

Genetics is the study of heredity, the process in which a parent passes certain genes onto their children. A person's appearance — height, hair color, skin color, and eye color — are determined by genes. Other characteristics affected by heredity:

- Likelihood of getting certain diseases
- Mental abilities
- Natural talents etc.

MENDEL'S EXPERIMENTS AND HEREDITY

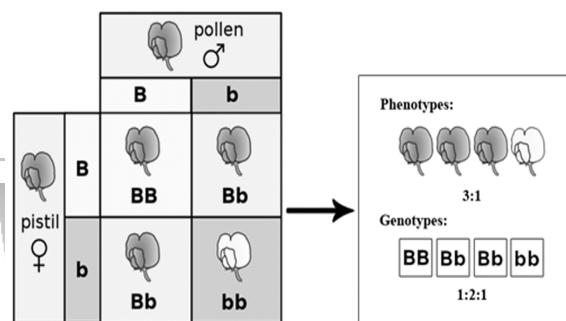
Introduction

Based on Gregor Mendel's work with pea plants, the principles of modern genetics were developed.

Gregor Mendel and the Study of Genetics

Genetics is the study of heredity, or the passing of traits from parents to offspring. Johann Gregor Mendel set the framework for genetics long before chromosomes or genes had been identified, at a time when meiosis was not well understood. For his work, Mendel is often referred to as the "father of modern genetics." Mendel selected a simple biological system, garden peas, and conducted methodical, quantitative analyses using large sample sizes. Mendel grew and studied around 29,000 garden pea plants in a monastery's garden, where he analyzed seven characteristics of the garden pea plants: flower color (purple or white), seed texture (wrinkled or round), seed color (yellow or green), stem length (long or short), pod color (yellow or green), pod texture (inflated or constricted), and flower position (axial or terminal). Based

on the appearance, or phenotypes, of the seven traits, Mendel developed genotypes for those traits .



Appearance and genetic makeup of garden pea plant flowers

Because of Mendel's work, the fundamental principles of heredity were revealed, which are often referred to as Mendel's Laws of Inheritance. The genes which are carried on chromosomes are the basic functional units of heredity with the capability to be replicated, expressed, or mutated. Today, the postulates put forth by Mendel form the basis of Classical or Mendelian genetics. Not all genes are transmitted from parents to offspring according to Mendelian genetics, but Mendel's experiments serve as an excellent starting point for thinking about inheritance.

Mendel's Model System

The garden pea has several advantageous characteristics that allowed Mendel to develop the laws of modern genetics. Mendel's seminal work was accomplished using the garden pea, *Pisum sativum*, to study inheritance . Pea plant reproduction is easily manipulated, large quantities of garden peas could be cultivated simultaneously, allowing Mendel to conclude

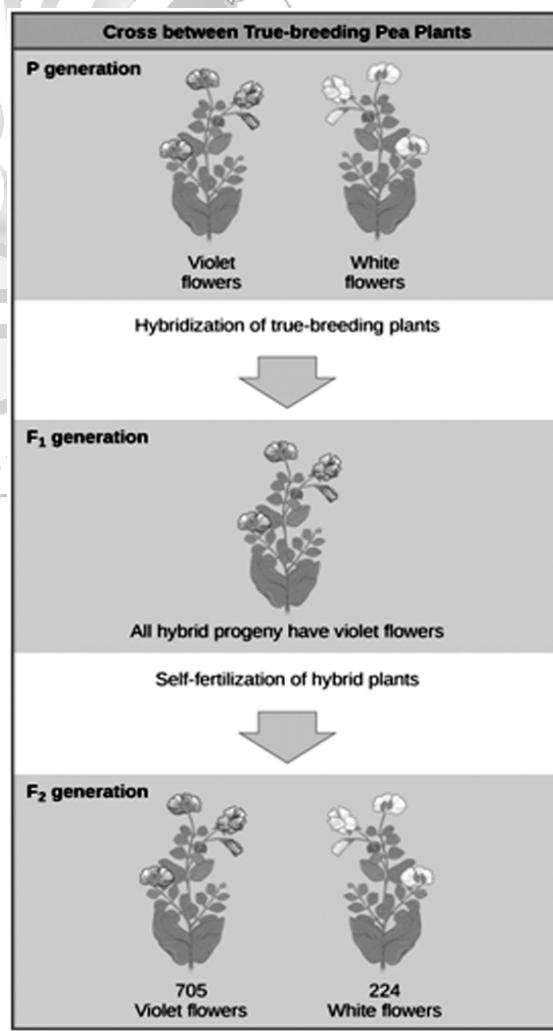


that his results did not occur simply by chance. The garden pea also grows to maturity within one season, several generations could be evaluated over a relatively short time. Pea plants have both male and female parts and can easily be grown in large numbers. For this reason, pea plants can either self-pollinate or cross-pollinate with other pea plants. This species naturally self-fertilizes i.e. pollen encounters ova within individual flowers. The flower petals remain sealed tightly until after pollination, preventing pollination from other plants. The result is highly inbred or "true-breeding," pea plants. These are plants that always produce offspring that look like the parent. In cross pollinating two true-breeding plants (for example, one that came from a long line of yellow peas and the other that came from a long line of green peas), the first generation of offspring always is all yellow peas. The following generations had a ratio of 3:1 yellow to green. In this and all other pea plant traits Mendel observed, one form was dominant over another so it masked the presence of the other (recessive) allele. Even if the phenotype (presence) is hidden, the genotype (allele) can be passed on to other generations. By experimenting with true-breeding pea plants, Mendel avoided the appearance of unexpected (recombinant) traits in offspring that might occur if the plants were not true breeding.

Mendelian Crosses

Mendel's crosses involved mating two true-breeding organisms that had different traits to produce new generations of pea plants. Mendel performed crosses, which involved mating two true-breeding individuals that have different traits. In the pea, which is a naturally self-pollinating plant, this is done by manually transferring pollen from the anther of a mature pea plant of one variety to the stigma of a separate mature pea plant of the second

variety. In plants, pollen carries the male gametes (sperm) to the stigma, a sticky organ that traps pollen and allows the sperm to move down the pistil to the female gametes (ova) below. To prevent the pea plant that was receiving pollen from self-fertilizing and confounding his results, Mendel painstakingly removed all of the anthers from the plant's flowers before they had a chance to mature. Plants used in first-generation crosses were called P₀, or parental generation one, plants. Mendel collected the seeds belonging to the P₀ plants that resulted from each cross and grew them the following season. These offspring were called the F₁, or the first filial (filial = offspring, daughter or son), generation.



