FEATURE ARTICLE

It's Not Your Grandmother's Genetics Anymore! (Part 2)

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Abstract

In a companion article, I discussed recent developments in genetics and the inadequacies of eight common claims made by biology teachers, followed by suggested replacement language for those statements. In the present article, I address nine more claims, about such topics as whether or not most human characteristics are inherited as simple Mendelian traits (determined by one gene with a dominant and a recessive allele), problems with the Central Dogma of Biology, misunderstandings about the inheritance of traits such as eye color, the relative importance of genetics versus the environment, "genes FOR" language, and junk DNA.

Key Words: *Genetics; genomics; non-Mendelian inheritance; epigenetics; genetic determinism; junk DNA.*

In the companion article in last month's *ABT*, I discussed recent developments in genetics and the inadequacies of common statements made by biology teachers, followed by suggested replacement language for these statements. Here, I address more genetics issues raised by current research.

> *Students need to understand that genes with multiple alleles, not simple pairs of alleles, are the typical case, not the exception.*

A Quick Genetics Quiz

Take the quick True/False quiz in Table 1. Some may be tricky, so read carefully. Once you have answered an item, don't go back to it because of what you read in a later item.

(*You will find the answers in the next paragraph. Don't peek! No one is grading you.*)

All these statements are FALSE in one way or another, but we have all made some of these statement in the classroom – or at least said something similar. Let's look at the difficulties in these statements individually.

1. Most genes have two alleles.

Most biology textbooks first present the simple Mendelian (monogenic, two-allele) case, and students somehow get the idea that genes with only two alleles are typical. Genes with multiple alleles such as the ABO blood system are presented, but only as the exception. In fact, most genes have many

Table 1. True/false quiz.

	Statement	True	False
1.	Most genes have two alleles.		
2.	Brown eye color is dominant to blue eye color.		
3.	The brown-eye gene codes for a brown pigment, and the blue-eye gene codes for a blue pigment.		
4.	Two blue-eyed people cannot have a brown-eyed child.		
5.	One gene can produce one, and only one, polypeptide.		
6.	Dominant traits are usually the most common in a population.		
7.	Most alleles are Mendelian dominants or recessives.		
8.	The gene for phenylketonuria (PKU), a serious genetic disorder that causes the accumulation of phenyl ketones in the urine, codes for phenyl ketones.		
9.	Most of the human genome is "junk DNA" (i.e., it is not transcribed and has no function).		

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different alleles. It should be simple to see this. Consider a gene determined by 700 codons. Isn't it possible that mutations in any of those codons could potentially result in the insertion of abnormal amino acids that could have varying impacts on the resulting phenotype? As an example, the human *PAH* gene involved in phenylketonuria (PKU), is known to have at least 67 different alleles (Online Mendelian Inheritance in Man, 2013). Students need to understand that genes with multiple alleles, not simple pairs of alleles, are the typical case, not the exception. (Teachers, of course, must always ensure that students understand that any one normal diploid *individual* can have only two alleles – one on each homologue.)

Replacement Language

Most genes have multiple alleles.

2. Brown eye color is dominant to blue eye color.

Eye color is one of the most commonly used examples of simple Mendelian inheritance in primary and secondary school genetics. Even a cursory examination of your own eyes in the mirror is likely to suggest that this statement is not true, however. Eye-color inheritance is not so simple (see Figure 1). First of all, the iris of the eye is clearly NOT a single color. Second, some people have one blue eye and one brown eye. Third, what about other colors such as hazel and green?

And if you look more carefully, you'll see that eye color comes in many shades along a continuum from pale blue to almost black. An excellent series of photographs of the range of variation in iris colors is found in Sturm and Frudakis (2004). Even a careful look at varieties of the garden pea – Mendel's choice of organism to study – shows not a dichotomy between smooth and wrinkled seeds, but a continuum of variation from one extreme to the other. An excellent photograph showing peas along this continuum can be found in Weldon (1902). (Much is now known about the molecular basis of the smooth/wrinkled trait; see Jamieson & Radick, 2013.) Students typically have an implicit understanding that human traits (such as height and weight) tend to exhibit such gradations of variability, not dichotomous extremes (Dougherty, 2009), and comparing the classical understanding with the molecular understanding can be a very interesting classroom activity.

