Closing the Gap: Inverting the Genetics Curriculum to Ensure an Informed Public

Michael J. Dougherty[1,*]

Over the past 20 years, the focus of national efforts to improve K-12 science education has ranged from curriculum and professional development of teachers to the adoption of science standards and high-stakes testing. In spite of this work, students in the United States continue to lag behind their peers in other countries. This underperformance is true for genetics, as well as for science and math in general, and is particularly worrisome given the accelerating need for scientists and engineers in our increasingly technology-driven economy. A scientifically literate public is essential if citizens are to engage effectively with policymakers on issues of scientific importance. Perhaps nowhere is this conjunction more personally meaningful than in human genetics and medicine. Rapid changes in our field have the potential to revolutionize healthcare, but the public is ill prepared to participate in this transformation. One potential solution is to modernize the genetics curriculum so that it matches the science of the 21st century. This paper highlights changes in human genetics that support a curricular reorganization, outlines the problems with current genetics instruction, and proposes a new genetics curriculum.

Introduction

With the completion of the sequencing phase of the Human Genome Project, genetic research has expanded to large-scale variation studies and functional genomics. One goal of that research is an improved understanding of the genetics of complex phenotypes, especially the genetic basis of health and disease. The earliest disorder to be recognized for its Mendelian inheritance pattern was alkaptonuria (MIM 203500), a single-gene, inborn error of metabolism.[1] Interestingly, even this iconoclastic example of a "simple" genetic condition—that is, one displaying Mendelian segregation—is itself genetically complex (e.g., multiple mutant alleles).[2,3] Similarly, several phenylalanine hydroxylase mutations (*PAH* [MIM 612349]) can now be correlated with variable expression at the metabolic level in phenylketonuria (PKU [MIM 261600]).[4] Recent studies of ataxia telangiectasia (MIM 208900), another classic recessive disorder, have shown that for certain molecular phenotypes, *ATM*-mutation heterozygotes (MIM 607585) resemble noncarriers, but for other phenotypes the heterozygotes resemble homozygous AT patients. Moreover, different expression profiles have revealed a regulatory pathway underlying the phenotypic differences.[5]

Some "monogenic" disorders are beginning to be understood at a molecular level in the context of phenotype "modifiers" that confuse the correlation between genotype and phenoytpe, for example as in the case of adrenal hypoplasia congenita (AHC [MIM 300200]).[6] Second-site polymorphisms in the *PRNP* gene (MIM 176640), which encodes the prion protein responsible for fatal familial insomnia (FFI [MIM 600072]) and familial Creutzfeld-Jakob disease (both autosomal-dominant disorders; CJD [MIM 123400]), were initially thought to determine which disease would manifest.[7] However, variation in pathological findings and clinical presentation (e.g., age of onset) now suggest that other factors influence phenotype, for example through protein processing.[8,9] Factors that modify phenotype also have been implicated for glycerol kinase deficiency (GK [MIM 307030]), an X-linked inborn error of metabolism that can result in either symptomatic or asymptomatic cases. In GK deficiency, variation in protein stability and RNA processing appear to modify phenotype.[10] The genetic underpinnings of Mendelian disease will continue to integrate with theoretical and experimental work in biochemistry to explicate phenotypic complexity, for example, by providing a better understanding of the kinetic behavior of enzyme reactions and metabolic flux, which behave as nonlinear systems.[11] However, the precise phenotypic outcomes will probably remain predictable only at low resolution because "for many diseases, only a subset of all mutations reliably predicts phenotypes."[12]

Recent discoveries about how single-nucleotide polymorphisms (SNPs) and copy number variants (CNVs) have contributed to "complex" disease further expand the palette of known, phenoytpically relevant genetic variation[13–15] and suggest that we have not exhausted the range of important genetic variation. Adding to the challenge of understanding how molecular markers might indicate predisposition to disease is the fact that phenotype is also influenced by the environment. Unfortunately, and unlike genetics, we have no governing, theory-based chain of causation to structure our thinking about *how* environment shapes traits. DNA methylation and chromatin remodeling have emerged as important mechanisms for understanding how epigenetic modification

