FEATURE ARTICLE

Missing Links in Genes to Traits: Toward Teaching for an Integrated Framework of Genetics

IGLIKA V. PAVLOVA, SCOTT A. KREHER

Abstract

Genetics, one of the most influential fields, underlies all of biology and produces discoveries that are in the news daily. However, many students leave introductory biology and genetics courses lacking a coherent framework of knowledge to use in their daily lives. We identify substantial "missing links" in the teaching of foundational concepts in genetics that should be addressed, as well as provide examples and suggest activities toward integration. Teaching in this manner can help students build on their knowledge in more advanced courses and allow them to use this knowledge throughout their lives.

Key Words: *Chemical interactions; classical genetics; mutations; dominant/recessive alleles; sickle cell disease.*

The many discoveries of the past century, centered around the expression of genetic potential into traits, have turned genetics into perhaps the most successful field of biology, and it ever-increasingly informs many disparate fields, from neuroscience and nutrition to medicine. The integrative nature of the discipline is behind this success, which has developed through the progressive convergence of initially separate areas of study: classical genetics, cell and molecular biology, population genetics, and evolution. The multiple interactions within modern genetics present wonderful teaching opportunities as well as some challenges we can avoid. Specifically, even though as experienced teachers we understand the interconnections within the field, these are often not clear to students.

The problems students have in synthesizing the material are compounded by the way we teach.

The problems students have in synthesizing the material are compounded by the way we teach. One aspect involves a curriculum that is not always well integrated. The explosion of information has been a subject of discussion and has led to efforts in curricular and textbook updating (e.g., Redfield, 2012; McElhinny et al., 2013). However, many textbooks have been modernized not by integrating newer with older information, but by adding new chapters (e.g., on genomics and informatics). Thus, paradoxically, the modernized textbooks promote teaching in the old way, without integration or with integration that may not be sufficiently explicit or emphasized for a newcomer, leaving students with a weak overall picture of how genes become expressed as traits. The strain from this abundance of information is so great that in *Introduction to Genetic Analysis* (Griffiths et al., 2012), one of the major college genetics textbooks, the previous, integrative Chapter 9 on how traits emerge from genes ("Genetics of DNA function") was removed from the current 10th edition, and the information was spread throughout the book.

With an eye toward integration, we identify the most critical "core" genetics concept as the expression of the genetic potential into traits, or [gene → trait] (Figure 1, Steps 1–3; referred to hereafter as "Steps"). In our own experience during a decade of teaching college and some high school, we have found that students are exposed piecemeal to this central genetics concept, leading to "missing links" (mostly regarding Steps 2–3). Students have a mixed bag of knowledge and implicit half-understandings, which they have trouble using in practice. Instead, we should teach in a way that helps students form an integrated view, or framework, of the most fundamental concepts. Such a coherent perspective can enable students to (1) understand popular science articles (as any citizen should) and (2) incorporate new knowledge, allowing them to understand ever more complex genetics information (especially important for biology or pre-health majors).

Here, we seek to promote discussion of what unites curricula, which is especially critical in the face of the recent unprecedented accumulation of new information. Without careful planning, we run the risk of creating hodge-podge curricula of "hot topics." By considering the common threads, we can instead incorporate the new material in a way that is meaningful to our students. Thinking about foundational concepts will also allow us to integrate curricula early on, starting in secondary schools, laying a foundation for further learning and in a way that students can use in their lives even if they do not take another science course.

To get a better view of how concepts related to our framework are taught, especially in introductory biology, we surveyed undergraduate professors from across the nation who teach courses that involve genetics (Figure 2A, B). Importantly, our sample is enriched in educators actively participating in professional associations and research on education.

Of the teachers who teach introductory biology, 85% responded that they teach how genes lead to proteins (Step 1), as expected for a

The American Biology Teacher, Vol. 75, No. 9, pages 641–649. ISSN 0002-7685, electronic ISSN 1938-4211.
DOI: 10.1525/abt.2013.75.9.4