Mendelian Crosses



Once Mendel examined the characteristics in the F1 generation of plants, he allowed them to self-fertilize naturally. He then collected and grew the seeds from the F1 plants to produce the F2, or second filial, generation. Mendel's experiments extended beyond the F2 generation to the F3 and F4 generations, and so on, but it was the ratio of characteristics in the P0" F1" F2 generations that were the most intriguing and became the basis for Mendel's postulates.

Garden Pea Characteristics Revealed the Basics of Heredity

Mendel's experiments with peas revealed the presence of dominant and recessive traits in the filial generations. To fully examine each of the seven traits in garden peas, Mendel generated large numbers of F1 and F2 plants, reporting results from 19,959 F2 plants alone. His findings were consistent. What results did Mendel find in his crosses for flower color? First, Mendel confirmed that he had plants that bred true for white or violet flower color. Regardless of how many generations Mendel examined, all self-crossed offspring of parents with white flowers had white flowers, and all self-crossed offspring of parents with violet flowers had violet flowers. In addition, Mendel confirmed that, other than flower color, the pea plants were physically identical. Once these validations were complete, Mendel applied the pollen from a plant with violet flowers to the stigma of a plant with white flowers. After gathering and sowing the seeds that resulted from this cross, Mendel found that 100 percent of the F1 hybrid generation had violet flowers. Conventional wisdom at that time would have predicted the hybrid flowers to be pale violet or for hybrid plants to have equal numbers of white and violet flowers. In other words, the contrasting parental traits were expected to blend in the offspring. Instead, Mendel's results demonstrated

that the white flower trait in the F1 generation had completely disappeared. Importantly, Mendel did not stop his experimentation there. He allowed the F1 plants to self-fertilize and found that, of F2-generation plants, 705 had violet flowers and 224 had white flowers. This was a ratio of 3.15 violet flowers per one white flower, or approximately 3:1. When Mendel transferred pollen from a plant with violet flowers to the stigma of a plant with white flowers and vice versa, he obtained about the same ratio regardless of which parent, male or female, contributed which trait. This is called a reciprocal cross: a paired cross in which the respective traits of the male and female in one cross become the respective traits of the female and male in the other cross. For the other six characteristics Mendel examined, the F1 and F2 generations behaved in the same way as they had for flower color. One of the two traits would disappear completely from the F1 generation only to reappear in the F2 generation at a ratio of approximately 3:1. Upon compiling his results for many thousands of plants, Mendel concluded that the characteristics could be divided into expressed and latent traits. He called these, respectively, dominant and recessive traits. Dominant traits are those that are inherited unchanged in a hybridization. Recessive traits become latent, or disappear, in the offspring of a hybridization. The recessive trait does, however, reappear in the progeny of the hybrid offspring. An example of a dominant trait is the violet-flower trait. For this same characteristic (flower color), white-colored flowers are a recessive trait. The fact that the recessive trait reappeared in the F2 generation meant that the traits remained separate (not blended) in the plants of the F1 generation. Mendel also proposed that plants possessed two copies of the trait for the flower-color characteristic and that each parent transmitted one of its two copies to



its offspring, where they came together. Moreover, the physical observation of a dominant trait could mean that the genetic composition of the organism included two dominant versions of the characteristic or that it included one dominant and one recessive version. Conversely, the observation of a recessive trait meant that the organism lacked any dominant versions of this characteristic.

The Results of Mendel's Garden Pea Hybridizations				
Characteristic	Contrasting P ₀ Traits	F ₁ Offspring Traits	F ₂ Offspring Traits	F ₂ Trait Ratios
Flower color	Violet vs. white	100 percent violet	705 violet 224 white	3.15:1
Flower position	Axial vs. terminal	100 percent axial	651 axial 207 terminal	3.14:1
Plant height	Tall vs. dwarf	100 percent tall	787 tall 277 dwarf	2.84:1
Seed texture	Round vs. wrinkled	100 percent round	5,474 round 1,850 wrinkled	2.96:1
Seed color	Yellow vs. green	100 percent yellow	6,022 yellow 2,001 green	3.01:1
Pea pod texture	Inflated vs. constricted	100 percent inflated	882 inflated 299 constricted	2.95:1
Pea pod color	Green vs. yellow	100 percent green	428 green 152 yellow	2.82:1

Probability Basics

The rules of probability can be applied to Mendelian crosses to determine the expected phenotypes and genotypes of offspring.

Probability Basics

Probabilities are mathematical measures of likelihood. The empirical probability of an event is calculated by dividing the number of times the event occurs by the total number of opportunities for the event to occur. Empirical probabilities come from observations such as those of Mendel. An example of a genetic event is a round seed produced by a pea plant. Mendel demonstrated that the probability of the event "round seed"

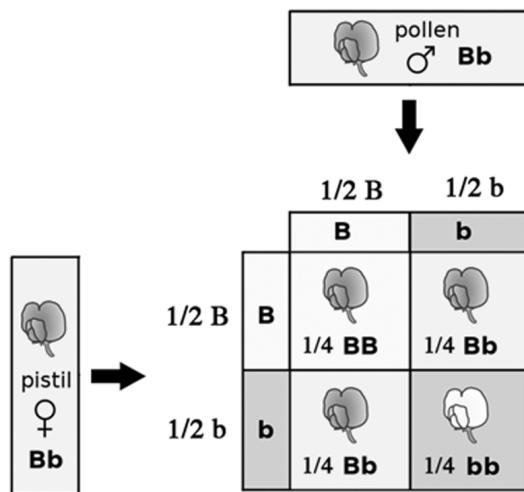
was guaranteed to occur in the F₁ offspring of true-breeding parents, one of which has round seeds and one of which has wrinkled seeds. When the F₁ plants were subsequently self-crossed, the probability of any given F₂ offspring having round seeds was now three out of four. In other words, in a large population of F₂ offspring chosen at random, 75 percent were expected to have round seeds, whereas 25 percent were expected to have wrinkled seeds. Using large numbers of crosses, Mendel was able to calculate probabilities and use these to predict the outcomes of other crosses.

