



# A Science Primer

National Center for Biotechnology Information

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Science Primer:

## A Basic Introduction to the Science Underlying NCBI Resources

Bioinformatics

Genome Mapping

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### WHAT IS A GENOME?

#### Mechanisms of Genetic Variation and Heredity

##### Does Everyone Have the Same Genes?

When you look at the human species, you see evidence of a process called **genetic variation**, that is, there are immediately recognizable differences in human traits, such as hair and eye color, skin pigment, and height. Then there are the not so obvious genetic variations, such as blood type. These expressed, or **phenotypic**, traits are attributable to **genotypic** variation in a person's DNA sequence. When two individuals display different phenotypes of the same trait, they are said to have two different **alleles** for the same gene. This means that the gene's sequence is slightly different in the two individuals, and the gene is said to be **polymorphic**, "poly" meaning many and "morph" meaning shape or form. Therefore, although people generally have the same genes, the genes do not have exactly the same DNA sequence. These polymorphic sites influence gene expression and also serve as markers for genomic research efforts.

##### Genetic Variation

The cell cycle is the process that a cell undergoes to replicate.

Most genetic variation occurs during the phases of the cell cycle when DNA is duplicated. Mutations in the new DNA strand can manifest as **base substitutions**, such as when a single base gets replaced with another; **deletions**, where one or more bases are left out; or **insertions**, where one or more bases are added. Mutations can

either be **synonymous**, in which the variation still results in a codon for the same amino acid or **non-synonymous**, in which the variation results in a codon for a different amino acid. Mutations can also cause a **frame shift**, which occurs when the variation bumps the reference point for reading the genetic code down a base or two and results in loss of part, or sometimes all, of that gene product. DNA mutations can also be introduced by toxic chemicals and, particularly in skin cells, exposure to ultraviolet radiation.

The manner in which a cell replicates differs with the various classes of life forms, as well as with the end purpose of the cell replication. Cells that compose tissues in multicellular organisms typically replicate by organized duplication and spatial separation of their cellular genetic material, a process called **mitosis**. **Meiosis** is the mode of cell replication for the formation of sperm and egg cells in plants, animals, and many other multicellular life forms. Meiosis differs significantly from mitosis in that the cellular progeny have their complement of genetic material reduced to half that of the parent cell.

Mutations that occur in **somatic cells**—any cell in the body except gametes and their precursors—will not be passed on to the next generation. This does not mean, however, that somatic cell mutations, sometimes called **acquired mutations**, are benign. For example, as your skin cells prepare to divide and produce new skin cells, errors may be inadvertently introduced when the DNA is duplicated, resulting in a daughter cell that contains the error. Although most defective cells die quickly, some can persist and may even become cancerous if the mutation affects the ability to regulate cell growth.

## Mutations and the Next Generation

There are two places where mutations can be introduced and carried into the next generation. In the first stages of development, a sperm cell and egg cell fuse. They then begin to divide, giving rise to cells that differentiate into tissue-specific cell types. One early type of differentiated cell is the germ line cell, which may ultimately develop into mature gametes. If a mutation occurs in the developing germ line cell, it may persist until that individual reaches reproductive age. Now the mutation has the potential to be passed on to the next generation.

Mutations may also be introduced during meiosis, the mode of cell replication for the formation of sperm and egg cells. In this case, the germ line cell is healthy, and the mutation is introduced during the actual process of gamete replication. Once again, the sperm or egg will contain the mutation, and during the reproductive process, this mutation may then be passed on to the offspring.

One should bear in mind that not all mutations are bad. Mutations also provide a species with the opportunity to adapt to new environments, as well as to protect a species from new pathogens. Mutations are what lie behind the popular saying of "**survival of the fittest**", the basic theory of evolution proposed by Charles Darwin in 1859. This theory proposes that as new environments arise, individuals carrying certain mutations that enable an evolutionary advantage will survive to pass this mutation on to its offspring. It does not suggest that a mutation is derived from the environment, but that survival in that environment is enhanced by a particular mutation. Some genes, and even some organisms, have evolved to tolerate mutations better than others. For example, some viral genes are known to have high mutation rates. Mutations serve the virus well by enabling adaptive traits, such as changes in the outer protein coat so that it can escape detection and thereby destruction by the host's immune system. Viruses also produce certain enzymes that are necessary for infection of a host cell. A mutation within such an enzyme may result in a new form that still allows the virus to infect its host but that is no longer blocked by an anti-viral drug. This will allow the virus to propagate freely in its environment.

## Mendel's Laws—How We Inherit Our Genes

In 1866, Gregor Mendel studied the transmission of seven different pea traits by carefully test-crossing many distinct varieties of peas. Studying garden peas might seem trivial to those of us who live in a modern world of cloned sheep and gene transfer, but Mendel's simple approach led to fundamental insights into genetic inheritance, known today as **Mendel's Laws**. Mendel did not actually know or understand the cellular mechanisms that produced the results he observed. Nonetheless, he correctly surmised the behavior of traits and the mathematical

predictions of their transmission, the independent segregation of alleles during gamete production, and the independent assortment of genes. Perhaps as amazing as Mendel's discoveries was the fact that his work was largely ignored by the scientific community for over 30 years!