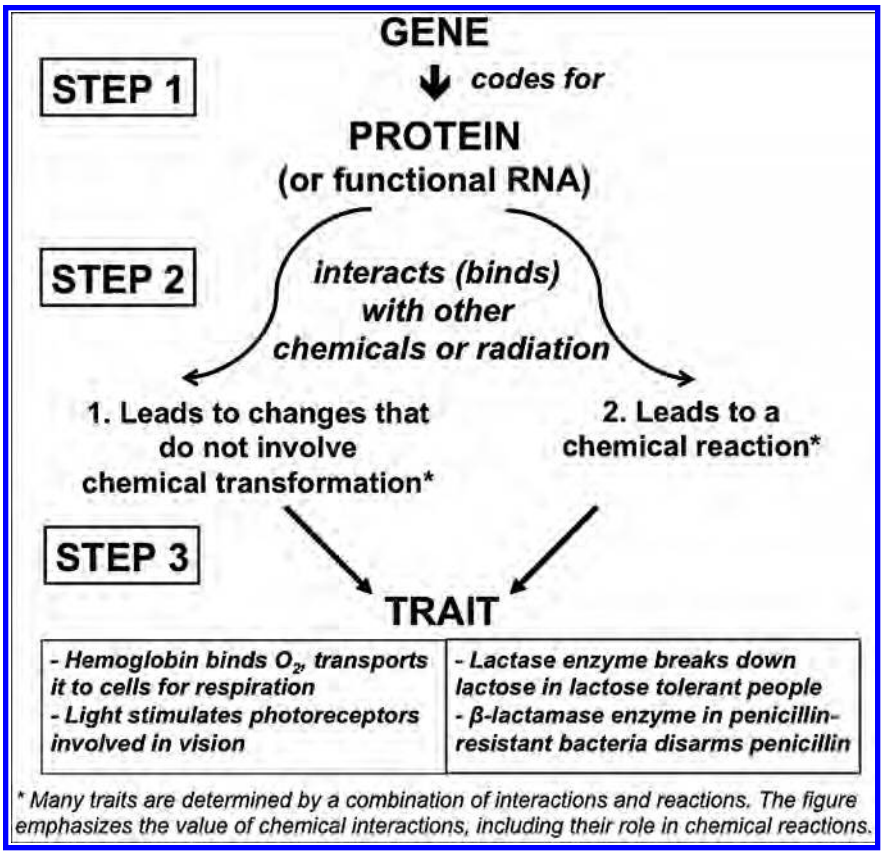

Figure 1. An integrated foundational framework of the steps that lead genes to become expressed as traits. We recommend that teachers not focus most or all of their teaching on the details of Step 1 at the expense of Steps 2 and 3. A bird's-eye view of all the Steps should be presented early, upon first exposure, starting in secondary school and continuing into college curricula.

traditionally emphasized topic (Figure 2C). In the same group, 79% reported teaching the topic of how proteins lead to traits, a surprisingly high number. Is the concept glanced over, or taught with emphasis? Although 60–80% of the respondents use a variety of teaching approaches (e.g., explicitly conceptualizing the topic, engaging students through activities and homework, and testing on exams) for Step 1 (how genes lead to traits), there is less of an emphasis on linking proteins to traits (Figure 2D). Furthermore, only about 50% teach either the molecular basis of dominant and recessive alleles or the role of gene regulation in determining trait variation (Figure 2C), two topics that allow integration; these topics are emphasized even less than the other topics (Figure 2D). While further studies can lead to better understanding of what is taught and learned, this survey supports the idea that, even in this group of perhaps more actively engaged instructors, most of the emphasis seems to be on Step 1, and not on the integration of Steps 1–3.

What, then, are the "missing links" and what approaches can we use to teach for an integrated framework of biology and genetics? We propose that the two most important "missing links" are those between (1) chemistry and genetics and (2) classical and molecular genetics, both of which address the underemphasized Steps 2–3. Appendix 1 compiles examples selected for their utility in making these "missing links." Instructors can use Appendix 1, and this article, as a guide for curriculum development. We introduce examples that are not as well known and that can enliven class through their novelty. Additionally, modern discoveries on the molecular basis of traits allow curricula to be modernized by addressing Steps 2–3 for familiar traits (e.g., wrinkled peas) that are traditionally taught in classical genetic units (see Appendix 1).

○ 1. A Chemistry Framework First: Linking Chemistry to Biology to Uncover the Molecular Basis Behind Traits

The first and most fundamental problem we encounter is that of a weakly represented chemistry framework that is not well linked to biology. In class, knocking on the bench with the words "everything is made of chemicals," I am invariably met with a whole class of wide eyes, with students exclaiming: "I didn't know the bench is made of chemicals! Sugars!" Even students with more solid chemistry knowledge enjoy puzzling over the relationships among chemicals, molecules, salts, organic molecules, proteins, sugars, fats, and DNA (Figure 3). Even though the material is taught, they have never been asked to make the links explicitly for themselves. This is compounded by the fact that in secondary schools organic chemistry is taught by biologists separately from chemistry; even in colleges organic chemistry is often not well integrated with biology.

A Simple Framework Links Chemistry to Biology, & Chemical Interactions & Reactions to Traits

Thus, students simply do not think on a chemical level in an everyday way, even though the basic chemical principles can help explain much of the biology they encounter, including how variations in proteins or protein levels determine traits. To link chemistry with biology, a fairly simple but well-represented framework of a few foundational chemical ideas (Points 1 and 2 below) should be incorporated into lesson plans. We present it here in a way that demonstrates the emphasis instructors need to make for students to make the connection between chemistry and traits:

1. All matter is made of chemicals, and in biology the most commonly discussed chemicals are organic molecules such as proteins, fats, sugars, etc. (Figure 3). Chemicals participate in any trait.
2. Chemicals can *interact* with each other, and this may or may not result in changes in their chemical composition (Figure 1). In particular:
   - 2.1. Chemical interactions that do *not* involve changes in chemical composition can still lead to changes that underlie the trait. For example, the *chemical/organic molecule* testosterone has to interact (without reacting) with another *chemical/organic molecule* that transports it to the nucleus, where the two induce protein expression, leading to an increase in muscle size.
   - 2.2. One possible result of a chemical interaction is a *chemical reaction*, which does change the chemical composition of the participating chemicals (but not the enzyme). For example, when the *chemical/molecule* that is the enzyme lactase binds to the *chemical/molecule* lactose (a milk sugar) in the intestines,