[1]Director of Education, ASHG, 9650 Rockville Pike, Bethesda, MD 20814
*Correspondence: mdougherty@ashg.org
DOI 10.1016/j.ajhg.2009.05.010.

of genes can lead to disease,[16] but environmental disruptions of homeostasis operate at many other levels, for example at the cell and tissue levels, without affecting gene expression, at least initially. Most researchers accept that complex traits are the result of multifactorial causation—that is, they are the product of multiple genes (polygeny) and a dynamic environment. Complexity at this level is of particular importance for common diseases, such as heart disease, cancer, stroke, and diabetes, which constitute the major public health concerns of developed countries.

Regardless of cause, complex traits tend to be quantitative in nature in that they lend themselves to physical and biochemical measurements, and at a population level they often display normal or near-normal distributions spanning a continuous range. This differs markedly from the discrete ("either/or") presentation typically seen in traits that show Mendelian segregation. Moreover, in cases where genetic markers are increasingly available, complex traits can often be linked to genotype with only low predictive power, unlike the relatively accurate predictions typical of segregating traits (and notwithstanding the variable expressivity often seen in those traits). Despite changes in our views of how genotype influences phenotype, the old paradigms have been enriched, not replaced. The same principles of Mendelian segregation that helped us make sense of alkaptonuria also govern the many genes influencing diabetes, heart disease, and schizophrenia.

The Current Status of Genetics Instruction and the Need for Change

According to a 2009 study by Battelle, the Biotechnology Industry Organization, and the Biotechnology Institute, only 28% of high-school students taking the American College Test (ACT) achieved a score indicating readiness for college biology. (The ACT is a standardized exam that provides subject-specific information for college admissions.)[17] In genetics, instruction continues to emphasize Mendelian ratios and monogenic traits and disorders, often to the exclusion of inherent complexity. Five out of six high-school biology textbooks recently analyzed lacked a sound discussion of incomplete penetrance, and "gene-environment interactions and the potential influence of these interactions on the development of disease" was also missing in the majority of texts (L. Doyle, personal communication). Students miss out on the richness and depth that characterizes our more complete and current understanding of genetics when we omit complexity. Worse, our emphasis on single-gene inheritance may inadvertently contribute to a poor understanding of genetics and encourage genetic determinism.

Over the course of two years, the American Society of Human Genetics (ASHG) collected data on student misconceptions about genetics as revealed in essays submitted by middle- and high-school students to ASHG's annual DNA Day Essay Contest. Many of the misconceptions have their roots in deterministic thinking and in an overly simplified view of patterns of inheritance.[18] In particular, many students view all phenotypes through the lens of Mendelian inheritance and fail to appreciate that most human traits are the product of polygenic expression modulated by the environment. Compounding the problem, or perhaps at its root, is the fact that only 10%–15% of state science standards specify that students should learn those concepts.[18] The National Science Education Standards include trait variation in the context of natural selection (although not in the context of inheritance), but not a single state specifies a standard dealing with genetics and continuous variation (M.J.D. and Wong, unpublished data). In a climate where high-stakes testing drives much of the curriculum, it is to be expected that standards will influence what gets taught and what does not.[19,20] Thus, there is a great need to involve geneticists in K-12 public education to help ensure that genetics is represented appropriately and that curricula are designed in ways that increase the chances of producing a well-informed public.

