Mendel's Laws

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Glossary

Dihybrid cross Crossing two individuals who are heterozygous for two genes of interest.
Dominant A trait that persists in the hybrid generation.
Genes Units of inheritance.
Genetics The study of the transmission of inherited traits from generation to generation.
Heterozygote An individual who has two different alleles of a particular gene.
Homozygote An individual who has two of the same alleles of a particular gene.
Independent assortment Random combination of alleles for genes carried on different chromosomes.
Monohybrid cross Crossing two individuals who are heterozygous for a gene of interest.
Recessive A trait that appears to vanish in the hybrid generation.
Segregation The distribution of alleles of a gene into separate sperm and egg.

Introduction

Over the past 20 years, the field of genetics has evolved into genomics, as researchers deciphered the 3.2 billion building blocks of the informational molecule deoxyribonucleic acid (DNA) that comprises the complete set of genetic instructions to maintain a human body – the genome. Yet, even as researchers today routinely compare DNA sequences at millions of places in the genome, many practical questions about heredity still ask how a single trait or medical condition is transmitted in a family. The answers require familiarity with the basic laws of inheritance that describe the patterns in which genes pass from parents to offspring. These principles were discovered more than 100 years ago.

Gregor Mendel: The Father of Genetics

Gregor Mendel (1822–84), an Augustinian monk living in what is now the Czech Republic, worked out the basic principles of inheritance in garden peas in a series of experiments conducted over 7 years in the monastery garden and greenhouse. Mendel, although not a trained scientist, instinctively followed the classic steps of scientific investigation. Drawing on coursework in mathematics, he methodically tested how certain traits seemingly vanish between generations, only to reappear. He repeated experiments to rule out the possibility of chance causing the results and carried out reciprocal crosses so that in one cross a male contributed a trait and in another, a female. Altogether, he looked at a variety of traits in an estimated 24 034 plants, even breeding some plants for up to seven generations (2 years) to demonstrate that a trait did not change with time.

Unlike investigators and philosophers who had pondered heredity before him, Mendel added a quantitative perspective to his experiments. He sought similarities and trends in the data, then proposed physical explanations for them. But when Mendel published his famous paper *Experiments in Plant Hybridization* in 1865, the world was not ready for the mathematical precision and clarity of his work.

Influences on Mendel

In Mendel's time, interest in inheritance centered on plant and animal breeding. Horticulturists sought new varieties of ornamental plants, after the explorers of the sixteenth and seventeenth centuries brought many new species to Europe. The late 1700s saw the proliferation of botanical gardens and parks, as interest in plant variants rose. In the late 1700s and early 1800s, 'agricultural science' courses at universities considered breeding an outgrowth of natural science. As the textile industry flourished in Mendel's hometown of Brno (Brünn), the capital of the province of Moravia, breeding sheep for their wool became a high priority. More art than science, agricultural experiments sought new varieties or new ways to better perpetuate existing favorites. Pursuit of valuable traits at this time was more qualitative than Mendel's statistical analyses.

Two researchers, J. G. Kölreuter and Andrew Knight in particular, influenced Mendel. They pioneered plant breeding by crossing pure varieties to obtain hybrids. Kölreuter (1733–1806) studied hybridization in 54 species at the University of Tübingen, publishing three reports from 1761 to 1766. He controlled breeding by placing pollen from one plant onto the female parts of another plant. Kölreuter noted that when he crossed hybrids to each other, traits in the parental plants reappeared in the third generation. Although Kölreuter was the first to systematically hybridize plants, he did not explain how they arose. He supported epigenesis, the idea that the new organism does not inherit discrete units or traits but forms from a homogeneous mix that specializes into distinctive characteristics during development.

Andrew Knight (1759–1838) recommended artificial pollination of fruit trees to yield more desired varieties. When he became more interested in trait transmission than in the particulars of fruit-raising, he switched to peas, which were an ideal experimental organism. Peas displayed many traits and had a short generation time and a flower form that allowed control over breeding. In experiments begun in 1787, Knight confirmed the creation of hybrids in a second generation and reappearance of the parental traits in the third. Other investigators made the same observations, but until Mendel, no one probed how and why this happened.