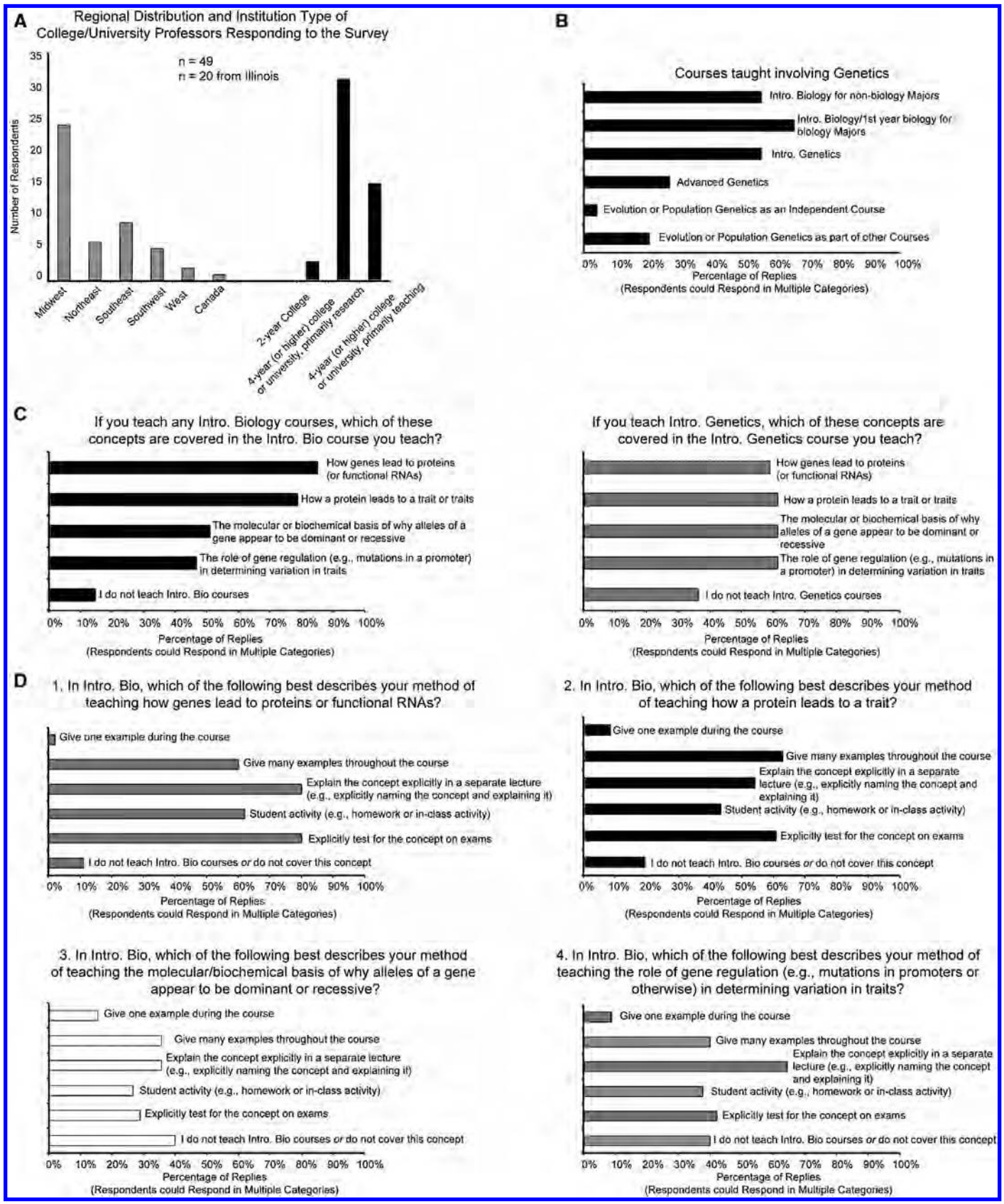

Figure 2. (A–D) A survey of undergraduate instructors teaching introductory courses that include genetics topics. In panel D, the survey indicates that instructors put more emphasis on Step 1 and less on Steps 2–3 (the molecular basis of traits and trait variation).

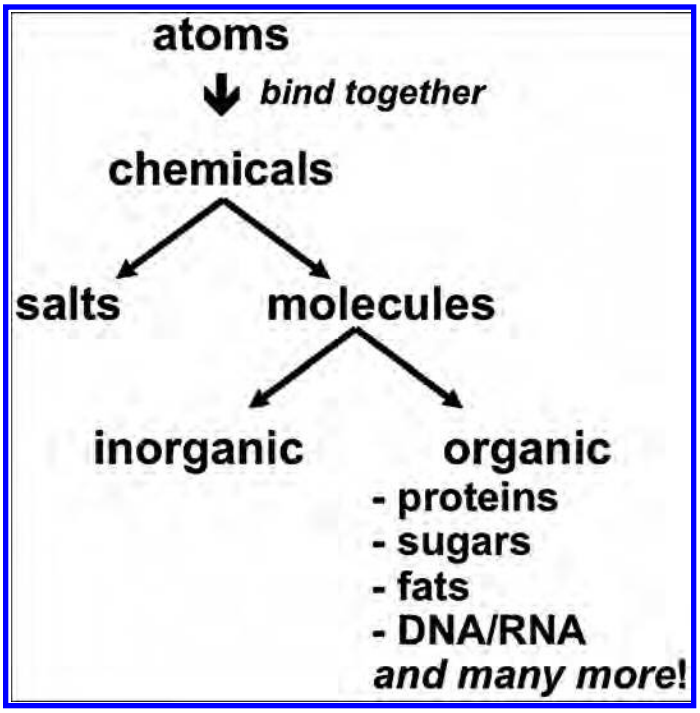

Figure 3. Linking chemistry to biology. All the molecules in living organisms are also chemicals.