Undergraduate genetics also appears to be falling short in that many teachers never introduce quantitative genetics or, if they do, they spend little time on it. A study of genetics instructors of undergraduate nonmajor biology courses found that instructors spent the greatest amount of genetics lecture time on meiosis and Mendel (the category classified as "transmission") and the least amount of lecture time on "gene regulation," the broad category that included multifactorial traits and the underlying genetics.[21]

The lack of emphasis on continuous variation and populations also impedes students' understanding of evolution. To truly understand how species change across time, students need a deep appreciation for the nearly infinite phenotypic variation in populations (because traits serve as the substrate for selection) and, of course, for the incredible genotypic variation at the foundation of those traits. Interestingly, virtually every discovery since Mendel, from recombination to imprinting to alternative splicing to SNPs and CNVs, has deepened our appreciation for nature's myriad ways of providing for phenotypic variation. Biologists may not be surprised by this (not after Theodosius Dobzhansky's essay "Nothing in biology makes sense except in the light of evolution"[22]), but many students miss the connection between genetics and evolution because their world of genetics is one of either/or traits, rather than quantitative characters, and individual organisms, rather than populations. Ultimately, poor instruction in genetics means students are not being prepared to understand how trait variation relates to genetic variation and consequently to evolution.

Perhaps even worse, the predominant mode of genetics instruction primes many students to think deterministically and with a confused understanding of risk. The use of

Punnett squares— wonderful heuristic tools when used properly—can become conceptually limiting when used excessively. When most or all of inheritance is explained with Punnett squares, should we be surprised when some of our students end up believing that two carriers of a mutated *CFTR* gene (MIM 602421) will always produce one child with cystic fibrosis for every four children (MIM 219700)? What the student sees is four discrete boxes with one shaded, not the representation of a probability function. One might argue that fundamentally this is a problem with students' grasp of simple statistical concepts, but genetics instructors contribute to the problem to the extent that they focus on individuals rather than populations. Deterministic thinking may affect attitudes toward genetic testing, with implications for genetics research and even social behaviors such as cheating.[23,24] Taken together, current teaching practices may be producing a public that is unprepared to participate effectively as medical consumers in a world where personalized medicine will rely increasingly on genetic testing, risk assessment, predispositions, and ranges of treatment options that include biological and behavioral components. Professional organizations such as ASHG and other leaders in genetics education must take responsibility for bringing genetics education to the same level as genetics research.

An Alternative Paradigm

The sequence of topics taught in most genetics courses roughly follows the historical development of genetics research: genes and alleles (particulate "factors"); dominance; independent assortment; meiosis and chromosome segregation; linkage; epistasis; molecular genetics; and then, if at all, brief treatment of complex traits. Geneticists have always been interested in complex traits, but the heavy focus on monogenic traits was a natural consequence of the fact that those were the phenomena we could best apprehend, a situation that is still true. However, given what we know about the deficiencies in the current curriculum and student understanding, and armed with an improved understanding of the genetics of complex traits, there is no longer a compelling reason to maintain the historical sequence of our syllabus. Indeed, the direction of genetics research and medicine suggests that an alternative may be in order.

Specifically, it may be preferable to "invert" the curriculum—that is, to begin genetics instruction with common quantitative traits, which might include health and disease traits but should not be limited to them, and to build the conceptual base for interpreting the genetic influences on those traits before immersing students in the genetics of rare, monogenic traits (Appendix A). There is still active debate about the relative contribution of different factors to variance in complex traits, for example additive models of genetic variance versus the effects of dominance and epistatic interactions,[25] but the fundamental contributors are generally accepted and the concepts are relatively accessible, even to middle- and high-school students.

This is not meant to imply that our understanding of the contributors to complex phenotypes is complete or as well developed as for single-gene traits. To the contrary, there is still the matter of missing heritability, and there are no complex traits for which all causative factors and pathways are known and fully explain the observed phenotypic variance. However, the latter can be said for single-gene traits as well. The degree of uncertainty is no doubt smaller for those, but uncertainty remains, which is why we are unable to predict the precise expression of symptoms and age of onset even for Mendelian disorders. PKU is often presented in high-school biology as an example of monogenic, fully penetrant inheritance, yet its heritability may be zero, through environmental modification alone, for a population that is adequately screened, informed, and compliant with dietary restrictions. Huntington disease (MIM 143100) and cystic fibrosis are also commonly taught, but the variability in their expression is not. We typically teach these examples incompletely. If we were more thorough, the conceptual difficulty would be no greater than that encountered in using complex traits as the entrée. With the latter approach, we gain the substantial benefit of not encouraging genetic determinism and an overly simplified view of inheritance.

