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Genetic Dominance & Cellular Processes

Robert D. Seager
University of Northern Iowa

FEATURE ARTICLE

Genetic Dominance & Cellular Processes

ROBERT D. SEAGER

Abstract

In learning genetics, many students misunderstand and misinterpret what "dominance" means. Understanding is easier if students realize that dominance is not a mechanism, but rather a consequence of underlying cellular processes. For example, metabolic pathways are often little affected by changes in enzyme concentration. This means that enzyme-producing alleles usually show complete dominance. For genes producing nonenzymatic proteins such as collagen or hemoglobin, the amount of product matters, and dominance relationships are more complicated. Furthermore, with hemoglobin, dominance can change depending on what aspect of the phenotype is being studied and on the environmental conditions. X-linked genes are a special case, whether enzymatic or not. Because of X-chromosome inactivation, only one X-linked allele can be active in a cell, which means that the concept of dominance cannot be applied at the cellular level. Instead, a type of dominance is demonstrated at the individual level; but even so, dominant traits may fail to be expressed, and recessive traits can be expressed. Teaching not only what is happening but why it's happening will give students a deeper understanding, not only of dominance relationships, but of the underlying cellular processes as well.

Key Words: *Dominance relationships; enzymes and structural proteins; X-chromosome genes and dominance; instruction.*

Dominance relationships are "commonly misunderstood and misinterpreted" by students learning genetics. Some believe that "dominance … depends on some mysterious, unknown and perhaps unknowable force" (Heim, 1991, p. 94). Others say that it is "based on power, strength and value," which leads to the misconceptions that *dominant* alleles *dominate* recessive alleles or that dominant alleles will naturally become more frequent in a population (Allchin, 2000, p. 633; for other examples of student misunderstandings of dominance, see Redfield, 2012; Smith, 2014a, b).

On the contrary, dominance is not a force or a power. Dominance is not a mechanism; rather, dominance relationships are a result. They are consequences of how gene products function in a cell. Understanding goes both ways – understanding dominance relationships helps students understand cellular processes, and understanding cellular processes helps students understand dominance relationships.

Dominance relationships are "commonly misunderstood and misinterpreted" by students learning genetics.

Dominance pertains only to the phenotype (observable characteristics) of a heterozygote (Table 1). It describes the relationship *between* allelic products, between products of different versions of the same gene in a heterozygous individual. Alleles by themselves do not have dominance; dominance/recessiveness is not built into our DNA. Referring to an allele *by itself* as dominant or recessive is misleading and can hamper understanding. In addition, dominance relationships apply only to a single gene; one gene cannot be dominant to a different gene, even though it may alter or even suppress the function of that gene.

I will discuss three types of dominance relationships here: (1) complete dominance (or being haplo-sufficient); (2) incomplete dominance (or being haplo-insufficient); and (3) the interesting and unusual case of X-chromosome genes. Table 2 explains the mechanisms underlying complete and incomplete dominance. Although the following examples are restricted to humans, the same principles apply to all diploids, with the exception of X-linked genes in organisms such as *Drosophila*, in which X-chromosome inactivation does not occur.

○ Genes That Code for an Enzyme: Complete Dominance

We often study traits in which different genotypes produce obvious and noticeably different phenotypes, as with albinism, Tay Sachs disease, phenylketonuria, and many others. For these, there is complete dominance because a single functional allele is sufficient to produce the nondisease phenotype (Table 2). This relationship is common in genes that code for enzymes, as in the three examples above (Lanza & Cress, 2001).

Students could be asked what this tells us about enzymes. First, it emphasizes that enzymes, by their nature, are not used up

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Table 1. Genes and alleles. The terms *gene* and *allele* are often used incorrectly. For example, there is no cystic fibrosis gene; instead, there is a gene that codes for a protein that regulates sodium and chloride transport across epithelial cell membranes. An individual with two altered or nonfunctional versions (alleles) of this gene has cystic fibrosis.