> it changes the chemical composition of lactose by converting it into two smaller sugars, glucose and galactose (when the enzyme is not active in lactose-intolerant people, microbes in the gut instead metabolize the lactose, producing gases that cause abdominal pain and other symptoms).

The ideas above are framed simply so that they are easy to remember and reference. Point 1 can help with a widespread difficulty that prevents students from understanding even simple science news – not recognizing the numerous names given to proteins (and genes) as those of proteins (or genes). Thus, the combination of explicit concepts and lively examples will allow students to transfer the knowledge so that they can *think* chemically beyond the classroom, in their daily encounters.

There are "missing links" as well about the role of enzymes for traits, as in the following prompt that students find difficult: "Genes code for proteins, but many traits are due to non-protein molecules, such as melanin (skin color) or antibiotics. How can this be?" (It's good to show students the chemical structures.) Only a few students among hundreds realize that genes can code for enzymes, which then act on chemicals precursors (e.g., for melanin or antibiotics) converting them into the chemicals that determine the trait. The focus on chemical interactions also drives home another "missing link," the idea that to speed up chemical reactions, enzymes must interact with the substrates (for an excellent introductory treatment, see Tobin & Dusheck, 2005).

Many Traits Are Not Physical Attributes & Have No Official or Popular Names

One of the major problems stems from the focus on using easy-to-think-about, visible, traits such as eye and hair color or Mendel's famous green/yellow or wrinkled/smooth peas. However, many traits are not physical attributes but involve behaviors (e.g., personality traits), disease states or risk (e.g., differing breast cancer risk), and metabolic or physiological processes, which can often be expressed as "abilities" (e.g., bacteria that have the "ability to produce antibiotics"). Furthermore, many traits (especially in the last category) do not have official names, or the names are at the biochemical level (e.g., antibiotic production). As students continue to encounter examples of other traits in the future, they are often not explicitly taught to think of these as traits; thus, only students with repeated exposure (e.g., in AP/Honors Biology or those specializing in biology) will eventually form the connection, implicit at first and maybe, eventually, explicit.

As good teachers, we should certainly not wait for *some* of our students to *eventually* make the link! Instead, an introduction to traits can start with a short activity: "Can you think of traits that are not about physical appearance?" (Activity 1, Appendix 2). Follow this with several examples of traits showing variation (see Appendix 1) and explicitly discuss the lack of a name, as well as all the relationships between gene and trait: "OK, we've talked about trait X. What is the gene, the protein, the trait, and how does the protein lead to the trait?" The familiar example of hemoglobin (used to teach sickle-cell disease) provides a fresh look at the issue (Activity 2, Appendix 2), as hemoglobin is involved in many different kinds of traits: physical appearance (skin color, blue-baby syndrome, blushing, flushing, erythema; through its breakdown products, hemoglobin gives color to urine and feces), disease (sickle-cell disease, thalassemias, and malaria resistance/sensitivity), and physiological functions (oxygen transport, O_2 and CO_2 blood concentrations, and respiration rate).

○ 2. Linking Classical to Modern Molecular Genetics: The Molecular Basis behind Trait Variation

Students often leave high schools with some understanding of both classical and molecular genetics, but without having been prompted to think about how the two disciplines are related. To integrate classical and molecular genetics, it is essential that students see how the same traits can be approached from both the classical and molecular viewpoints. For example, return to a trait already covered in the classical genetics lesson (e.g., round/wrinkled peas) and explicitly describe how, at the molecular level, the phenotype emerges. The recessive wrinkled allele of the gene for a starch branching enzyme contains a transposon that causes reduced enzyme levels, which leads developing peas to have more sucrose and increased osmotic pressure, which, in turn, leads to increased water accumulation. As peas mature, the extra water is lost, and the previously overstretched membranes wrinkle. Appendix 1 contains a rich set of other engaging examples to teach the integration of molecular and classical genetics.

By integrating classical with molecular genetics, we are restoring the proper emphasis on Steps 2–3 and addressing the central issue of how variation in traits arises. Even if some of the details may not be taught in an introductory class, the overall picture of the major contributors to trait variation should still be presented (Figure 4A), with an example for each (see Appendix 1). The basic framework can be further expanded by linking to the rest of biology (e.g., population genetics, development, and evolution).

What Is the Molecular Basis of Dominant & Recessive Alleles?

The concept of dominant/recessive alleles is introduced with Mendelian inheritance, but the connection with molecular interactions is never

made. This omission leads to common misconceptions, such as that each gene has one dominant and one recessive allele, and that being dominant or recessive is an absolute state. These misconceptions will not arise when traits and trait variation are seen as the result of chemical interactions, reactions, and levels of proteins.

Using a traditional, classical genetics example, red flowers are produced when an enzyme transforms a colorless chemical precursor into a red pigment. The gene that codes for the enzyme has two alleles: one (R) encodes the normal enzyme, and the other allele (r) has a mutation that leads to an absence of the enzyme in the flower. When the flower has at least one R allele (RR or Rr), *enough* enzyme is produced to allow the red chemical to form. If both alleles are "rr", the enzyme is not produced, and the flower appears white instead of red.

In the simplified case above, the gene has only two alleles, and the recessive allele leads to loss of function (because no enzyme is produced). It is important to begin with such a simple example, but the complexity must also be taught. Many recessive alleles do not lead to complete loss of function; in fact, much understanding of traits comes from "weaker" partial alleles. Furthermore, some dominant alleles are dominant only when combined with specific alleles and not others (e.g., the fruit fly Toll gene; Schneider et al., 1991). Finally, loss-of-function alleles can be dominant and can lead to traits because protein levels are reduced below a critical threshold level required for function (known as *haploinsufficiency*).