Our incompleteness of understanding and the messiness of complex-trait examples are poor arguments for maintaining the status quo in our genetics classrooms. We know on theoretical grounds that the entirety of phenotype is defined by genes and environment, and substantial uncertainty still characterizes both. To pretend such uncertainty does not exist is to deprive students of an appreciation of both modern genetics and the nature of science. To delay reform of the genetics curriculum until we understand the genetics of complex traits completely is to allow the perfect to be the enemy of the good. If future research identifies the source of missing heritability, for example, through a deeper understanding of CNVs or epistasis, the curriculum, which should be dynamic, should be modified accordingly.

A New Curriculum

Students recognize that certain normal traits, such as height and weight, are fundamentally different from the discrete traits commonly discussed in genetics courses. If a teacher asks a naive class to generate graphs illustrating continuous variation in height or arm length (concept 1), they can do so easily. (Preferably, they will do this after measuring these characters themselves by using their own population as a sample and taking the opportunity to both collect and analyze data.) They can then be asked to contemplate whether genetics might explain such a distribution. Students have an intuitive understanding that such traits are heritable; for example, they know that tall parents tend to have tall children and short parents tend to have short children and that most people cluster

around bimodal averages (by sex). Making this implicit understanding explicit is the first, crucial step in teaching the genetics of complex traits.

Students also know intuitively that the environment influences complex traits (concept 2). If a teacher asks them what factors, besides parents, influence height or weight, they volunteer answers such as nutrition, hormones, and drugs. Unfortunately, most do *not* know, because they are generally not taught, that environment also affects the expression of many monogenic disorders, leading to, for example, the range of phenotypes observed in PKU, which is determined by the amount of dietary phenylalanine as well as PAH mutations. The absence of examples of environmental modulators of commonly taught phenotypes reinforces students' tendency to think deterministically about genes. Conversely, many students (even undergraduates) doubt that there is any genetic contribution at all to certain rarely taught complex traits such as personality, addiction, and cardiovascular efficiency. In these cases, many students believe that environmental factors alone explain variation, for example, through peer groups, will power, and exercise, respectively.

A very small number of evidence-based lessons that could help to correct these misconceptions already exist, but we need far more. For example, in *Genes, Environment, and Human Behavior*, a free module funded by the Department of Energy, students can model twin studies and genetic-association studies.[26] If the genetics research and teaching communities expressed strong support for teaching the genetic basis of complex traits, curriculum developers and publishers would be encouraged to incorporate these concepts into commonly used textbooks.

If we succeed in helping students appreciate that complex traits are the result of multifactorial causation, then we can begin to move them toward real understanding. For instance, continuously distributed traits can be described by the basic statistics of normal distributions (e.g., mean, variance, and standard deviation). In this case, an inversion of the genetics curriculum can take advantage of state mathematics standards. Every state specifies the teaching of these basic statistical concepts, often beginning as early as the fifth grade. Moreover, a simplified model of polygenic inheritance, such as Nilsson-Ehle's additive model (number of discrete phenotypes = $2n + 1$, where n = number of genes[27]), is sufficient to illustrate the concept that the number of inherited "contributing factors" can correlate with the extent of a trait (concept 3). These factors, harkening back to Mendel, need not be defined as segregating alleles or independently assorting genes at the first presentation of the concept (indeed probably *should not* be so defined, at this time, in order to keep the focus on the broader concepts). That said, even middle-school students understand at a general level that things called genes, which come from parents, influence inherited traits.

For an example of how to teach about additive polygenic inheritance, consider a lesson where students model weight by using offspring that inherit red and white marbles from hypothetical parents. Offspring inheriting six red glass marbles (e.g., contributing genes or alleles) and two white plastic marbles (noncontributing genes or alleles) would be heavier than offspring inheriting four red and four white. And from a population of equal numbers of red and white, more combinations of eight lead to weights around the average than lead to extremes of high or low, something the students would discover as they conducted this exercise. These phenotype-contributing factors will be no more abstract to most students than the concept of alleles is in the current curriculum, and students do not have to understand meiosis yet to learn the basic concept of additive inheritance. Students can simply select marbles at random from a jar knowing that half would be from one parent and half from the other.