The Product Rule

Mendel demonstrated that the pea-plant characteristics he studied were transmitted as discrete units from parent to offspring. Mendel also determined that different characteristics were transmitted independently of one another and could be considered in separate probability analyses. For instance, performing a cross between a plant with green, wrinkled seeds and a plant with yellow, round seeds produced offspring that had a 3:1 ratio of green:yellow seeds and a 3:1 ratio of round:wrinkled seeds. The characteristics of color and texture did not influence each other. The product rule of probability can be applied to this phenomenon of the independent transmission of characteristics. It states that the probability of two independent events occurring together can be calculated by multiplying the individual probabilities of each event occurring alone. Imagine that you are rolling a six-sided die (D) and flipping a penny (P) at the same time. The die may roll any number from 1–6 (D#), whereas the penny may turn up heads (PH) or tails (PT). The outcome of rolling the die has no effect on the outcome of flipping the penny and vice versa. There are 12 possible outcomes, and each is expected to occur with equal probability: D1PH, D1PT, D2PH,



D2PT, D3PH, D3PT, D4PH, D4PT, D5PH, D5PT, D6PH, D6PT. Of the 12 possible outcomes, the die has a $2/12$ (or $1/6$) probability of rolling a two, and the penny has a $6/12$ (or $1/2$) probability of coming up heads. The probability that you will obtain the combined outcome 2 and heads is: $(D2) \times (PH) = (1/6) \times (1/2)$ or $1/12$. The word "and" is a signal to apply the product rule. Consider how the product rule is applied to a dihybrid: the probability of having both dominant traits in the F₂ progeny is the product of the probabilities of having the dominant trait for each characteristic.



Role of probability in segregation of alleles and fertilization

The Sum Rule

The sum rule is applied when considering two mutually-exclusive outcomes that can result from more than one pathway. It states that the probability of the occurrence of one event or the other, of two mutually-exclusive events, is the sum of their individual probabilities. The word "or" indicates that you should apply the sum rule. Let's imagine you are flipping a penny (P) and a quarter (Q). What is the probability of one coin coming up heads and one coming up tails? This can be achieved by

two cases: the penny is heads (PH) and the quarter is tails (QT), or the quarter is heads (QH) and the penny is tails (PT). Either case fulfills the outcome. We calculate the probability of obtaining one head and one tail as $[(PH) \times (QT)] + [(QH) \times (PT)] = [(1/2) \times (1/2)] + [(1/2) \times (1/2)] = 1/2$. You should also notice that we used the product rule to calculate the probability of PH and QT and also the probability of PT and QH, before we summed them. The sum rule can be applied to show the probability of having just one dominant trait in the F₂ generation of a dihybrid cross. To use probability laws in practice, it is necessary to work with large sample sizes because small sample sizes are prone to deviations caused by chance. The large quantities of pea plants that Mendel examined allowed him to calculate the probabilities of the traits appearing in his F₂ generation. This discovery meant that when parental traits were known, the offspring's traits could be predicted accurately even before fertilization.

Pairs of Unit Factors, or Genes

Genes exist in pairs within an organism, with one of each pair inherited from each parent. Mendel proposed that paired unit factors of heredity were transmitted faithfully from generation to generation by the dissociation and reassociation of paired factors during gametogenesis and fertilization, respectively. After he crossed peas with contrasting traits and found that the recessive trait resurfaced in the F₂ generation, Mendel deduced that hereditary factors must be inherited as discrete units. This finding contradicted the belief at that time that parental traits were blended in the offspring. A gene is made up of short sections of DNA that are contained on a chromosome within the nucleus of a cell. Genes control the development and function of all organs and all working systems in the



body. A gene has a certain influence on how the cell works; the same gene in many different cells determines a certain physical or biochemical feature of the whole body (e.g., eye color or reproductive functions). All human cells hold approximately 21,000 different genes. Genetics is the science of the way traits are passed from parent to offspring. For all forms of life, continuity of the species depends upon the genetic code being passed from parent to offspring. Evolution by natural selection is dependent on traits being heritable. Genetics is very important in human physiology because all attributes of the human body are affected by a person's genetic code. It can be as simple as eye color, height, or hair color. Or it can be as complex as how well your liver processes toxins, whether you will be prone to heart disease or breast cancer, and whether you will be color blind. Genetic inheritance begins at the time of conception. You inherited 23 chromosomes from your mother and 23 from your father. Together they form 22 pairs of autosomal chromosomes and a pair of sex chromosomes (either XX if you are female, or XY if you are male). Homologous chromosomes have the same genes in the same positions, but may have different alleles (varieties) of those genes. There can be many alleles of a gene within a population, but an individual within that population only has two copies and can be homozygous (both copies the same) or heterozygous (the two copies are different) for any given gene.

Alleles Can Be Dominant or Recessive

In a heterozygote, the allele which masks the other is referred to as dominant, while the allele that is masked is referred to as recessive. Most familiar animals and some plants have paired chromosomes and are described as diploid. They have two versions of each chromosome: one contributed by the female parent in her