In any case, wherever there is gradation in the phenotype, the trait is likely to be polygenic (and perhaps also multifactorial). So it is with human eye color, which is determined by how much melanin (the pigment in the eye and skin) is present and by the packaging and quality of the melanin.

Replacement Language

Eye color is a polygenic trait and is therefore not an example of simple Mendelian inheritance.

3. The brown-eye gene codes for a brown pigment, and the blue-eye gene codes for a blue pigment.

4. Two blue-eyed people cannot have a brown-eyed child.

There is no blue pigment in the eye. In people whose irises contain little or no melanin, minute protein particles in the iris reflect the short blue wavelengths to the surface of the iris, making the iris appear blue to the observer. This is, of course, why albino individuals have blue eyes even though their irises have little or no melanin.

There are, in fact, two known forms of melanin in the melanosomes (pigment-bearing cells) of the iris, eumelanin (brown-black) and pheomelanin (a red-yellow pigment), and the catalytic conversion pathway from tyrosine and DOPA into these forms of melanin is known to involve several different enzymes (Figure 2; Sturm & Frudakis, 2004). Each enzyme is coded by a different gene, and

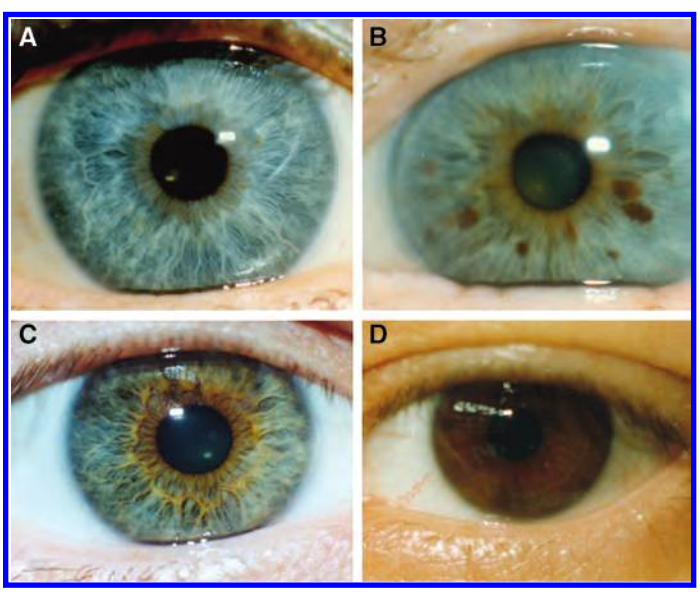

Figure 1. Different eye-color phenotypes. (A) Blue without brown areas. (B) Blue with brown spots. (C) Brown-green/hazel. (D) Brown. Reproduced with permission.