Now, with a broader perspective on the role of genes and the environment in complex traits, students will be better prepared to experience the elegance of transmission genetics and our familiar Mendelian examples (concepts 4–8). They can be introduced to a selection of relatively rare single-gene traits and how they beautifully exemplify meiotic segregation, independent assortment, and Mendelian ratios. Moreover, if teachers place greater emphasis on the environment's influence on genetically encoded traits, they will help to combat students' tendency to think about genes deterministically. Instead of leaving the example of height in Mendel's pea plants as tall or short, instructors can ask students what would happen if a population of plants with identical genotypes was subdivided and grown under different conditions. What would the population look like if a dozen different concentrations of fertilizer were used, or varying amounts of sunlight and water? What would happen if two true-breeding populations (e.g., tall and short) experienced a similar mix of environmental variation? Such elaborations would suffice to help students see that discrete phenotypes can be broadened, perhaps until they overlap with one another, even in single-gene cases, yielding distributions that are more complex than the typical binary categories.

At the end of the unit, teachers would return to complex traits to reinforce the idea that genes and alleles behave according to the principles Mendel observed, regardless of whether they are contributing to traits with continuous (when polygenic) or discrete inheritance patterns (concept 9). In the end, there would be no diminution of Mendel but rather an application of his principles to a more sophisticated genetics. Genome-wide association studies might be modeled to emphasize how phenotypic variation can lead to gene discovery, genetic predisposition, and risk prediction, further de-emphasizing deterministic thinking. With a proper foundation, students would recognize that particulate inheritance of digital information can produce the analog hues of continuous phenotypes, an abstraction that

captivates genetics instructors but rarely their students.

An alternative model is possible. After introducing concepts 1–3 but before introducing concepts 4–8, teachers could discuss the basics of gene expression, which would establish the idea that genes give rise to proteins that act in signaling, structure, and catalysis to make traits manifest. Brief overviews of molecular genetics are becoming common as the very first chapter in introductory genetics texts (i.e., before transmission genetics). The rationale behind this evolution in genetics texts is that the connection between genes, protein structure and function, and phenotype is more concrete than the less-direct genotype-phenotype connection associated with presentations of Mendel's work; it acknowledges a mechanism of causation (e.g., the *SBE* locus and starch-branching enzyme's influence on pea texture is sometimes used). If the connection between genes and proteins is taught first, the additive model becomes an example of phenotype linked to gene and protein dosage, a limited but accurate view of inheritance for at least some complex traits, for example certain threshold-expression mitochondrial diseases and size-related traits in *Drosophila*.[28] (Indeed, Correns' discovery of incomplete dominance and intermediate phenotypes, as in the classic example of carnation color, is the limiting test case (i.e., a single gene with two alleles) for this phenomenon.) Later, after students understand the difference between genes and alleles, the additive model can be elaborated to include the fact that different alleles *and* different genes might contribute to the same trait. Likewise, the same gene might influence more than one trait (i.e., in pleiotropy).

Why "invert" when we could "supplement"? Couldn't these lessons on complex traits be added at the end of the normal genetics units? Unfortunately, if students have already spent four or five weeks learning nothing but single-gene traits that exhibit Mendelian segregation (i.e., if they have experienced a typical genetics unit in high-school general biology) and then spend only a few days on quantitative traits, the teachers will have a very difficult time convincing students of the prevalence and importance of complex-trait genetics. The message would be incommensurate with the delivery. To help students appreciate the current state of genetics research and the proper balance of genetic and environmental influences, the curriculum should present these topics in a new sequence and different proportion. A radically different approach would have the greatest ability to convince teachers that dramatic change is needed in instruction, not just refinement at the margins.