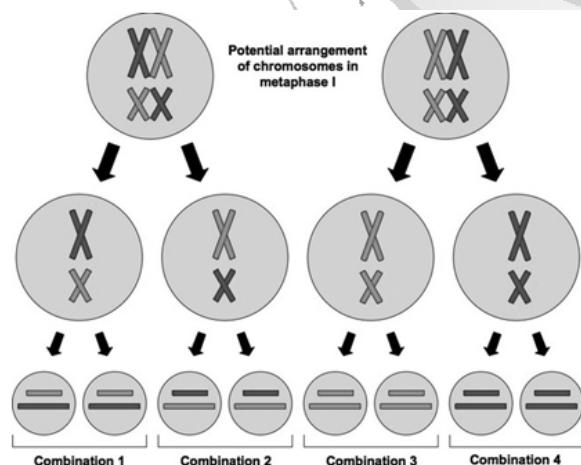
ovum and one by the male parent in his sperm. These are joined at fertilization. The ovum and sperm cells (the gametes) have only one copy of each chromosome and are described as haploid. Mendel's law of dominance states that in a heterozygote, one trait will conceal the presence of another trait for the same characteristic. Rather than both alleles contributing to a phenotype, the dominant allele will be expressed exclusively. The recessive allele will remain "latent," but will be transmitted to offspring by the same manner in which the dominant allele is transmitted. The recessive trait will only be expressed by offspring that have two copies of this allele; these offspring will breed true when self-crossed. By definition, the terms dominant and recessive refer to the genotypic interaction of alleles in producing the phenotype of the heterozygote. The key concept is genetic: which of the two alleles present in the heterozygote is expressed, such that the organism is phenotypically identical to one of the two homozygotes. It is sometimes convenient to talk about the trait corresponding to the dominant allele as the dominant trait and the trait corresponding to the hidden allele as the recessive trait. However, this can easily lead to confusion in understanding the concept as phenotypic. For example, to say that "green peas" dominate "yellow peas" confuses inherited genotypes and expressed phenotypes. This will subsequently confuse discussion of the molecular basis of the phenotypic difference. Dominance is not inherent. One allele can be dominant to a second allele, recessive to a third allele, and codominant to a fourth. If a genetic trait is recessive, a person needs to inherit two copies of the gene for the trait to be expressed. Thus, both parents have to be carriers of a recessive trait in order for a child to express that trait. Since Mendel's experiments with pea plants, other researchers have found that the



law of dominance does not always hold true. Instead, several different patterns of inheritance have been found to exist.

Equal Segregation of Alleles

Mendel's Law of Segregation states that a diploid organism passes a randomly selected allele for a trait to its offspring, such that the offspring receives one allele from each parent. Observing that true-breeding pea plants with contrasting traits gave rise to F1 generations that all expressed the dominant trait and F2 generations that expressed the dominant and recessive traits in a 3:1 ratio, Mendel proposed the law of segregation. The law of segregation states that each individual that is a diploid has a pair of alleles (copy) for a particular trait. Each parent passes an allele at random to their offspring resulting in a diploid organism. The allele that contains the dominant trait determines the phenotype of the offspring. In essence, the law states that copies of genes separate or segregate so that each gamete receives only one allele.



The Law of Segregation states that alleles segregate randomly into gametes

For the F2 generation of a monohybrid cross, the following three possible combinations of genotypes could result: homozygous dominant, heterozygous, or homozygous recessive.

Because heterozygotes could arise from two different pathways (receiving one dominant and one recessive allele from either parent), and because heterozygotes and homozygous dominant individuals are phenotypically identical, the law supports Mendel's observed 3:1 phenotypic ratio. The equal segregation of alleles is the reason we can apply the Punnett square to accurately predict the offspring of parents with known genotypes. The physical basis of Mendel's law of segregation is the first division of meiosis in which the homologous chromosomes with their different versions of each gene are segregated into daughter nuclei. The behavior of homologous chromosomes during meiosis can account for the segregation of the alleles at each genetic locus to different gametes. As chromosomes separate into different gametes during meiosis, the two different alleles for a particular gene also segregate so that each gamete acquires one of the two alleles. In Mendel's experiments, the segregation and the independent assortment during meiosis in the F1 generation give rise to the F2 phenotypic ratios observed by Mendel. The role of the meiotic segregation of chromosomes in sexual reproduction was not understood by the scientific community during Mendel's lifetime.

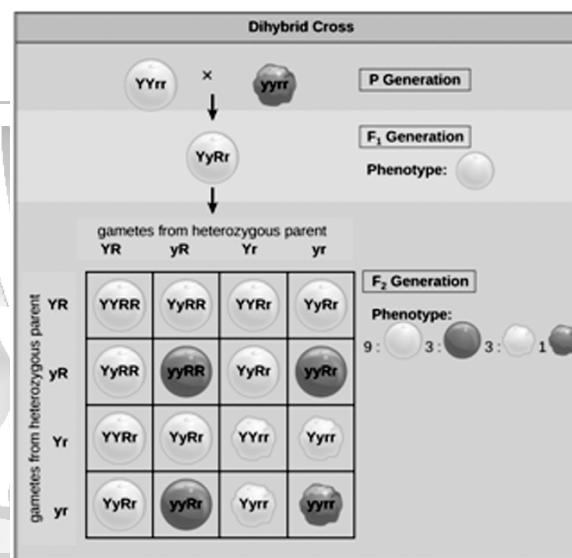
Independent Assortment

Independent assortment allows the calculation of genotypic and phenotypic ratios based on the probability of individual gene combinations. Mendel's law of independent assortment states that genes do not influence each other with regard to the sorting of alleles into gametes: every possible combination of alleles for every gene is equally likely to occur. The independent assortment of genes can be illustrated by the dihybrid cross: a cross between two true-breeding parents that express different traits for two characteristics. Consider the characteristics of seed color and



seed texture for two pea plants: one that has green, wrinkled seeds (yyrr) and another that has yellow, round seeds (YYRR). Because each parent is homozygous, the law of segregation indicates that the gametes for the green/wrinkled plant all are yr, while the gametes for the yellow/round plant are all YR. Therefore, the F₁ generation of offspring all are YyRr. For the F₂ generation, the law of segregation requires that each gamete receive either an R allele or an r allele along with either a Y allele or a y allele. The law of independent assortment states that a gamete into which an r allele sorted would be equally likely to contain either a Y allele or a y allele. Thus, there are four equally likely gametes that can be formed when the YyRr heterozygote is self-crossed as follows: YR, Yr, yR, and yr. Arranging these gametes along the top and left of a 4 × 4 Punnett square gives us 16 equally likely genotypic combinations. From these genotypes, we infer a phenotypic ratio of 9 round/yellow:3 round/green:3 wrinkled/yellow:1 wrinkled/green. These are the offspring ratios we would expect, assuming we performed the crosses with a large enough sample size. Because of independent assortment and dominance, the 9:3:3:1 dihybrid phenotypic ratio can be collapsed into two 3:1 ratios, characteristic of any monohybrid cross that follows a dominant and recessive pattern. Ignoring seed color and considering only seed texture in the above dihybrid cross, we would expect that three-quarters of the F₂ generation offspring would be round and one-quarter would be wrinkled. Similarly, isolating only seed color, we would assume that three-quarters of the F₂ offspring would be yellow and one-quarter would be green. The sorting of alleles for texture and color are independent events, so we can apply the product rule. Therefore, the proportion of round and yellow F₂ offspring is expected to be $(3/4) \times (3/4) = 9/16$, and the proportion

