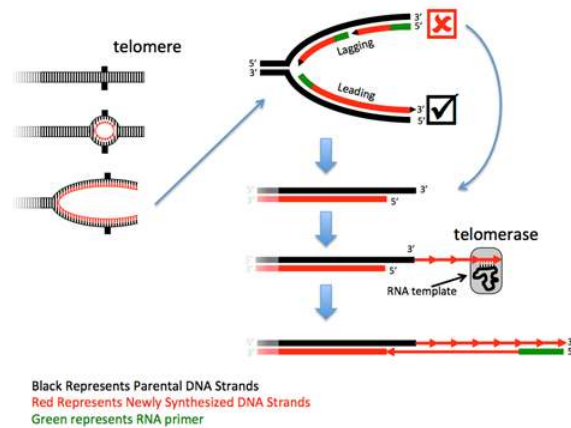


Figure 6.1.8: Telomere replication showing the completion of the leading strand and incomplete replication of the lagging strand. The gap is replicated by the extension of the 3' end by telomerase and then filled in by extension of an RNA primer. (Original-Locke-CC:AN)

In the absence of telomerase, as is the case in human somatic cells, repeated cell division leads to the “**Hayflick limit**”, where the telomeres shorten to a critical limit and then the cells enter a senescence phase of non-growth. The activation of telomerase expression permits a cell and its descendants to become immortal and bypass the Hayflick limit. This happens in cancer cells, which can form tumours as well as in cells in culture, such as **HeLa cells**, which can be propagated essentially indefinitely. HeLa cells have been kept in culture since 1951.

6.1.6: Eukaryote Chromosomes have Multiple Origins of Replication

In prokaryotes, with a small, simple, circular chromosome, only one origin of replication is needed to replicate the whole genome. For example, *E. coli* has a ~4.5 Mb genome (chromosome) that can be duplicated in ~40 minutes assuming a single origin, bi-directional replication, and a speed of ~1000 bases/second/fork for the polymerase.

However, in larger, more complicated eukaryotes, with multiple linear chromosomes, more than one origin of replication is required per chromosome to duplicate the whole chromosome set in the 8-hours of S-phase of the cell cycle. For example, the human diploid genome has 46 chromosomes (6×10^9 basepairs). The shortest chromosomes are ~50 Mbp long and so could not possibly be replicated from one origin. Additionally, the rate of replication fork movement is slower, only ~100 base/second. Thus, eukaryotes contain multiple origins of replication distributed over the length of each chromosome to enable the duplication of each chromosome within the observed time of S-phase (Fig 2.9).

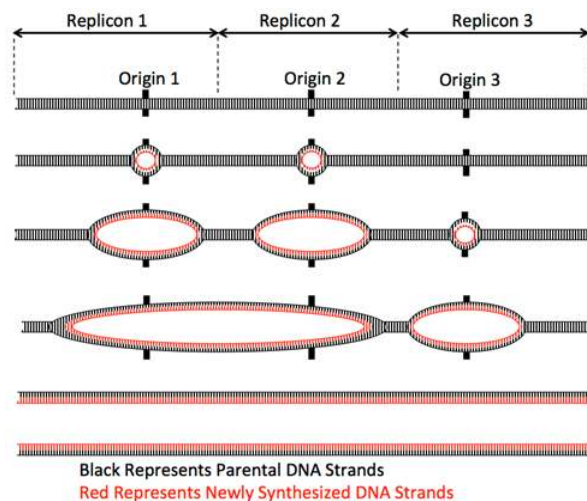


Figure 6.1.9: Part of a eukaryote chromosome showing multiple Origins (1, 2, 3) of Replication, each defining a **replicon** (1, 2, 3). Replication may start at different times in S-phase. Here #1 and #2 begin first then #3. As the replication forks proceed bi-directionally, they create what are referred to as “**replication bubbles**” that meet and form larger bubbles. The end result is two semi-conservatively replicated duplex DNA strands. (Original-Locke-CC:AN)

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6.2: Mitosis

Cell growth and division is essential to asexual reproduction and the development of multicellular organisms. Accordingly, the primary function of mitosis is to ensure that at division each daughter cell inherits identical genetic material, i.e. exactly one copy of each chromosome. To make this happen, replicated chromosomes condense (**prophase**), and are positioned near the middle of the dividing cell (**metaphase**), and then each of the sister chromatids from each chromosome migrates towards opposite poles of the dividing cell (**anaphase**), until the identical sets of unreplicated chromosomes are completely separated from each other within the two newly formed daughter cells (**telophase**) (Figures 2.10 and 2.11). This is followed by the division of the cytoplasm (**cytokinesis**) to complete the process. The movement of chromosomes occurs through microtubules that attach to the chromosomes at the centromeres.

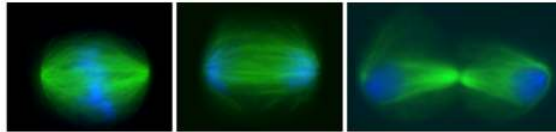


Figure 6.2.10: Mitosis in arabidopsis showing fluorescently labeled chromosomes (blue) and microtubules (green) at metaphase, anaphase and telophase (from left to right). (PLoS Genetics-Somma MP et al. (2008) PLoS Genets 4(7): e1000126 – PD).

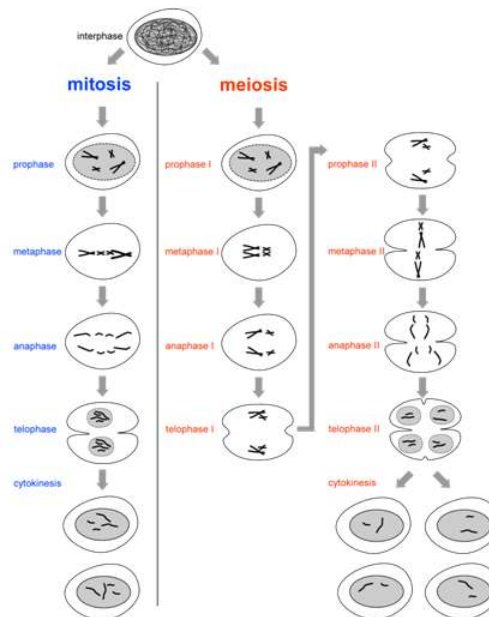


Figure 6.2.11: Mitosis and meiosis. Note the similarities and differences between metaphase in mitosis and metaphase I and II of meiosis. (Original-Deyholos-CC:AN)

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6.3: Meiosis

Most eukaryotes replicate sexually - a cell from one individual joins with a cell from another to create the next generation. For this to be successful, the cells that fuse must contain half the number of chromosomes as in the adult organism. Otherwise, the number of chromosomes would double with each generation! The reduction in chromosome number is achieved by the process of **meiosis**. In meiosis, there are usually two steps, Meiosis I and II. In Meiosis I homologous chromosomes segregate, while in Meiosis II sister chromatids segregate. Most multicellular organisms use meiosis to produce **gametes**, the cells that fuse to make offspring. Some single celled eukaryotes such as yeast also use meiosis.

6.3.1: Meiosis I and II

Meiosis begins similarly to mitosis (a cell has replicated its chromosomes and grown large enough to divide), but requires two rounds of division (Figure 6.3.8). In the first, known as meiosis I, the homologous chromosomes separate and segregate. During meiosis II the sister chromatids separate and segregate. Note how meiosis I and II are both divided into prophase, metaphase, anaphase, and telophase. After two rounds of cytokinesis, four cells will be produced, each with a single copy of each chromosome.

Cells that will undergo the process of meiosis are called **meiocytes** and are diploid ($2N$). Meiosis is divided into two stages designated by the roman numerals I and II. Meiosis I is called a **reductional** division, because it reduces the number of chromosomes inherited by each of the daughter cells. Meiosis I is further divided into Prophase I, Metaphase I, Anaphase I, and Telophase I, which are roughly similar to the corresponding stages of mitosis, except that in Prophase I and Metaphase I, homologous chromosomes pair with each other, or **synapse**, and are called **bivalents** (Figs. 2.12). This is an important difference between mitosis and meiosis, because it affects the segregation of alleles, and also allows for recombination to occur through crossing-over, as described later. During Anaphase I, one member of each pair of homologous chromosomes migrates to each daughter cell ($1N$). Meiosis II resembles mitosis, with one sister chromatid from each chromosome separating to produce two daughter cells. Because Meiosis II, like mitosis, results in the segregation of sister chromatids, Meiosis II is called an **equational** division.

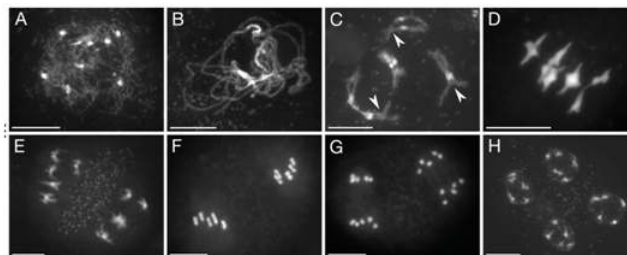


Figure 6.3.12: Meiosis in Arabidopsis ($n=5$). Panels A-C show different stages of prophase I, each with an increasing degree of chromosome condensation. Subsequent phases are shown: metaphase I (D), telophase I (E), metaphase II (F), anaphase II (G), and telophase II (H). (PLoS Genetics-Chelysheva, L. et al (2008) PLoS Genetics-PD)

In meiosis I replicated, homologous chromosomes **pair up**, or **synapse**, during prophase I, lining up in the middle of the cell during metaphase I, and separating during anaphase I. For this to happen the homologous chromosomes need to be brought together while they condense during prophase I. These attachments are formed in two ways. Proteins bind to both homologous chromosomes along their entire length and form the **synaptonemal complex** (synapse means junction). These proteins hold the chromosomes in a transient structure called a **bivalent**. The proteins are released when the cell enters anaphase I.

Within the synaptonemal complex a second event, **crossingover**, occurs. These are places where DNA repair enzymes break the DNA two non-sister chromatids in similar locations and then covalently reattach non-sister chromatids together to create a crossover between non-sister chromatids. This reorganization of chromatids will persist for the remainder of meiosis and result in recombination of alleles in the gametes.

Crossovers function to hold homologous chromosomes together during meiosis I so they segregate successfully and they also cause the reshuffling of gene/allele combinations to create genetic diversity, which can have an important effect on evolution (see Chapter 7).

6.3.2: Stages of Prophase I

In meiosis, Prophase I is divided up into five visual stages, that are steps along a continuum of events. Leptotene, zygotene, pachytene, diplotene and diakinesis. From interphase, a cell enters **leptotene** as the nuclear material begins to condense into long visible threads (chromosomes). During **Zygotene** homologous chromosomes begin to pair up (synapse) and form an elaborate structure called the synaptonemal complex along their length. At **pachytene** homologous chromosomes are fully synapsed (two chromosomes and four chromatids) to form **bivalents**. **Crossing over** takes place in pachytene. After this, the pairing begins to loosen and individual chromatids become apparent in **diplotene**. This is when the consequences of each crossing over event can be seen as a **chiasma** (plural: **chiasmata**). **Diakinesis** follows as the chromosomes continue to condense and individualize. This is followed by metaphase I where the paired chromosomes orient on the metaphase plate in preparation for segregation (reductional).

6.3.3: Meiosis II and Gamete Maturation

At the completion of meiosis I there are two cells, each with one, replicated copy of each chromosome (1N). Because the number of chromosomes per cell has decreased ($2 \rightarrow 1$), meiosis I is called a **reductional cell division**. In the second part of meiosis the chromosomes will once again be brought to the middle of the cell, but this time it is the sister chromatids that will segregate during anaphase.

After cytokinesis there will be four cells, each containing only one unreplicated chromosome of each type. Meiosis II resembles mitosis in that the number of chromosomes per cell is unchanged - both are **equational cell divisions** – but in meiosis II all cells won't have the same genetic composition. There will be allelic differences among the gametes.

In animals and plants the cells produced by meiosis need to mature before they become functional gametes. In male animals the four products of meiosis are called spermatids. They grow tails and become functional sperm cells. In female animals the gametes are eggs. In order that each egg contains the maximum amount of nutrients only one of the four products of meiosis becomes an egg. The other three cells end up as tiny disposable cells called **polar bodies**. In plants the products of meiosis reproduce a few times using mitosis as they develop into functional male or female gametes.

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6.4: Karyotypes Describe Chromosome Number and Structure

6.4.1: Karyograms are images of real chromosomes

Each eukaryotic species has its nuclear genome divided among a number of chromosomes that is characteristic of that species. For example, a haploid human nucleus (i.e. sperm or egg) normally has 23 chromosomes ($n=23$), and a diploid human nucleus has 23 pairs of chromosomes ($2n=46$). A **karyotype** is the complete set of chromosomes of an individual. The cell was in metaphase so each of the 46 structures is a replicated chromosome even though it is hard to see the two sister chromatids for each chromosome at this resolution. As expected there are 46 chromosomes. Note that the chromosomes have different lengths. In fact, human chromosomes were named based upon this feature. Our largest chromosome is called 1, our next longest is 2, and so on. By convention the chromosomes are arranged into the pattern shown in Figure 6.4.15 and the resulting image is called a **karyogram**. A karyogram allows a geneticist to determine a person's karyotype - a written description of their chromosomes including anything out of the ordinary.

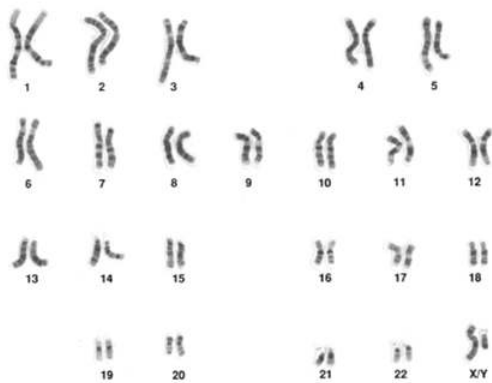


Figure 6.4.15: Karyogram of a normal human male karyotype.(Wikipedia-NHGRI-PD)

Various stains and fluorescent dyes are used to produce characteristic banding patterns to distinguish all 23 chromosomes. The number of chromosomes varies between species, but there appears to be very little correlation between chromosome number and either the complexity of an organism or its total amount genomic DNA.

6.4.2: Autosomes and Sex Chromosomes

In the figure above note that most of the chromosomes are paired (same length, centromere location, and banding pattern). These chromosomes are called **autosomes**. However note that two of the chromosomes, the X and the Y do not look alike. These are **sex chromosomes**. In humans males have one of each while females have two X chromosomes. Autosomes are those chromosomes present in the same number in males and females while sex chromosomes are those that are not. When sex chromosomes were first discovered their function was unknown and the name X was used to indicate this mystery. The next ones were named Y, then Z, and then W.

The combination of sex chromosomes within a species is associated with either male or female individuals. In mammals, fruit flies, and some flowering plants embryos, those with two X chromosomes develop into females while those with an X and a Y become males. In birds, moths, and butterflies males are ZZ and females are ZW. Because sex chromosomes have arisen multiple times during evolution the molecular mechanism(s) through which they determine sex differs among those organisms. For example, although humans and *Drosophila* both have X and Y sex chromosomes, they have different mechanisms for determining sex.

In mammals, the sex chromosomes evolved just after the divergence of the monotreme lineage from the lineage that led to placental and marsupial mammals. Thus nearly every mammal species uses the same sex determination system. During embryogenesis the gonads will develop into either ovaries or testes. A gene present only on the Y chromosome called *TDF* encodes a protein that makes the gonads mature into testes. XX embryos do not have this gene and their gonads mature into ovaries instead (default). Once formed the testes produce sex hormones that direct the rest of the developing embryo to become male, while the

ovaries make different sex hormones that promote female development. The testes and ovaries are also the organs where gametes (sperm or eggs) are produced.

How do the sex chromosome behave during meiosis? Well, in those individuals with two of the same chromosome (i.e. **homogametic** sexes: XX females and ZZ males) the chromosomes pair and segregate during meiosis I the same as autosomes do. During meiosis in XY males or ZW females (**heterogametic** sexes) the sex chromosomes pair with each other (Figure 6.4.16). In mammals the consequence of this is that all egg cells will carry an X chromosome while the sperm cells will carry either an X or a Y chromosome. Half of the offspring will receive two X chromosomes and become female while half will receive an X and a Y and become male.

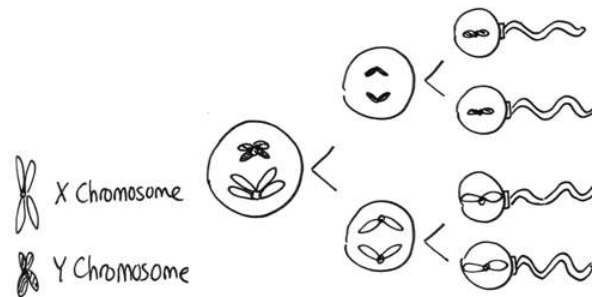


Figure 6.4.16: Meiosis in an XY mammal. The stages shown are anaphase I, anaphase II, and mature sperm. Note how half of the sperm contain Y chromosomes and half contain X chromosomes. (Original-Harrington-CC:AN)

6.4.3: Aneuploidy - Changes in Chromosome Number

Analysis of karyotypes can identify chromosomal abnormalities, including **aneuploidy**, which is the addition or subtraction of a chromosome from a pair of homologs. More specifically, the absence of one member of a pair of homologous chromosomes is called **monosomy** (only one remains). On the other hand, in a **trisomy**, there are three, rather than two (disomy), homologs of a particular chromosome. Different types of aneuploidy are sometimes represented symbolically; if $2n$ symbolizes the normal number of chromosomes in a cell, then $2n-1$ indicates monosomy and $2n+1$ represents trisomy. The addition or loss of a whole chromosome is a mutation, a change in the genotype of a cell or organism.

The most familiar human aneuploidy is trisomy-21 (i.e. three copies of chromosome 21), which is one cause of **Down syndrome**. Most (but not all) other human aneuploidies are lethal at an early stage of embryonic development. Note that aneuploidy usually affects only one set of homologs within a karyotype, and is therefore distinct from **polyploidy**, in which the entire chromosome set is duplicated (see below). Aneuploidy is almost always deleterious, whereas polyploidy appears to be beneficial in some organisms, particularly many species of food plants.