Fixing State Science Standards to Support Improved Genetic Literacy

Beyond revising the curriculum (and developing teachers' ability to use it), there is another obstacle standing in the way of improved genetic literacy. High-stakes testing associated with No Child Left Behind and state science standards are increasingly distorting the science curriculum nationwide. States and districts now prescribe the public-school curriculum in ways that constrain teachers to a limited set of standards-based genetics topics, which usually lack concepts related to complex traits, as described above. As a result, many teachers complain that they do not have flexibility to teach the concepts they think are most important. Thus, regardless of teachers' desire to improve their genetics instruction to reflect modern understandings, their goodwill, professionalism, and an improved curriculum will be insufficient to ensure success. Geneticists around the country must become involved as content experts in their state's processes of standards revision and in outreach to help promote the inclusion of critical genetics concepts, such as continuous phenotypic variation, polygenic inheritance, and multifactorial causation. Currently, only eight out of 31 states in the Battelle study indicated that research scientists played a major role in the development of science standards.[17] The American Society of Human Genetics has taken some initial steps in this direction through the assembly and preliminary analysis of a database of state science standards for genetics. By coupling that standards analysis with revision schedules and the appropriate administrative contacts in each state, geneticists linked through ASHG's Genetics Education Outreach Network (GEON) could become a cadre of Society members devoted to the improvement of state standards.

Summary

The rare, single-gene traits commonly taught in middle and high school allow an elegant explication of the genotype-phenotype connection, but too often instruction ends at that point, leaving students with the mistaken assumption that this fully describes inheritance. Such a misconception is clearly not compatible with modern understandings of genetics. Eventually, it will interfere with students' comprehension of genetic risk and predisposition as medicine becomes more informed by the genetics of complex, common diseases. If the recent pace of technology growth in genetics is any guide, the thousand-dollar genome may be here even sooner than its target date of 2014. Regardless of when it arrives, that capability will surely accelerate the push toward the use of genetic information as a guide to prevention and disease management. If we want the public to participate meaningfully in genetics-centered health-care decisions, we must begin preparing them now for a dramatically different view of genetics than is de rigueur in today's middle- and high-school classrooms. Similarly, students in our universities and graduate and professional schools need a curriculum that is up to the task of dealing with the genetics of the 21st century.

Inverting the sequence of topics and emphasizing complex traits could be the best way to accomplish these

goals, but it will require a new curriculum, professional development, and a concerted effort to improve the standards that drive teaching and learning. Whether students actually learn genetics better with an inverted curriculum than with a standard one is, of course, a testable question, and one that should be answered before implementing any large-scale changes in instruction. However, evaluation is difficult when the curriculum and teachers necessary for conducting this type of educational research are absent. As such, the ASHG has proposed a pilot project to develop sample curricula, provide professional development for teachers, and to evaluate learning outcomes for test and control classes.

Appendix A. Simplified Conceptual Flow for an Inverted Genetics Curriculum

1. Many traits show continuous variation (e.g., height, weight, forearm length, extroversion, etc).
2. Such traits (quantitative, or complex, traits) can be inherited and are strongly influenced by the environment.
3. The level of a quantitative trait can be understood in terms of "contributing factors" that offspring receive from parents.
   a. many contributing factors (in an additive model) lead to greater manifestation of a trait;
   b. fewer factors lead to less manifestation; and
   c. most combinations lead to an intermediate level of manifestation.