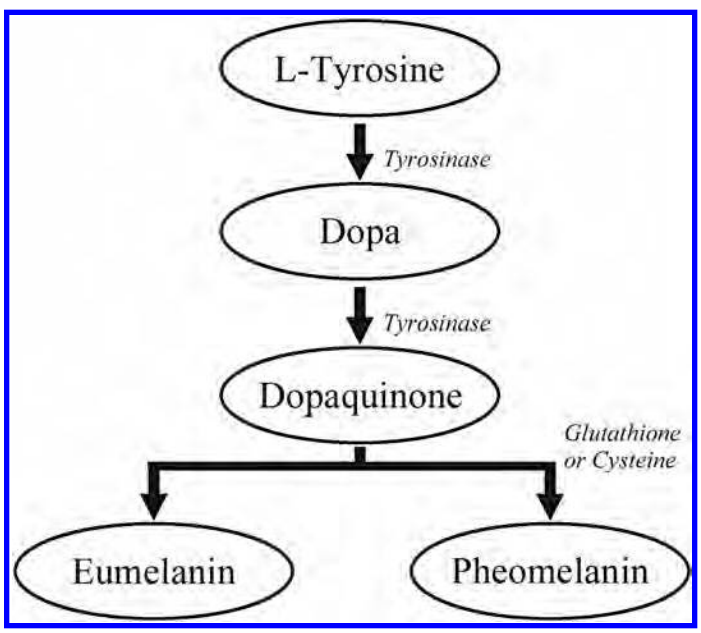

Figure 2. L-tyrosine pathway to eye color. Reproduced with permission.

mutations in any one of these could potentially result in a change in the color of the iris. Sturm and Frudakis (2004) reported at least 15 different proteins (from 15 different genes) that influence the color of the iris in humans. That is to say, we know iris color to be polygenic, and many if not all of these genes are likely to have multiple alleles. Unusual combinations of various alleles of these genes have been reported (in cases where paternity was not in question) to result in the birth of a dark-eyed child from two individuals with blue eyes!

Replacement Language

Human eye color is polygenic. Although it is rare, if mutations in different eye-color genes are involved, two blue-eyed parents can produce a brown-eyed child.

5. One gene can produce one, and only one, polypeptide.

This claim, which is a partial restatement of the "Central Dogma of Biology," is also inconsistent with modern genetic understanding. The Central Dogma (Figure 3) is usually interpreted to mean that information flows from DNA to RNA to protein and not in the reverse direction. The Central Dogma, as originally formulated, was "not only too simple, but also did not begin to do justice to the wealth of possibilities this molecule [DNA] actually offers" (Keller, 2010). Today we know of many exceptions. For example, certain viruses (like HIV) have RNA genomes that are transcribed "in reverse" to make DNA copies when they enter a host cell. (For more on conceptual difficulties with the Central Dogma, see Smith & Adkison, 2010.)

The bigger problem with this particular statement, however, is the "one and only one" phrase. There are, in fact, several ways that genes can make more than one polypeptide. The common occurrence

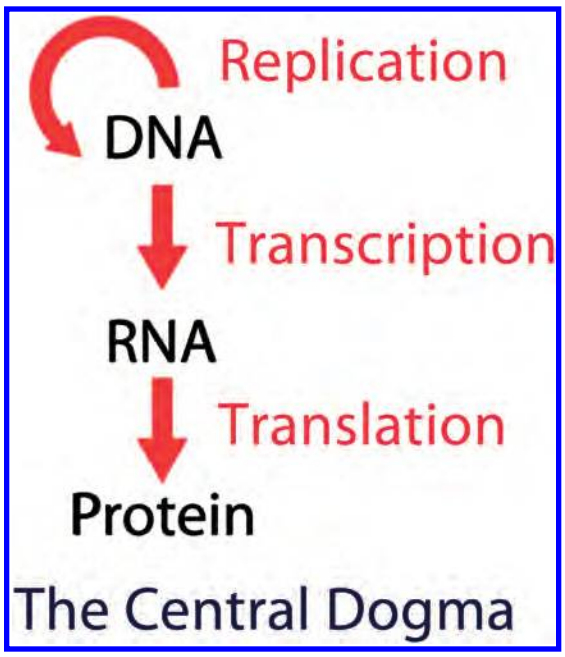

Figure 3. The (outdated) Central Dogma of Biology (modified from Anderson Lab, 2013).