The English biologist William Bateson (1861–1926) coined the term 'genetics' in 1906, but it had actually been used earlier. In 1819, Count E. Festetics, a prominent sheep breeder from Hungary, published 'genetic laws' which included the observations that progeny inherit traits from their parents, and that traits of grandparents can reappear in the offspring of their offspring.

Mendel's Early Life

Gregor Mendel was born on 22 July 1822 in the tiny village of Hynčice, to Anton, a peasant farmer, and Rosine, who was the daughter of a gardener. His given birth name was Johann Mendel. Young Mendel learned from an early age to care for fruit trees, both because of his mother's background and because the family ate the fruit. He excelled in school, and in the third grade was sent away to a 'Gymnasium' for gifted students. With little financial help from his ailing father, Mendel had to earn his own way by tutoring for 6 years he spent there. By age 16, he supported himself.

After the Gymnasium, Mendel spent 2 years at a 'philosophical study' (a 2-year preparatory program before college), but it took an extra year because he had to return home to care for his father, and his own health was not good. He grew intensely interested in physics and mathematics, but did not, at that point, continue to college. His parents encouraged him to enter the priesthood, and in 1843, at the age of 21, Mendel entered the Augustinian monastery of St. Thomas in Brno, where he took the name Gregor. It was an unusual monastery, in that the members taught in public schools and maintained plant and mineral collections. They were encouraged to investigate nature. From 1843 until 1848, Mendel attended lectures in agricultural science, learning how to artificially pollinate plants to produce higher yielding varieties. He worked briefly at a hospital, quickly realizing that he had not the stomach for it after witnessing surgery performed without anesthesia. Then, he was briefly hospitalized for what some sources report as a nervous breakdown. Finally, Mendel received a valued assignment: teaching latin, greek, and mathematics in the seventh grade.

Mendel secured the teaching post because a revolution had led to an increased interest in education. But he had no formal training as a teacher and had to take an exam for certification. A curriculum vitae which he attached to his application has supplied much of what we know of Mendel's early years. Mendel wanted to teach natural history. But he suffered from test anxiety and failed because he had had no experience taking examinations and he had not prepared sufficiently. A zoologist who graded one essay was especially harsh, criticizing Mendel's ideas on evolution and speciation that would turn out, in light of Darwin's contributions 8 years later, to have been brilliant. Mendel was told to retake the examination 1 year later.

He never retook the examination, but instead luck intervened. In 1851, Mendel substituted for a sick teacher at the Brno Technical School, and made such a good impression that he was sent to the University of Vienna to complete his education. He was 29 then. At the university, Mendel supplemented his knowledge of language and philosophy with courses in chemistry, botany, and zoology, becoming very interested in plant hybridization. A course in 'combinatorial analysis' would prove particularly valuable later on as Mendel devised and carried out his breeding experiments with peas. Also at this time, scientists, both amateur and professional, were turning from observation toward experimentation.

Three years later, Mendel switched to a new type of institution in Brno for the children of factory workers called a 'Realschule'. Here, he taught his beloved natural history and physics. At this time, Mendel began to formulate what was missing from the experiments of Kölreuter, Knight, and others and, more importantly, to plan how he would reveal the mechanisms behind trait transmission through a hybrid generation. He recognized the compelling need for a statistical analysis of the problem. It was a new way to look at an old question.

Mendel's Paper

Mendel read his famous paper describing experiments conducted from 1857 to 1863 at two meetings of the Brno Natural History Society on 8 February and 8 March 1865. The paper was published in the proceedings of that organization in the following year, and Bateson translated it into English in 1901. This paper has been reprinted in many collections of historical papers of scientific importance.