Gene	The unit of heredity; all genes discussed here code for a polypeptide/protein.
Alleles	Different versions of the same gene; genes have many alleles.
Homozygote/homozygous	The two alleles are the same (homo).
Heterozygote/heterozygous	The two alleles are different (hetero).

Table 2. Gene action and dominance. "A1" and "A2" are used for the alleles because using "A" and "a" is appropriate only when there is complete dominance.

Alleles	A1	Produces a functional product/protein
	A2	Produces a nonfunctional product or no product at all
Genotypes	A1 A1 homozygote	Produces functional product
	A1 A2 heterozygote	Produces about half as much functional product as A1 A1
	A2 A2 homozygote	No functional product (or no product at all) produced

Notes: Dominance pertains to the phenotype of the heterozygote. Complete (or full) dominance describes the situation when the heterozygote and the A1 A1 homozygote have the same phenotype. This happens if "about half as much functional product" is enough for full functioning. Since only one functional allele (A1) is sufficient for full functioning, this can also be called **haplo-sufficient** (= **"one allele is sufficient"**). If "about half as much functional product" is not enough for full functioning, the heterozygote will have a different phenotype than either homozygote. This is incomplete dominance; the functional allele (A1) is **haplo-insufficient**.

during a reaction. From this, it follows that in many cases, not a lot of enzyme is necessary for proper functioning, given that decreasing the amount of available enzyme by half has no effect. An overall conclusion is that enzymatic (metabolic) pathways in general are not particularly sensitive to changes in enzyme concentration. But what about proteins that are not enzymes and that are needed in large quantities, such as collagen and hemoglobin (Wilkie, 1994)?

○ Genes That Do Not Code for an Enzyme: When the Amount Matters

Type I Collagen

There are many collagen genes and many different collagen proteins. Collagens hold our bodies together ("collagen" means "glue producing"); for example, collagens are essential components of bones and tendons. A critical collagen is Type I, the major component of connective tissue and the most abundant protein found in humans (Prockop & Kivirikko, 1995).

Collagen is also the largest, most complex macromolecule found in humans. The Type I collagen genes are correspondingly large, and they frequently mutate as a consequence, leading to >300 known connective-tissue disorders in humans (Di Lullo et al., 2002). A single Type I collagen disorder, osteogenesis imperfecta (see below), is associated with >800 independent mutations (Marini et al., 2007). What is the effect of these mutations?

Type I collagen is a structural protein that helps support the body, just as beams and columns provide structural support for a building. (Enzymes, by contrast, are analogous to building tools, like hammers and saws, which are reused many times.) What would happen if there were no structural support at all? There would be no building, and no body. Homozygotes that lack any functional Type I collagen do not survive. Heterozygotes produce about half of the structurally sound columns and beams the building (body) needs (see Table 2); the other half is either missing or defective (the mutated Type I collagen allele either makes no product at all or makes a defective one). Students should expect dire consequences in this case.

What does this predict about dominance relationships, about the phenotype of the heterozygote? The amount of functional protein matters; a Type I collagen heterozygote should be affected. The fragile-bone disorder osteogenesis imperfecta Type I is an example of this; the body is unsound and may even collapse – some Type I collagen mutations are lethal (Marini et al., 2007). For further information on Type I collagen and human genetics in general, see Online Mendelian Inheritance in Man (http://www.omim.org).

Hemoglobins: An Overview

Hemoglobin consists of two different proteins and is thus the product of two different genes; in adults, these are the hemoglobin α and hemoglobin β genes. Adult hemoglobin ($\alpha_2\beta_2$) consists of two copies of each protein. Three other functional hemoglobin genes in humans, γ, δ and ε, are variants of the β gene – $\alpha_2\varepsilon_2$ appears in the embryo, $\alpha_2\gamma_2$ in the fetus, and $\alpha_2\delta_2$ comprises a small portion of adult hemoglobin (Barton et al., 2007, and accompanying website).