Aneuploidy can arise due to a **non-disjunction** event, which is the failure of at least one pair of chromosomes or chromatids to segregate during mitosis or meiosis. Non-disjunction will generate gametes with extra and missing chromosomes.

6.4.4: Chromosomal abnormalities

Structural defects in chromosomes are another type of abnormality that can be detected in karyotypes (Fig 2.17). These defects include **deletions**, **duplications**, and **inversions**, which all involve changes in a segment of a single chromosome. **Insertions** and **translocations** involve two non-homologous chromosomes. In an insertion, DNA from one chromosome is moved to a non-homologous chromosome in a unidirectional manner. In a translocation, the transfer of chromosomal segments is bidirectional and reciprocal – a reciprocal translocation.

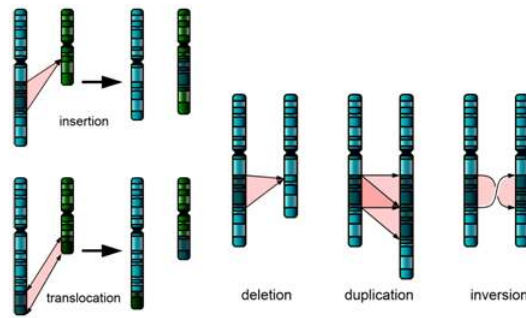


Figure 6.4.17: Structural aberrations in chromosomes.(Wikipedia-Zephyris-GFDL)

Structural defects affect only part of a chromosome (a subset of genes), and so tend to be less harmful than aneuploidy. In fact, there are many examples of ancient chromosomal rearrangements in the genomes of species including our own. Duplications of some small chromosomal segments, in particular, may have some evolutionary advantage by providing extra copies of some genes, which can then evolve in new, potentially beneficial, ways.

Chromosomal abnormalities arise in many different ways, some of which can be traced to rare errors in natural cellular processes such as DNA replication. **Chromosome breakage** also occurs infrequently as the result of physical damage (such as ionizing radiation), movement of some types of transposons, and other factors. During the repair of a broken chromosome, deletions, insertions, translocations and even inversions can be introduced.

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6.5: Polyploidy Arises from Changes in Whole Sets of Chromosomes

If you refer back to Figure 6.5.15 you can see that humans, like most animals and most eukaryotic genetic model organisms, have two copies of each autosome. This situation is called **diploidy**. This means that most of their cells have two homologous copies of each chromosome. In contrast, many plant species and even a few animal species are **polyploids**. This means they have more than two chromosome sets, and so have more than two homologs of each chromosome in each cell.

When the nuclear content changes by a whole chromosome set we call it a change in ploidy. Gametes are haploid ($1n$) and thus most animals are diploid ($2n$), formed by the fusion of two haploid gametes. However, some species can exist as monoploid ($1x$), triploid ($3x$), tetraploid ($4x$), pentaploid ($5x$), hexaploid ($6x$), or higher.

6.5.1: Notation of ploidy

When describing polyploids, we use the letter “**x**” (not “**n**”) to define the level of ploidy. A diploid is $2x$, because there are two basic sets of chromosomes, and a tetraploid is $4x$, because it contains four chromosome sets. For clarity when discussing polyploids, geneticists will often combine the “**x**” notation with the “**n**” notation already defined previously in this chapter. Thus for both diploids and polyploids, “**n**” is the number of chromosomes in a gamete, and “ $2n$ ” is the number of chromosomes following fertilization. For a diploid, therefore, $n=x$, and $2n=2x$. But for a tetraploid, $n=2x$, and $2n=4x$ and for a hexaploid, $n=3x$, and $2n=6x$.

6.5.2: Male Bees are Monoploid

Monoploids, with only one set, are usually inviable in most species, however, in many species of hymenoptera (bees, wasps, ants) the males are monoploid and develop from unfertilized eggs. These males don’t undergo meiosis for gametes; mitosis produces sperm. Females are diploid (from fertilized eggs) and produce eggs via meiosis. This is the basis for the haploid-diploid sex determination system (not the X/Y chromosome system). Female bees are diploid ($2n=32$) and are formed when an egg ($n=16$) is fertilized by a sperm ($n=16$). If an egg isn’t fertilized it can still develop and the result is a $n=16$ male drone. Males are described as haploid (because they have the same number of chromosomes as a gamete) or monoploid (because they have only one chromosome set). Females produce eggs by meiosis while males produce sperm by mitosis. This form of sex determination produces more females – workers, which do the work (Figure 2-18) than males, who are only needed for reproduction.



Figure 6.5.18: A worker caste European honey bee, which is female and diploid. Male drones are haploid. (Wikipedia-J. Severns-PD)

6.5.3: Polyploids can be stable or sterile

Like diploids ($2n=2x$), stable polyploids generally have an even number of copies of each chromosome: tetraploid ($2n=4x$), hexaploid ($2n=6x$), and so on. The reason for this is clear from a consideration of meiosis. Remembering that the purpose of meiosis is to reduce the sum of the genetic material by half, meiosis can equally divide an even number of chromosome sets, but not an odd number. Thus, polyploids with an odd number of chromosomes (e.g. triploids, $2n=3x$) tend to be **sterile**, even if they are otherwise healthy.

The mechanism of meiosis in stable polyploids is essentially the same as in diploids: during metaphase I, homologous chromosomes pair with each other. Depending on the species, all of the homologs may be aligned together at metaphase, or in multiple separate pairs. For example, in a tetraploid, some species may form **tetravalents** in which the four homologs from each chromosome align together, or alternatively, two pairs of homologs may form two bivalents. Note that because that mitosis does not involve any pairing of homologous chromosomes, mitosis is equally effective in diploids, even-number polyploids, and odd-number polyploids.

6.5.4: Many Crop Plants are Hexaploid or Octoploid

Polyploid plants tend to be larger and healthier than their diploid counterparts. The strawberries sold in grocery stores come from **octoploid** (8x) strains and are much larger than the strawberries formed by wild diploid strains. An example is bread wheat which is a **hexaploid** (6x) strain. This species is derived from the combination of three other wheat species, *T. monococcum* (chromosome sets = AA), *T. searsii* (BB), and *T. tauschii* (DD). Each of these chromosome sets has 7 chromosomes so the diploid species are $2n=2x=14$ and bread wheat is $2n=6x=42$ and has the chromosome sets AABBDD. Bread wheat is viable because each chromosome behaves independently during mitosis. The species is also fertile because during meiosis I the A chromosomes pair with the other A chromosomes, and so on. Thus, even in a polyploid, homologous chromosomes can segregate equally and gene balance can be maintained.

6.5.5: Bananas, Watermelons, and Other Seedless Plants are Triploid

The bananas found in grocery stores are a seedless variety called Cavendish. They are a **triploid** variety (chromosome sets = AAA) of a normally diploid species called *Musa acuminata* (AA). Cavendish plants are viable because mitosis can occur. However they are sterile because the chromosomes cannot pair properly during meiosis I. During prophase I there are three copies of each chromosome trying to “pair” with each other. Because proper chromosome segregation in meiosis fails, seeds cannot be made and the result is a fruit that is easier to eat because there are no seeds to spit out. Seedless watermelons (Figure 6.5.19) have a similar explanation.



Figure 6.5.19: Seedless watermelon is triploid, with the white, aborted seeds within the flesh. (Flickr-

Darwin Bell-CC:AN)

If triploids cannot make seeds, how do we obtain enough triploid individuals for cultivation? The answer depends on the plant species involved. In some cases, such as banana, it is possible to propagate the plant asexually; new progeny can simply be grown from cuttings from a triploid plant. On the other hand, seeds for seedless watermelon are produced sexually: a tetraploid watermelon plant is crossed with a diploid watermelon plant. Both the tetraploid and the diploid are fully fertile, and produce gametes with two ($1n=2x$) or one ($1n=1x$) sets of chromosomes, respectively. These gametes fuse to produce a zygote ($2n=3x$) that is able to develop normally into an adult plant through multiple rounds of mitosis, but is unable to compete normal meiosis or produce seeds.

Polyploids are often larger in size than their diploid relatives (Figure 6.5.20). This feature is used extensively in food plants. For example, most strawberries you eat are not diploid, but octoploid (8x).

Polyploidy in animals is rare, essentially limited to lower forms, which often reproduce by parthenogenesis.

Credit: www.jamesandthegiantcorn.com/wp-content/uploads/2009/11/strawberries2.jpg



Figure 6.5.20: Polyploidy in Strawberries. The sweet, flavorful, wild diploid is on the left, while the huge, cultivated octoploid is on the right.

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6.6: Sex-Linkage- An Exception to Mendel's First Law

In the previous chapter we introduced sex chromosomes and autosomes. For loci on autosomes, the alleles follow the normal Mendelian pattern of inheritance. However, for loci on the sex chromosomes this is mostly not true, because most of the loci on the typical X-chromosome are absent from the Y-chromosome, even though they act as a homologous pair during meiosis. Instead, they will follow a **sex-linked** pattern of inheritance.

6.6.1: X-Linked Genes: the *white* gene in *Drosophila melanogaster*

A well-studied sex-linked gene is the *white* gene on the X chromosome of *Drosophila melanogaster*. Normally flies have red eyes but flies with a mutant allele of this gene called *white*⁻ (*w*⁻) have white eyes because the red pigments are absent. Because this mutation is recessive to the wild type *w*⁺ allele females that are heterozygous have normal red eyes. Female flies that are homozygous for the mutant allele have white eyes. Because there is no *white* gene on the Y chromosome, male flies can only be hemizygous for the wild type allele or the mutant allele.

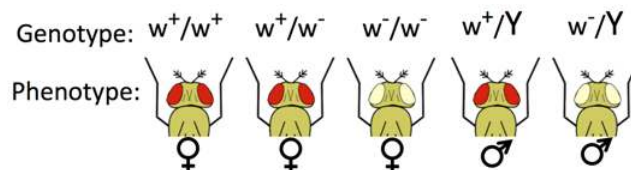


Figure 6.6.9: Relationship between genotype and phenotype for the *white* gene on the X-linked gene in *Drosophila melanogaster*. The Y chromosome is indicated with a capital Y because it does not have a copy of the *white* gene. (Original-Harrington/Locke-CC:AN)

A researcher may not know beforehand whether a novel mutation is sex-linked. The definitive method to test for sex-linkage is **reciprocal crosses** (Figure 6.6.10). This means to cross a male and a female that have different phenotypes, and then conduct a second set of crosses, in which the phenotypes are reversed relative to the sex of the parents in the first cross. For example, if you were to set up reciprocal crosses with flies from pure-breeding *w*⁺ and *w*⁻ strains the results would be as shown in Figure 6.6.10. Whenever reciprocal crosses give different results in the F1 and F2 and whenever the male and female offspring have different phenotypes the usual explanation is sex-linkage. Remember, if the locus were autosomal the F1 and F2 progeny would be different from either of these crosses.

A similar pattern of sex-linked inheritance is seen for X-chromosome loci in other species with an XX-XY sex chromosome system, including mammals and humans. The ZZ-ZW system is similar, but reversed (see below).

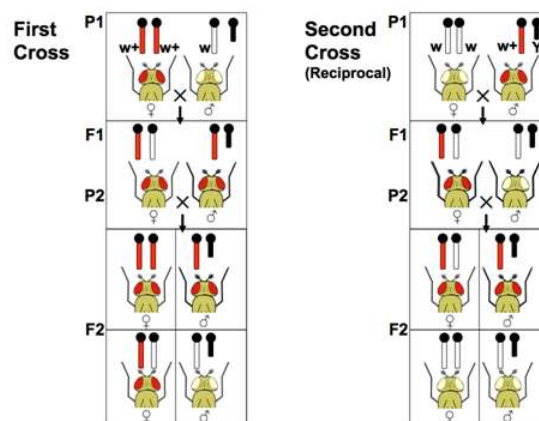


Figure 6.6.10: Reciprocal crosses involving an X-linked gene in *Drosophila melanogaster*. In the first cross (left) all of the offspring have red eyes. In second (reciprocal) cross (right) all of the female offspring have red eyes and the male offspring all have white eyes. If the F1 progeny are crossed (to make the P2), the F2 progeny will be different in each cross. The first cross has all red-eyed females and half red-eyed males. The reciprocal cross has half red-eyed males and females. Thomas Morgan won the Nobel Prize for using these crosses to demonstrate that genes (such as *white*) were on chromosomes (in this case the X-chromosome). (Wikipedia-PAR-PD)

6.6.2: Sex Determination in animals.

There are various mechanisms for sex determination in animals. These include sex chromosomes, chromosome dosage, and environment.

For example in humans and other mammals XY embryos develop as males while XX embryos become females. This difference in development is due to the presence of only a **single gene**, the TDF-Y gene, on the Y-chromosome. Its presence and expression dictates that the sex of the individual will be male. Its absence results in a female phenotype.

Although *Drosophila melanogaster* also has an XX-XY sex chromosomes, its sex determination system uses a different method, that of **X:Autosome (X:A) ratio**. In this system it is the ratio of autosome chromosome sets (A) relative to the number of X-chromosomes (X) that determines the sex. Individuals with two autosome sets and two X-chromosomes (2A:2X) will develop as females, while those with only one X-chromosome (2A:1X) will develop as males. The presence/absence of the Y-chromosome and its genes are not significant.

In other species of animals the number of chromosome sets can determine sex. For example the **haploid-diploid system** is used in bees, ants, and wasps. Typically haploids are male and diploids are female.

In other species, the environment can determine an individual's sex. In alligators (and some other reptiles) the temperature of development dictates the sex, while in many reef fish, the population sex ratio can cause some individuals to change sex.

6.6.3: Dosage Compensation for Loci on Sex Chromosomes.

Mammals and *Drosophila* both have XX - XY sex determination systems. However, because these systems evolved independently they work differently with regard to compensating for the difference in gene dosage (and sex determination – see above). Remember, in most cases the sex chromosomes act as a homologous pair even though the Y-chromosome has lost most of the loci when compared to the X-chromosome. Typically, the X and the Y chromosomes were once similar but, for unclear reasons, the Y chromosomes have degenerated, slowly mutating and losing its loci. In modern day mammals the Y chromosomes have very few genes left while the X chromosomes remain as they were. This is a general feature of all organisms that use chromosome based sex determination systems. Chromosomes found in both sexes (the X or the Z) have retained their genes while the chromosome found in only one sex (the Y or the W) have lost most of their genes. In either case there is a gene dosage difference between the sexes: e.g. XX females have two doses of X-chromosome genes while XY males only have one. This gene dosage needs to be compensated in a process called **dosage compensation**. There are two major mechanisms.

In *Drosophila* and many other insects, to make up for the males only having a single X chromosome the genes on it are expressed at twice the normal rate. This mechanism of dosage compensation restores a balance between proteins encoded by **X-linked genes** and those made by **autosomal genes**.

In mammals a different mechanism is used, called **X-chromosome inactivation**.

6.6.4: X-chromosome Inactivation in Mammals

In mammals the dosage compensation system operates in females, not males. In XX embryos one X in each cell is randomly chosen and marked for inactivation. From this point forward this chromosome will be inactive, hence its name X_{inactive} (X_i). The other X chromosome, the X_{active} (X_a), is unaffected. The X_i is replicated during S phase and transmitted during mitosis the same as any other chromosome but most of its genes are never allowed to turn on. The chromosome appears as a condensed mass within interphase nuclei called the Barr body. With the inactivation of genes on one X-chromosome, females have the same number of functioning X-linked genes as males.

This random inactivation of one X-chromosome leads to a commonly observed phenomenon in cats. A familiar X-linked gene is the *Orange* gene (O) in cats. The O^O allele encodes an enzyme that results in orange pigment for the hair. The O^B allele causes the hairs to be black. The phenotypes of various genotypes of cats are shown in Figure 6.6.11. Note that the heterozygous females have an orange and black mottled phenotype known as tortoiseshell. This is due to patches of skin cells having different X-chromosomes inactivated. In each orange hair the X_i chromosome carrying the O^B allele is inactivated. The O^O allele on the X_a is functional and orange pigments are made. In black hairs the reverse is true, the X_i chromosome with the O^O allele is inactive and the X_a chromosome with the O^B allele is active. Because the inactivation decision happens early during embryogenesis, the cells continue to divide to make large patches on the adult cat skin where one or the other X is inactivated.

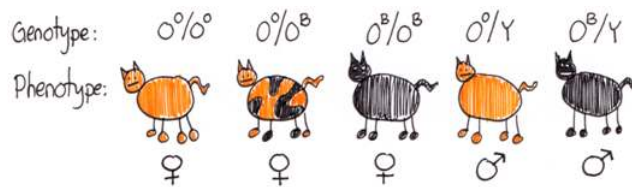


Figure 6.6.11: Relationship between genotype and phenotype for an X-linked gene in cats. The O^O allele = orange while the O^B allele = black. (Original-Harrington-CC:AN)

The *Orange* gene in cats is a good demonstration of how the mammalian dosage compensation system affects gene expression. However, most X-linked genes do not produce such dramatic mosaic phenotypes in heterozygous females. A more typical example is the *F8* gene in humans. It makes Factor VIII blood clotting proteins in liver cells. If a male is hemizygous for a mutant allele the result is hemophilia type A. Females homozygous for mutant alleles will also have hemophilia. Heterozygous females, those people who are $F8^+/F8^-$, do not have hemophilia because even though half of their liver cells do not make Factor VIII (because the X with the $F8^+$ allele is inactive) the other 50% can (Figure 6.6.12). Because some of their liver cells are exporting Factor VIII proteins into the blood stream they have the ability to form blood clots throughout their bodies. The genetic mosaicism in the cells of their bodies does not produce a visible mosaic phenotype.