Choosing Traits to Follow

Mendel's paper is organized logically into 11 sections. It begins by questioning the nature of hybridization, based on observations on ornamental plants. Why and how do some parental traits reappear in the third generation, and why do some crosses produce the same proportion of hybrids time after time? In the next section, Mendel extols the virtues of the garden pea as an experimental organism, citing much the same reasons as Andrew Knight had years earlier. The third section then lists the 'differentiating characters', or traits, that Mendel considered as the subjects of his study. He whittled down several dozen possible traits to 15 (**Table 1**), then selected seven to pursue because they appeared in two distinct forms, rather than the 'more or less' nature of the others (**Table 2**). For each cross of one type with the second type for a given trait, he conducted 23–60 artificial fertilizations and

Table 1 Traits in the garden pea *Pisum sativum* Mendel considered

Stem length[a]	*Unripe pod color*
Stem color	Pod form[a]
Leaf size	Pod size
Leaf form	Seed form[a]
Flower position[a]	Seed size
Flower color	Seed coat color[a]
Flower size	Seed color[a]
Length of flower stalk	

[a]Those selected for experiments.

Table 2 Dominant and recessive traits used in Mendel's experiments

Trait	*Dominant expression*	*Recessive expression*
Seed form	Round (*R*)	Wrinkled (*r*)
Seed color	Yellow (*I*)	Green (*i*)
Seed coat color	Gray or gray-brown (*A*)	White (*a*)
Pod form	Inflated (*V*)	Constricted (*v*)
Unripe pod color	Green (*Gp*)	Yellow (*gp*)
Flower position	Axial (along stem; *Fa*)	Terminal (on top; *fa*)
Stem length	Long (6–7 feet; *Le*)	Short (3/4 to 1 1/2 feet; *le*)

varied whether the female or the male transmitted each variant. Then, he selected the 'most vigorous' hybrids for further study. Mendel used the tools of the backyard gardener, working with plants 'maintained in their natural upright position by means of sticks, twigs, and taut strings'. Certain experiments were replicated in a greenhouse to avoid insect disturbances.

In his first experiment, Mendel crossed plants bearing the two forms of each trait and observed the hybrid progeny. He thus established the concepts of dominance and recessiveness. A dominant trait is the one that appears in the hybrid, and the recessive trait is the one that seemingly vanishes. Mendel's own words describe his conclusions best:

> In the case of each of the 7 crosses, the hybrid character resembles that of one of the parental forms so closely that the other either escapes observation completely or cannot be detected with certainty. … The expression 'recessive' has been chosen because the characters thereby designated withdraw or entirely disappear in the hybrids, but nevertheless reappear unchanged in their progeny.

The First Generation from the Hybrids, and Beyond

The fifth section of Mendel's paper shows, repeatedly, that the dominant and recessive forms of each trait appear in a 3:1 ratio in the progeny of hybrids crossed to each other. The numbers speak for themselves in **Table 3**. Mendel showed the classic 3:1 phenotypic ratio of a monohybrid cross (one trait present in two forms, or alleles), although the terms 'phenotype' (an individual's appearance) and 'genotype' (the gene variants present) were not yet in use. This observation would become known as Mendel's first law, or the law of segregation, years later (**Figure 1**). The ratios that Mendel chronicled were actually the result of meiosis, the type of cell division that gives rise to gametes. When a sperm or egg forms, the chromosome pairs (homologous pairs), whose DNA has been replicated, separate. Likewise, the pairs of genes that comprise the chromosomes separate and are distributed into different gametes. The part of meiosis that determines the gene combinations that will enter gametes, and eventually be expressed in organisms, is called metaphase, when chromosomes align down the center of the cell.

Table 3 The 'first generation from the hybrids' experiments reveal a 3:1 dominant-to-recessive phenotypic ratio

Experiment	*Total*	*Dominant*	*Recessive*	*Ratio*
Seed form	7324	5474	1850	2.96:1
Seed color	8023	6022	2001	3.01:1
Seed coat color	929	705	224	3.15:1
Pod form	1181	882	299	2.95:1
Unripe pod color	580	428	152	2.82:1
Flower position	858	651	207	3.14:1
Stem length	1064	787	277	2.84:1
Average				2.98:1

Mendel followed crosses beyond the third generation, determining that the dominant-appearing individuals among the progeny of the hybrids had 'double signification', meaning that they were of two types. He wrote, "… of those forms which possess the dominant character in the first generation, two-thirds have the hybrid character, while one-third remains constant with the dominant character." One type bred true, always yielding the dominant phenotype in further crosses. The second type, when crossed to hybrids, produced both the dominant and recessive phenotypes. The plants that did not breed true outnumbered the other plants two to one.