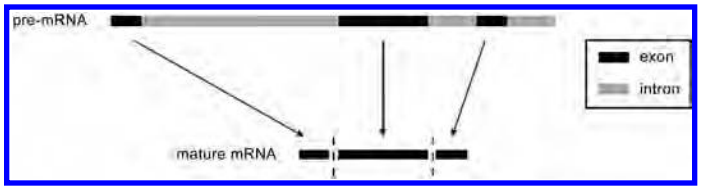

Figure 4. RNA transcript being processed to remove exons. Reproduced with permission.

of splicing together exons in mRNA was mentioned in the previous article (see Figure 4). Geneticists have discovered that this splicing is not identical every time a transcript is spliced. Sometimes, different introns are removed, producing different proteins (e.g., the gene that codes the human thyroid hormone calcitonin; Leff et al., 1986). Sometimes the splicing does not involve exactly the same point at a given exon–intron junction. If the mRNA produced has one or two additional bases, a nonfunctional molecule will of course be produced, but if the triplet nature of mRNA is maintained, this "alternative splicing" will produce proteins that have slightly different amino acid sequences. Each is a slightly different polypeptide and thus may function differently.

Remember now that introns must be spliced out of the RNA transcript in order for it to be translated. So, splicing itself is not some sort of exceptional event. And, surprisingly perhaps, the phenomenon of alternative splicing is also common. Recent studies have shown that fully 95% of human multi-exon genes are alternatively spliced (Pan et al., 2008).

Splicing also occurs at the DNA level. Splicing out different DNA fragments in different copies of the genes that code human antibodies explains, in part, why so few copies of such genes can produce the multitudes of different antibodies that make our immune system successful against the plethora of possible antigens we encounter. One gene can also consistently produce a given protein at one time and a different protein after a new (somatic) mutation in the gene, a phenomenon known as "class switching" in antibody-producing genes (Market & Papavasiliou, 2003).

Replacement Language

One gene typically codes for one polypeptide, but splicing in mRNA or DNA can result in the production of different polypeptides from a single DNA sequence.

Remember: Alternative splicing is a common occurrence, not the exception, and is therefore important for understanding genetics.

6. Dominant traits are usually the most common in a population.

7. Most alleles are Mendelian dominants or recessives.

These statements are examples of a common misconception. The error likely stems from the vernacular association of the word "dominant" with "strong" or "overpowering" (Figure 5). Add that to the misunderstanding of "survival of the fittest" as survival of the strongest, and the obvious (incorrect) conclusion is that dominant traits are more likely to survive and, thus, become the most frequent (Offner, 2011).

Figure 5. Strength.

In the same vein, a typical presentation of Mendelian inheritance can lead students to believe, not only that most traits are monogenic, but also that most alleles are dominant or recessive. In fact, we now understand that simple Mendelian dominance is the exception, not the rule, in nature.

These misunderstandings can be made clear by considering common recessive traits such as O blood type (the most common blood type). Of course, discussion of the ABO blood system is a common feature of introductory genetics instruction, but as noted above, this trait is typically presented as an example of multiple alleles (with codominance between two) and as an exception to Mendelian monogenic/dominant traits. What is needed is a presentation that makes it clear that few traits follow the simple dominance inheritance pattern. In addition, the fact that the homozygous recessive genotype is the most common is rarely, if ever, noted. Discussion of how this can be true will help address the confusion over dominance and prevalence.

Students (and even teachers) may harbor these misconceptions, and, as with most misconceptions, the person may not be aware of it. When the teacher is aware that students may have a misconception, she can ask about it, address it directly, and give clear counterexamples. This approach can be an effective strategy for teaching about genetics and evolution.

Replacement Language

The frequency of an allele in a population is not related to its mode of inheritance. Most alleles are not simple Mendelian dominants or recessives.

8. The gene for phenylketonuria (PKU), a serious genetic disorder that causes the accumulation of phenyl ketones in the urine, codes for phenyl ketones.

As discussed in the companion article, this language is deterministic – it ignores epigenetic influences. Thus, "gene for" should be "allele that codes for." But there is another, more serious, problem here. We often assume that an allele codes for a protein that results in the phenotype: pp codes for phenylketonuria, and aa codes for albinism – but again, this is only shorthand. It is important to remember that what we typically know as a "genetic disorder" is caused by a mutation that *damages* a protein with a normal function, not by the (normal) gene itself. Otherwise, for example, why would humans have genes "for cancer" or "for PKU"? Such statements make no sense and, again, may confuse students.