### Mendel's Principles of Genetic Inheritance

**Law of Segregation:** Each of the two inherited factors (alleles) possessed by the parent will segregate and pass into separate gametes (eggs or sperm) during meiosis, which will each carry only one of the factors.

**Law of Independent Assortment:** In the gametes, alleles of one gene separate independently of those of another gene, and thus all possible combinations of alleles are equally probable.

**Law of Dominance:** Each trait is determined by two factors (alleles), inherited one from each parent. These factors each exhibit a characteristic dominant, co-dominant, or recessive expression, and those that are dominant will mask the expression of those that are recessive.

### How Does Inheritance Work?

Our discussion here is restricted to sexually reproducing organisms where each gene in an individual is represented by two copies, called **alleles**—one on each chromosome pair. There may be more than two alleles, or **variants**, for a given gene in a population, but only two alleles can be found in an individual. Therefore, the probability that a particular allele will be inherited is 50:50, that is, alleles randomly and independently segregate into daughter cells, although there are some exceptions to this rule.

The term **diploid** describes a state in which a cell has two sets of homologous chromosomes, or two chromosomes that are the same. The maturation of germ line stem cells into gametes requires the diploid number of each chromosome be reduced by half. Hence, gametes are said to be **haploid**—having only a single set of homologous chromosomes. This reduction is accomplished through a process called meiosis, where one chromosome in a diploid pair is sent to each daughter gamete. Human gametes, therefore, contain 23 chromosomes, half the number of somatic cells—all the other cells of the body.

Because the chromosome in one pair separates independently of all other chromosomes, each new gamete has the potential for a totally new combination of chromosomes. In humans, the independent segregation of the 23 chromosomes can lead to as many as 16 to 17 million different combinations in one individual's gametes. Only one of these gametes will combine with one of the nearly 17 million possible combinations from the other parent, generating a staggering potential for individual variation. Yet, this is just the beginning. Even more variation is possible when you

consider the recombination between sections of chromosomes during meiosis as well as the random mutation that can occur during DNA replication. With such a range of possibilities, it is amazing that siblings look so much alike!

## Expression of Inherited Genes

Gene expression, as reflected in an organism's phenotype, is based on conditions specific for each copy of a gene. As we just discussed, for every human gene there are two copies, and for every gene there can be several variants or alleles. If both alleles are the same, the gene is said to be **homozygous**. If the alleles are different, they are said to be **heterozygous**. For some alleles, their influence on phenotype takes precedence over all other alleles. For others, expression depends on whether the gene appears in the homozygous or heterozygous state. Still other phenotypic traits are a combination of several alleles from several different genes. Determining the allelic condition used to be accomplished solely through the analysis of pedigrees, much the way Mendel carried out his experiments on peas. However, this method can leave many questions unanswered, particularly for traits that are a result of the interaction between several different genes. Today, molecular genetic techniques exist that can assist researchers in tracking the transmission of traits by pinpointing the location of individual genes, identifying allelic variants, and identifying those traits that are caused by multiple genes.

The Nature of Alleles
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A **dominant allele** is an allele that is almost always expressed, even if only one copy is present. Dominant alleles express their phenotype even when paired with a different allele, that is, when heterozygous. In this case, the phenotype appears the same in both the heterozygous and homozygous states. Just how the dominant allele overshadows the other allele depends on the gene, but in some cases the dominant gene produces a gene product that the other allele does not. Well-known dominant alleles occur in the human genes for Huntington disease, a form of dwarfism called achondroplasia, and polydactylism (extra fingers and toes).

On the other hand, a **recessive allele** will be expressed only if there are two identical copies of that allele, or for a male, if one copy is present on the X chromosome. The phenotype of a recessive allele is only seen when both alleles are the same. When an individual has one dominant allele and one recessive allele, the trait is not expressed because it is overshadowed by the dominant allele. The individual is said to be a carrier for that trait. Examples of recessive disorders in humans include sickle cell anemia, Tay-Sachs disease, and phenylketonuria (PKU).

A particularly important category of genetic linkage has to do with the **X and Y sex chromosomes**. These chromosomes not only carry the genes that determine male and female traits, but also those for some other characteristics as well. Genes that are carried by either sex chromosome are said to be **sex linked**. Men normally have an X and a Y combination of sex chromosomes, whereas women have two X's. Because only men inherit Y chromosomes, they are the only ones to inherit **Y-linked traits**. Both men and women can have **X-linked traits** because both inherit X chromosomes.

X-linked traits not related to feminine body characteristics are primarily expressed in the phenotype of men. This is because men have only one X chromosome. Subsequently, genes on that chromosome that do not code for gender are expressed in the male phenotype, even if they are recessive. In women, a recessive allele on one X chromosome is often masked in their phenotype by a dominant normal allele on the other. This explains why women are frequently carriers of X-linked traits but more rarely have them expressed in their own phenotypes. In humans, at least 320 genes are X-linked. These include the genes for **hemophilia**, **red-green color blindness**, and **congenital night blindness**. There are at least a dozen Y-linked genes, in addition to those that code for masculine physical traits.

