Polygenic inheritance and environmental effects

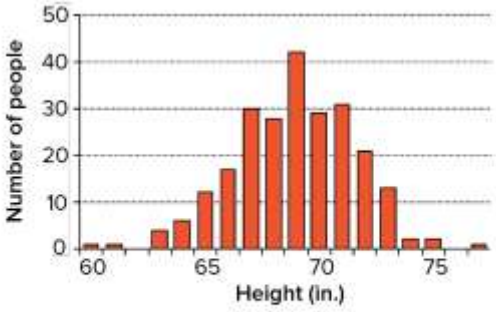
Traits that are controlled by multiple genes and/or influenced by the environment. Penetrance and expressivity.

How is height inherited?

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

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

Continuous variation. Unlike Mendel's pea plants, humans don't come in two clear-cut "tall" and "Short" varieties. In fact, they don't even come in four heights, or eight, or sixteen. Instead, it's possible to get humans of many different heights, polygenic inheritance and environmental effects and height can vary in increments of inches or fractions of inches.



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

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

Simple models involving one or two genes can't accurately predict all of these inheritance patterns.

How, then, is height inherited?

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

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

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

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

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

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

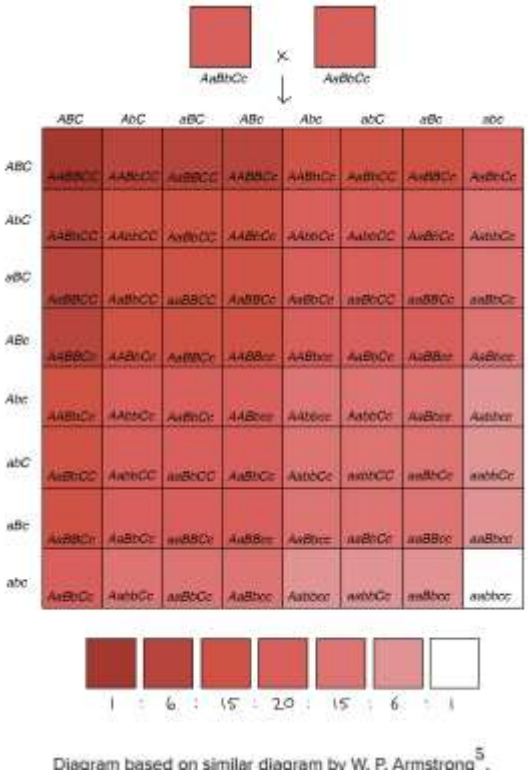


Diagram based on similar diagram by W. P. Armstrong[5].

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

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

Environmental effects

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

One striking example of how environment can affect phenotype comes from the hereditary disorder Phenylketonuria (PKU). People who are homozygous for disease alleles of the PKU gene lack activity of an enzyme that breaks down the amino acid phenylalanine. Because people with this disorder

cannot get rid of ex cess phenylalanine, it rapidly builds up to toxic levels in their bodies.

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

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

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

Variable penetrance, incomplete expressivity

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

In variable expressivity, a phenotype may be stronger or weaker in different people with the same genotype.

For instance, in a group of people with a disease causing genotype, some might develop a severe form of the disorder, while others might have a milder form. The idea of expressivity is illustrated in the diagram below, with the shade of green representing the strength of the phenotype.

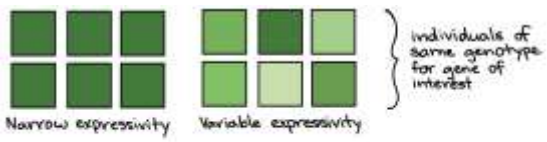


Illustration modeled after similar image by Steven M. Carr[10].

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

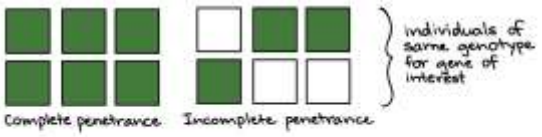


Illustration modeled after similar image by Steven M. Carr[10].

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