Consider PKU. One of three recognized forms of PKU is determined by a mutation in phenylalanine hydroxylase (PAH), an enzyme that converts phenylalanine to tyrosine, an amino acid found in proteins, melanin, neurotransmitters, and other molecules (see Figure 6). This is an important pathway for *normal* functioning; it is the mutation-caused blockage of this step that leads to the abnormal buildup of the precursor phenylalanine, which is excreted in the form of phenyl ketones in the urine. Similarly, in their unmutated form, many of the so-called "genes for cancer" are involved in the normal control of cell division – that is, they turn mitosis on when growth is needed ("proto-oncogenes" such as *myc*, *ras*, and *src*) or stop mitosis when that is appropriate ("tumor suppressors" or "anti-oncogenes" such as *Rb* and *p53*) (Lodish et al., 2012).

In other words, most of what we know about the normal functioning of a gene has come from what we have learned by studying mutations of that gene. In those cases, "phenotypic differences are not due to the presence of two qualitatively different capabilities, but rather the *absence* of the ability to make the so-called normal protein" (Moss, 2004, p. 45; emphasis added).

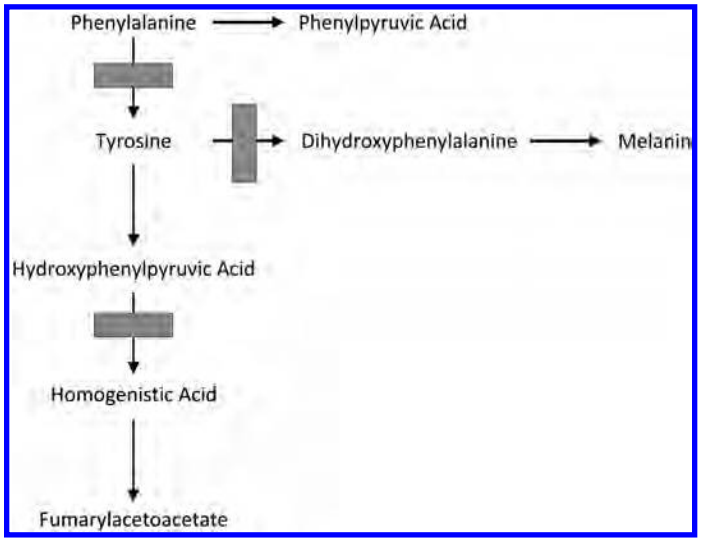

Figure 6. Metabolic pathway from phenylalananine, showing three mutations that can cause types of PKU.

Replacement Language

A mutation in one of three genes that code for enzymes involved in normal phenylalanine metabolism typically results in phenylketonuria (PKU). For example, a mutation in human PAH, which codes for the enzyme phenylalanine hydroxylase that converts phenylalanine to tyrosine, typically results in the accumulation of the phenyl ketones in the urine typical of PKU.

9. Most of the human genome is "junk DNA" (i.e., it is not transcribed and has no function).

In the not-too-distant past, geneticists knew that most of the human genome consisted of long DNA stretches that did not include open reading frames (ORFs) and, thus, could not code for proteins. Such sequences were called "junk DNA." One of the more surprising findings from the Human Genome Project was the discovery that only 1–2% of the human genome contains ORF protein-coding sequences (Baltimore, 2001). How could 98% of our DNA be "junk"?

As the genomes of more and more species were sequenced, geneticists were also surprised to find that much of this "junk DNA" was well conserved across species. Also, the vast majority of the DNA was found to be transcribed. All of these findings would make no sense if this DNA were biologically inactive. These findings strongly suggest that these DNA sequences are indeed functional (and, thus, could be conserved by evolution). Recent studies suggest that this DNA is likely involved in epigenetic control (Harmon, 2012). This conclusion marks one of the major new understandings about genetics.

Replacement Language

Most of the human genome is composed of non-protein-coding sequences that are assumed to have other functions.