Gain-of-function mutations can drive home the point that dominant/recessive alleles are not absolute but depend on the particulars of the chemical interaction between their gene products. The "sickle-cell" mutation of hemoglobin (Hb) replaces a charged amino acid with a hydrophobic one (valine), which leads to a change in the interactions such that a new ability (a "gain of function") comes about. Specifically, because of the hydrophobic interaction between the valines, the hemoglobin-S tetramers (Hb-S) have a higher propensity to clump ("polymerize") under low oxygen partial pressures. The long polymers of Hb-S cause red blood cells to distort into a sickled shape, which in turn leads to the multitude of consequences in sickle-cell disease and a much shortened life span. Because Hb-S can still bind oxygen at high oxygen partial pressures (as "normal" hemoglobin, Hb-A, does), the new ability, to polymerize, is a gain of function. Is the "sickle-cell" mutation recessive or dominant? Hb-A molecules act to dilute Hb-S, preventing the interaction – indeed, AS heterozygotes have normal life span and are largely symptom free – and, thus, the Hb-S mutation is a gain-of-function mutation that is recessive!

Role of Mutations in Coding vs. Regulatory Regions

The effect of mutations in coding regions on Step 1 is usually well covered (e.g., that silent mutations do not change the protein), but the effect of such mutations on protein interactions and function and, ultimately, traits (Steps 2–3) is not discussed (Figure 4B). Moreover, mutations in regulatory regions (e.g., promoters and introns) are also important contributors to trait variation. A basic framework for the role of mutations in trait variation would make the distinction between the differing effects

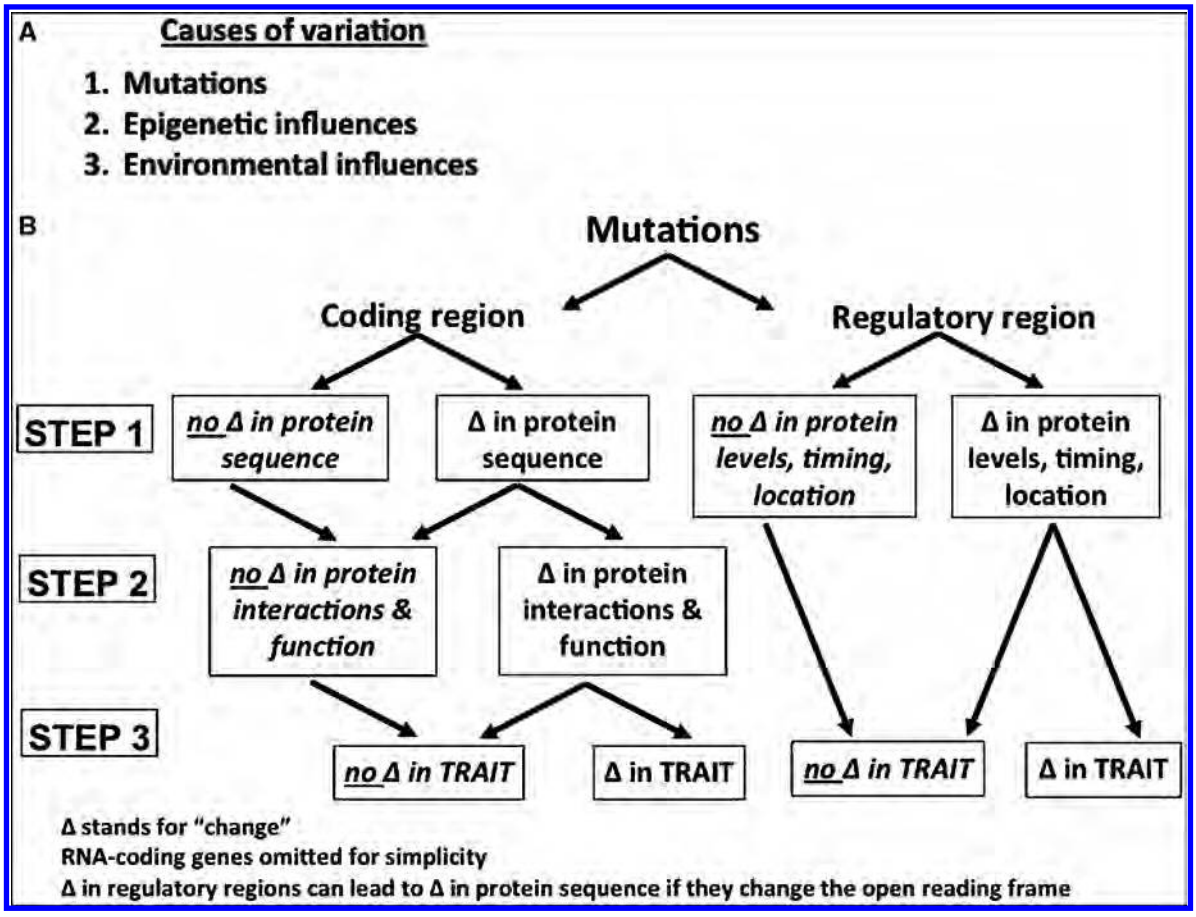

Figure 4. An integrated foundational framework for trait variation to use in introductory curricula. (A) The three major causes of trait variation. Students should be exposed to some examples in each category (Appendix 1). (B) Effects of mutations on [gene → trait], Steps 1–3 from Figure 1.

of mutation in coding and regulatory regions. The critical idea is that changes in regulatory regions typically do not affect protein sequence (though they may lead to use of alternative reading frames), instead influencing the levels, timing, or location of protein expression (Figure 4B).