of wrinkled and green offspring is expected to be $(1/4) \times (1/4) = 1/16$. These proportions are identical to those obtained using a Punnett square. Round/green and wrinkled/yellow offspring can also be calculated using the product rule as each of these genotypes includes one dominant and one recessive phenotype. Therefore, the proportion of each is calculated as $(3/4) \times (1/4) = 3/16$.



Independent assortment of 2 genes

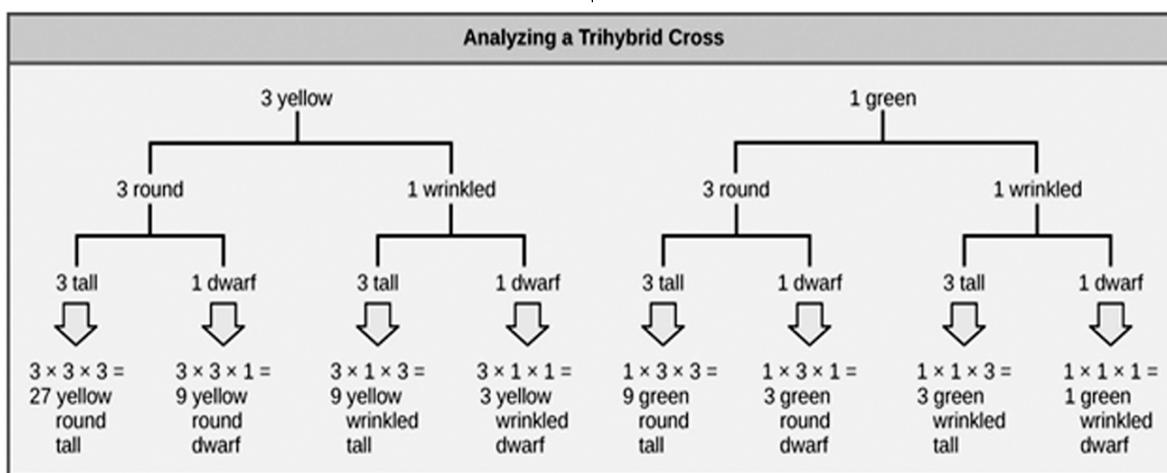
Forked-Line Method

When more than two genes are being considered, the Punnett-square method becomes unwieldy. For instance, examining a cross involving four genes would require a 16 × 16 grid containing 256 boxes. It would be extremely cumbersome to manually enter each genotype. For more complex crosses, the forked-line and probability methods are preferred. To prepare a forked-line diagram for a cross between F₁ heterozygotes resulting from a cross between AABBCC and aabbcc parents, we first create rows equal to the number of genes being considered and then segregate the alleles in each row on forked lines according to the probabilities for individual monohybrid crosses. We then



multiply the values along each forked path to obtain the F₂ offspring probabilities. Note that this process is a diagrammatic version of the product rule. The values along each

forked pathway can be multiplied because each gene assorts independently. For a trihybrid cross, the F₂ phenotypic ratio is 27:9:9:9:3:3:3:1.



Independent assortment of 2 genes

Probability Method

While the forked-line method is a diagrammatic approach to keeping track of probabilities in a cross, the probability method gives the proportions of offspring expected to exhibit each phenotype (or genotype) without the added visual assistance. To fully demonstrate the power of the probability method, however, we can consider specific genetic calculations. For instance, for a tetrahybrid cross between individuals that are heterozygotes for all four genes, and in which all four genes are sorting independently in a dominant and recessive pattern, what proportion of the offspring will be expected to be homozygous recessive for all four alleles? Rather than writing out every possible genotype, we can use the probability method. We know that for each gene the fraction of homozygous recessive offspring will be 1/4. Therefore, multiplying this fraction for each of the four genes, $(1/4) \times (1/4) \times (1/4) \times (1/4)$, we determine that 1/256 of the offspring will be quadruply homozygous recessive.

Linked Genes Violate the Law of Independent Assortment

Genes that are on the same chromosome, or "linked", do not assort independently, but can be separated by recombination. Although all of Mendel's pea characteristics behaved according to the law of independent assortment, we now know that some allele combinations are not inherited independently of each other. Genes that are located on separate non-homologous chromosomes will always sort independently. However, each chromosome contains hundreds or thousands of genes organized linearly on chromosomes like beads on a string. The segregation of alleles into gametes can be influenced by linkage, in which genes that are located physically close to each other on the same chromosome are more likely to be inherited as a pair. However, because of the process of recombination, or "crossover," it is possible for two genes on the same chromosome to behave independently, or as if they are not linked. To understand this, let's consider the



biological basis of gene linkage and recombination. Homologous chromosomes possess the same genes in the same linear order. The alleles may differ on homologous chromosome pairs, but the genes to which they correspond do not. In preparation for the first division of meiosis, homologous chromosomes replicate and synapse. Like genes on the homologs align with each other. At this stage, segments of homologous chromosomes exchange linear segments of genetic material. This process is called recombination, or crossover, and it is a common genetic process. Because the genes are aligned during recombination, the gene order is not altered. Instead, the result of recombination is that maternal and paternal alleles are combined onto the same chromosome. Across a given chromosome, several recombination events may occur, causing extensive shuffling of alleles.