Concepts 4–8 are part of a traditional genetics unit:

4. Contributing factors that offspring receive from parents are called genes and are carried on the chromosomes passed from parents to offspring;
5. Genes exist in different forms called alleles;
6. Alleles are passed from generation to generation through the processes of meiosis and fertilization;
7. The movement of chromosomes (and the alleles they carry) during meiosis and fertilization leads to characteristic patterns of inheritance;
8. Following the inheritance of one gene (one pair of alleles) or two genes (two different pairs of alleles) reveals the patterns of inheritance first identified by Mendel:
   a. monohybrid crosses result in a 3:1 phenotypic ratio and reveal segregation of alleles; and
   b. dihybrid crosses result in a 9:3:3:1 phenotypic ratio and reveal independent assortment of genes.
9. The genes and alleles contributing to complex traits segregate and assort according to the same patterns identified by Mendel except that:
   a. in complex traits, many genes and alleles contribute to one trait rather than each gene contributing to a separate single-gene trait (e.g., as in dihybrid crosses); and
   b. when only one gene or allele primarily determines a trait (e.g., smooth pea texture vs. wrinkled), the resulting trait shows a rare pattern of variation (i.e., discrete, not continuous).

Acknowledgments

The author would like to thank Wylie Burke, Edward McCabe, and Joseph McInerney for helpful discussions and reviews.

Received: March 12, 2009
Revised: May 19, 2009
Accepted: May 21, 2009
Published online: June 25, 2009

Web Resources

The URLs for data presented herein are as follows:

Battelle/BIO/Biotechnology Institute report on bioscience education, http://www.battelle.org/spotlight/5-18-09BioEd09.aspx

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/omim/

References

1. Garrod, A. (1902). The incidence of alkaptonuria: A study in chemical individuality. Lancet *2*, 1616–1620.
2. Fernández-Cañón, J.M., Granadino, B., Beltrán-Valero de Bernabé, D., Renedo, M., Fernández-Ruiz, E., Peñalva, M.A., and Rodríguez de Córdoba, S. (1996). The molecular basis of alkaptonuria. Nat. Genet. *14*, 19–24.
3. Beltrán-Valero de Bernabé, D., Granadino, B., Chiarelli, I., Porfirio, B., Mayatepek, E., Aquaron, R., Moore, M.M., Festen, J.J., Sanmartí, R., Peñalva, M.A., and de Córdoba, S.R. (1998). Mutation and polymorphism analysis of the human homogentisate 1, 2-dioxygenase gene in alkaptonuria patients. Am. J. Hum. Genet. *62*, 776–784.
4. Bercovich, D., Elimelech, A., Zlotogora, J., Korem, S., Yardeni, T., Gal, N., Goldstein, N., Vilensky, B., Segev, R., Avraham, S., et al. (2008). Genotype-phenotype correlations analysis of mutations in the phenylalanine hydroxylase (PAH) gene. J. Hum. Genet. *53*, 407–418.
5. Smirnov, D.A., and Cheung, V.G. (2008). ATM gene mutations result in both recessive and dominant expression phenoytpes of genes and microRNAs. Am. J. Hum. Genet. *83*, 243–253.
6. McCabe, E.R.B. (2007). DAX1: Increasing complexity in the roles of this novel nuclear receptor. Mol. Cell. Endocrinol. *265–266*, 179–182.
7. Petersen, R.B., Parchi, P., Richardson, S.L., Urig, C.B., and Gambetti, P. (1996). Effect of the D178N mutation and the codon 129 polymorphism on the metabolism of the prion protein. J. Biol. Chem. *271*, 12661–12668.
8. Harder, A., Jendroska, K., Kreuz, F., Wirth, T., Schafranka, C., Karnatz, N., Théallier-Janko, A., Dreier, J., Lohan, K., Emmerich, D., et al. (1999). Novel twelve-generation kindred of fatal familial insomnia from Germany representing the entire spectrum of disease expression. Am. J. Med. Genet. *87*, 311–316.
9. Kovacs, G.G., Trabattoni, G., Hainfellner, J.A., Ironside, J.W., Knight, R.S., and Budka, H. (2002). Mutations of the prion protein gene phenotypic spectrum. J. Neurol. *249*, 1567–1582.