One engaging example for students is variation in dogs' body size. Although there are probably multiple factors that underlie size variation in dogs, one important cause is variation in the promoter of the insulin-like growth factor (IGF) gene, which affects levels of the IGF protein: big dogs have higher blood levels of IGF protein than small dogs (Sutter et al., 2007). A suggested exercise is to show students a graph of IGF levels in large and small dogs, and to ask how this could be caused by gene variation. After students propose multiple explanations, give them the clue that the IGF protein coding regions are identical between dogs: what could the explanation be? Guide students to understand how mutations outside of coding regions can have huge effects on traits. This example also serves to integrate the concepts through the steps (Steps 1 through 3): how do mutations affect IGF protein levels, and how do differing protein levels affect dog body size?

The large variety of regulatory units and elements within them (e.g., TATA box), and their ever growing number, presents a problem when teaching introductory courses. It is most helpful if we group them all under "regulatory elements"; particular examples can then be covered as deemed appropriate, but students should be specifically trained to look for the functional category "regulatory elements" in order to recognize an unfamiliar element.

○ Integrating with Existing Curricula & Thinking of the Future

The idea of teaching for a framework and addressing the "missing links" may sound scary: we are all so busy, would it require a complete overhaul of the way we teach? No; instead we propose that, by modifying the way one already teaches, the information can be integrated effectively. Foremost, it involves presenting the material in an integrative way upon first exposure. For example, when introducing gene expression, instead of the typical and immediate focus on transcription and translation, the whole outline of [gene → trait] is presented, along with a few lively examples of what a protein does to lead to a trait (Figure 1 and Appendix 1).

Similarly, one can start by providing a bird's-eye view of the complexity in trait variation (Figure 4), instead of leaving the topic for later or skipping it altogether. Even the simplest of traits – such as sickle-cell disease and other "single-gene" traits – are due to a combination of genetic and environmental influences (see Appendix 1). Moreover, commonly used "fun" traits (e.g., eye color, attached ear lobes, and tongue rolling) are actually polygenic. All genes interact; this is the rule, not the exception! Gene interactions are traditionally difficult for students, and epistatic interactions are typically restricted to college genetics courses. An integrative framework primes even introductory-level students to think about protein interactions and enzyme pathways, which is one step away from thinking about gene interactions, making the topic easier to learn (and teach!) and connect to other biological topics (e.g., physiology).

Teaching for an overarching framework requires incorporating some topics that may be considered too complex for introductory students (e.g., gene regulation), yet are essential to form a complete view. A reassessment of learning goals can help: what do we want students to learn? For example, should we be teaching the specifics of transcription and translation (e.g., Step 1) – a topic that even exemplary teachers find difficult to have all their students learn – and to the detriment of the full picture (Steps 1 through 3)? In our opinion, it is most important to begin with the bird's-eye view, laying a solid foundation for further understanding, while at the same time providing a coherent structure that has enough real-life complexity to be usable immediately. A "big picture" approach also helps put ideas in their context, so that students can see the purpose of learning seemingly endless details. A further benefit of a clear framework is that topics that are considered too difficult or unnecessary distractions (e.g., various complexities in trait determination such as pleiotropy), especially given the amount of material, become instead naturally integrated and more easily understood. Moreover, students become interested and start asking the questions themselves: "How do dominant alleles come about? What are the effects of mutations (or the environment) on promoters and proteins?"

Modifications can range from incorporating mini-modules that are only part of a class period (e.g., a discussion of Figure 1 or 4) to using larger modules that take one or two class periods, which would typically replace existing units that are not integrative (thus not requiring extra time). We have exemplified ways of talking about the material with more emphasis and clarity, and enlivening interest through activities. Appendix 2 presents the activities discussed throughout the paper, together with more suggestions. Particularly engaging are unusual or unfamiliar examples (see Appendix 1); through their novelty these allow thinking from the "ground up."

We can show our students the large universe waiting to be discovered by pointing out the many unknown aspects of how the genome is expressed into traits (see Appendix 1). Discussing how much is known for even one such example can help students not only to solidify the links for [gene → trait], but also to experience the process of thinking and using evidence (e.g., what is known about the role of apolipoprotein-E [APOE] in Alzheimer's disease?). By remembering that the success of genetics relies on its integrative nature, we can convey the wonderful complexity of nature, the joy of discovery, and the benefit to humans.

References

Griffiths, A.J.F., Wessler, S.R. & Carroll, S.B. (2012). *Introduction to Genetic Analysis.* New York, NY: W.H. Freeman.

McElhinny, T.L., Dougherty, M.J., Bowling, B.V. & Libarkin, J.C. (2013). The status of genetics curriculum in higher education in the United States: goals and assessment. *Science & Education*, *22*, in press.

Redfield, R.J. (2012). "Why do we have to learn this stuff?" – A new genetics for 21st century students. *PLoS Biology*, *10*(7), e1001356.

Schneider, D.S., Hudson, K.L., Lin, T.-Y. & Anderson, K.V. (1991). Dominant and recessive mutations define functional domains of Toll, a transmembrane protein required for dorsal–ventral polarity in the *Drosophila* embryo. *Genes and Development*, *5*, 797–807.