		<i>Ttii</i>			
		<i>TT</i>	<i>Tt</i>	<i>tT</i>	<i>tt</i>
<i>Ttii</i>	<i>TT</i>	<i>TTII</i>	<i>TTIi</i>	<i>TtII</i>	<i>TtIi</i>
	<i>Tt</i>	<i>TTIi</i>	<i>TTii</i>	<i>Ttii</i>	<i>Ttii</i>
	<i>tT</i>	<i>TtII</i>	<i>TtIi</i>	<i>ttII</i>	<i>ttIi</i>
	<i>tt</i>	<i>TtIi</i>	<i>Ttii</i>	<i>ttII</i>	<i>ttii</i>
	<i>tt</i>	<i>ttII</i>	<i>ttIi</i>	<i>ttii</i>	<i>ttii</i>

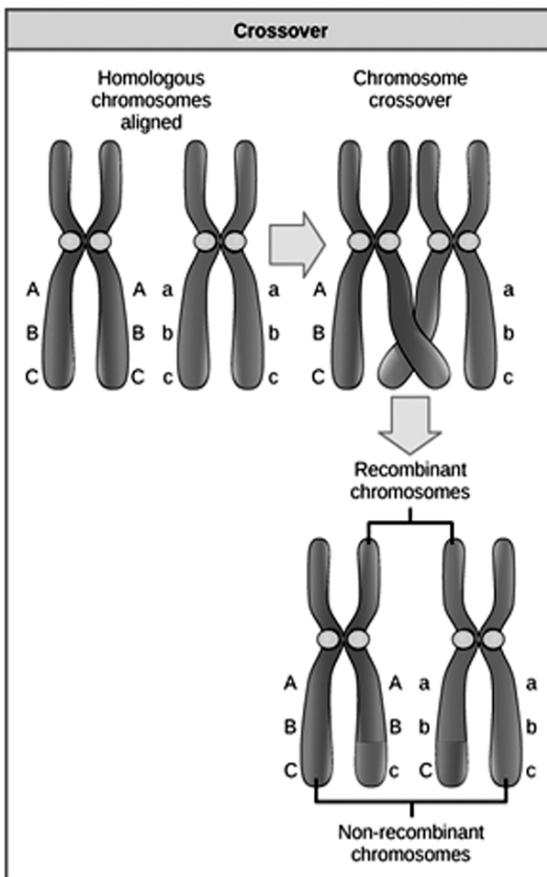
Unlinked genes assort independently

When two genes are located in close proximity on the same chromosome, they are considered linked, and their alleles tend to be transmitted through meiosis together. To exemplify this, imagine a dihybrid cross involving flower color and plant height in which the genes are next to each other on the chromosome. If one

homologous chromosome has alleles for tall plants and red flowers, and the other chromosome has genes for short plants and yellow flowers, then when the gametes are formed, the tall and red alleles will go together into a gamete and the short and yellow alleles will go into other gametes. These are called the parental genotypes because they have been inherited intact from the parents of the individual producing gametes. But unlike if the genes were on different chromosomes, there will be no gametes with tall and yellow alleles and no gametes with short and red alleles. If you create the Punnett square with these gametes, you will see that the classical Mendelian prediction of a 9:3:3:1 outcome of a dihybrid cross would not apply. As the distance between two genes increases, the probability of one or more crossovers between them increases, and the genes behave more like they are on separate chromosomes. Geneticists have used the proportion of recombinant gametes (the ones not like the parents) as a measure of how far apart genes are on a chromosome. Using this information, they have constructed elaborate maps of genes on chromosomes for well-studied organisms, including humans.

Mendel's seminal publication makes no mention of linkage, and many researchers have questioned whether he encountered linkage, but chose not to publish those crosses out of concern that they would invalidate his independent assortment postulate. The garden pea has seven chromosomes and some have suggested that his choice of seven characteristics was not a coincidence. However, even if the genes he examined were not located on separate chromosomes, it is possible that he simply did not observe linkage because of the extensive shuffling effects of recombination.





Linked genes can be separated by recombination

MODERN UNDERSTANDINGS OF INHERITANCE

Chromosomal Theory of Inheritance

The Chromosomal Theory of Inheritance identified chromosomes as the genetic material responsible for Mendelian inheritance. The speculation that chromosomes might be the key to understanding heredity led several scientists to examine Mendel's publications and re-evaluate his model in terms of the behavior of chromosomes during mitosis and meiosis. In 1902, Theodor Boveri observed that proper embryonic development of sea urchins does not occur unless chromosomes are present. That same year, Walter Sutton observed the separation of chromosomes into daughter cells during meiosis. Together, these observations led to the development of the Chromosomal

Theory of Inheritance, which identified chromosomes as the genetic material responsible for Mendelian inheritance. During meiosis, homologous chromosome pairs migrate as discrete structures that are independent of other chromosome pairs. The sorting of chromosomes from each homologous pair into pre-gametes appears to be random. Each parent synthesizes gametes that contain only half of their chromosomal complement. Even though male and female gametes (sperm and egg) differ in size and morphology, they have the same number of chromosomes, suggesting equal genetic contributions from each parent. The gametic chromosomes combine during fertilization to produce offspring with the same chromosome number as their parents. Despite compelling correlations between the behavior of chromosomes during meiosis and Mendel's abstract laws, the Chromosomal Theory of Inheritance was proposed long before there was any direct evidence that traits were carried on chromosomes. Critics pointed out that individuals had far more independently segregating traits than they had chromosomes. It was only after several years of carrying out crosses with the fruit fly, *Drosophila melanogaster*, that Thomas Hunt Morgan provided experimental evidence to support the Chromosomal Theory of Inheritance. In 1910, Thomas Hunt Morgan started his work with *Drosophila melanogaster*, a fruit fly. He chose fruit flies because they can be cultured easily, are present in large numbers, have a short generation time, and have only four pairs of chromosomes that can be easily identified under the microscope. They have three pairs of autosomes and a pair of sex chromosomes. At that time, he already knew that X and Y have to do with gender. He used normal flies with red eyes and mutated flies with white eyes and cross-bred them. In flies, the wild type eye color is red (X^W) and is dominant to white eye color (X^w). He was able to conclude



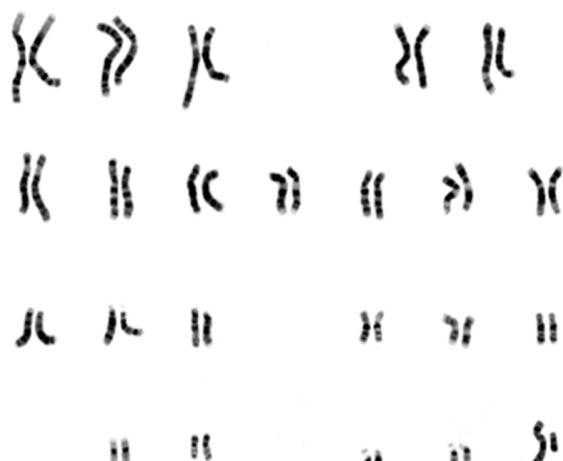
that the gene for eye color was on the X chromosome. This trait was thus determined to be X-linked and was the first X-linked trait to be identified. Males are said to be hemizygous, in that they have only one allele for any X-linked characteristic.