A good question for students is "Why are there so many hemoglobins?" More precisely, "What are the differences among the different hemoglobins, and are these differences appropriate for their different developmental environments?" For example, $\alpha_2\gamma_2$ (fetal hemoglobin) has a slightly higher affinity for oxygen than the adult hemoglobin ($\alpha_2\beta_2$) that later replaces it. How is this difference tied to the different oxygen needs of the fetus versus the adult?

Fetal hemoglobin's higher affinity for oxygen helps the fetus by making oxygen transport across the placenta more efficient

(Elmissbah & Abdalla, 2012). Outside of the uterus, this can cause problems. If the amount of oxygen in the body is low (hypoxia), fetal hemoglobin is harmful. Because it holds onto its oxygen more strongly than adult hemoglobin, fetal hemoglobin would release less oxygen to the body to counter the hypoxia.

A further, seemingly simple question: Can any vertebrate survive without hemoglobin? All vertebrates require oxygen, and all vertebrates started out with hemoglobin. Are there conditions in which hemoglobin actually became harmful and was selected against?

Surprisingly, yes: There is a group of fish living in very cold Antarctic waters. Under these conditions, hemoglobin would make the blood too viscous (too thick) and thus extremely hard to circulate. A good analogy is how slowly syrup kept in the refrigerator (the "Antarctic") pours, compared with syrup kept at room temperature. Indeed, it was selection against hemoglobin and for reduced blood viscosity that allowed these fish to expand into and inhabit Antarctic waters in the first place (di Prisco et al., 2007 [more technical]; Carroll, 2009 [less technical]). In every other case, as with Type I collagen, survival is impossible without hemoglobin; having no hemoglobin at all is lethal.

β hemoglobin & sickle cell anemia

The β hemoglobin variant associated with sickle cell anemia (Medzhitov et al., 2012) is well known and displays complex dominance relationships. The sickle cell allele codes for an altered, less functional β hemoglobin ("S"), and as with Type I collagen, the amount of fully functional β hemoglobin ("A") matters (Table 3).

Homozygosity for the altered β hemoglobin (SS; sickle cell anemia) causes severe health risks and is often lethal: in sub-Saharan Africa, an estimated 50–80% of individuals with sickle cell anemia die before adulthood. The World Health Organization estimates that 70% of these deaths could be avoided by the use of simple, cost-effective intervention strategies available in countries such as the United States, where up to 94% of individuals with sickle cell anemia survive to at least 18 years of age (Makani et al., 2011).

Students can be challenged to explain why S hemoglobin is such a problem. A good way to start is to compare the chemical composition of A versus S hemoglobin. As is well documented, there is only a single amino acid difference: Glutamic acid in the fully functional A molecule has been replaced by valine in the S variant. Why is this change so significant?

First, the relevant amino acid is exposed on the surface of the hemoglobin molecule. This means that it can interact both with the aqueous cellular environment and with other hemoglobin molecules. Second, the glutamic acid side group in the nonmutated A hemoglobin ends in carboxylic acid (–COOH). Since acids are soluble in water, A type hemoglobin is water soluble or hydrophilic ("water loving").

By contrast, valine, its replacement in S hemoglobin, ends with non-water-soluble methyl groups ($-CH_3$). Thus, S hemoglobin is less water-soluble or hydrophobic ("water hating") and, therefore, harder to move around within the cell than A hemoglobin (Mosby, 2009).

This amino acid difference is not much of a problem when S hemoglobin is carrying oxygen. However, when the oxygen is released, both S and A hemoglobin molecules change shape, exposing a formerly hidden and hydrophobic part of the molecule.

This is not a problem with the hydrophilic A hemoglobin, but it is with S hemoglobin. The hydrophobic valine of S hemoglobin is attracted to the newly exposed hydrophobic part of adjacent hemoglobins. This continues until insoluble, and unusable, clumps of hemoglobin are formed within the red blood cells (RBCs). An excellent illustration of this is on a website maintained by the University of Wisconsin (2012).