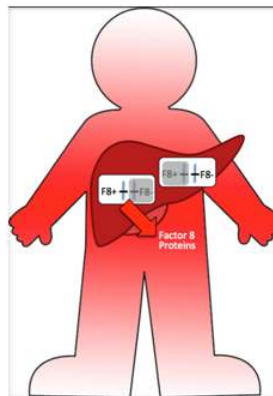


Figure 6.6.12: This figure shows the two types of liver cells in females heterozygous for an *F8* mutation. Because people with the $F8^+/F8^-$ genotype have the same phenotype, normal blood clotting, as $F8^+/F8^+$ people the $F8^-$ mutation is classified as recessive. (Original-Harrington/Locke-CC:AN)

6.6.5: Other Sex-Linked Genes – Z-linked genes

One last example is a **Z-linked gene** that influences feather colour in turkeys. Turkeys are birds, which use the ZZ-ZW sex chromosome system. The *E* allele makes the feathers bronze and the *e* allele makes the feathers brown (Figure 6.6.13). Only male turkeys can be heterozygous for this locus, because they have two Z chromosomes. They are also uniformly bronze because the *E* allele is completely dominant to the *e* allele and birds use a dosage compensation system similar to *Drosophila* and not mammals. Reciprocal crosses between turkeys from pure-breeding bronze and brown breeds would reveal that this gene is in fact Z-linked.

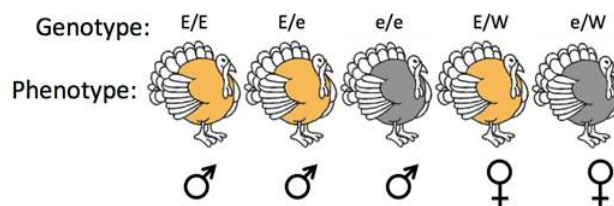


Figure 6.6.13: Relationship between genotype and phenotype for a Z-linked gene in turkeys. The W chromosome does not have an *E/e*-gene so it is just indicated with a capital W. (Original-Harrington/Locke-CC:AN)

6.6.6: Mechanisms of Sex Determination Systems

Sex is a phenotype. Typically, in most species, there are multiple characteristics, in addition to sex organs, that distinguish male from female individuals (although some species are normally **hermaphrodites** where both sex organs are present in the same

individual). The morphology and physiology of male and females is a phenotype just like hair or eye colour or wing shape. The sex of an organism is part of its phenotype and can be genetically (or environmentally) determined.

For each species, the genetic determination relies on one of several gene or chromosome based mechanisms. See Figure 6.6.14 for a summary. There are, for other species, also a variety of environmental mechanisms, too (rearing temperature, social interactions, **parthenogenesis**). Whatever the sex choice mechanism, however, there are two different means by which the cells of an organism carry out this decision: **hormonal** or **cell-autonomous**

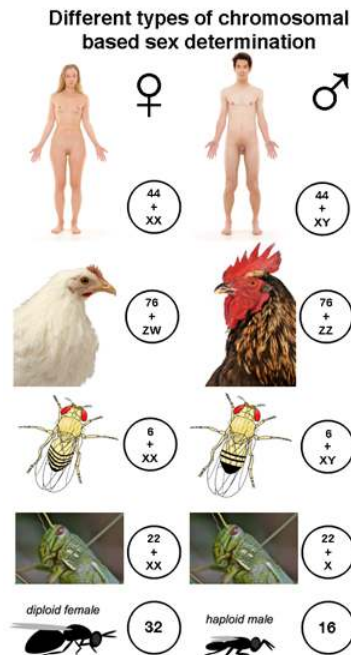


Figure 6.6.14: – Different types of chromosomal (or gene) based sex determination. From top to bottom, there is the archetypal XX/XY system found in humans (and most mammals) with the TDF-Y gene leading to a male phenotype; the ZW/ZZ system found in chickens (birds, moths, and butterflies); the same XX/XY system in *Drosophila* (sex is determined by the X-chromosome:autosome ratio); the XX/XO system as found in grasshoppers; and the diploid/haploid system as found in bees (and ants, and wasps). Also, the hormonal mechanism is used in humans, while all the other examples use the cell-autonomous mechanism for development of the male or female sex phenotype. (Wikipedia+original - CFCF with additions and corrections by J. Locke- CC:AN)

Hormonal mechanism: With this system, used by mammals for example, including humans, the zygote initially develops into a sexually undifferentiated embryo that can become either sex. Then, depending on the sex choice of the genital ridge cells, they will grow and differentiate into male (testis) or female (ovary) gonads, which will then produce the appropriate hormones (e.g. testosterone or estrogen). This hormone will circulate throughout the body and cause all the other tissues to develop and differentiate accordingly, into a male or female phenotype for that individual. Thus, the circulating hormone “tells” all the cells and tissues what sex to be and which sexual phenotype to be.

A **freemartin** is a type of **chimera** found in cattle (and some other mammals). Externally it appears as a female but is infertile, and has masculinized behavior and non-functioning ovaries. The animal originates as a female (XX), but acquires male (XY) cells or tissues *in utero* by exchange of some cellular material from a male twin. The female reproductive development is altered by anti-Müllerian hormone from the male twin, acquired via vascular connections between placentas.

Cell-autonomous mechanism: With this system, used by many animals, including birds and insects, the zygote cell initially has a sex phenotype set at the cell level. All cells intrinsically know, individually, which sex they are and develop accordingly, giving the appropriate sexual characteristics and phenotype. Each cell is autonomous with respect to its sex; there are no sex hormone cues to determine the sex expressed. This autonomy can lead to **sexual gynandromorphs**, which are **mosaics** that display both male and female characteristics in a mosaic fashion, typically split down the midline of the organism. These rare individuals are thought to be the result of an improper sex chromosome segregation that occurs in a cell very early in development so that one half of the individual has cells with a male chromosome set while the other half has cells with a female set. If the species is **sexually**

dimorphic (external morphology easily distinguishes males from females) they are easily visible and are even sometimes seen in the wild. See Figure 6.6.15 for a local example. A search on the internet will bring up many more examples.



Figure 6.6.15: – *Drosophila* sexual gynandromorph. The left side is female with the most distal abdominal segments being not heavily pigmented, while the right is male and the two most distal segments are heavily pigmented (arrow). This example was found by a U. of Alberta student in the GENET 375 lab course, Introductions to Molecular Genetic Techniques. (Original – Locke – CC:AN)

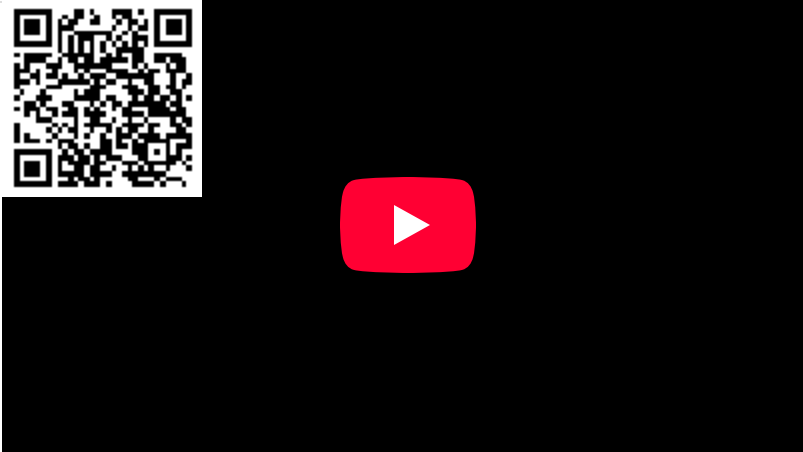
While gynandromorphs are seen in cell-autonomous species, such as insects and birds, they are not seen in hormonally determined species, such as mammals, because all the cells display the same sex phenotype caused by the circulating sex hormones. Sexual gynandromorphs appear to be absent in reptiles, amphibians, and fish indicating that they don't use a cell-autonomous mechanism. Nevertheless, there are genetic mosaic individuals in these groups but they do not appear to involve sex determined traits, which is required for a true gynandromorph. They often involve mosaicism of alleles at a single gene locus that affect external morphology (e.g. color).

- A **gynandromorph** is an organism that made up of mosaic tissues of male and female genotypes and displays both male and female characteristics.
- A **mosaic** is an organism or a tissue that contains two or more types of genetically different cells derived from the same zygote.
- A **chimera** is a single organism composed of genetically distinct cells derived from different zygotes.

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6.7: Example punnet square for sex-linked recessive trait



Example punnet square for sex-linked recessive trait.

6.7.1: Contributors and Attributions

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6.8: X-linked inheritance

6.8.1: Key points:

- In humans and other mammals, biological sex is determined by a pair of **sex chromosomes**: XY in males and XX in females.
- Genes on the X chromosome are said to be **X-linked**. X-linked genes have distinctive inheritance patterns because they are present in different numbers in females (XX) and males (XY).
- X-linked human genetic disorders are much more common in males than in females due to the X-linked inheritance pattern.

6.8.2: Introduction

If you're a human being (which seems like a good bet!), most of your chromosomes come in **homologous pairs**. The two chromosomes of a homologous pair contain the same basic information – that is, the same genes in the same order – but may carry different versions of those genes.

Are all of your chromosomes organized in homologous pairs? The answer depends on whether you're (chromosomally) male.

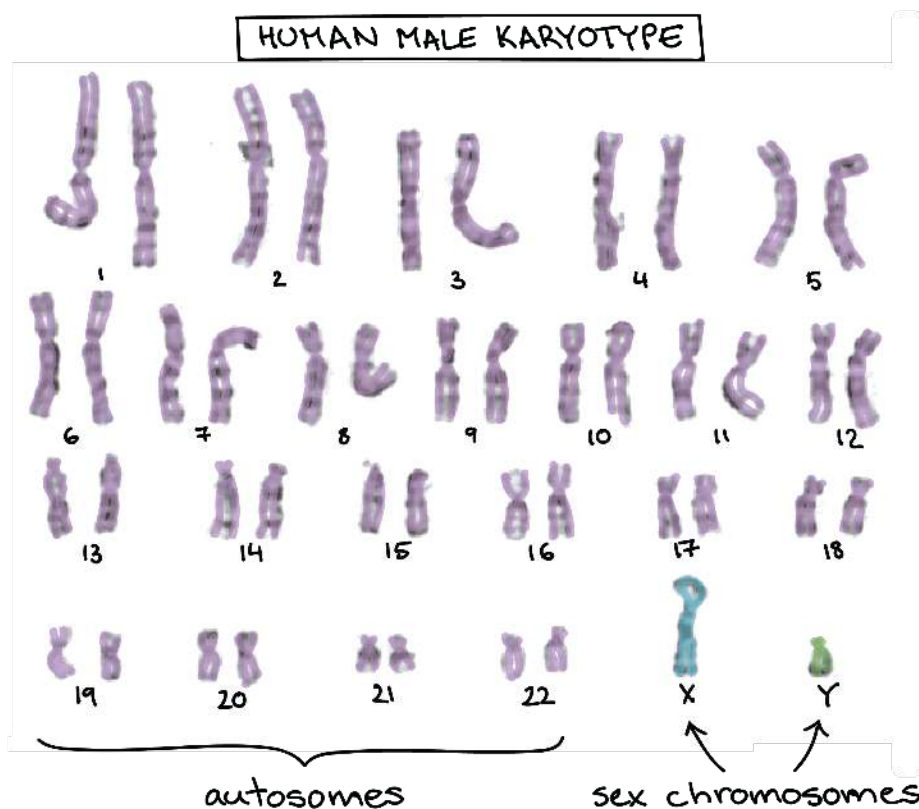


Image modified from "Karyotype," by Can H. (CC BY 2.0).

- A human male has two **sex chromosomes**, the X and the Y. Unlike the 44 **autosomes** (non-sex chromosomes), the X and Y don't carry the same genes and aren't considered homologous.
- Instead of an X and a Y, a human female has two X chromosomes. These X chromosomes do form a *bona fide* homologous pair.

Because sex chromosomes don't always come in homologous pairs, the genes they carry show unique, distinctive patterns of inheritance.

6.8.3: Sex chromosomes in humans

Human X and Y chromosomes determine the biological sex of a person, with XX specifying female and XY specifying male. Although the Y chromosome contains a small region of similarity to the X chromosome so that they can pair during meiosis, the Y chromosome is much shorter and contains many fewer genes.

To put some numbers to it, the X chromosome has about 800-900 protein-coding genes with a wide variety of functions, while the Y chromosome has just 60-70 protein-coding genes, about half of which are active only in the testes (sperm-producing organs)^{1,2,3,4}.

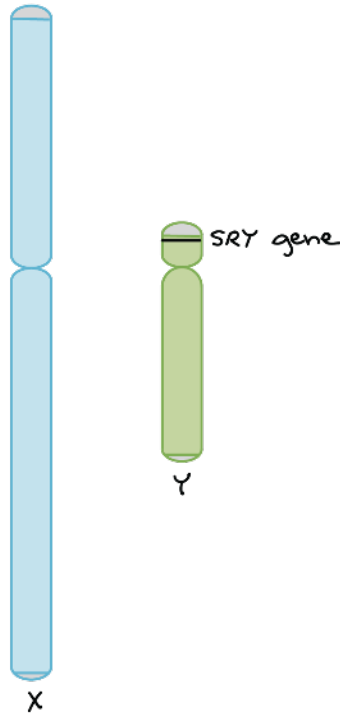


Image based on ideograms from the [Genome Decoration Page](#), maintained by the U.S. NCBI.

The human Y chromosome plays a key role in determining the sex of a developing embryo. This is mostly due to a gene called *SRY* (“sex-determining region of Y”). *SRY* is found on the Y chromosome and encodes a protein that turns on other genes required for male development^{5,6}.

- XX embryos don't have *SRY*, so they develop as female.
- XY embryos do have *SRY*, so they develop as male.

In rare cases, errors during meiosis may transfer *SRY* from the Y chromosome to the X chromosome. If an *SRY*-bearing X chromosome fertilizes a normal egg, it will produce a chromosomally female (XX) embryo that develops as a male⁷. If an *SRY*-deficient Y chromosome fertilizes a normal egg, it will produce a chromosomally male embryo (XY) that develops as a female⁸.

[Do all species with X and Y chromosomes have the *SRY* gene?]

No, not all of them. The molecular mechanisms of sex determination vary greatly among species, even those that use an X-Y sex determination system. In most placental mammals, *SRY* is found on the Y chromosome and is used for sex determination. However, the *SRY* gene is not present in other species with X-Y sex determination systems, such as fruit flies and other insects⁹.

6.8.3.1: X and Y chromosomes have evolved independently many times

To understand how this is possible, it's useful to keep in mind that “X” and “Y” are just generic labels applied to the dimorphic (*di-* = two, *-morphe* = form), or dissimilar, chromosomes found in species with X-Y sex determination systems¹⁰. X is whatever chromosome the female has two of, while Y is the chromosome paired with a single X in the male. The nature of the chromosomes — what genes are on them, and how they determine maleness or femaleness — may be quite different between species.

Sex chromosomes have evolved independently many times¹¹. Thus, although fruit flies and humans both have X and Y chromosomes that match the above definition, and although XY and XX chromosome combinations correspond to maleness and femaleness, respectively, in both species, the sex determination mechanism in flies is very different from that of humans.

6.8.3.2: Example: Humans vs. fruit flies

In humans, as described above, the Y chromosome specifies maleness through the action of the SRY gene, a master regulator of male development.

In flies, the presence of a single X chromosome specifies maleness, while the presence of two Xs specifies femaleness, regardless of the presence or absence of a Y chromosome. (More specifically, it appears that sex is determined by the ratio of X chromosomes to autosomes, with a 1:2 ratio specifying maleness and a 2:2 ratio specifying femaleness. These ratios are "measured" through the levels of proteins produced by specific genes on the X chromosome and on autosomes.)¹²

Because of these differences in sex determination mechanisms, an XXY fly will develop as a female (see article on [Thomas Hunt Morgan's experiments](#)), while an XXY human will develop as a male (in a condition known as Klinefelter syndrome; see article on [large-scale chromosomal changes](#)).

6.8.4: X-linked genes

When a gene is present on the X chromosome, but not on the Y chromosome, it is said to be **X-linked**. X-linked genes have different inheritance patterns than genes on non-sex chromosomes (autosomes). That's because these genes are present in different copy numbers in males and females.

[What about genes on the Y?]

Genes on either the X or the Y have unusual inheritance patterns and are called **sex-linked**, but X-linkage is much more common than Y-linkage (since there are many more genes on the X than the Y).

Since a female has two X chromosomes, she will have two copies of each X-linked gene. For instance, in the fruit fly *Drosophila* (which, like humans, has XX females and XY males), there is an eye color gene called *white* that's found on the X chromosome, and a female fly will have two copies of this gene. If the gene comes in two different alleles, such as X^W (dominant, normal red eyes) and X^w (recessive, white eyes), the female fly may have any of three genotypes: $X^W X^W$ (red eyes), $X^W X^w$ (red eyes), and $X^w X^w$ (white eyes).

A male has different genotype possibilities than a female. Since he has only one X chromosome (paired with a Y), he will have only one copy of any X-linked genes. For instance, in the fly eye color example, the two genotypes a male can have are $X^W Y$ (red eyes) and $X^w Y$ (white eyes). Whatever allele the male fly inherits for an X-linked gene will determine his appearance, because he has no other gene copy—even if the allele is recessive in females. Rather than homozygous or heterozygous, males are said to be **hemizygous** for X-linked genes.