Today, we call the dominant-appearing plants that are 'constant' homozygous dominant. They have two copies of the dominant allele. The hybrids, called heterozygotes, have one dominant and one recessive allele. Individuals expressing the recessive trait constitute the homozygous recessive class, and they too breed true. That is, when crossed among themselves, they yield only homozygous recessive individuals. A monohybrid cross results in a phenotypic ratio of 3:1 (dominant to recessive), and a genotypic ratio of 1:2:1 (homozygous dominant to heterozygous to homozygous recessive).

Mendel carried out crosses for four to six generations for each of the seven traits, each time self-crossing the individuals that 'bred true' (the homozygous dominants and homozygous recessives) as well as self-crossing the hybrids. When he did this repeatedly, the proportion of hybrids decreased by 50% at each generation. By the 10th generation, only two hybrids would remain for every 1023 individuals of each homozygous class.

Tracking More Than One Trait

Next, Mendel set up crosses and followed more than one trait. Again, he began with a general observation – when he crossed individuals that were hybrid for two traits, most of the offspring resembled the original parent (that gave rise to the hybrids) that had two dominant alleles, one for each gene.

Mendel's crosses involving two or more traits reveal the detail of his mathematical analyses. In one experiment, he crossed round yellow seeds (genotype *RRYY*) to wrinkled

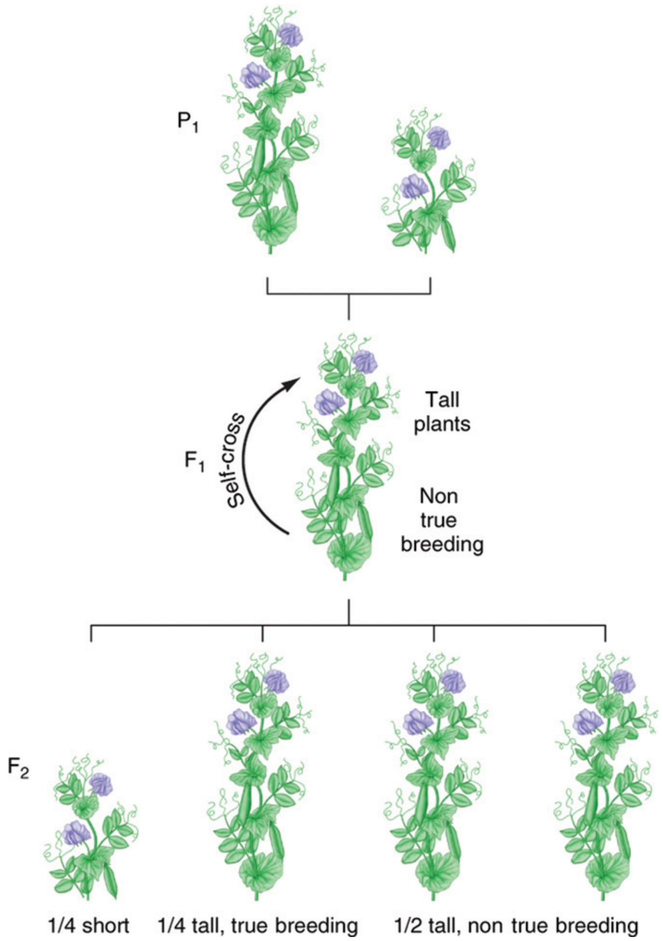

Figure 1 Mendel derived what would become known as his first law, the law of segregation, by crossing plants that 'bred true' for tall to plants that bred true for short, in the parental or P_1 generation. All the plants of the first filial (F_1) generation were tall. Allowing the F_1 plants to self-fertilize yielded an F_2 generation of plants in which tall plants outnumbered short plants three to one. By conducting further crosses of the F_2 plants to short plants, Mendel deduced the genotypic ratio in the F_2 generation to be one short to two tall non-true-breeding hybrids to one tall true-breeding. Reproduced with permission from Lewis R (2010) *Human Genetics: Concepts and Applications*, 9th edn. New York: McGraw-Hill.