Identification of Chromosomes

The isolation and microscopic observation of chromosomes forms the basis of cytogenetics and is the primary method by which clinicians detect chromosomal abnormalities in humans. A karyotype is the number and appearance of chromosomes. To obtain a view of an individual's karyotype, cytologists photograph the chromosomes and then cut and paste each chromosome into a chart, or karyogram, also known as an ideogram. In a given species, chromosomes can be identified by their number, size, centromere position, and banding pattern. In a human karyotype, autosomes or "body chromosomes" (all of the non-sex chromosomes) are generally organized in approximate order of size from largest (chromosome 1) to smallest (chromosome 22). However, chromosome 21 is actually shorter than chromosome 22. This was discovered after the naming of Down syndrome as trisomy 21, reflecting how this disease results from possessing one extra chromosome 21 (three total). Not wanting to change the name of this important disease, chromosome 21 retained its numbering, despite describing the shortest set of chromosomes. The X and Y chromosomes are not autosomes and are referred to as the sex chromosomes. The chromosome "arms" projecting from either end of the centromere may be designated as short or long, depending on their relative lengths. The short arm is abbreviated p (for "petite"), whereas the long arm is abbreviated q (because it follows "p" alphabetically). Each arm is further subdivided and denoted by a number. Using this naming system, locations

on chromosomes can be described consistently in the scientific literature. Although Mendel is referred to as the "father of modern genetics," he performed his experiments with none of the tools that the geneticists of today routinely employ. One such powerful cytological technique is karyotyping, a method in which traits characterized by chromosomal abnormalities can be identified from a single cell. To observe an individual's karyotype, a person's cells (like white blood cells) are first collected from a blood sample or other tissue. In the laboratory, the isolated cells are stimulated to begin actively dividing. A chemical called colchicine is then applied to cells to arrest condensed chromosomes in metaphase. Cells are then made to swell using a hypotonic solution so the chromosomes spread apart. Finally, the sample is preserved in a fixative and applied to a slide. The geneticist then stains chromosomes with one of several dyes to better visualize the distinct and reproducible banding patterns of each chromosome pair. Following staining, the chromosomes are viewed using bright-field microscopy. A common stain choice is the Giemsa stain. Giemsa staining results in approximately 400–800 bands (of tightly coiled DNA and condensed proteins) arranged along all of the 23 chromosome pairs. An experienced geneticist can identify each chromosome based on its characteristic banding pattern. In addition to the banding patterns, chromosomes are further identified on the basis of size and centromere location. To obtain the classic depiction of the karyotype in which homologous pairs of chromosomes are aligned in numerical order from longest to shortest, the geneticist obtains a digital image, identifies each chromosome, and manually arranges the chromosomes into this pattern .

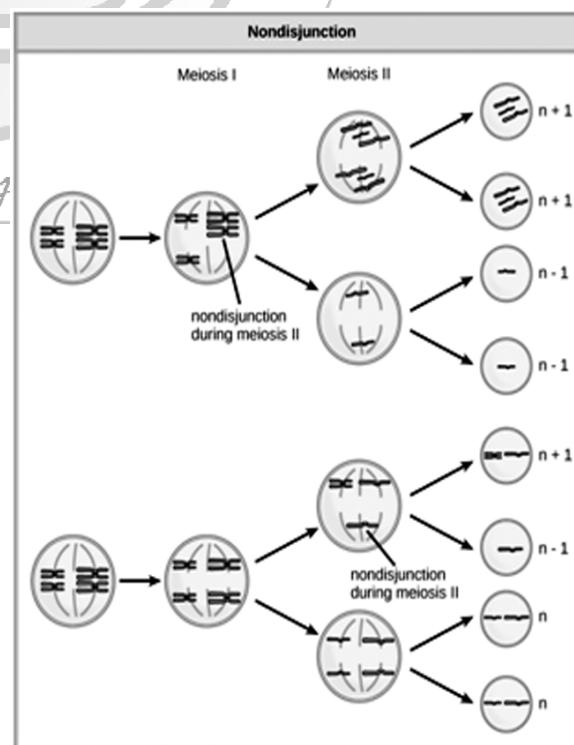


*A human karyotype*

At its most basic, the karyotype may reveal genetic abnormalities in which an individual has too many or too few chromosomes per cell. Examples of this are Down Syndrome, which is identified by a third copy of chromosome 21, and Turner Syndrome, which is characterized by the presence of only one X chromosome in women instead of the normal two. Geneticists can also identify large deletions or insertions of DNA. For instance, Jacobsen Syndrome, which involves distinctive facial features as well as heart and bleeding defects, is identified by a deletion on chromosome 11. Finally, the karyotype can pinpoint translocations, which occur when a segment of genetic material breaks from one chromosome and reattaches to another chromosome or to a different part of the same chromosome. Translocations are implicated in certain cancers, including chronic myelogenous leukemia. During Mendel's lifetime, inheritance was an abstract concept that could only be inferred by performing crosses and observing the traits expressed by offspring. By observing a karyotype, today's geneticists can actually visualize the chromosomal composition of an individual to confirm or predict genetic abnormalities in offspring, even before birth.