We can see how sex linkage affects inheritance patterns by considering a cross between two flies, a white-eyed female ($X^w X^w$) and a red-eyed male ($X^W Y$). If this gene were on a non-sex chromosome, or autosome, we would expect all of the offspring to be red-eyed, because the red allele is dominant to the white allele. What we actually see is the following:

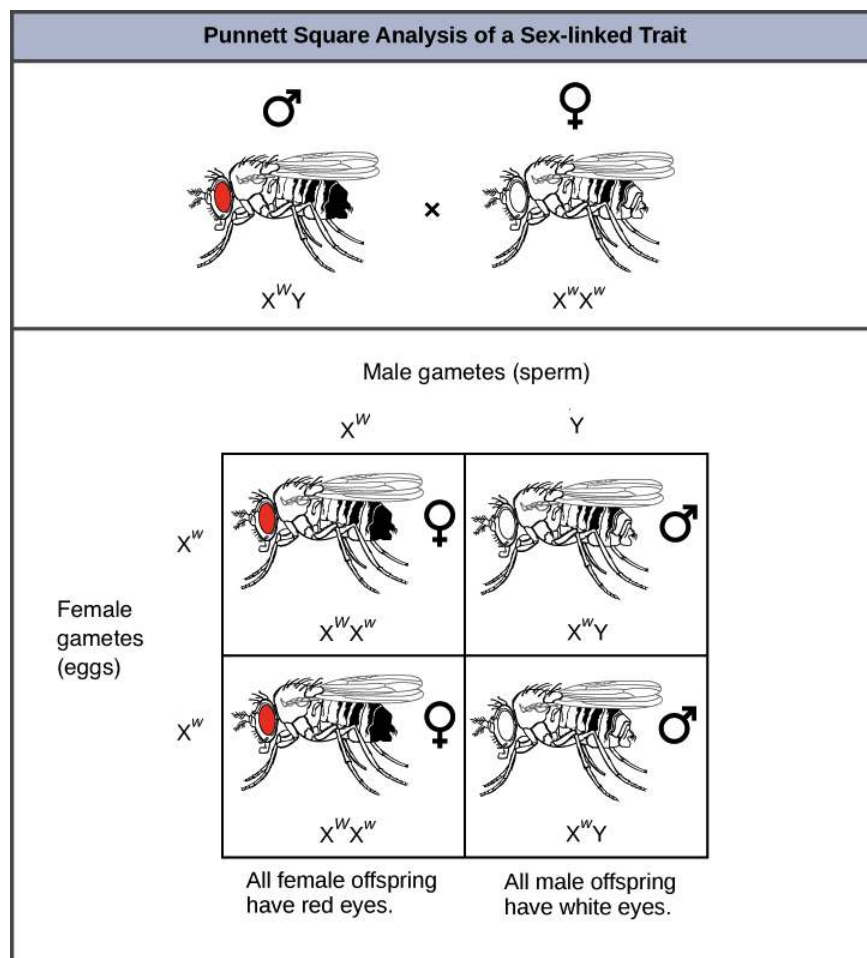


Image credit: "Characteristics and traits: Figure 10," by OpenStax College, Biology, CC BY 4.0

However, because the gene is X-linked, and because it was the female parent who had the recessive phenotype (white eyes), all the male offspring—who get their only X from their mother—have white eyes ($X^w Y$). All the female offspring have red eyes because they received two Xs, with the X^W from the father concealing the recessive X^w from the mother.

6.8.5: X-linked genetic disorders

The same principles we see at work in fruit flies can be applied to human genetics. In humans, the alleles for certain conditions (including some forms of color blindness, hemophilia, and muscular dystrophy) are X-linked. These diseases are much more common in men than they are in women due to their X-linked inheritance pattern.

Why is this the case? Let's explore this using an example in which a mother is heterozygous for a disease-causing allele. Women who are heterozygous for disease alleles are said to be **carriers**, and they usually don't display any symptoms themselves. Sons of these women have a 50% chance of getting the disorder, but daughters have little chance of getting the disorder (unless the father also has it), and will instead have a 50% chance of being carriers.

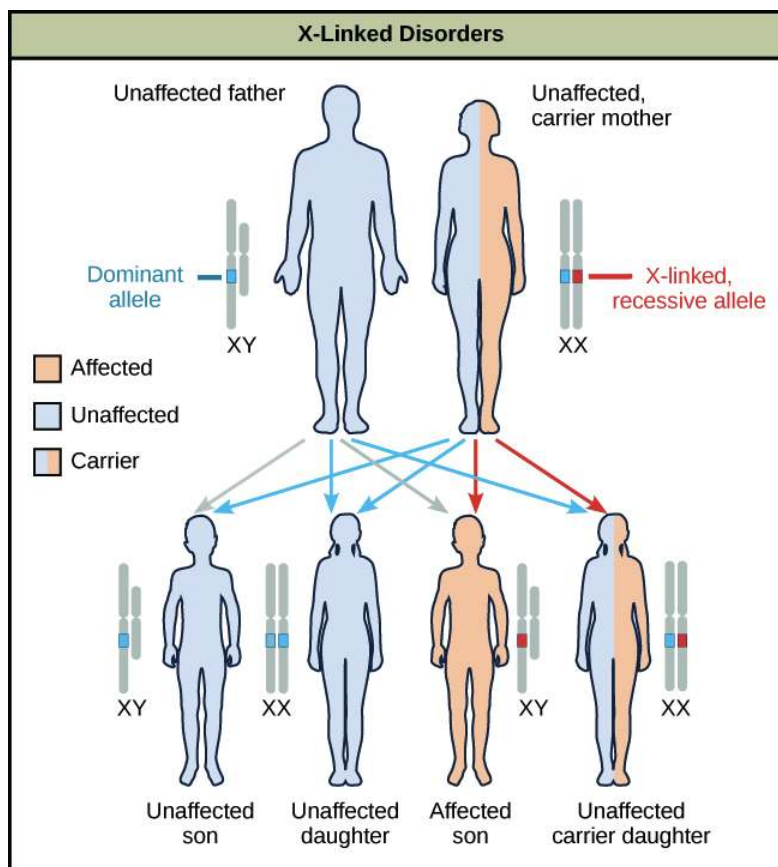


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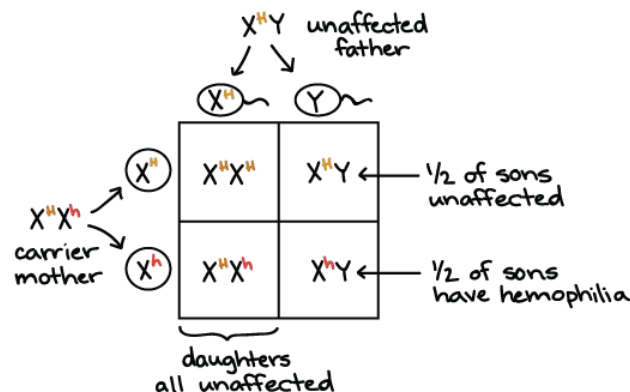
Why is this the case? Recessive X-linked traits appear more often in males than females because, if a male receives a "bad" allele from his mother, he has no chance of getting a "good" allele from his father (who provides a Y) to hide the bad one. Females, on the other hand, will often receive a normal allele from their fathers, preventing the disease allele from being expressed.

6.8.6: Case study: Hemophilia

Let's look at a Punnett square example using an X-linked human disorder: hemophilia, a recessive condition in which a person's blood does not clot properly¹³. A person with hemophilia may have severe, even life-threatening, bleeding from just a small cut.

Hemophilia is caused by a mutation in either of two genes, both of which are located on the X chromosome. Both genes encode proteins that help blood clot¹⁴. Let's focus on just one of these genes, calling the functional allele X^H and the disease allele X^h .

In our example, a woman who is heterozygous for normal and hemophilia alleles ($X^H X^h$) has children with a man who is hemizygous for the normal form ($X^H Y$). Both parents have normal blood clotting, but the mother is a carrier. What is the chance of their sons and daughters having hemophilia?



Since the mother is a carrier, she will pass on the hemophilia allele (X^h) on to half of her children, both boys and girls.

- None of the daughters will have hemophilia (zero chance of the disorder). That's because, in order to have the disorder, they must get a X^h allele from both their mother and their father. There is 0 chance of the daughters getting an X^h allele from their father, so their overall chance of having hemophilia is zero.
- The sons get a Y from their father instead of an X, so their only copy of the blood clotting gene comes from their mother. The mother is heterozygous, so half of the sons, on average, will get an X^h allele and have hemophilia (1/2 chance of the disorder).

[Can a woman ever have hemophilia?]

Yes, it's possible for a woman to have a recessive, X-linked condition such as hemophilia. However, she must get two recessive copies of the X-linked gene (one from each parent) in order to have the condition. The odds of this are much lower than the odds of a man getting just one recessive disease allele from his mother.

6.8.7: Check your understanding

6.8.8: Contributors and Attributions

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CHAPTER OVERVIEW

7: Chi Square Analysis

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CHAPTER OVERVIEW

8: Gene Mapping and Recombination

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8.1: Linkage

As we learned in Chapter 6, Mendel reported that the pairs of loci he observed behaved independently of each other; for example, the segregation of seed color alleles was independent from the segregation of alleles for seed shape. This observation was the basis for his Second Law (Independent Assortment), and contributed greatly to our understanding of heredity. However, further research showed that Mendel's Second Law did not apply to every pair of genes that could be studied. In fact, we now know that alleles of loci that are located close together on the same chromosome tend to be inherited together. This phenomenon is called **linkage**, and is a major exception to Mendel's **Second Law of Independent Assortment**. Researchers use linkage to determine the location of genes along chromosomes in a process called genetic mapping. The concept of gene linkage is important to the natural processes of heredity and evolution.

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8.2: Recombination

The term “recombination” is used in several different contexts in genetics. In reference to heredity, **recombination** is defined as any process that results in gametes with combinations of alleles that were not present in the gametes of a previous generation (see Figure 8.2.2). **Interchromosomal recombination** occurs either through **independent assortment** of alleles whose loci are on different chromosomes (Chapter 6). **Intrachromosomal recombination** occurs through **crossovers** between loci on the same chromosomes (as described below). It is important to remember that in both of these cases, recombination is a process that occurs during meiosis (mitotic recombination may also occur in some species, but it is relatively rare). If meiosis results in recombination, the products are said to have a **recombinant genotype**. On the other hand, if no recombination occurs during meiosis, the products have their original combinations and are said to have a non-recombinant, or **parental genotype**. Recombination is important because it contributes to the genetic variation that may be observed between individuals within a population and acted upon by selection to produce evolution.

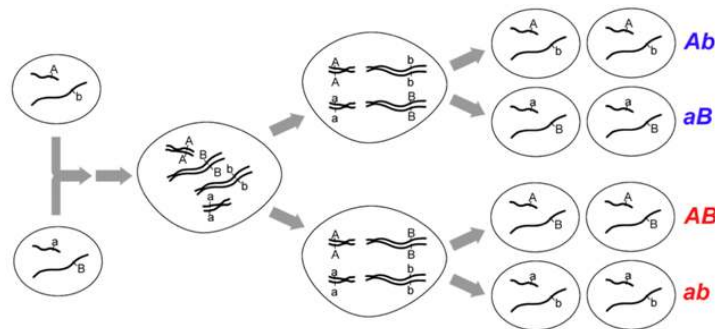


Figure 8.2.2: When two loci are on non-homologous chromosomes, their alleles will segregate in combinations identical to those present in the parental gametes (Ab, aB), and in recombinant genotypes (AB, ab) that are different from the parental gametes. (Original-Deyholos-CC:AN)

As an example of interchromosomal recombination, consider loci on two different chromosomes as shown in Figure 8.2.2. We know that if these loci are on different chromosomes, there are no physical connections between them, so they are **unlinked** and will segregate independently as did Mendel’s traits. The segregation depends on the relative orientation of each pair of chromosomes at metaphase. Since the orientation is random and independent of other chromosomes, each of the arrangements (and their meiotic products) is equally possible for two unlinked loci as shown in Figure 8.2.2. More precisely, there is a 50% probability for recombinant genotypes, and a 50% probability for parental genotypes within the gametes produced by a meiocyte with unlinked loci. Indeed, if we examined all of the gametes that could be produced by this individual (which are the products of multiple independent meioses), we would note that approximately 50% of the gametes would be recombinant, and 50% would be parental. **Recombination frequency** (RF) is simply the number of recombinant gametes, divided by the total number of gametes. A frequency of approximately 50% recombination is therefore a defining characteristic of unlinked loci. Thus the greatest recombinant frequency expected is ~50%.

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8.3: Linkage Reduces Recombination Frequency

Having considered unlinked loci above, let us turn to the opposite situation, in which two loci are so close together on a chromosome that the parental combinations of alleles always segregate together (Figure 8.3.3). This is because during meiosis they are so close that there are no crossover events between the two loci and the alleles at the two loci are physically attached on the same chromatid and so they always segregate together into the same gamete. In this case, no recombinants will be present following meiosis, and the recombination frequency will be 0%. This is **complete** (or **absolute**) **linkage** and is rare, as the loci must be so close together that crossovers are never detected between them.

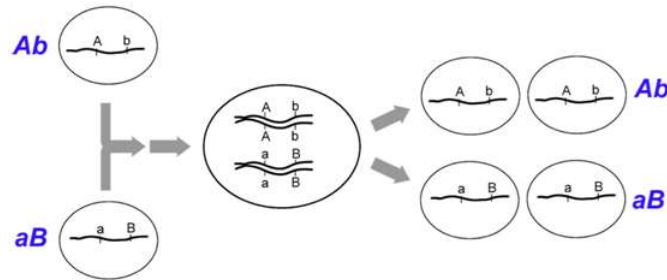


Figure 8.3.3: If two loci are completely linked, their alleles will segregate in combinations identical to those present in the parental gametes (Ab, aB). No recombinants will be observed. (Original-Deyholos-CC:AN)

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8.4: Crossovers Allow Recombination of Linked Loci

Thus far, we have only considered situations with either no linkage (50% recombination) or complete linkage (0% recombination). It is also possible to obtain recombination frequencies between 0% and 50%, which is a situation we call **incomplete** (or **partial**) **linkage**. Incomplete linkage occurs when two loci are located on the same chromosome but the loci are far enough apart so that crossovers occur between them during some, but not all, meioses. Genes that are on the same chromosome are said to be **syntenic** regardless of whether they are completely or incompletely linked. All linked genes are syntenic, but not all syntenic genes are linked, as we will learn later.

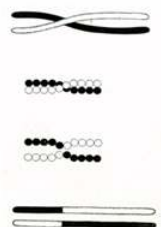


Figure 8.4.4: A depiction of a crossover from Morgan's 1916 manuscript. Only one pair of non-sister chromatids is shown, but remember there are 4 chromatids for each homologous pair in meiosis. (Wikipedia-Morgan-PD)

Crossovers occur during prophase I of meiosis, when pairs of homologous chromosomes have aligned with each other in a process called **synapsis**. Crossing over begins with the breakage of DNA of a pair of non-sister chromatids. The breaks occur at corresponding positions on two non-sister chromatids, and then the ends of non-sister chromatids are connected to each other resulting in a reciprocal exchange of double-stranded DNA (Figure 8.4.4). Generally every pair of chromosomes has at least one (and often more) crossovers during meiosis (Figure 8.4.5).

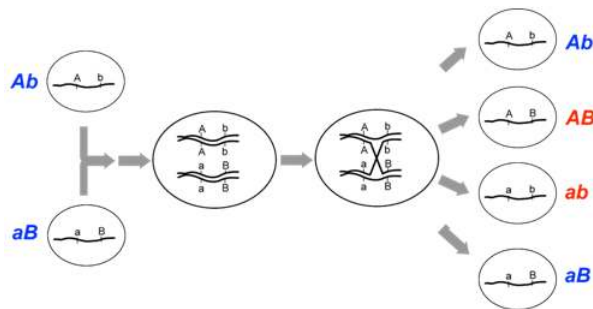


Figure 8.4.5: A crossover between two linked loci can generate recombinant genotypes (AB, ab), from the chromatids involved in the crossover. Remember that multiple, independent meioses occur in each organism, so this particular pattern of recombination will not be observed among all the meioses from this individual. (Original-Deyholos-CC:AN)

Because the location of crossovers is essentially random along the chromosome, the greater the distance between two loci, the more likely a crossover will occur between them. Furthermore, loci that are on the same chromosome, but are sufficiently far apart from each other, will on average have multiple crossovers between them and they will behave as though they are completely unlinked. A recombination frequency of 50% is therefore the maximum recombination frequency that can be observed, and is indicative of loci that are either on separate chromosomes, or are located very far apart on the same chromosome.

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8.5: Inferring Recombination From Genetic Data

In the preceding examples, we had the advantage of knowing the approximate chromosomal positions of each allele involved, before we calculated the recombination frequencies. Knowing this information beforehand made it relatively easy to define the parental and recombinant genotypes, and to calculate recombination frequencies. However, in most experiments, we cannot directly examine the chromosomes, or even the gametes, so we must infer the arrangement of alleles from the phenotypes over two or more generations. Importantly, it is generally not sufficient to know the genotype of individuals in just one generation; for example, given an individual with the genotype $AaBb$, we do not know from the genotype alone whether the loci are located on the same chromosome, and if so, whether the arrangement of alleles on each chromosome is AB and ab or Ab and aB (Figure 8.5.6). The top cell has the two dominant alleles together and the two recessive alleles together and is said to have the genes in the **coupling** (or **cis**) **configuration**. The alternative shown in the cell below is that the genes are in the **repulsion** (or **trans**) **configuration**.

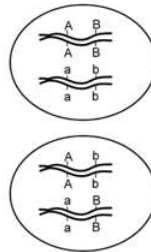


Figure 8.5.6: Alleles in coupling configuration (top) or repulsion configuration (bottom). (Original-Deyholos-CC:AN)

Fortunately for geneticists, the arrangement of alleles can sometimes be inferred if the genotypes of a previous generation are known. For example, if the parents of $AaBb$ had genotypes $AABB$ and $aabb$ respectively, then the parental gametes that fused to produce $AaBb$ would have been genotype AB and genotype ab . Therefore, prior to meiosis in the dihybrid, the arrangement of alleles would likewise be AB and ab (Figure 8.5.7). Conversely, if the parents of $AaBb$ had genotypes $aaBB$ and $AAbb$, then the arrangement of alleles on the chromosomes of the dihybrid would be aB and Ab . Thus, the genotype of the previous generation can determine which of an individual's gametes are considered recombinant, and which are considered parental.