green seeds (*rryy*) and obtained heterozygotes of genotype *RrYy*. (Mendel used the letters *A* and *B* to denote all traits. The round/wrinkled gene was named '*r*' in 1917, for 'rugosus'.) He then crossed the heterozygotes, and found a 9:3:3:1 phenotypic ratio of plants with the following types of seeds:

- 315 round yellow
- 101 wrinkled yellow
- 108 round green
- 32 wrinkled green

Further crosses established the genotypes of these phenotypic classes. Figure 2 shows a tool called a Punnett square that displays gene combinations from generation to generation, which can be used to demonstrate Mendel's laws. Mendel identified nine genotypic classes among the 16 combinations. There were four ways to generate offspring with both genes heterozygous (*RrYy*); two ways to produce each of four types of individuals with one gene heterozygous and the other homozygous (*RRYy*, *RrYY*, *Rryy*, and *rrYy*); and four ways to produce offspring with no heterozygotes (*RRYY*, *RRyy*, *rrYY*, and *rryy*).

Mendel deduced from the ratios of progeny classes that the different genes were inherited separately. All combinations of the variants appeared in predictable ratios. He wrote, "… the relation of each pair of different characters in hybrid union is independent of the other differences in the two original parental stocks." This observation became known as Mendel's second law, or the law of independent assortment. It, too, has its roots in meiosis. We know today that Mendel observed these results because the seven traits he studied are carried on different chromosomes. Had they not been, certain traits would have appeared together more often than predicted, because they are physically conveyed to the next generation on the same chromosome. This phenomenon is called linkage.

Mendel's Conclusions

The ninth part of Mendel's paper reads like an introduction because it was the first part of his second lecture. He related the ratios seen in his crosses to events in the pollen and eggs, writing that "… the hybrids produce egg cells and pollen cells