Disorders in Chromosome Number

Of all of the chromosomal disorders, abnormalities in chromosome number are the most obviously identifiable from a karyotype and are referred to as aneuploidy. Aneuploidy is a condition in which one or more chromosomes are present in extra copies or are deficient in number, but not a complete set. To be more specific, the loss of a single chromosome from a diploid genome is called monosomy ($2n-1$). The gain of one chromosome is called trisomy ($2n+1$). They are caused by nondisjunction, which occurs when pairs of homologous chromosomes or sister chromatids fail to separate during meiosis. Misaligned or incomplete synapsis, or a dysfunction of the spindle apparatus that facilitates chromosome migration, can cause nondisjunction. The risk of nondisjunction occurring increases with the age of the parents. Nondisjunction can occur during either meiosis I or II, with differing results. If homologous

*Nondisjunction in Meiosis*

chromosomes fail to separate during meiosis I, the result is two gametes that lack that particular chromosome and two gametes with two copies of the chromosome. If sister chromatids fail to separate during meiosis II, the result is one gamete that lacks that chromosome, two normal gametes with one copy of the chromosome, and one gamete with two copies of the chromosome. If a gamete with two copies of the chromosome combines with a normal gamete during fertilization, the result is trisomy; if a gamete with no copies of the chromosomes combines with a normal gamete during fertilization, the result is monosomy.

Aneuploidy often results in serious problems such as Turner syndrome, a monosomy in which females may contain all or part of an X chromosome. Monosomy for autosomes is usually lethal in humans and other animals. Klinefelter syndrome is a trisomy genetic disorder in males caused by the presence of one or more X chromosomes. The effects of trisomy are similar to those of monosomy. Down syndrome is the only autosomal trisomy in humans that has a substantial number of survivors one year after birth. Trisomy in chromosome 21 is the cause of Down syndrome; it affects 1 infant in every 800 live births.

Sex Chromosome Nondisjunction in Humans

Humans display dramatic deleterious effects with autosomal trisomies and monosomies. Therefore, it may seem counterintuitive that human females and males can function normally, despite carrying different numbers of the X chromosome. Rather than a gain or loss of autosomes, variations in the number of X chromosomes are associated with relatively mild effects. In part, this occurs because of a molecular process called X inactivation. Early in development, when

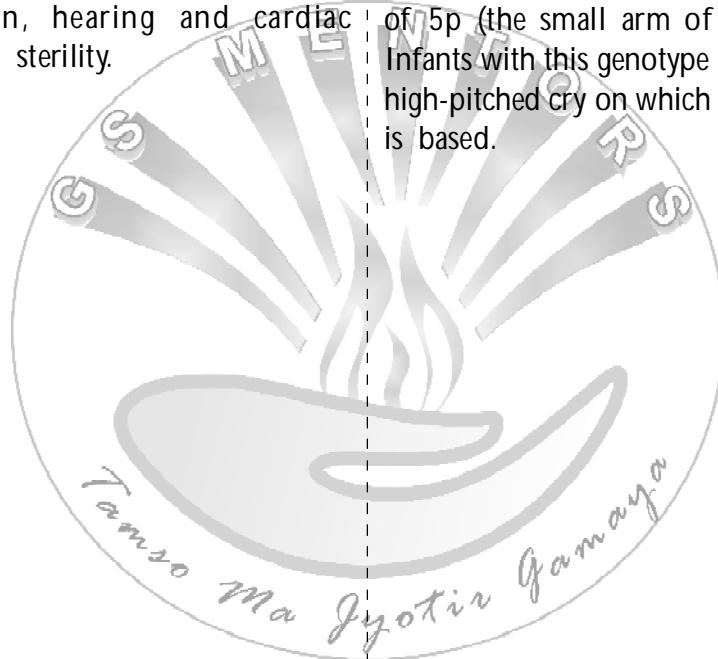
female mammalian embryos consist of just a few thousand cells (relative to trillions in the newborn), one X chromosome in each cell inactivates by tightly condensing into a quiescent (dormant) structure called a Barr body. The chance that an X chromosome (maternally or paternally derived) is inactivated in each cell is random, but once the inactivation occurs, all cells derived from that single cell will have the same inactive X chromosome or Barr body. By this process, a phenomenon called dosage compensation is achieved. Females possess two X chromosomes, while males have only one; therefore, if both X chromosomes remained active in the female, they would produce twice as much product from the genes on the X chromosomes as males. So how does X-inactivation help alleviate the effects of extra X chromosomes? An individual carrying an abnormal number of X chromosomes will inactivate all but one X chromosome in each of her cells. If three X chromosomes are present, the cell will inactivate two of them. If four X chromosomes are present, three will be inactivated, and so on. This results in an individual that is relatively phenotypically normal. However, even inactivated X chromosomes continue to express a few genes, and X chromosomes must reactivate for the proper maturation of female ovaries. As a result, X-chromosomal abnormalities are typically associated with mild mental and physical defects, as well as sterility. If the X chromosome is absent altogether, the individual will not develop in utero. Several errors in sex chromosome number have been characterized. Individuals with three X chromosomes, called triplo-X, are phenotypically female, but express developmental delays and reduced fertility. The XXY genotype, corresponding to one type of Klinefelter syndrome, corresponds to phenotypically male individuals with small



testes, enlarged breasts, and reduced body hair. More complex types of Klinefelter syndrome exist in which the individual has as many as five X chromosomes. In all types, every X chromosome except one undergoes inactivation to compensate for the excess genetic dosage. This can be seen as several Barr bodies in each cell nucleus. Turner syndrome, characterized as an X0 genotype (i.e., only a single sex chromosome), corresponds to a phenotypically female individual with short stature, webbed skin in the neck region, hearing and cardiac impairments, and sterility.

Duplications and Deletions

In addition to the loss or gain of an entire chromosome, a chromosomal segment may be duplicated or lost. Duplications and deletions often produce offspring that survive but exhibit physical and mental abnormalities. Duplicated chromosomal segments may fuse to existing chromosomes or may be free in the nucleus. Cri-du-chat (from the French for "cry of the cat") is a syndrome associated with nervous system abnormalities and identifiable physical features that result from a deletion of most of 5p (the small arm of chromosome 5). Infants with this genotype emit a characteristic high-pitched cry on which the disorder's name is based.



■ ■ ■