Sutter, N.B., Bustamante, C.D., Chase, K., Gray, M.M., Zhao, K., Zhu, L. & others. (2007). A single IGF1 allele is a major determinant of small size in dogs. *Science*, *316*, 112–115.

Tobin, A.J. & Dusheck, J. (2005). *Asking about Life, 3rd Ed.* Bellmont, CA: Thomson Brooks/Cole.

IGLIKA V. PAVLOVA is a Lecturer in Biological Sciences at the University of Chicago, 924 E. 57th St., BSLC Rm. 208, Chicago, IL 60637; e-mail: iglikap@uchicago.edu. SCOTT A. KREHER is Assistant Professor of Biology at Dominican University, 203 Parmer Hall, 7900 W. Division, River Forest, IL 60305; e-mail: skreher@dom.edu.

Appendix 1. A pool of examples to draw on in teaching within an integrated framework that can provide the "missing links" (Steps 2–3 in Figure 1) of how genes lead to traits. A balance of better-known examples (which are easier to incorporate) and lesser-known examples (which are attention-grabbing) is presented. The table, and all references, can be found at http://domin.dom.edu/faculty/skreher/.

Example of Trait with Variation	Organism	Gene/Alleles	Protein	Trait Category[a]	Use in Framework: Linking Genes to Proteins to Traits & Explaining Trait Variation
I. Trait Variation due to Mutations in Coding Region ("Gene")					
Round/wrinkled peas[b]	Peas	Rugosus gene	Starch branching enzyme	Physical	See text for details. Example of classical trait that we understand molecularly.
Fruit fly body axis development	Fruit flies	Toll	Membrane receptor protein	Physical	Signaling through Toll communicates cell fate. Example of interesting D/R relationships.[c]
The "waltzing" mouse[b]	Mouse	Snell's waltzer deafness gene	Myosin VI	Behavior	Not completely understood. Myosin VI is important for sensory hair cell development in the inner ear, which is linked to balance.
C. elegans roller phenotype[b]	*C. elegans* worms	rol-6	Collagen	Behavior	Mutations change interactions between collagen molecules in the cuticle, causing animals to roll.
Bitter taste sensitivity[b]	Humans	TAS2R38 *≥5 alleles*	Taste Receptor Protein	Biochemical/ Physiological	Bitter substances such as PTC bind to this taste receptor. Different alleles linked to differential sensitivity to bitter compounds.
Resistance to penicilin family antibiotics	Various bacteria	β-lactamase	β-lactamase	Biochemical/ Physiological	The β-lactamase enzyme modifies β-lactam-containing antibiotics. Different alleles linked to differential activity and specificity (can disarm either some or many family members).
Resistance to rifamycin family antibiotics	Various bacteria	rpoB	RNA polymerase	Biochemical/ Physiological	Rifamycin antibiotics inhibit transcription by binding to RNA polymerase. Resistance mutations reduce binding to RNA polymerase.
Organ transplant compatibility	Humans	HLA/MHC *several genes 100s of alleles*	MHC proteins	Biochemical/ Physiological	Degree of match between MHC proteins in transplant vs. recipient determines immune response. MHC alleles are also linked to differential ability to respond to infections.
Inherited breast cancer risk[b]	Humans	BRCA1 *Many alleles*	DNA repair enzyme	Disease/Risk	Defective DNA repair increases chance of cancer mutations. Mutation is a dominant loss of function – example of haploinsufficiency.
Inherited risk for Alzheimer's disease	Humans	APOE-ε 4 *≥4 alleles*	Apolipoprotein E	Disease/Risk	Strong genetic association; but role of APOE, found in amyloid plagues in brain, is not completely understood.
Sickle cell disease[b]	Humans	β-globin *Many alleles*	Globin protein of hemoglobin	Disease/Risk	See text for details. Many alleles also cause different thalassemias, which range in severity.

Appendix 1. Continued

Example of Trait with Variation	Organism	Gene/Alleles	Protein	Trait Category[a]	Use in Framework: Linking Genes to Proteins to Traits & Explaining Trait Variation
II. Trait Variation due to Mutations in Regulatory Regions					
Human eye-color variation[b]	Humans	OCA-2 *Many alleles*	Membrane protein	Physical	Role of protein not completely understood.
Dog size variation	Dogs	IGF-1	Insulin-like growth factor	Physical	IGF-1 induces cell mitosis. Alleles with higher growth-factor levels linked to larger dog size.
Monogamy in voles	Voles *Interspecies*	V1aR	Vasopressin receptor	Behavior	Vasopressin released during mating activates reward areas in brain in monogamous prairie voles, but not in montane or meadow voles.
Human lactose intolerance	Humans	LCT	Lactase enzyme	Metabolism and Disease	See text for details.
Sickle cell disease[b]	Humans	β-globin *Many alleles*	Globin protein of hemoglobin	Disease/Risk	Hereditary mutations related to the fetal hemoglobin (HbF) gene lead to continued HbF expression in adults, ameliorating SCD.[d]
III. Trait Variation due to Epigenetics					
Agouti coat color in mice	Mice	Viable yellow Agouti allele	Signaling protein	Physical	Epigenetic modification (DNA methylation) regulates deposition of color pigment.
Flowering time in *Arabidopsis*	Thale cress plants	PCG and FLC	Polycomb and flowering locus	Physical	Polycomb proteins regulate gene expression by regulating overall chromatin structure.
Prader-Willi and Angleman Syndromes	Humans	Probably several genes	Probably several proteins	Disease/Risk	Inherit epigenetically imprinted (differentially between the sexes) version from one parent and version with large deletion from the other.
IV. Trait Variation due to Environmental Influences					
Sun tanning	Humans	Many genes		Physical	UV light induces skin darkening. Also, example of mutations linked to evolutionary adaptation.
Respiration capacity at high altitudes	Humans	Many genes		Biochemical/ Physiological	Multiple physiological responses to high altitudes. Also example of mutations linked to evolutionary adaptation.
Sickle cell disease[b]	Humans	β globin	Globin protein of hemoglobin	Disease/Risk	High altitudes, exercise, level of hydration, and drugs (hydroxyurea) influence hemoglobin interactions or fetal hemoglobin gene expression, which affects symptom frequency and severity.