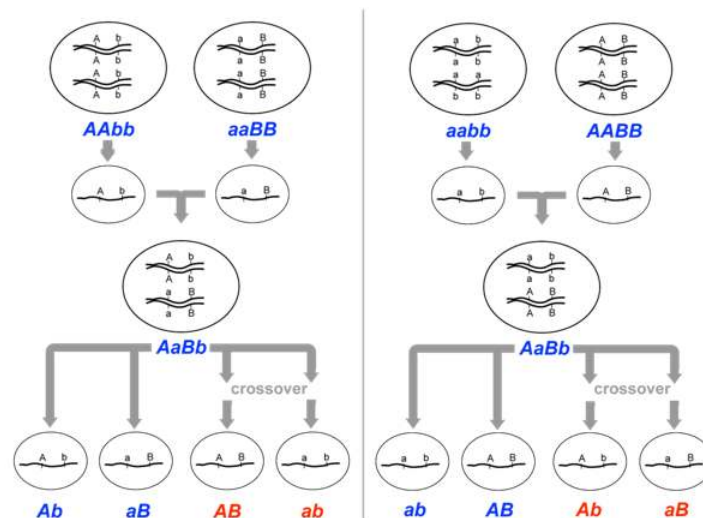


Figure 8.5.7: The genotype of gametes can be inferred unambiguously if the gametes are produced by homozygotes. However, recombination frequencies can only be measured among the progeny of heterozygotes (i.e. dihybrids). Note that the dihybrid on the left contains a different configuration of alleles than the dihybrid on the right due to differences in the genotypes of their respective parents. Therefore, different gametes are defined as recombinant and parental among the progeny of the two dihybrids. In the cross at left, the recombinant gametes will be genotype AB and ab , and in the cross on the right, the recombinant gametes will be Ab and aB . (Original-Deyholos-CC:AN)

Let us now consider a complete experiment in which our objective is to measure recombination frequency (Figure 8.5.8). We need at least two alleles for each of two genes, and we must know which combinations of alleles were present in the parental gametes. The simplest way to do this is to start with pure-breeding lines that have contrasting alleles at two loci. For example, we could

cross short-tailed mice, brown mice ($aaBB$) with long-tailed, white mice ($AAbb$). Based on the genotypes of the parents, we know that the parental gametes will be aB or Ab (but not ab or AB), and all of the progeny will be dihybrids, $AaBb$. We do not know at this point whether the two loci are on different pairs of homologous chromosomes, or whether they are on the same chromosome, and if so, how close together they are.

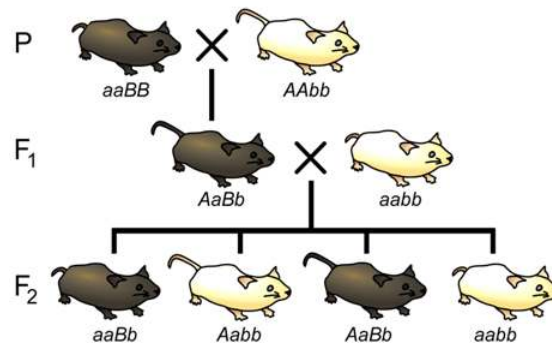


Figure 8.5.8: An experiment to measure recombination frequency between two loci. The loci affect coat color (B/b) and tail length (A/a). (Wikipedia-Modified Deyholos-CC:AN)

The recombination events that may be detected will occur during meiosis in the dihybrid individual. If the loci are completely or partially linked, then prior to meiosis, alleles aB will be located on one chromosome, and alleles Ab will be on the other chromosome (based on our knowledge of the genotypes of the gametes that produced the dihybrid). Thus, recombinant gametes produced by the dihybrid will have the genotypes ab or AB , and non-recombinant (i.e. parental) gametes will have the genotypes aB or Ab .

How do we determine the genotype of the gametes produced by the dihybrid individual? The most practical method is to use a testcross (Figure 8.5.8), in other words to mate $AaBb$ to an individual that has only recessive alleles at both loci ($aabb$). This will give a different phenotype in the F₂ generation for each of the four possible combinations of alleles in the gametes of the dihybrid. We can then infer unambiguously the genotype of the gametes produced by the dihybrid individual, and therefore calculate the recombination frequency between these two loci. For example, if only two phenotypic classes were observed in the F₂ (i.e. short tails and brown fur ($aaBb$), and white fur with long tails ($Aabb$)) we would know that the only gametes produced following meiosis of the dihybrid individual were of the parental type: aB and Ab , and the recombination frequency would therefore be 0%. Alternatively, we may observe multiple classes of phenotypes in the F₂ in ratios such as shown in Table 8.5.1:

Table 8.5.1: An example of quantitative data that may be observed in a genetic mapping experiment involving two loci. The data correspond to the F₂ generation in the cross shown in Figure 8.5.8.

tail phenotype	fur phenotype	number of progeny	gamete from dihybrid	genotype of F ₂ from test cross	(P)arental or (R)ecombinant
short	brown	48	aB	$aaBb$	P
long	white	42	Ab	$Aabb$	P
short	white	13	ab	$aabb$	R
long	brown	17	AB	$AaBb$	R

Given the data in Table 8.5.1, the calculation of recombination frequency is straightforward:

$$\text{recombination frequency} = \frac{\text{number of recombinant gametes}}{\text{total number of gametes scored}} \quad (8.5.1)$$

$$\text{R.F.} = \frac{13 + 17}{48 + 42 + 13 + 17} \quad (8.5.2)$$

$$= 25\% \quad (8.5.3)$$

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8.6: Genetic Mapping

Because the frequency of recombination between two loci (up to 50%) is roughly proportional to the chromosomal distance between them, we can use recombination frequencies to produce genetic maps of all the loci along a chromosome and ultimately in the whole genome. The units of genetic distance are called **map units** (mu) or **centiMorgans** (cM), in honor of **Thomas Hunt Morgan** by his student, **Alfred Sturtevant**, who developed the concept. Geneticists routinely convert recombination frequencies into cM: the recombination frequency in percent is approximately the same as the map distance in cM. For example, if two loci have a recombination frequency of 25% they are said to be ~25cM apart on a chromosome (Figure 8.6.9). Note: this approximation works well for small distances (RF<30%) but progressively fails at longer distances because the RF reaches a maximum at 50%. Some chromosomes are >100 cM long but loci at the tips only have an RF of 50%. The method for mapping of these long chromosomes is shown below.

Note that the map distance of two loci alone does not tell us anything about the orientation of these loci relative to other features, such as centromeres or telomeres, on the chromosome.

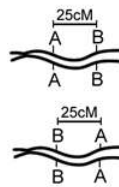


Figure 8.6.9: Two genetic maps consistent with a recombination frequency of 25% between A and B. Note the location of the centromere. (Original-Deyholos-CC:AN)

Map distances are always calculated for one pair of loci at a time. However, by combining the results of multiple pairwise calculations, a **genetic map** of many loci on a chromosome can be produced (Figure 8.6.10). A genetic map shows the map distance, in cM, that separates any two loci, and the position of these loci relative to all other mapped loci. The genetic map distance is roughly proportional to the physical distance, i.e. the amount of DNA between two loci. For example, in *Arabidopsis*, 1.0 cM corresponds to approximately 150,000bp and contains approximately 50 genes. The exact number of DNA bases in a cM depends on the organism, and on the particular position in the chromosome; some parts of chromosomes (“crossover hot spots”) have higher rates of recombination than others, while other regions have reduced crossing over and often correspond to large regions of heterochromatin.

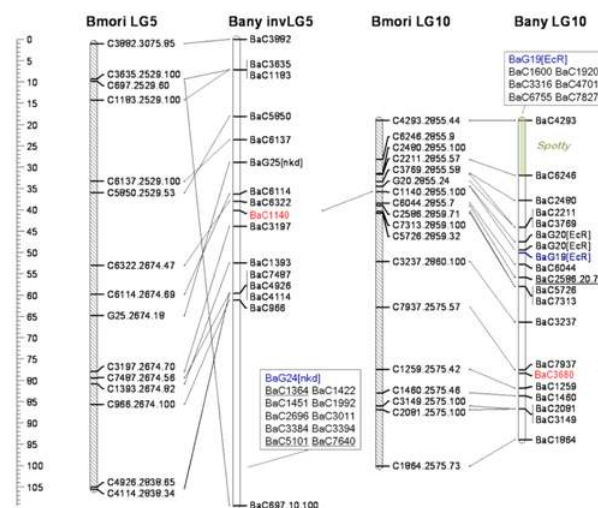


Figure 8.6.10: Genetic maps for regions of two chromosomes from two species of the moth, *Bombyx*. The scale at left shows distance in cM, and the position of various loci is indicated on each chromosome. Diagonal lines connecting loci on different chromosomes show the position of corresponding loci in different species. This is referred to as regions of **conserved synteny**. (NCBI-NIH-PD)

When a novel gene or locus is identified by mutation or polymorphism, its approximate position on a chromosome can be determined by crossing it with previously mapped genes, and then calculating the recombination frequency. If the novel gene and

the previously mapped genes show complete or partial linkage, the recombination frequency will indicate the approximate position of the novel gene within the genetic map. This information is useful in isolating (i.e. cloning) the specific fragment of DNA that encodes the novel gene, through a process called **map-based cloning**.

Genetic maps are also useful to track genes/alleles in breeding crops and animals, in studying evolutionary relationships between species, and in determining the causes and individual susceptibility of some human diseases.

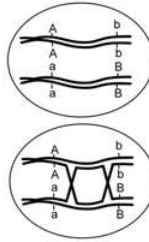


Figure 8.6.11: A double crossover between two loci will produce gametes with parental genotypes. (Original-Deyholos-CC:AN)

Genetic maps are useful for showing the order of loci along a chromosome, but the distances are only an approximation. The correlation between recombination frequency and actual chromosomal distance is more accurate for short distances (low RF values) than long distances. Observed recombination frequencies between two relatively distant markers tend to underestimate the actual number of crossovers that occurred. This is because as the distance between loci increases, so does the possibility of having a second (or more) crossovers occur between the loci. This is a problem for geneticists, because with respect to the loci being studied, these **double-crossovers** produce gametes with the same genotypes as if no recombination events had occurred (Figure 8.6.11) – they have parental genotypes. Thus a double crossover will appear to be a parental type and not be counted as a recombinant, despite having two (or more) crossovers. Geneticists will sometimes use specific mathematical formulae to adjust large recombination frequencies to account for the possibility of multiple crossovers and thus get a better estimate of the actual distance between two loci.

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8.7: Mapping With Three-Point Crosses

A particularly efficient method of mapping three genes at once is the **three-point cross**, which allows the order and distance between three potentially linked genes to be determined in a single cross experiment (Figure 8.7.12). This is particularly useful when mapping a new mutation with an unknown location to two previously mapped loci. The basic strategy is the same as for the dihybrid mapping experiment; pure breeding lines with contrasting genotypes are crossed to produce an individual heterozygous at three loci (a trihybrid), which is then testcrossed to determine the recombination frequency between each pair of genes.

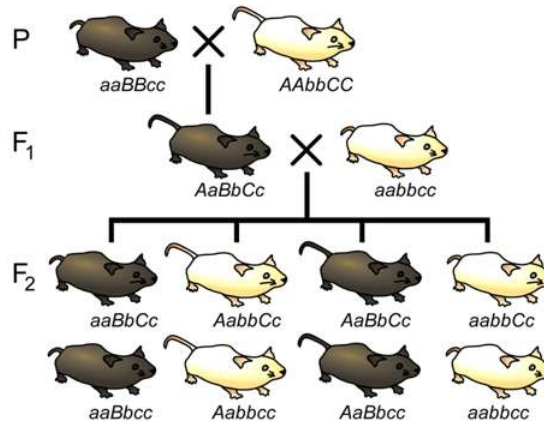


Figure 8.7.12: A three point cross for loci affecting tail length, fur color, and whisker length. (Original-Modified Deyholos-CC:AN)

One useful feature of the three-point cross is that the order of the loci relative to each other can usually be determined by a simple visual inspection of the F₂ segregation data. If the genes are linked, there will often be two phenotypic classes that are much more infrequent than any of the others. In these cases, the rare phenotypic classes are usually those that arose from two crossover events, in which the locus in the middle is flanked by a crossover on either side of it. Thus, among the two rarest recombinant phenotypic classes, the one allele that differs from the other two alleles relative to the parental genotypes likely represents the locus that is in the middle of the other two loci. For example, based on the phenotypes of the pure-breeding parents in Figure 8.7.12, the parental genotypes are *aBC* and *AbC* (remember the order of the loci is unknown, and it is not necessarily the alphabetical order in which we wrote the genotypes). Because we can deduce from the outcome of the testcross (Table 8.7.2) that the rarest genotypes were *abC* and *ABc*, we can conclude that locus *A* that is most likely located between the other two loci, since it would require a recombination event between both *A* and *B* and between *A* and *C* in order to generate these gametes. Thus, the order of loci is *BAC* (which is equivalent to *CAB*).

Table 8.7.2: An example of data that might be obtained from the F₂ generation of the three-point cross shown in Figure 8.7.12. The rarest phenotypic classes correspond to double recombinant gametes *ABc* and *abC*. Each phenotypic class and the gamete from the trihybrid that produced it can also be classified as parental (P) or recombinant (R) with respect to each pair of loci (A,B), (A,C), (B,C) analyzed in the experiment.

tail phenotype	fur phenotype	whisker phenotype	number of progeny	gamete from trihybrid	genotype of F ₂ from test cross	loci A, B	loci A, C	loci B, C
short	brown	long	5	<i>aBC</i>	<i>aaBbCc</i>	P	R	R
long	white	long	38	<i>AbC</i>	<i>AabbCc</i>	P	P	P
short	white	long	1	<i>abC</i>	<i>aabbCc</i>	R	R	P
long	brown	long	16	<i>ABC</i>	<i>AaBbCc</i>	R	P	R
short	brown	short	42	<i>aBc</i>	<i>aaBbcc</i>	P	P	P
long	white	short	5	<i>Abc</i>	<i>Aabbcc</i>	P	R	R
short	white	short	12	<i>abc</i>	<i>aabbcc</i>	R	P	R
long	brown	short	1	<i>ABc</i>	<i>AaBbcc</i>	R	R	P

Recombination frequencies may be calculated for each pair of loci in the three-point cross as we did before for one pair of loci in our dihybrid (Figure 7. 8).

$$\text{loci A,B R.F.} = \frac{1 + 16 + 12 + 1}{120} = 25\% \quad (8.7.1)$$

$$\text{loci A,C R.F.} = \frac{1 + 5 + 1 + 5}{120} = 10\% \quad (8.7.2)$$

$$\text{loci B,C R.F.} = \frac{5 + 16 + 12 + 5}{120} = 32\% \quad (8.7.3)$$

$$\text{(not corrected for double crossovers)} \quad (8.7.4)$$

$$(8.7.5)$$

However, note that in the three point cross, the sum of the distances between A-B and A-C (35%) is less than the distance calculated for B-C (32%)(Figure 8.7.13). this is because of **double crossovers** between B and C, which were undetected when we considered only pairwise data for B and C. We can easily account for some of these double crossovers, and include them in calculating the map distance between B and C, as follows. We already deduced that the map order must be *BAC* (or *CAB*), based on the genotypes of the two rarest phenotypic classes in Table 8.7.2. However, these double recombinants, *Abc* and *abC*, were not included in our calculations of recombination frequency between loci *B* and *C*. If we included these double recombinant classes (multiplied by 2, since they each represent two recombination events), the calculation of recombination frequency between B and C is as follows, and the result is now more consistent with the sum of map distances between A-B and A-C.

$$\text{loci B,C R.F.} = \frac{5 + 16 + 12 + 5 + 2(1) + 2(1)}{120} = 35\% \quad (8.7.6)$$

$$\text{(corrected for double recombinants)} \quad (8.7.7)$$

$$(8.7.8)$$

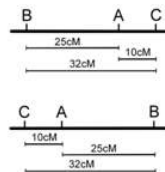


Figure 8.7.13: Equivalent maps based on the data in Table 8.7.2 (without correction for double crossovers). (Original-Deyholos-CC:AN)

Thus, the three point cross was useful for:

1. determining the order of three loci relative to each other,
2. calculating map distances between the loci, and
3. detecting some of the double crossover events that would otherwise lead to an underestimation of map distance.

However, it is possible that other, double crossovers events remain undetected, for example double crossovers between loci A,B or between loci A,C. Geneticists have developed a variety of mathematical procedures to try to correct for things like double crossovers during large-scale mapping experiments.

As more and more genes are mapped a better genetic map can be constructed. Then, when a new gene is discovered, it can be mapped relative to other genes of known location to determine its location. All that is needed to map a gene is two alleles, a wild type allele (e.g. A) and a mutant allele (e.g. 'a').

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8.E: Linkage and Mapping (Exercises)

These are homework exercises to accompany Nickle and Barrette-Ng's "Online Open Genetics" TextMap. Genetics is the scientific study of heredity and the variation of inherited characteristics. It includes the study of genes, themselves, how they function, interact, and produce the visible and measurable characteristics we see in individuals and populations of species as they change from one generation to the next, over time, and in different environments.

8.E.1: Study Questions

7.1 Compare recombination and crossover. How are these similar? How are they different?

7.2 Explain why it is usually necessary to start with pure-breeding lines when measuring genetic linkage by the methods presented in this chapter.

7.3 If you knew that a locus that affected earlobe shape was tightly linked to a locus that affected susceptibility to cardiovascular disease in humans, under what circumstances would this information be clinically useful?

7.4 In a previous chapter, we said a 9:3:3:1 phenotypic ratio was expected among the progeny of a dihybrid cross, in absence of gene interaction.

a) What does this ratio assume about the linkage between the two loci in the dihybrid cross?

b) What ratio would be expected if the loci were completely linked? Be sure to consider every possible configuration of alleles in the dihybrids.

7.5 Given a dihybrid with the genotype *CcEe*:

a) If the alleles are in coupling (cis) configuration, what will be the genotypes of the parental and recombinant progeny from a test cross?

b) If the alleles are in repulsion (trans) configuration, what will be the genotypes of the parental and recombinant progeny from a test cross?

7.6 Imagine the white flowers are recessive to purple flowers, and yellow seeds are recessive to green seeds. If a green-seeded, purple-flowered dihybrid is testcrossed, and half of the progeny have yellow seeds, what can you conclude about linkage between these loci? What do you need to know about the parents of the dihybrid in this case?