10. Zhang, Y.H., Huang, B.L., Jialal, I., Northrup, H., McCabe, E.R., and Dipple, K.M. (2006). Aysmptomatic isolated human glycerol kinase deficiency associated with splice-site mutations and nonsense-mediated decay of mutant RNAs. Pediatr. Res. *59*, 590–592.
11. Porteous, J.W. (2004). A rational treatment of mendelian genetics. Theor. Biol. Med. Model. *1*, 6–23.
12. Dipple, K.M., and McCabe, E.R.B. (2000). Phenotypes of patients with "simple" mendelian disorders are complex traits: Thresholds, modifiers, and systems dynamics. Am. J. Hum. Genet. *66*, 1729–1735.
13. De Gobbi, M., Viprakasit, V., Hughes, J.R., Fisher, C., Buckle, V.J., Ayyub, H., Gibbons, R.J., Vernimmen, D., Yoshinaga, Y., de Jong, P., et al. (2006). A regulatory SNP causes a human genetic disease by creating a new transcriptional promoter. Science *312*, 1215–1217.
14. Stranger, B.E., Forrest, M.S., Dunning, M., Ingle, C.E., Beazley, C., Thorne, N., Redon, R., Bird, C.P., de Grassi, A., Lee, C., et al. (2007). Relative impact of nucleotide and copy number variation on gene expression phenotypes. Science *315*, 848–853.
15. McCarroll, S.A., and Altschuler, D.M. (2007). Copy number variation and association studies of human disease. Nat. Genet. *39*, S37–S42.
16. Liu, L., Li, Y., and Tollefsbol, T.O. (2008). Gene-environment interactions and epigenetic basis of human diseases. Curr. Issues Mol. Biol. *10*, 25–36.
17. Battelle, BIO, and Biotechnology Institute. (2009). Taking the pulse of bioscience education in America: A state by state analysis. http://www.battelle.org/spotlight/5-18-09BioEd09.aspx
18. Mills Shaw, K.R., Van Horner, K., Zhang, H., and Boughman, J. (2008). Essay contest reveals misconceptions of high school students in genetics content. Genetics *178*, 1157–1168.
19. Popham, W.J. (2004). Curriculum matters. Am. Sch. Board J. *191*, 30–33.
20. Swanson, C.B. (2006). Making the connection: A decade of standards-based reform and achievement. Editorial Projects in Education Research. http://www.edweek.org/media/ew/qc/2006/MakingtheConnection.pdf.
21. Hott, A.M., Huether, C.A., McInerney, J.D., Christianson, C., Fowler, R., Bender, R., Jenkins, J., Wysocki, A., Markle, G., and Karp, R. (2002). Genetics content in introductory biology courses for non-science majors: Theory and practice. Bioscience *52*, 1024–1035.
22. Dobzhansky, T.G. (1973). Nothing in biology makes sense except in the light of evolution. Am. Biol. Teach. *35*, 125–129.
23. Wang, S.S., Fridinger, F., Sheedy, K.M., and Khoury, M.J. (2001). Public attitudes regarding the donation and storage of blood specimens for genetic research. Community Genet. *4*, 18–26.
24. Vohs, K.D., and Schooler, J.W. (2008). The value of believing in free will: Encouraging a belief in determinism increases cheating. Psychol. Sci. *19*, 49–54.
25. Hill, W.G., Goddard, M.E., and Visscher, P.M. (2008). Data and theory point to mainly additive genetic variance for complex traits. PLoS Genet. *4*, e1000008.
26. Bloom, M.V., Cutter, M.A., Davidson, R., Dougherty, M.J., Drexler, E., Gelernter, J., McCullough, L.B., McInerney, J.D., Murray, J., Vogler, G.P., and Zola, J. (2000). Genes, Environment, and Human Behavior. (Colorado Springs, CO: BSCS).
27. Nilsson-Ehle, H. (1914). Zur Kenntnis der mit der keimungsphysiologie des weizens in zusammenhang stehenden inneren faktoren. Zeitschrift für Planzenzüctung *2*, 153–187.
28. David, J.R., Gibert, P., Peatavy, G., and Moreteau, B. (2002). Variable modes of inheritance of morphometrical traits in hybrids between *Drosophila melanogaster* and *Drosophila simulans*. Proc. Biol. Sci. *269*, 127–135.