○ Summary

Once upon a time, maybe when your grandmother learned about genetics, we thought that most traits were determined by single genes, each of which had two alleles that were inherited as either dominant or recessive. Students learned that eye color was a simple Mendelian trait and that one gene can produce only one polypeptide. Somehow, students often got the idea that Mendelian "dominant traits" were the strongest – and thus must be the most common in the population – and that most alleles have a simple dominant or recessive character. We spoke about certain diseases or other phenotypes (PKU, cancer, etc.) as if the mutant gene coded for a protein that caused the disease instead of coding for a protein that did not function normally (or maybe even no protein at all, as in an early frame-shift mutation). We endorsed the Central Dogma of Biology, and we thought that most of human DNA was junk.

Boy, have things changed! Like most sciences today, genetics is growing at an exponential rate, but it is likely growing even faster because genetics is such a relatively young science. This fact places a great burden on both teachers and textbook developers to keep up.

On the other hand, genetics also provides an excellent opportunity for students to see how exciting science is, instead of their common view of moldy old specimens in display cabinets and lists of impossible words to memorize. We owe it to our students to be accurate and avoid sloppy use of language in our teaching. The discussion above calls for a substantial shift in our own genetic understanding. The replacement language provided for each statement should help teachers explain modern genetics more accurately and effectively.

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References

Anderson Lab, University of California Berkeley. (2013). Basic molecular biology: the Central Dogma. [Online.] Available at http://andersonlab.qb3.berkeley.edu/.

Baltimore, D. (2001). Our genome unveiled. *Nature, 409,* 814–816.

Dougherty, M.J. (2009). Closing the gap: inverting the genetics curriculum to ensure an informed public. *American Journal of Human Genetics, 85,* 6–12.

Harmon, K. (2012). "Junk" DNA holds clues to common diseases. *Scientific American*. [Online.] Available at http://www.scientificamerican.com/article.cfm?id=junk-dna-encode.

Jamieson, A. & Radick, G. (2013). Putting Mendel in his place: how curriculum reform in genetics and counterfactual history of science can work together. In K. Kampourakis (Ed.), *The Philosophy of Biology: A Handbook for Educators*. New York, NY: Springer.

Keller, E.F. (2010). *The Mirage of a Space between Nature and Nurture*. Durham, NC: Duke University Press.

Leff, S.E., Rosenfeld, M.G. & Evans, R.M. (1986). Complex transcriptional units: diversity in gene expression by alternative RNA processing. *Annual Review of Biochemistry, 55,* 1091–1117.

Lodish, H., Berk, A., Kaiser, C.A., Krieger, M., Bretscher, A., Ploegh, H. & Scott, M.P. (2012). *Molecular Cell Biology, 7th Ed.* Cranbury, NJ: W.H. Freeman.

Market, E. & Papavasiliou, F.N. (2003). V(D)J recombination and the evolution of the adaptive immune system. *PLoS Biology, 1,* e16.

Moss, L. (2004). *What Genes Can't Do.* Cambridge, MA: MIT Press.

Offner, S. (2011). Mendel's peas & the nature of the gene: genes code for proteins & proteins determine phenotype. *American Biology Teacher, 73,* 382–387.

Online Mendelian Inheritance in Man. (2013). Phyenylketonuria; PKU. [Online.] Available at http://omim.org/entry/261600.

Pan, Q., Shai, O., Lee, L.J., Frey, B.J. & Blencowe, B.J. (2008). Deep surveying of alternative splicing complexity in the human transcriptome by high-throughput sequencing. *Nature Genetics, 40,* 1413–1415.

Smith, M.U. &. Adkison, L.R. (2010). Updating the model definition of the gene in the modern genomic era with implications for instruction. *Science & Education, 19,* 1–20.

Sturm, R.A. & Frudakis, T.N. (2004). Eye colour: portals into pigmentation genes and ancestry. *TRENDS in Genetics, 20,* 327–332.

Weldon, W.F.R. (1902). Mendel's laws of alternative inheritance in peas. *Biometrika, 1,* 228–254.

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