7.7 In corn (i.e. maize, a diploid species), imagine that alleles for resistance to a particular pathogen are recessive and are linked to a locus that affects tassel length (short tassels are recessive to long tassels). Design a series of crosses to determine the map distance between these two loci. You can start with any genotypes you want, but be sure to specify the phenotypes of individuals at each stage of the process. Outline the crosses similar to what is shown in Figure 7.8, and specify which progeny will be considered recombinant. You do not need to calculate recombination frequency.

7.8 In a mutant screen in *Drosophila*, you identified a gene related to memory, as evidenced by the inability of recessive homozygotes to learn to associate a particular scent with the availability of food. Given another line of flies with an autosomal mutation that produces orange eyes, design a series of crosses to determine the map distance between these two loci. Outline the crosses similar to what is shown in Figure 7.8, and specify which progeny will be considered recombinant. You do not need to calculate recombination frequency.

7.9 Imagine that methionine heterotrophy, chlorosis (loss of chlorophyll), and absence of leaf hairs (trichomes) are each caused by recessive mutations at three different loci in *Arabidopsis*. Given a triple mutant, and assuming the loci are on the same chromosome, explain how you would determine the order of the loci relative to each other.

7.10 If the progeny of the cross *aaBB* x *AAbb* is testcrossed, and the following genotypes are observed among the progeny of the testcross, what is the frequency of recombination between these loci?

AaBb 135

Aabb 430

aaBb 390

7.11 Three loci are linked in the order B-C-A. If the A-B map distance is 1cM, and the B-C map distance is 0.6cM, given the lines *AaBbCc* and *aabbcc*, what will be the frequency of *Aabb* genotypes among their progeny if one of the parents of the dihybrid had the genotypes *AABBCC*?

7.12 Genes for body color (B black dominant to b yellow) and wing shape (C straight dominant to c curved) are located on the same chromosome in flies. If single mutants for each of these traits are crossed (i.e. a yellow fly crossed to a curved-wing fly), and their progeny is testcrossed, the following phenotypic ratios are observed among their progeny.

	black, straight	17
	yellow, curved	12
	black, curved	337
	yellow, straight	364

a) Calculate the map distance between B and C.

b) Why are the frequencies of the two smallest classes not exactly the same?

7.13 Given the map distance you calculated between B-C in question 12, if you crossed a double mutant (i.e. yellow body and curved wing) with a wild-type fly, and testcrossed the progeny, what phenotypes in what proportions would you expect to observe among the F_2 generation?

7.14 In a three-point cross, individuals *AaBbcc* and *aaBBCC* are crossed, and their F_1 progeny is testcrossed. Answer the following questions based on these F_2 frequency data.

<i>aaBbCc</i>	480
<i>AaBbcc</i>	15
<i>AaBbCc</i>	10
<i>aaBbcc</i>	1
<i>aabbCc</i>	13
<i>Aabbcc</i>	472
<i>AabbCc</i>	1
<i>aabbcc</i>	8

a) Without calculating recombination frequencies, determine the relative order of these genes.

b) Calculate pair-wise recombination frequencies (without considering double cross overs) and produce a genetic map.

c) Recalculate recombination frequencies accounting for double recombinants.

7.15 Wild-type mice have brown fur and short tails. Loss of function of a particular gene produces white fur, while loss of function of another gene produces long tails, and loss of function at a third locus produces agitated behaviour. Each of these loss of function alleles is recessive. If a wild-type mouse is crossed with a triple mutant, and their F_1 progeny is test-crossed, the following recombination frequencies are observed among their progeny. Produce a genetic map for these loci.

8.E.2: Chapter 7 - Answers

7.1

Crossovers are defined cytologically; they are observed directly under the microscope.

Recombination is defined genetically; it is calculated from observed phenotypic proportions.

Some crossovers lead to recombination, but not all crossovers result in recombination.

Some recombinations involve crossovers, but not all recombinations result from crossovers.

Crossovers happen between sister and non-sister chromatids. If the chromatids involved the crossover have identical alleles, there will not be any recombination.

Crossovers can also happen without causing recombination when there are two crossovers between the loci being scored for recombination.

Recombination can occur without crossover when loci are on different chromosomes.

7.2

The use of pure breeding lines allows the researcher to be sure that he/she is working with homozygous genotypes. If a parent is known to be homozygous, then all of its gametes will have the same genotype. This simplifies the definition of parental genotypes and therefore the calculation of recombination frequencies.

7.3

This would suggest that individuals with a particular earlobe phenotype may also carry one or more alleles that increased their risk of cardiovascular disease. These individuals could therefore be informed of their increased risk and have an opportunity to seek increased monitoring and reduce other risk factors.

7.4 a)

It assumes that the loci are completely unlinked.

b)

If the parental gametes were *AB* and *ab*, then the gametes produced by the dihybrids would also be *AB* and *ab*, and the offspring of a cross between the two dihybrids would all be genotype *AABB:AaBb:aabb*, in a 1:2:1 ratio.

If the parental gametes were *Ab* and *aB*, then the gametes produced by the dihybrids would also be *Ab* and *aB*, and the offspring of a cross between the two dihybrids would all be genotype *AAbb:AaBb:aaBB*, in a 1:2:1 ratio.

fur	tail	behaviour	
white	short	normal	16
brown	short	agitated	0
brown	short	normal	955
white	short	agitated	36
white	long	normal	0
brown	long	agitated	14
brown	long	normal	46
white	long	agitated	933

7.5 a) Parental: *CcEe* and *ccee*; Recombinant: *Ccee* and *ccEe*.

b) Parental: *Ccee* and *ccEe*; Recombinant: *CcEe* and *ccee*.

7.6 Let *WwYy* be the genotype of a purple-flowered (*W*), green seeded (*Y*) dihybrid. Half of the progeny of the cross *WwYy* × *wwyy* will have yellow seeds whether the loci are linked or not. The proportion of the seeds that are also either white or purple flowered would help you to know about the linkage between the two loci only if the genotypes of the parents of the dihybrid were also known.

7.7

Let tt be the genotype of a short tassels, and rr is the genotype of pathogen resistant plants. We need to start with homozygous lines with contrasting combinations of alleles, for example:

P: $RRtt$ (pathogen sensitive, short tassels) $\times$ $rrTT$ (pathogen resistant, long tassels)

F_1 : $RrTt$ (sensitive, long) $\times$ $rrtt$ (resistant, short)

F_2 : parental $Rrtt$ (sensitive, short) , $rrTt$ (resistant, long)

Recombinant $rrtt$ (resistant, short) , $RrTt$ (sensitive, long)

7.8 Let mm be the genotype of a mutants that fail to learn, and ee is the genotype of orange eyes. We need to start with homozygous lines with contrasting combinations of alleles, for example (wt means wild-type):

P: $MMEE$ (wt eyes, wt learning) $\times$ mme (orange eyes, failure to learn)

F_1 : $MmEe$ (wt eyes, wt learning) $\times$ mme (orange eyes, failure to learn)

F_2 : parental $MmEe$ (wt eyes, wt learning) , mme (orange eyes, failure to learn)

Recombinant $Mmee$ (wt eyes, failure to learn) , $mmEe$ (orange eyes, wt learning)

7.9 Given a triple mutant $aabbcc$, cross this to a homozygote with contrasting genotypes, i.e. $AABBCC$, then testcross the trihybrid progeny, i.e.

P: $AABBCC \times aabbcc$

F_1 : $AaBbCc \times aabbcc$

Then, in the F_2 progeny, find the two rarest phenotypic classes; these should have reciprocal genotypes, e.g. $aaBbCc$ and $AAbbcc$. Find out which of the three possible orders of loci (i.e. $A-B-C$, $B-A-C$, or $B-C-A$) would, following a double crossover that flanked the middle marker, produce gametes that correspond to the two rarest phenotypic classes. For example, if the rarest phenotypic classes were produced by genotypes $aaBbCc$ and $AAbbcc$, then the dihybrid's contribution to these genotypes was aBC and Abc . Since the parental gametes were ABC and abc the only gene order that is consistent with aBC and Abc being produced by a double crossover flanking a middle marker is $B-A-C$ (which is equivalent to $C-A-B$).

7.10 If the progeny of the cross $aaBB \times Aabb$ is testcrossed, and the following genotypes are observed among the progeny of the testcross, what is the frequency of recombination between these loci?

$AaBb$ 135

$Aabb$ 430

$aaBb$ 390

$aabb$ 120

$(135 + 120)/(135+120+390+430)= 24\%$

7.11

Based on the information given, the recombinant genotypes with respect to these loci will be $Aabb$ and $aaBb$. The frequency of recombination between A-B is $1cM=1\%$, based on the information given in the question, so each of the two recombinant genotypes should be present at a frequency of about 0.5%. Thus, the answer is 0.5%.

7.12

a) 4cM

b) Random sampling effects; the same reason that many human families do not have an equal number of boys and girls.

7.13

There would be approximately 2% of each of the recombinants: (yellow, straight) and (black, curved), and approximately 48% of each of the parentals: (yellow, curved) and (black, straight).

7.14

a) Without calculating recombination frequencies, determine the relative order of these genes.

A-C-B

b)

A-B 4.6%

A-C 2%

B-C 3%

B C A

|-----|-----|

3cM 2cM

	A-B	A-C	B-C
<i>aBC</i>	0	0	0
<i>ABc</i>	15	0	15
<i>ABC</i>	10	10	0
<i>aBc</i>	0	1	1
<i>abC</i>	13	0	13
<i>Abc</i>	0	0	0
<i>AbC</i>	0	1	1
<i>abc</i>	8	8	0
TOTAL	46	20	30
%	4.6	2	3

c) Recalculate recombination frequencies accounting for double recombinants

	A-B	A-C	B-C
<i>aBC</i>	0	0	0
<i>ABc</i>	15	0	15
<i>ABC</i>	10	10	0
<i>aBc</i>	1 x 2	1	1
<i>abC</i>	13	0	13
<i>Abc</i>	0	0	0
<i>AbC</i>	1 x 2	1	1
<i>abc</i>	8	8	0
TOTAL	50	20	30
%	5	2	3

7.15

A is fur color locus

B is tail length locus

C is behaviour locus

fur (A)	tail (B)	behaviour (C)			AB	AC	BC
white	short	normal	16	<i>aBC</i>	R	R	P
brown	short	agitated	0	<i>ABc</i>	P	R	R
brown	short	normal	955	<i>ABC</i>	P	P	P
white	short	agitated	36	<i>aBc</i>	R	P	R
white	long	normal	0	<i>abC</i>	P	R	R
brown	long	agitated	14	<i>Abc</i>	R	R	P
brown	long	normal	46	<i>AbC</i>	R	P	R
white	long	agitated	933	<i>abc</i>	P	P	P

B C A

|-----|-----|

4.1cM 1.5cM

Pairwise recombination frequencies are as follows (calculations are shown below):

A-B 5.6%

A-C 1.5%

B-C 4.1%

AB	AC	BC
16	16	0
0	0	0
0	0	0
36	0	36
0	0	0
14	14	0
46	0	46
0	0	0
112	30	82
5.6%	1.5%	4.1%

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8.S: Linkage and Mapping (Summary)

- Recombination is defined as any process that results in gametes with combinations of alleles that were not present in the gametes of a previous generation.
- The recombination frequency between any two loci depends on their relative chromosomal locations.
- Unlinked loci show a maximum 50% recombination frequency.
- Loci that are close together on a chromosome are linked and tend to segregate with the same combinations of alleles that were present in their parents.
- Crossovers are a normal part of most meioses, and allow for recombination between linked loci.
- Measuring recombination frequency is easiest when starting with pure-breeding lines with two alleles for each locus, and with suitable lines for test crossing.
- Because recombination frequency is usually proportional to the distance between loci, recombination frequencies can be used to create genetic maps.
- Recombination frequencies tend to underestimate map distances, especially over long distances, since double crossovers may be genetically indistinguishable from non-recombinants.
- Three-point crosses can be used to determine the order and map distance between of three loci, and can correct for some of the double crossovers between the two outer loci.

8.S.1: Key Terms

linkage	complete (absolute) linkage	repulsion
recombination	incomplete (partial) linkage	map units (mu)
independent assortment	syntenic	centiMorgans (cM)
crossover	synapsis	genetic map
recombinant genotype	coupling (cis) configuration	conserved syteny
parental genotype	repulsion(trans) configuration	double-crossover
unlinked		three-point cross
recombination frequency (RF)		

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CHAPTER OVERVIEW

9: Chromosomal Disorders

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9.1: Changes in Chromosome Number

If something goes wrong during cell division, an entire chromosome may be lost and the cell will lack all of these genes. The causes behind these chromosome abnormalities and the consequences they have for the cell and the organism is the subject of this section.

9.1.1: Cause: Nondisjunction During Mitosis or Meiosis

Segregation occurs in anaphase. In mitosis and meiosis II, sister chromatids (of replicated chromosomes) are normally pulled to opposite ends of the cell (see Figure 9.1.1a). In Meiosis I, it is homologous chromosomes, which are synapsed at that time, that segregate and move apart.

In rare cases, the sister chromatids (or paired chromosomes in Meiosis I) fail to separate, or dis-join. This failure to segregate properly is called **nondisjunction** and it can happen during mitosis, meiosis I, or meiosis II. This nondisjunction results in both chromatids (or chromosomes) moving to one pole and none at the other. One cell will have an extra copy and the other will lack a copy. Thus failure to segregate properly leads to unbalanced products.

9.1.2: Consequence: Decreased Viability

The result of a non-disjunction event is daughter cells that have an abnormal number of chromosomes. Cells, such as the parent cell in Figure 9.1.1a, which have the proper number of chromosomes, are said to be **euploid**. The daughter cells have one too many or one too few chromosomes and are thus **aneuploid**. Even though both product cells have at least one copy of all genes, both cells will probably die. The reason is due to the loss or gain of a large number of genes. Genes produce a standard amount of product - either functional RNAs or proteins. The parent cell shown has a **balanced** genotype because it has two copies of all of its genes. Each of its genes produces half of the products needed by the cell. But if one of these cells suddenly had only one copy (or three copies) of an important gene, the amount of product would be either 50% (or 150%) of what was required. Such a change for a single gene could probably be tolerated by the cell and it would probably survive. But the sudden change to one copy (or three copies) of the hundreds or thousands of genes on an entire chromosome the results would be more than tolerable and be catastrophic for the daughter cells. They have what's called an **unbalanced** genotype, which usually decreases their viability.

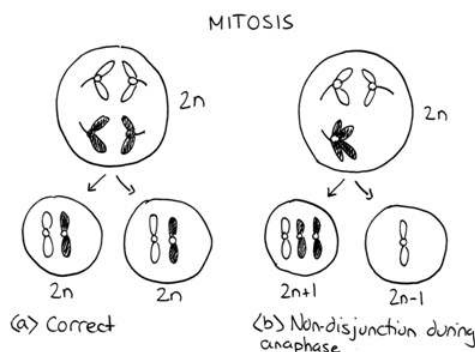


Figure 9.1.1: Mitosis done successfully (a) and unsuccessfully (b). The cell is diploid and the homologs of one chromosome are shown in white and black. (Original-Harrington-CC:AN)

If a **first division** or **second division nondisjunction** event occurs during meiosis the result is an unbalanced gamete (Figure 9.1.2b and 9.1.2c). The gamete will often be functional, but after fertilization the embryo will be genetically unbalanced. This usually leads to the death of the embryo. There are some exceptions to this in humans and these will be presented later in this chapter.

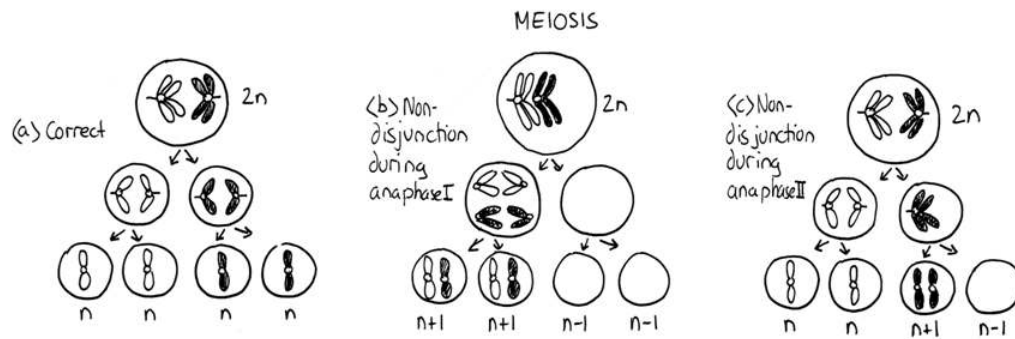


Figure 9.1.2: Meiosis done successfully (a) and unsuccessfully (b and c). (Original-Harrington-CC:AN)

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9.2: Changes in Chromosome Structure

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

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

A chromosome is a very long but very thin molecule. In the phosphodiester backbone there are only two covalent bonds holding each base pair to the next. If one of these covalent bonds is broken the chromosome will still remain intact, although a DNA Ligase will be needed to repair the nick (Figure 9.2.1a). Problems arise when both strands are broken at or near the same location. This **double strand break** will cleave the chromosome into two independent pieces (Figure 9.2.1b). Because these events do occur in cells there is a repair system called the **non-homologous end joining (NHEJ) system** to fix them. Proteins bind to each broken end of the DNA and reattach them with new covalent bonds. This system is not perfect and sometimes leads to **chromosome rearrangements** (see next section).