It is now known that one of the X chromosomes in the cells of human females is completely, or mostly, inactivated early in embryonic life. This is a normal self-preservation action to prevent a potentially harmful double dose of genes. Recent research points to the **"Xist" gene** on the X chromosome as being responsible for a sequence of events that silences one of the X chromosomes in women. The inactivated X chromosomes become highly compacted structures known as **Barr bodies**. The presence of Barr bodies has been used at international sport competitions as a test to determine whether an athlete is a male or a female.

## Exceptions to Mendel's Laws

There are many examples of inheritance that appear to be exceptions to Mendel's laws. Usually, they turn out to represent complex interactions among various allelic conditions. For example, **co-dominant alleles** both contribute to a phenotype. Neither is dominant over the other. Control of the human blood group system provides a good example of co-dominant alleles.

### The Four Basic Blood Types

There are four basic blood types, and they are O, A, B, and AB. We know that our blood type is determined by the "alleles" that we inherit from our parents. For the blood type gene, there are three basic blood type alleles: A, B, and O. We all have two alleles, one inherited from each parent. The possible combinations of the three alleles are OO, AO, BO, AB, AA, and BB. **Blood types A and B are "co-dominant" alleles**, whereas **O is "recessive"**. A codominant allele is apparent even if only one is present; a recessive allele is apparent only if two recessive alleles are present. Because blood type O is recessive, it is not apparent if the person inherits an A or B allele along with it. So, the possible allele combinations result in a particular blood type in this way:

OO = blood type O  
AO = blood type A  
BO = blood type B  
AB = blood type AB  
AA = blood type A  
BB = blood type B

You can see that a person with blood type B may have a B and an O allele, or they may have two B alleles. If both parents are blood type B and both have a B and a recessive O, then their children will either be BB, BO, or OO. If the child is BB or BO, they have blood type B. If the child is OO, he or she will have blood type O.

**Pleiotropism, or pleiotrophy**, refers to the phenomenon in which a single gene is responsible for producing multiple, distinct, and apparently unrelated phenotypic traits, that is, an individual can exhibit many different phenotypic outcomes. This is because the gene product is active in many places in the body. An example is **Marfan's syndrome**, where there is a defect in the gene coding for a connective tissue protein. Individuals with Marfan's syndrome exhibit abnormalities in their eyes, skeletal system, and cardiovascular system.

Some genes mask the expression of other genes just as a fully dominant allele masks the expression of its recessive counterpart. A gene that masks the phenotypic effect of another gene is called an **epistatic gene**; the gene it subordinates is the **hypostatic gene**. The gene for **albinism** in humans is an epistatic gene. It is not part of the interacting skin-color genes. Rather, its dominant allele is necessary for the development of any skin pigment, and its recessive homozygous state results in the albino condition, regardless of how many other pigment genes may be present. Because of the effects of an epistatic gene, some individuals who inherit the dominant, disease-causing gene show only partial symptoms of the disease. Some, in fact, may show no expression of the disease-causing gene, a condition referred to as

**nonpenetrance.** The individual in whom such a nonpenetrant mutant gene exists will be phenotypically normal but still capable of passing the deleterious gene on to offspring, who may exhibit the full-blown disease.

Then we have traits that are **multigenic**, that is, they result from the expression of several different genes. This is true for human eye color, in which at least three different genes are responsible for determining eye color. A brown/blue gene and a central brown gene are both found on chromosome 15, whereas a green/blue gene is found on chromosome 19. The interaction between these genes is not well understood. It is speculated that there may be other genes that control other factors, such as the amount of pigment deposited in the iris. This multigenic system explains why two blue-eyed individuals can have a brown-eyed child.

Speaking of eye color, have you ever seen someone with one green eye and one brown eye? In this case, **somatic mosaicism** may be the culprit. This is probably easier to describe than explain. In multicellular organisms, every cell in the adult is ultimately derived from the single-cell fertilized egg. Therefore, every cell in the adult normally carries the same genetic information. However, what would happen if a mutation occurred in only one cell at the two-cell stage of development? Then the adult would be composed of two types of cells: cells with the mutation and cells without. If a mutation affecting melanin production occurred in one of the cells in the cell lineage of one eye but not the other, then the eyes would have different genetic potential for melanin synthesis. This could produce eyes of two different colors.

**Penetrance** refers to the degree to which a particular allele is expressed in a population phenotype. If every individual carrying a dominant mutant gene demonstrates the mutant phenotype, the gene is said to show complete penetrance.

## **Molecular Genetics: The Study of Heredity, Genes, and DNA**

As we have just learned, DNA provides a blueprint that directs all cellular activities and specifies the developmental plan of multicellular organisms. Therefore, an understanding of DNA, gene structure, and function is fundamental for an appreciation of the molecular biology of the cell. Yet, it is important to recognize that progress in any scientific field depends on the availability of experimental tools that allow researchers to make new scientific observations and conduct novel experiments. The [last section of the genetic primer](#) concludes with a discussion of some of the laboratory tools and technologies that allow researchers to study cells and their DNA.

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