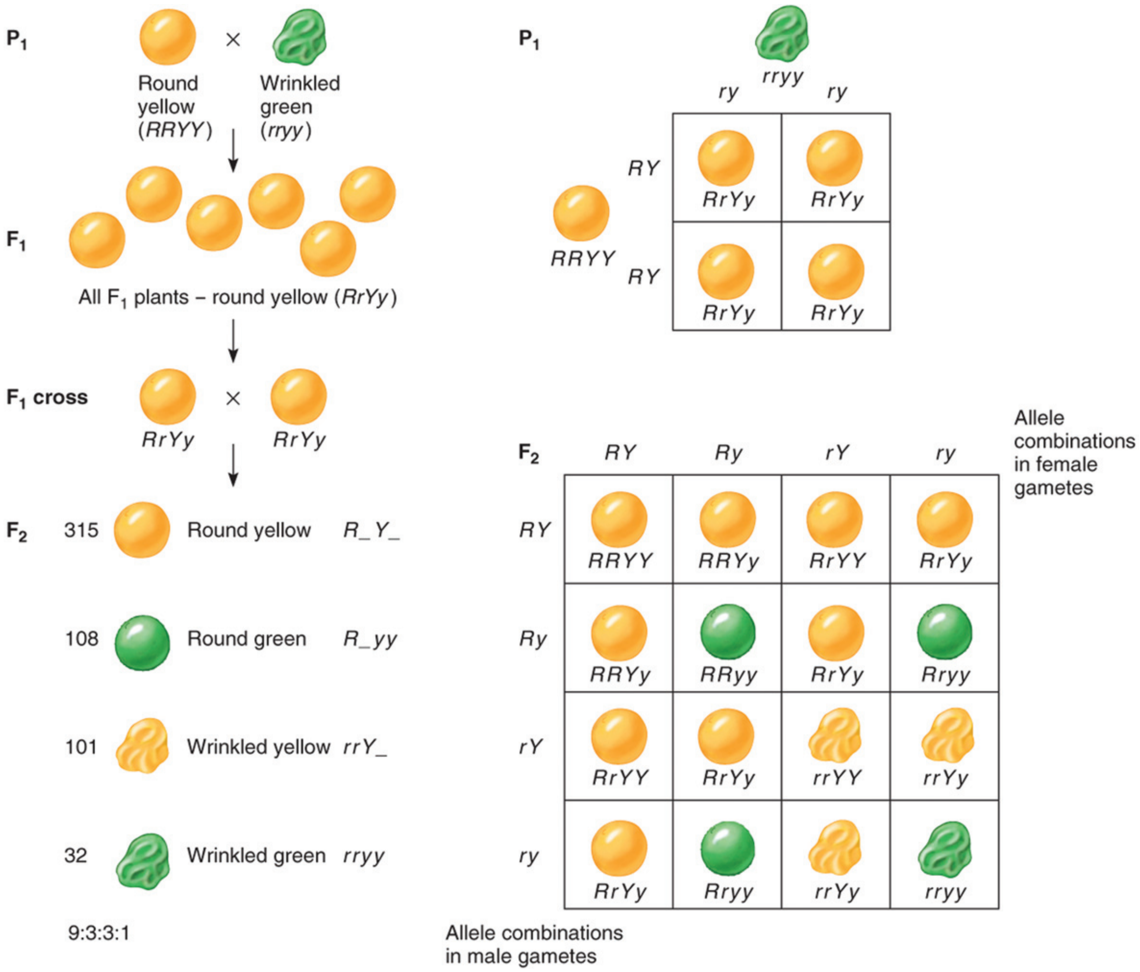

Figure 2 Mendel's dihybrid cross (*RrYy* × *RrYy*) yielded a 9:3:3:1 ratio, as shown in the Punnett Square in the lower right. P_1, F_1, and F_2 indicate successive generations. The illustrations show the phenotypes of seed color and shape. Reprinted from *Human Genetics: Concepts and Applications*, 9/e, by Ricki Lewis, figure 4.12, p. 81 (need to add art).

which in equal numbers represent all constant forms which result from the combination of the characters brought together in fertilization."

Mendel used this hypothesis to predict the outcome of a cross: round yellow dihybrids (*RrYy*) fertilized with pollen from plants that had wrinkled green (*rryy*) seeds. If the four types of gametes from the female plant (*RY*, *Ry*, *rY*, and *ry*) formed in equal numbers and were then fertilized by *ry* pollen, then four progeny classes (*RrYy*, *Rryy*, *rrYy*, and *rryy*) should appear in approximately equal numbers. They did so, as Table 4 shows.

Table 4 Gametes form in equal numbers

Parental cross	*RrYy (round yellow)*	×	*rryy (wrinkled green)*
Gametes	*RY Ry rY ry*		*Ry*
Progeny			
Phenotype	Genotype		#
Round yellow	*RrYy*		31
Round green	*Rryy*		26
Wrinkled yellow	*rrYy*		27
Wrinkled green	*rryy*		26

The 10th part of the paper details Mendel's attempts to repeat certain pea experiments with the bean plants *Phaseolus vulgaris* and *Phaseolus nanus*. Mendel concluded that the principles he had demonstrated in peas still applied, but were obscured by the complexity of pigmentation. The 11th and final section of the paper eloquently summarizes the overall findings of the experiments: "With *Pisum* it was shown by experiment that the hybrids form egg and pollen cells of different kinds, and that herein lies the reason of the variability of their offspring."

Mendel Is Ignored, Then Rediscovered

It is astounding, in retrospect, that Mendel's paper initially failed to attract attention at a time when Darwin's *On the Origin of Species* was an overnight sensation. Mendel himself sought support for his work by a frustrating correspondence with Karl Wilhelm von Nägeli, a noted Swiss botanist. Nägeli, whose thinking sometimes veered from science to mysticism, dismissed Mendel's work because he was uncomfortable with the mathematics and logic, and because it lacked speculation, according to historians of science. Noted scientist and science writer Isaac Asimov called Nägeli's harsh treatment of the sensitive Mendel his 'most far-reaching mistake', and accused him of delaying the recognition of genetics as a discipline for a full generation.

Perhaps Mendel's results were simply not as exciting or colorful as those of his contemporary, Darwin. Mendel's vision of discrete, measurable traits also did not fit Darwin's gradual view of evolution. It would be years before geneticists would understand that discrete factors can combine and interact to produce graded phenotypes.