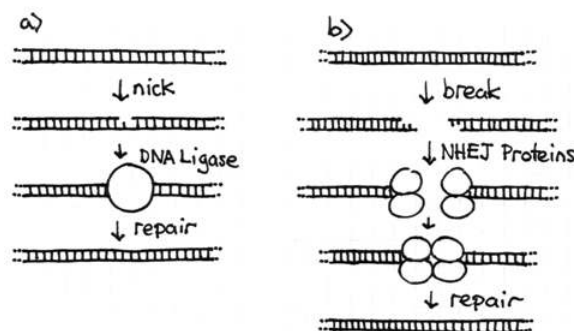


Figure 9.2.1: Repair of single strand nicks and double strand breaks in DNA. (Original-Harrington-CC:AN)

The NHEJ system proteins only function if required. If the chromosomes within an interphase nucleus are all intact the system is not active. The telomeres at the natural ends of chromosomes prevent the NHEJ system from attempting to join the normal ends of chromosomes together. If there is one double strand break the two broken ends can be recognized and joined. But if there are two double strand breaks at the same time there will be four broken ends in total. The NHEJ system proteins may join the ends together correctly but if they do not the result is a **chromosome rearrangement** (Figure 9.2.2).

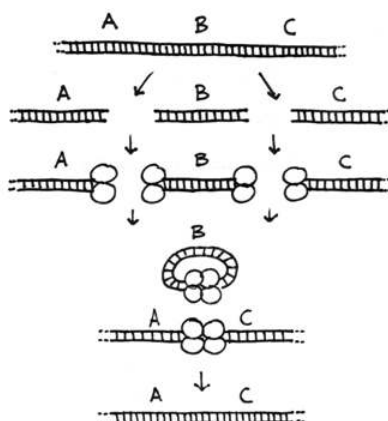


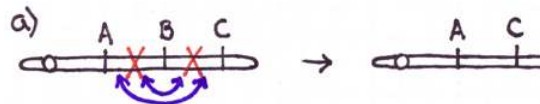
Figure 9.2.2 there has been breaks in the DNA, recruitment of NHEJ proteins, and repair. After the repairs are completed the small piece of DNA with gene B is lost and the chromosome now has genes A and C. (Original-Harrington-CC:AN)

9.2.2: The Four Types of Chromosome rearrangements

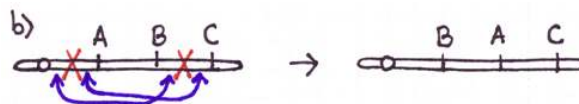
Errors during the repair of multiple double strand breaks can cause four types of chromosome rearrangements. The type of chromosome rearrangement is dependent upon where the two breaks were originally and how they are rejoined. Figure 9.2.5 shows some possibilities but more are shown below. In these there is a double strand DNA break between the B and C genes (shown here as a red X). A second DNA break occurs and the NHEJ proteins mend the damage incorrectly by joining the ends shown with the blue arrows. The chromosomes are drawn unreplicated as they are in G₁ phase but these events can happen anytime during interphase.

There are four major types of rearrangements:

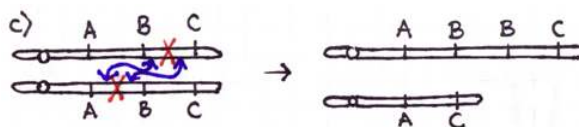
a) Deletions arise when both breaks are on one chromosome. If the ends are joined in this way the piece of DNA with the B gene on it does not have a centromere and will be lost during the next cell division.



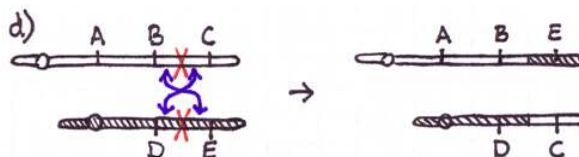
b) Inversions also occur when both breaks are on one chromosome. If the ends are joined in this way, part of the chromosome is inverted. This example shows a **paracentric inversion**, named because the inverted section does not include the centromere (para = beside). If the breaks occur on different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



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



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



9.2.3: Cause #2: Incorrect Crossovers During Meiosis

Meiotic crossovers occur at the beginning of meiosis for two reasons. They help hold the homologous chromosomes together until separation occurs during anaphase I (see Chapter 2). They also allow recombination to occur between linked genes (see Chapter 7). The event itself takes place during prophase I when a double strand break on one piece of DNA is joined with a double strand break on another piece of DNA and the ends are put together (Figure 9.2.3a). Most of the time the breaks are on non-sister chromatids and most of the time the breaks are at the same relative locations.

Problems occur when the wrong pieces of DNA are matched up along the chromosomes during crossover events. This can happen if the same or similar DNA sequence is found at multiple sites on the chromosomes (Figure 9.2.3b). For example, if there are two

Alu transposable elements on a chromosome. When the homologous chromosomes pair during prophase I the wrong *Alu* sequences might line up. A crossover may occur in this region. If so, when the chromosomes separate during anaphase I one of the chromatids will have a duplication and one will have a deletion. Ultimately, of the four cells produced by this meiosis, two will be normal, one will have a chromosome with extra genes, and one will have a chromosome missing some genes. Errors of this type can also cause inversions and translocations.

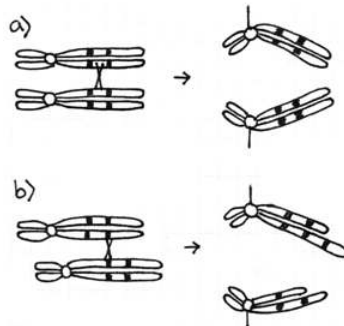


Figure 9.2.3: Errors during meiotic crossovers can cause duplications and deletions. This diagram shows homologous chromosomes pairing in prophase I and then separating in anaphase I. The shaded boxes are alu transposable elements. a) The homologous chromosomes pair properly, a crossover occurs, and all four chromatids in anaphase I are normal. b) The pairing is incorrect, a crossover occurs in the mispaired region, and in anaphase I one chromatid has a duplication and another has a deletion. (Original-Harrington-CC:AN)

9.2.4: Consequence #1 - Rearrangements Show Abnormal pairing at Meiosis

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

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

When an **inversion** chromosome is paired up in meiosis there is an **inversion loop** formed. If there is a crossover within the loop then abnormal products will result and abnormal, unbalanced gametes will be produced. For example, a crossover event within the loop of a **paracentric inversion** will lead to a di-centric product that will break into deletion products and produce unbalanced gametes (Figure 9.2.4). Similarly, with a **pericentric inversion**, a crossover event leads to duplicate/deletion products that are unbalanced (Figure 9.2.5).

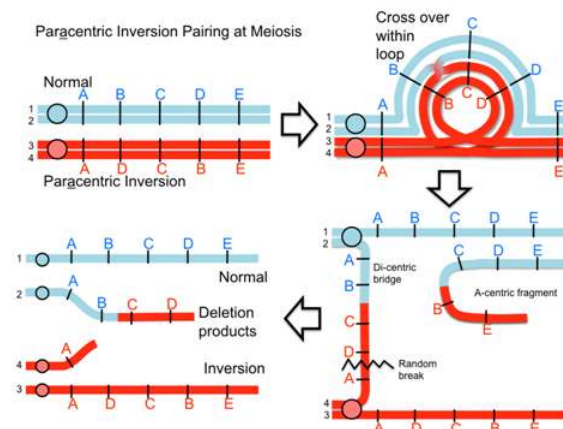


Figure 9.2.4: A paracentric inversion pairing at meiosis. A crossover within the loop causes the production of an acentric and a dicentric chromatids which leads to deletion product.(Original-Locke-CC:AN)

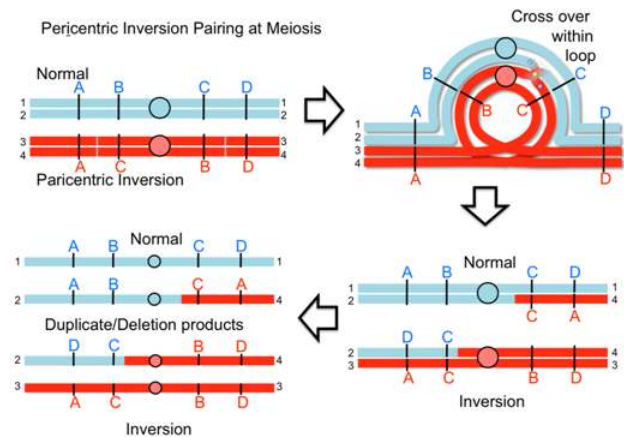


Figure 9.2.5: A pericentric inversion pairing at meiosis. A crossover within the loop causes the production of duplicate and deletion products. (Original-Locke-CC:AN)

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

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

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

For **translocations**, a consequence for the two chromosomes involved is that when they pair at meiosis both replicated chromosome pairs will be together, which can be seen cytologically as a **tetrad**. This tetrad can segregate in three ways. Two of which are shown below. This set of paired, replicated chromosomes can segregate as **Alternate** (balanced) where both normal and both translocated chromosomes go to the same poles. Or the chromosomes can segregate as **Adjacent-1** (unbalanced) where the normal and translocation chromosomes segregate as shown below. Each of these possibilities is approximately equally frequent and thus only about half the time do the gametes end up unbalanced (Figure 9.2.6).

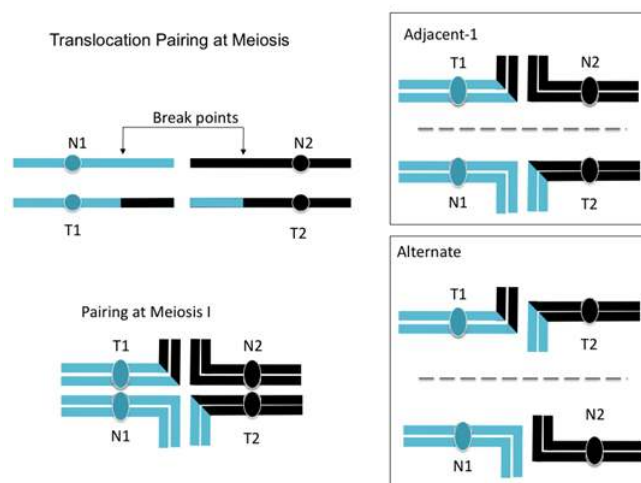


Figure 9.2.6: A reciprocal translocation pairing at meiosis. There are two main avenues for segregation: Adjacent-1 and Alternate. Adjacent-1 results in duplication and deletion for part of the chromosome segments. Alternate doesn't. (Original-Locke-CC:AN)

9.2.5: Consequence #2: Decreased Viability

All of the chromosome rearrangements shown above produce functional chromosomes. Each has one centromere, two telomeres, and thousands of origins of replication. Because inversions and translocations do not change the number of genes in a cell or

organism they are said to be balanced rearrangements. Unless one of the breakpoints occurred in the middle of a gene the cells will not be affected. On the other hand, deletions and duplications are unbalanced rearrangements. The larger they are (more genes involved) the more disruption they cause to the proper functioning of the cell or organism. As explained in Section 9.1.2 above having too much or too little gene action for a large number of genes can disrupt the cellular metabolism to generate a phenotype or reduce viability.

9.2.6: Consequence #3: Decreased Fertility

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

Cells heterozygous for balanced rearrangements actually have more difficulties in prophase I. Consider the chromosomes shown in Figure 9.2.7. There are different ways they might pair during prophase I - one is shown in Figure 9.2.8. But if a crossover occurs in the inverted region the result will be unbalanced gametes. Embryos made with unbalanced gametes rarely survive. The consequence is that the heterozygous organism will have **reduced fertility**.

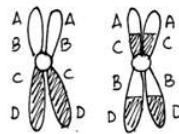


Figure 9.2.7: An unrearranged chromosome (left) and a homolog with a pericentric inversion (right). (Original-Harrington-CC:AN)

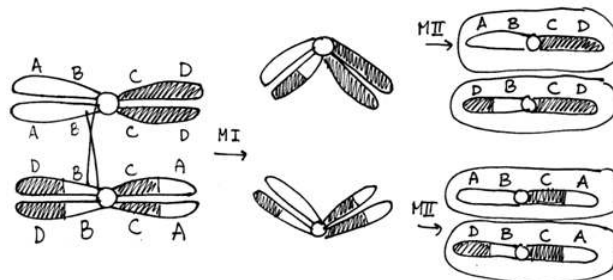


Figure 9.2.8: Meiosis in a cell heterozygous for the chromosomes shown in Figure 9.2.11. Note that of the four gametes one has a deletion of the A gene and a duplication of the D gene while another gamete has a duplication of A and a deletion of D. (Original-Harrington-CC:AN)

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

9.2.7: Consequence #4: Cancer

Some chromosome rearrangements have breakpoints within genes leading to the creation of hybrid genes – the first part of one gene with the last part of another. If the hybrid gene inappropriately promotes cell replication, the cell can become cancerous. An example of this is shown in Figure 9.2.1 where the chromosomes are from a patient with leukemia caused by a translocation between chromosomes 9 and 22 (the red and green spots side-by-side).

9.2.8: Consequence #5: Evolution

Those chromosome changes that duplicate genes are important for evolution. If an organism has an extra copy of important genes, one gene can be retained for their original function while others can mutate and potentially acquire new functions (Figure 9.2.9). An example of this is the multiple copies of the globin genes found in mammals (see Figure 9.2.13).

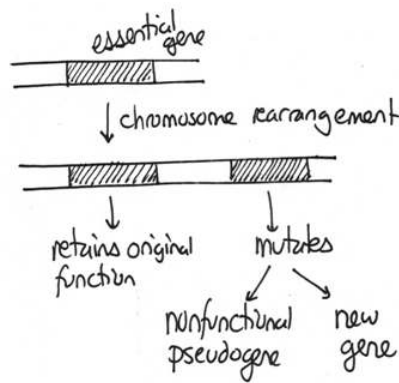


Figure 9.2.9: Duplicated genes can mutate without compromising the viability of the organism. Occasionally the result is a new gene. (Original-Harrington-CC:AN)

Chromosome rearrangements that decrease fertility are also important for the origin of new species. If a rearrangement, such as the inversion shown in Figure 9.2.9, becomes common in a small isolated population, that population has 100% fertility if they mate within their group, but a reduced fertility if they mate with members of the larger population. As rearrangements accumulate the small population will become more and more reproductively isolated. When members are incapable of forming viable, fertile offspring with the original population the group will have become a new species.

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9.3: Chromosome Abnormalities in Humans

The problems described above can affect all eukaryotes, unicellular and multicellular. To better understand the consequences let us consider those that affect people. As you will recall from Figure 9.3.12, humans are $2n=46$. The convention when describing a person's **karyotype** (chromosome composition) is to list the total number of chromosomes, then the sex chromosomes, and then anything out of the ordinary. Most of us are 46,XX or 46,XY. What follows are some examples of chromosome number and chromosome structure abnormalities.

9.3.1: Down Syndrome

The most common chromosome number abnormality is trisomy-21 or, as it is more commonly known, **Down syndrome**. Having an extra copy of the smallest human chromosome, chromosome 21, causes substantial health problems. It is present in about 1 in 800 births. Infants with this condition have three copies of chromosome 21 rather than the normal two. Don't confuse **trisomy** - having three copies of one chromosome (i.e. $2n+1$) with triploidy - having three entire chromosome sets ($3x$; see Section 2.6.) Females with trisomy-21 are 47,XX,+21 while males are 47,XY,+21. In general, people with Down syndrome are 47,sex,+21 where the word 'sex' signifies that the sex chromosomes may be XX or XY.

Trisomy-21 may arise from a nondisjunction event during meiosis in either parent or during mitosis very early during embryogenesis. However, most cases are due to a first division non-disjunction event occurring in the female parent (Figure 9.3.1).

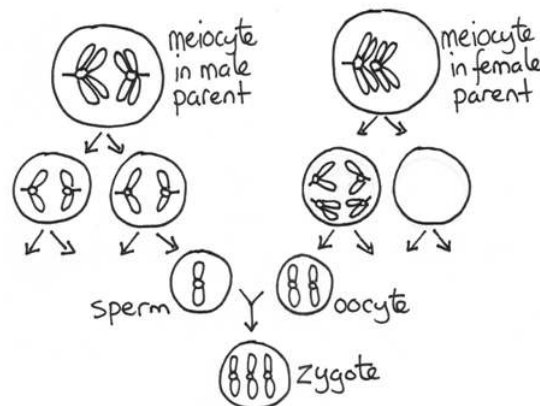


Figure 9.3.1: This diagram shows the errors during chromosome segregation that cause Down syndrome during meiosis in both parents and fusion of the gametes. Note that the cells that begin meiosis are called meiocytes and that this diagram only shows one of the four cells produced by meiosis. Meiosis occurred properly in the male parent but there was a nondisjunction event in the female parent in anaphase I. (Original-Harrington-CC:AN)

Having an extra copy of the smallest human chromosome, chromosome 21, causes substantial health problems. People with Down syndrome have various degrees of intellectual disability and often have other health problems such as heart defects. The disease was first described by John Down in 1866 but it was not until 1959 when its chromosomal basis was discovered. Current research suggests that at least some of the mental problems are due to having three copies of the *DYRK* gene on chromosome 21. This gene is active in the brain and there is evidence from humans and from mice that neurons are damaged if there is too much DYRK protein synthesized.

9.3.2: XYY and XXX

While fetuses trisomic for one of the other larger autosomes seldom survive to term, the situation is quite different for the sex chromosomes. Approximately 1 in 1000 males have an extra Y chromosome and yet most are unaware of it! There is little harm in having two Y chromosomes because they have relatively few genes. Similarly, 1 in 1000 females have an extra X chromosome. This situation is also relatively harmless although for a different reason. Normally in female mammals one of the two X chromosomes is inactivated in each cell so that there can be genetic balance (Figure 9.3.2 and see Section 3.5.2). In 46,XX females one of the X chromosomes is inactivated while in 47,XXX females two are inactivated.

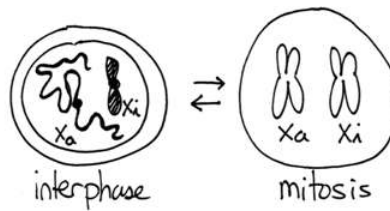


Figure 9.3.2: A simplified view of dosage compensation in mammals. Because females have more X chromosomes than males in females one X chromosome is marked as inactive (X_i). It is replicated and transmitted during cell division but most of its genes are silent. It appears as a condensed mass called the Barr body within the interphase nucleus. (Original-Harrington-CC:AN)

9.3.3: Turner Syndrome

Monosomy ($2n-1$) for autosomal chromosomes does occur at conception, but these embryos almost never survive to term. Similarly, embryos that are 45,Y are also non-viable because they lack many essential genes found on the X chromosome. The only viable monosomy in humans is 45,X, also known as **Turner syndrome**. These people are phenotypically female because they do not have a Y chromosome (Section 2.5.2). They are viable because in females only one X is active in most cells anyway. People with this condition do have health problems though: they are shorter than average, they have an elevated risk of heart defects, and they are infertile.