The consequence for SS homozygous individuals is sickle cell anemia, in which the oxygen-carrying capacity of RBCs is greatly reduced. Making things worse, S hemoglobin releases its oxygen more easily, and thus changes shape more easily, than A hemoglobin (Riggs & Wells, 1961). Therefore, in SS people, the clumping problem will happen fairly quickly. The RBCs become distorted and relatively inflexible, and some become sickle shaped. Students can be directed to an excellent website created by Harvard University (2002), which helps explain this situation.

The consequences are more complicated for heterozygous individuals (AS – sickle cell trait). Questions of dominance pertain to the phenotype of the heterozygote (see Table 2). It is critical to remember, when studying dominance relationships, that phenotypes result from a combination of genetic and environmental influences. AS heterozygotes provide a good example of this. When oxygen levels are sufficient, a single functional allele (A) is enough to supply the body with adequate oxygen; A is dominant to S.

This situation reverses for AS heterozygotes when there is less oxygen in the air because of high altitude, a higher metabolic need for oxygen because of physical exertion, or both. In these cases, there is not enough fully functional A hemoglobin to supply the body with adequate oxygen, and S becomes dominant to A. The problems associated with the S allele occur as they do in SS homozygotes; hemoglobin is less likely to be fully oxygenated, hemoglobin aggregates are more likely to form, and many of the red blood cells sickle. A heterozygous individual experiences symptoms similar to sickle cell anemia (see Table 3).

This environmentally altered phenotype is a serious public health issue. Sickle cell trait (AS) is often undiagnosed unless a problem occurs, and this has led to military recruits dying during basic training (Eckart et al., 2004) and athletes dying during intense workouts (Eichner, 2007). Recently the National Athletic Trainers' Association issued a position statement on preventing sudden death in sports, including appropriate standards for working with athletes with sickle cell trait (Casa et al., 2012).

The harmful effects of high altitude and physical exertion were experienced by Ryan Clark, a defensive back with the Pittsburgh Steelers football team. Clark has the sickle

Table 3. "A" is fully functional β hemoglobin. This can be confusing; "A" has nothing to do with α hemoglobin. "S" is sickle cell β hemoglobin.

Genotype	Phenotype
AA	No problems with hemoglobin (no sickle cell problems)
AS	*Sickle cell trait:* sickle cell problems under oxygen stress, otherwise OK
SS	*Sickle cell anemia:* severe sickle cell problems in all environments

cell trait (AS), and in 2007, he played football at the high-altitude Mile High Stadium in Denver, Colorado. The consequences were devastating. Clark almost died and had to have his spleen and gallbladder removed (Quick, 2012).

Table 4. The effect of malaria on people with different β hemoglobin genotypes (this is an extension of Table 3).

Genotype	Phenotype
AA	No problems with hemoglobin (no sickle cell problems), no increased resistance to malaria
AS	*Sickle cell trait:* sickle cell problems when oxygen levels are low, otherwise OK; increased resistance to malaria
SS	*Sickle cell anemia:* severe sickle cells problems in all environments; probably some resistance to malarial infections but not to malaria itself

Hemoglobin, sickle cell, & malaria

There is a further complication. The reason for the relatively high frequency of S, the sickle allele, is that AS heterozygotes have an increased resistance to malaria. In malarial environments (which typically occur at low altitudes), S is dominant to A for malarial resistance (the AS heterozygote is more malarial resistant than the AA homozygote). By contrast, S is recessive to A for sickle cell anemia unless there is significant physical exertion (given that the altitudes are low; Table 4).

What about SS homozygotes? If one S allele offers protection against malaria, wouldn't two of them be even better? The answer is paradoxical: A 5-year study in Tanzania found that individuals with sickle cell anemia (SCA) indeed had lower levels of the malarial parasite than individuals without SCA, but SCA individuals were at a higher risk for severe anemia and death than those without SCA (Makani et al., 2010).