Mendel's ideas were also ahead of the times. Before the 'golden age of cytology', it was difficult to picture a physical basis for his 'characters'. It was not until 1903 that Walter S. Sutton and Theodor Boveri independently deduced that chromosomes carry the units of inheritance, which would later come to be called genes. Mendel could not have known that the patterns of inheritance he observed reflect the apportionment of chromosomes into sex cells, because it was not until 1882 that Walther Flemming described the maintenance of chromosome number as a cell divides. The chemical nature of the gene would not be described until James Watson and Francis Crick assembled the clues contributed by many others to depict the double helix of DNA, in 1953.

As the twentieth century began, three botanists independently and unknowingly rediscovered Mendel's laws. They were the Dutchman Hugo de Vries, the German Karl Franz Joseph Erich Correns, and the Austrian von Seysenegg Tschermak. Each credited the discovery of the principles of inheritance to Gregor Mendel.

Influences on Mendelian Ratios

In the first years of the twentieth century, researchers confirmed Mendel's work in different species. However, further experimentation revealed that gene transmission is not always as clear-cut as Mendel's crosses indicated. Genes inherited on different chromosomes can yield non-Mendelian phenotypic ratios if more than two alleles are at play. Allele combinations incompatible with life appear as a missing predicted progeny class.

Other circumstances do not negate Mendel's laws, but make them more difficult to observe. For example, the actions of different genes can contribute to the same phenotype. Some effects that seem to blur Mendel's ratios reflect the fact that genes do not function alone: the actions of other genes or the environment can influence their expression. Activity of one gene can mask the effect of another. Some traits may appear to be inherited but instead reflect the exposure of several family members to the same environmental influence, such as pathogens.

A Molecular View of the Traits Mendel Studied

Researchers are turning the tools of molecular biology to some of the traits in garden peas that Mendel immortalized in his experiments. This type of investigation reveals how the phenotypes that Mendel studied arise.

In 1990, investigators at the John Innes Institute and the Agricultural and Food Research Council (AFRC) Institute of Plant Science Research in Norwich, UK, identified the protein difference that distinguishes round (*RR* or *Rr*) from wrinkled (*rr*) peas. The functional *R* allele encodes a form of starch-branching enzyme, which normally links sugars with longer carbohydrates. Developing seeds (peas) of *rr* plants lack this enzyme, so they contain many free sugars. This draws water into the cells, which swells the seeds. When the pea matures, the water exits the cells, and the seeds wrinkle. Peas of genotype *rr* also have less protein and more lipid than *Rr* or *RR* peas.

In 1997, researchers at the University of Tasmania in Australia identified the product of the *Le* gene, which determines stem length, and therefore whether a plant is short or tall. The functional allele encodes an enzyme necessary for synthesis of gibberellin, a plant hormone that elongates stems. A change in the gene (a mutation) replaces one amino acid with another in the encoded enzyme product at its active site, impairing its function. With the enzyme disabled, gibberellin is in short supply, and the plant is stunted.

Mendel's Laws Today

Mendel's laws are laws because they apply to all diploid organisms (those with two copies of each chromosome). His and others' observation that a trait can reappear in the generation following the hybrids is echoed every time a child is born with a recessive disease, but there is no recent family history of the condition. It was inherited from two carriers. Online Mendelian Inheritance in Man catalogs single-gene, or Mendelian, traits.

The most recent type of genetic study is a genome-wide association study (GWAS). Unlike Mendel, who looked at one trait at a time, a GWAS compares as many as a million sites in a genome that may vary among thousands of individuals, tracking the DNA base at each site rather than a physical trait. But Mendel's first law is still in effect. That is, these single base sites, called single-nucleotide polymorphisms (SNPs), segregate at each generation and assort independently. GWASs follow the linkage of SNPs on a chromosome, which do not segregate and assort independently. More than a century after the rediscovery of Mendel's report, his explanations are as valid as ever. That is the definition of a law – persistence.

See also: Independent Assortment; Meiosis; Mendel, Gregor; Mendelian Genetics; Mendelian Inheritance; Mendelian Population; Mendelian Ratio; Recessive; Segregation.

Further Reading

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