[a]Many traits do not have official or popular names – and may rely on descriptions at the biochemical level such as metabolic abilities or physiological functions. Most of these are categorized in this table as "Biochemical/Physiological" traits; this does not mean that they do not affect organisms more widely (e.g., tasting ability affects behavior and antibiotic production and antibiotic resistance is critical for bacterial survival). Also, a trait can belong in more than one category; for example, bitter taste sensitivity may be linked to behaviors such as food choice and tobacco use.
[b]Marks classical traits – examples from classical genetics described at the phenotypic level. As we understand better their molecular basis, classical traits are important in making the link between molecular and classical genetics.
[c]D/R = dominant/recessive.
[d]SCD = sickle-cell disease.

Appendix 2. Suggestions for activities to engage introductory students. We have used all suggested activities with our students, including high school students and science teachers.

Issue	Activity Prompt or Description
What are traits?	Can you think of examples of traits that are not about physical appearance?*
Making link [Protein → Trait]	Think of as many traits that are linked to [protein of choice] as you can.* [Text describes hemoglobin example] [Demonstrates pleiotropy]
Making link [Protein → Trait] Enzymes	Show how a chemical interaction (without chemical transformation) leads to a trait. Show how a chemical interaction leads to a chemical reaction that leads to the trait. Who is interacting and what happens?
Making link [Protein → Trait]	Are we talking about the chemistry behind traits or the molecular basis behind traits? Which description do you think is better? [Open-ended] [Helps make link with chemistry]
Linking names to genes and proteins	Show a picture of a complex pathway, a short news piece or abstract from a paper, or a dozen examples of proteins or genes from the textbook and ask: "What are all these names?"
Making all links [Gene → → Trait] Enzymes	Some traits are linked to a molecule that is not a protein. For example, melanin for skin color or antibiotics is not a protein. How can that be? How does it work? • Can genes code for non-protein molecules that "do things" in the cell? • In the two examples above, the gene does actually code for a protein. But the trait is based on a non-protein molecule. What is the link?
Making all links [Gene → → Trait]	We have been discussing [trait X]. Shows all the links from gene to trait. How much do we [scientists] know about how the protein leads to the trait? What information is missing?
Making all links [Gene → → Trait]	Provide students with descriptions of a protein function (e.g., IGF-1 promotes mitosis) and an associated trait (dog size). Ask them to describe how the protein function could cause the trait. The function could be more or less removed from the trait – there could be more or fewer steps and, depending on students' knowledge, more or less detailed descriptions could be required.
Making all links [Gene → → Trait]	For a trait that varies by degrees (e.g., fruit fly eye color), give students phenotypes (e.g., red, orange, and white) associated with mutations in a gene linked to the trait (e.g., alleles of the white gene: wild type, one amino acid change, premature stop codon) and have students match the alleles to the phenotypes, and explain their thinking.
D/R basis Making all links [Gene → → Trait]	Explain how the results of the cross between AA and aa for [classical trait of choice] can be explained by what the proteins are doing. Why does A appear to be dominant?
D/R basis Making all links [Gene → → Trait]	What could be happening to a protein that can lead to incomplete dominance? What kinds of mutations could lead to partial protein function? Think widely about mutations in both coding and regulatory regions, and their effects – and think of as many different possibilities as you can.
D/R basis Making all links [Gene → → Trait]	You now know the chemical interactions that lead to [trait of choice]. Do you predict that the [allele X] will be dominant or recessive? [Text describes sickle-cell disease example]
D/R basis Making all links [Gene → → Trait]	Will a "loss-of-function" mutation always be recessive? Give one example of a loss-of-function allele that is recessive, and one that is dominant. Similarly, will a gain-of-function mutation be recessive or dominant? Can you give an example (real or hypothetical) for each case?
D/R basis Making all links [Gene → → Trait]	Give students the multiple alleles (and associated phenotypes) of a certain gene (Toll is good for this), and ask them to classify the alleles as D/R. For Toll, some alleles appear to be dominant when paired with one allele, but recessive when paired with another (Scheider et al., 1991).
D/R basis Making all links [Gene → → Trait]	MHC alleles present an interesting example.* Different alleles are linked with the ability to stimulate immune responses against different infections such that some alleles protect against one pathogen, while others protect against another kind of pathogen. Ask students to think about D/R relationships here. Are some mutations dominant in some environments, but not others?

*Activity particularly promotes thinking "from the ground up": pooling information already available on one's own to come up with a new understanding, and conceptualizing in a way that is different from previous exposures.