The best explanation of this paradox is that individuals with SCA do have some protection from malarial infection (lower parasitemia). However, because of their generally weakened condition, they have a much lower tolerance for malaria itself. In addition, malaria itself can cause anemia, greatly worsening the anemia already present.

To summarize, the β hemoglobin sickle allele (S), when homozygous, is both harmful and, in malarial regions, somewhat helpful, because it apparently confers some resistance to malaria. However, the benefits of this resistance are overshadowed by the greater vulnerability of SS homozygotes to the effects of malaria. When paired with a functional β hemoglobin allele (AS), S is beneficial in malarial regions, neutral if malaria is absent, and harmful if the individual is undergoing oxygen stress.

○ X-linked Genes: A Special Case

In mammals, both males and females have only one active (functional) X chromosome per cell. Although this occurs no matter how many X chromosomes are present (e.g., in XXX or XXY individuals), the following discussion is restricted to XX females and XY males. If an XX female is genetically heterozygous, in each of her cells only one of her two X-linked alleles is expressed. The other X chromosome coils up and becomes inactive (i.e. becomes a Barr body).

This happens independently in each initial cell, which means that some cells will have one of the alleles inactivated and other cells will have the other allele inactivated. Heterozygous females thus have two different cell populations. This initial inactivation happens only once, and which allele is inactive is stably inherited. All future cells will have the same active (expressed) and inactive (not expressed) X chromosome (and X-linked allele) as the initial cell.

Remember that dominance relationships are a function of the phenotype of a heterozygote (see Table 2). X-linked heterozygotes do not exist at the cellular level because both alleles are not expressed; therefore, traditional dominance relationships for X-linked genes do not exist either.

Even though no single cell is functionally heterozygous, an XX female can be heterozygous as a whole, but with a crucial difference. In an autosomal (non-sex-chromosome) heterozygote, if one allele is defective, every cell will produce functional product. In an X-linked heterozygote, if one allele is defective and the other functional, the consequence of X-chromosome inactivation is that some cells will produce only the functional product, whereas other cells will produce only a defective product or no product at all.

There is another important consideration. Human X-chromosome inactivation occurs very early in development, when the embryo has few cells (Lyon, 2002). In a heterozygote, which X chromosome/allele is inactivated in any given cell is random, but random does not necessarily mean equal, especially when the sample size is small. Students can visualize this with sets of 20 coins, corresponding to X-chromosome inactivation at the 20-cell stage. Each coin represents a cell, and the two sides of the coin represent the different alleles – the coin is "heterozygous." When flipped, only one allele (one side) is seen; the face-down side represents the inactivated allele in the Barr body.

Students could be asked how often they expect an equal number of heads and tails – this can help them understand probability. The different sets of coins will display different patterns, and – perhaps surprisingly – seldom will there be an equal number of heads and tails. The coins will be binomially distributed; using this distribution, it can be calculated that only 18% of the time will there be an equal division of coins/cells.

The consequences of this can be observed in Lesch-Nyhan syndrome. Lesch-Nyhan is the result of a defective allele of an X-linked enzyme-producing gene involved in purine metabolism. Because males have only one X chromosome, affected males will show symptoms, the severity of which depends on the specific nature of the mutation. More than 300 different disease-associated mutations have been identified (Torres et al., 2013). The least affected individuals build up uric acid, and the associated gout can be successfully treated. Lesch-Nyhan syndrome is the most severe manifestation – which, in addition to the buildup of uric acid, involves poor muscle control, mental impairment, and self-mutilation. While the uric acid problem is amenable to treatment, the cause of the neurological problems is poorly understood, and effective treatments do not exist (Torres et al., 2012).