The reason for the health problems is that there are a few genes that are found on both the X and the Y chromosome. Because these genes are found in two copies in both XY males and XX females they are in what is called the **pseudoautosomal region**. This region escapes X chromosome inactivation. One of the genes in this region is called *SHOX*. It makes a protein that promotes bone growth. 46,XX and 46,XY people have two functioning copies and have average height. People with 47,XYY and 47,XXX genomes have three copies and are taller than average. And people with 45,X have one copy and are short. It is the single copy of *SHOX* and a few of the other genes in the pseudoautosomal region that causes health problems for women with Turner syndrome.

The reason for the infertility is that the X chromosome inactivation system only acts in somatic cells - it is not needed in the germline cells. Ovaries naturally have two functional X chromosomes. Women with Turner syndrome can not perform oogenesis because this process only works if there are two active X chromosomes. Recently, it has become possible for these women to become pregnant with donated eggs and in vitro fertilization.

9.3.4: Klinefelter Syndrome

There are four common sex-chromosome aneuploidies: 47,XYY, 47,XXX, 45,X, and 47,XXY. This last situation is known as **Klinefelter syndrome**. These people are male (because they have a Y chromosome) and tall (because they have three *SHOX* genes). They do not have health problems because the X chromosome inactivation system is independent of sex. In the embryonic nuclei the X chromosome are counted and all but one are shut down. It does not matter whether the embryo is male or female. Men with Klinefelter syndrome have a Barr bodies in their nuclei, the same as 46,XX females. They do have fertility problems because there are two active X chromosome in their testes and this interferes with spermatogenesis. They make enough sperm to conceive children using intracytoplasmic sperm injection though.

9.3.5: Cri-du-Chat Syndrome

Cri-du-chat syndrome occurs when a child inherits a defective chromosome 5 from one parent (Figure 9.3.16n). This condition is rare - it is present in only 1 in 20,000 to 1 in 50,000 births but it does account for 1% of cases of profound intellectual disability. The specific defect is a deletion that removes 2 Mb or more from the tip of the short arm of the chromosome. In most cases the deletion is the result of a chromosomal rearrangement in one of the parent's germ line cells. People with cri-du-chat have a karyotype of 46,sex,deletion(5).

As with Down syndrome this condition is associated with intellectual disability and other health problems. These problems include an improperly formed larynx which leads to infants making high pitched cat-like crying sounds (hence the name "cry of the cat"). It is suspected that at least some of the intellectual disability phenotype is due to having only a single copy of the *CTNND2* gene. This gene is active during embryogenesis and makes a protein essential for neuron migration. Down syndrome and cri-du-chat syndrome are two examples of the need for genomes to contain the proper number of genes. Having too many copies of key genes (Down syndrome) or too few (cri-du-chat syndrome) can lead to substantial developmental problems.



Figure 9.3.3: A boy with cri-du-chat syndrome. The pictures were taken at 8 months (A), 2 years (B), 4 years (C), and 9 years (D). (Wikipedia-Paola Cerruti Mainardi-CC:AN)

9.3.6: Inversion(9)

The most common chromosome rearrangements in humans are inversions of chromosome 9. About 2% of the world's population is heterozygous or homozygous for inversion(9). This rearrangement does not affect a person's health because the genes on the chromosome are all present - all that has changed is their relative locations. Inversion(9) is different from deletion(5) in two main respects. As mentioned above because it is a balanced rearrangement it does not cause harm. And because of this nearly everyone with an inversion(9) chromosome has inherited it from a parent who had inherited it from one of their parents and so on. In contrast, most cases of deletion(5) are due to new mutations occurring in a parent.

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9.4: Diagnosing Human Chromosome Abnormalities

9.4.1: Bright Field Microscopy

How can we confirm that a person has a specific chromosomal abnormality? The first method was simply to obtain a sample of their cells, stain the chromosomes with **Giemsa** dye, and examine the results with a light microscope (Figure 9.4.1). Each chromosome can be recognized by its length, the location of its centromere, and the characteristic pattern of purple bands produced by the Giemsa. For example, if mitotic cells from a person consistently contained forty seven chromosomes in total with three chromosome 21s this would be indicative of Down syndrome. Bright field microscopy does have its limitations though - it only works with mitotic chromosomes and many chromosome rearrangements are either too subtle or too complex for even a skilled cytogeneticist to discern.

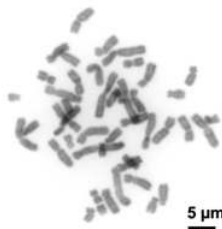


Figure 9.4.1: Human chromosomes. One way to obtain chromosomes is to take a blood sample, culture the cells for three days in the presence of a T-cell growth factor, arrest the cells in metaphase with a microtubule inhibitor, and then drop the cells onto a slide. The cells burst and the chromosomes stick to the slide. The chromosomes can then be stained or probed. Because the cells are in metaphase it is possible to see 46 replicated chromosomes here. There will be dozens of collections of chromosomes like this over the entire slide. (Wikipedia-Steffen Dietzel-CC:AS)

9.4.2: Fluorescence In Situ Hybridization

The solution to these problems was **fluorescence in situ hybridization** (FISH). The technique is similar to a Southern blot in that a single stranded **DNA probe** is allowed to hybridize to denatured target DNA (see Section 8.6). However, instead of the probe being radioactive it is fluorescent and instead of the target DNA being restriction fragments on a nylon membrane it is denatured chromosomes on a glass slide. Because there are several fluorescent colours available it is common to use more than one probe at the same time. Typically the chromosomes are also labeled with a fluorescent stain called **DAPI** which gives them a uniform blue colour. If the chromosomes have come from a mitotic cell it is possible to see all forty six of them spread out in a small area. Alternatively, if the chromosomes are within the nucleus of an interphase cell they appear together within a large blue circle.

9.4.3: Using FISH to Diagnose Down Syndrome

Most pregnancies result in healthy children. However in some cases there is an elevated chance that the fetus has trisomy-21. Older women are at a higher risk because the non-disjunction events that lead to trisomy become more frequent with age. The second consideration is what the fetus looks like during an ultrasound examination. Fetuses with trisomy-21 and some other chromosome abnormalities have a swelling in the back of the neck called a nuchal translucency. If either or both factors is present the woman may choose amniocentesis. In this test some amniotic fluid is withdrawn so that the fetal cells within it can be examined. Figure 9.4.2 shows a positive result for trisomy-21. Based upon this image the fetus has two X chromosomes and three chromosome 21s and therefore has a karyotype of 47,XX,+21.

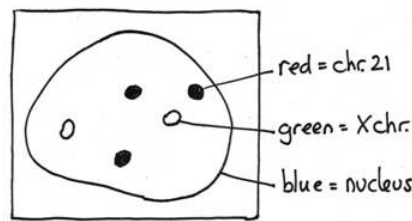


Figure 9.4.2: Confirmation of Down syndrome in a fetal cell. This diagram is based upon actual results. The DNA has been stained blue with DAPI. A red fluorescent probe is binding to the centromeres of chromosome 21 (shown here as filled circles). A green fluorescent probe is binding to the centromeres of the X chromosome (open circles). Source: Figure 4 in Antonarakis, S. E. et al. 2004. Chromosome 21 and Down syndrome: From genomics to pathophysiology. *Nature Reviews Genetics* 5:725-738 PubMed ID: 15510164.

9.4.4: Using FISH to Diagnose Cri-du-Chat Syndrome

A physician may suspect that a patient has a specific genetic condition based upon the patient's physical appearance, mental abilities, health problems, and other factors. FISH can be used to confirm the diagnosis. For example, Figure 9.4.3 shows a positive result for cri-du-chat syndrome. The probes are binding to two long arms of chromosome 5 but only one short arm. One of the chromosome 5s must therefore be missing part of its short arm.

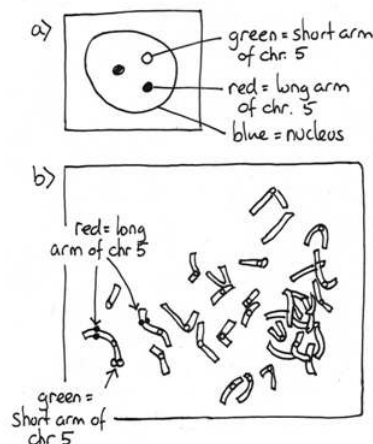


Figure 9.4.3: A positive result for cri-du-chat syndrome. This diagram is based upon actual results. Cells from a patient's blood were prepared to show an interphase nucleus (a) and mitotic chromosomes (b). The DNA has been coloured blue with DAPI. The green fluorescent probe is binding to the tip of the short arm of chromosome 5 (shown here as open circles). This is the region absent in cri-du-chat. The red fluorescent probe is binding to the middle of the long arm of the same chromosome (filled circles). This probe is used as a control. Source: Figure 1 in Fang J.-S. et al. 2008 Cytogenetic and molecular characterization of three-generation family with chromosome 5p terminal deletion. *Clinical Genetics* 73:585-590 PubMed ID: 18400035.

9.4.5: Newer Techniques

FISH is an elegant technique that produces dramatic images of our chromosomes. Unfortunately, FISH is also expensive, time consuming, and requires a high degree of skill. For these reasons, FISH is slowly being replaced with PCR and DNA chip based methods. Versions of these techniques have been developed that can accurately quantify a person's DNA. For example a sample of DNA from a person with Down syndrome will contain 150% more DNA from chromosome 21 than the other chromosomes. Likewise DNA from a person with cri-du-chat syndrome will contain 50% less DNA from the end of chromosome 5. These techniques are very useful if the suspected abnormality is a deletion, a duplication, or a change in chromosome number. They are less useful for diagnosing chromosome inversions and translocations because these rearrangements often involve no net loss or gain of genes.

In the future all of these techniques will likely be replaced with DNA sequencing. Each new generation of genome sequencing machines can sequence more DNA in less time. Eventually it will be cheaper just to sequence a patient's entire genome than to use FISH or PCR to test for specific chromosome defects.

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9.5: Gene Balance

Why do trisomies, duplications, and other chromosomal abnormalities that alter gene copy number often have a negative effect on the normal development or physiology of an organism? This is particularly intriguing because in many species, aneuploidy is detrimental or lethal, while polyploidy is tolerated or even beneficial. The answer probably differs in each case, but is probably related to the concept of **gene balance**, which can be summarized as follows: genes, and the proteins they produce, have evolved to function in complex metabolic and regulatory networks. Some of these networks function best when certain enzymes and regulators are present in specific ratios to each other. Increasing or decreasing the gene copy number for just one part of the network may throw the whole network out of balance, leading to increases or decreases of certain metabolites, which may be toxic in high concentrations or which may be limiting in other important processes in the cell. The activity of genes and metabolic networks is regulated in many different ways besides changes in gene copy number, so duplication of just a few genes will usually not be harmful. However, trisomy and large segmental duplications of chromosomes affect the dosage of so many genes that **cellular networks** are unable to compensate for the changes and an abnormal or lethal phenotype results.

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9.6: X-inactivation

9.6.1: Introduction

Having [extra or missing chromosomes](#) is not usually a good thing. In fact, for most chromosomes, having an extra or missing copy is lethal to humans (causing an embryo to die early in development).

Yet, human females have two X chromosomes (XX), while human males have just one (XY). Why doesn't it cause problems for men to have just one copy of the X chromosome, while women have two?

9.6.2: X-inactivation

As it turns out, the level of gene activity produced by a single X chromosome is the normal "dosage" for a human. Men have this dosage because, well, they only have one X chromosome! Women have the same dosage for a different reason: they shut down one of their two X chromosomes in a process called X-inactivation.

In **X-inactivation**, an X chromosome is compacted (or, as my intro bio professor liked to say, "crumpled up into a ball"), to make a small, dense structure called a **Barr body**. Most of the genes on the Barr body are inactive, meaning that they are not transcribed. The process of X-inactivation was discovered by the British geneticist Mary F. Lyon and is sometimes called **lyonization** in her honor¹.



Image modified from "Photo of an English geneticist, Mary Frances Lyon," by Jane Gitschier (CC BY 2.5).

A woman has two X chromosomes, one from each parent. Which one will she inactivate? X-inactivation is a random process that happens separately in individual cells during embryonic development. One cell might shut down the paternal X, while its next-door neighbor might shut down the maternal X instead. All the cells descended from each of these original cells will maintain the same pattern of X-inactivation.

Interesting note: if you were a kangaroo, what I just said would not be true! In kangaroos and other marsupials, it is always the paternal X chromosome that undergoes X-inactivation².

9.6.3: X-inactivation example: Calico cat

A classic example of X-inactivation is seen in cats. If a female cat is heterozygous for black and tan alleles of a coat color gene found on the X, she will inactivate her two Xs (and thus, the two alleles of the coat color gene) at random in different cells during development.

The result is a tortoiseshell coat pattern, made up of alternating patches of black and tan fur. The black patches come from groups of cells in which the X with the black allele is active, while the tan patches come from cells in which the X with the tan allele is

active.

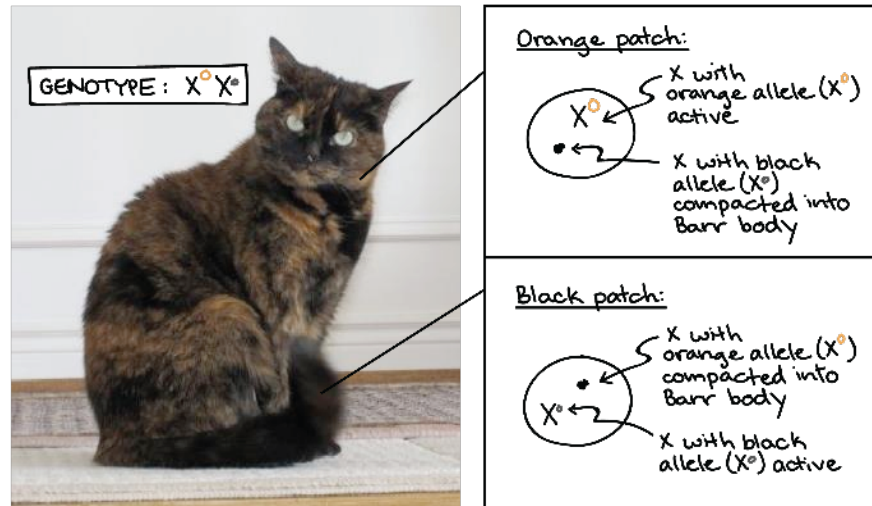


Image modified from "6-year old tortoiseshell cat," by Michael Bodega (public domain).

Although it's rarely as easy to see as in the case of the tortoiseshell cat, human females are also "mosaic" for any genes that are present in different alleles on their two X chromosomes.

[If that's true, why don't female carriers show X-linked disorders?]

At this point, you may be wondering why women heterozygous for a recessive, X-linked allele don't display the associated condition. After all, roughly half of their cells will inactivate the normal allele, leaving only the disorder-causing allele active.

In many cases, it appears that having 50% of cells with a normal copy of a gene is sufficient to produce a normal, or close to normal, phenotype.

A good example of this comes from the X-linked condition of red-green color vision deficiency (colorblindness). Women who are carriers for red-green color vision deficiency alleles have a mixture of working and non-working photoreceptor cells in their eyes. However, the working cells allow them to perceive red and green well enough to function normally in daily life. In more sensitive tests in a laboratory setting, these women actually do show subtle color vision deficiencies relative to women who are not carriers³.

9.6.3.1: Sex chromosome aneuploidies

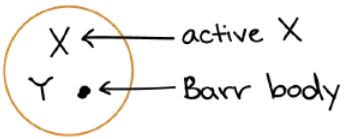
When an organism has an extra or missing copy of a chromosome, it is said to be **aneuploid**. Aneuploidies involving autosomes (non-sex chromosomes), especially large ones, are usually so harmful to development that an aneuploid embryo can't survive to birth.

Aneuploidies of X chromosomes, however, tend to be much less harmful, despite the fact that the X is a large chromosome. This is mostly thanks to X inactivation. Although the purpose of the X-inactivation system is to shut down the second X of an XX female, it can also do a pretty good job of shutting down more X chromosomes if they are present.

Examples of X chromosome aneuploidies include:

- **Triple X syndrome**, in which a woman has an XXX genotype, which occurs in about 1 out of every 1,000 female newborns⁴. Women with an XXX genotype have female sex characteristics and are fertile (able to have children). In some cases, triple X syndrome may be associated with learning difficulties, late development of motor skills in infants, and problems with muscle tone⁴.
- **Klinefelter syndrome**, in which males have an extra X chromosome, leading to a genotype of XXY. (In rarer cases, Klinefelter syndrome can involve several extra Xs, leading to an XXXY or XXXXY genotype.) Affected men may be infertile or develop less dense body and facial hair than other men. Klinefelter syndrome is thought to affect 1 out of every 500 to 1,000 male newborns⁵.

Like females, XXY males with Klinefelter syndrome will convert one X to a Barr body in each cell. Triple X females (as well as Klinefelter males with more than two X chromosomes) neutralize their extra Xs by forming additional Barr bodies. For example, there would be two Barr bodies in a cell from an XXX female or XXXY male.

XX female	
XY male	
XXY male (Klinefelter)	
XXX female (triple X)	

In **Turner syndrome**, a woman lacks part or all of one of her X chromosomes (leaving her with just one functional X). People with this disorder develop as females, but often have short stature and may exhibit symptoms like infertility and learning difficulties. Turner syndrome is thought to occur in about 1 out of every 2,500 female births⁶. It has relatively mild effects because humans normally have only one X active in the cells of their body anyway.

9.6.4: Check your understanding

9.6.5: Contributors and Attributions

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