As far as females are concerned, recall that a single functional allele of an enzyme-producing gene is most often completely dominant over a nonfunctional allele (see Table 1). Because males with a

single functional allele do not show symptoms, it might be expected that the same is true for females – while homozygous females should be affected, heterozygous females with their single functional allele should not be.

But they often are. Because the gene is X-linked, some cells will produce functional enzyme and others will not. Remind students of the skewed ratios frequently produced when 20 coins are flipped; if the ratio is skewed toward cells that do not produce functional enzyme, heterozygous females can be affected.

A particularly instructive case involves identical twin (monozygotic) females, one of whom is clinically normal while the other has Lesch-Nyhan. The twins are identical in their DNA and identical in their genotypes – both are heterozygous for the same mutation (De Gregorio et al., 2005), so something else must be happening.

Students with a good understanding of the material should be able to explain this finding. X-chromosome inactivation, even in genetically identical twins, is different in each of them because it is random. The affected twin had a skewed pattern of inactivation in which the chromosome carrying the functional allele was preferentially inactivated; the unaffected twin had the opposite.

What about a nonenzymatic X-linked structural protein such as dystrophin, the lack of which causes muscular dystrophy? Dystrophin is part of the cell membranes of striated muscle fibers (Campbell & Kahl, 1989). It helps link muscle cells to the extracellular matrix, thereby helping maintain muscle integrity (Ibraghimov-Beskrovnaya et al., 1992). Unlike Type I collagen, in which the amount of product matters, a single functional allele produces enough dystrophin for full functioning, as shown by males who have a single functional allele but not muscular dystrophy.

Heterozygous females with some degree of muscular dystrophy are relatively common. Dubowitz in 1960 described ~40 such heterozygous females (by contrast, only a few heterozygous females have been identified with Lesch-Nyhan syndrome). As with Lesch-Nyhan, in a pair of identical (monozygotic) twin girls, one twin had muscular dystrophy whereas the other did not (Richards et al., 1990). Many, but not all, of the muscle fibers in the twin with muscular dystrophy lacked dystrophin.

This illustrates another complication when considering females heterozygous for X-linked genes. During differentiation, different cell lineages lead to different structures. When X-chromosome inactivation occurs, not only can the overall ratio be skewed between cells expressing and cells not expressing the functional allele, but there can be different ratios in different parts of the body. For example, if most of the cells destined to become muscle fibers have a highly skewed ratio, with an even greater frequency of cells unable to make dystrophin, the muscular dystrophy symptoms will be even more severe.

This can also be illustrated with sets of 20 coins. Recall that the two sides of the coin represent the two different alleles, and when the coin is flipped, only one allele (one side) is seen; the face-down side represents the Barr body. Now (without looking) separate out five or six of these as muscle progenitor cells and look at the ratio; it may be the same as the overall ratio, but it also might be skewed toward more or fewer functional alleles.

○ Conclusions

Biology (and science in general) can be mysterious (and boring) if students do not adequately understand the mechanisms underlying what they are studying. As teachers, we need to go beyond *what* is happening and teach *why* it's happening. Unfortunately, biology can be taught as a "what subject" – as a memorization of facts without appropriate context.

It is important to remember that concepts come first and terms later; terms enable us to talk about concepts, but they are secondary to understanding the concepts themselves. For example, a student who can diagram cell division but cannot name the different stages knows most of what is necessary for a good understanding of cell division. A student who has memorized the names of the stages but cannot draw cell division knows nothing of worth about the process.

Such is the case with dominance relationships – they can seem like magic (Heim, 1991). Understanding the *why* of dominance requires understanding the underlying genetic/cellular processes, such as the distinction between enzymes and structural proteins and the effects of X-chromosome inactivation. Students will then understand that dominance relationships are the *consequence* of cellular processes and, as such, are themselves understandable.

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ROBERT D. SEAGER is a Professor of Genetics and Evolutionary Biology in the Department of Biology at the University of Northern Iowa, Cedar Falls, IA 50614; e-mail: seager@uni.edu.