GENETIC EXPLANATIONS

Sense and Nonsense

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Big B, Little b

Myth #1 Is That Mendelian Genes Actually Exist

DAVID S. MOORE

WHILE I WAS WAITING to catch a flight out of Columbus, Ohio, I heard an evening news story about the discovery of a genetic mutation that supposedly allows affected individuals to get away with fewer than eight hours of sleep each night. Beyond the specifics of the story, there was nothing particularly special about it; these days, it is difficult to pass through a 24-hour news cycle without some reference being made to a new discovery in the realm of genetics. But the story drew my attention because there was a central assumption buried in it, one that most people now share, namely, that there are genes that determine aspects of our behaviors, appearance, and health. However, in general, most scientists who actually study the genetic material, DNA, no longer believe that genes single-handedly determine any of these sorts of characteristics.[1] Amazingly, there is also a growing consensus among these scientists that we need to rethink one of the assumptions at the center of that assumption: namely, that there are such things as genes in the first place.[2]

Our modern notion of genetics has a long and interesting history, but for most people, it is rooted in the work of Gregor Mendel, a monk who lived in the nineteenth century in a monastery in what is now the Czech Republic. Mendel's experiments with pea plants are famous because they are often described for us in school science classes when we are relatively young; in fact, for many people, this is the only work in genetics to which they are ever exposed.

Mendel's basic research question can be construed as follows: why is it that if parents are different from each other in one of their traits—say, their

coloration—their child sometimes looks like only one of the parents, and not like a blend of the parents? Although it is certainly sometimes the case that the offspring of a darker-skinned father and a lighter-skinned mother will have a skin tone midway between those of her parents, it is also the case that the child of a brown-eyed father and a blue-eyed mother does not typically have eyes that are colored midway between brown and blue, but instead has eyes that are as blue or brown as those of one of her parents. In Mendel's day almost everyone believed that parental traits—for example, height, body shape, and the color of things like skin, hair, and eyes—were blended in offspring, but this view was not consistent with Mendel's observations.[3] A particularly troubling sort of question for Mendel was why plants with purely red or purely white flowers can sometimes be the offspring of parent plants that grow only pink flowers; if inheritance works by a process of blending, two pink-flowered plants should never produce offspring with red or white flowers.

To study this question, Mendel bred generations of pea plants and examined such characteristics as the colors of the peas and how wrinkled they were.[4] In order to explain his observations—that inheritance was not working by a process of blending—he felt the need to posit the existence of material entities that (1) could be inherited, (2) dictated the characteristics of the pea plants, and (3) were effectively indivisible. We have come to know these entities as "genes," and the idea that they are indivisible means that if you have blue eyes, your children's children's children could have eyes every bit as blue as yours, even if your children and your children's children all have brown eyes and find themselves reproducing with brown-eyed mates.

The standard story we encounter in school tells of "genes for brown eyes" and "genes for blue eyes" that are not equally strong; using the same terminology that Mendel (1866) chose to use (but translated into English), we say that the genes for brown eyes are "dominant." The idea that genes for brown eyes are dominant comes from the observation that when individuals in a group of randomly chosen brown-eyed people mate with the individuals in a group of randomly chosen blue-eyed people, most of the children of those unions wind up with brown eyes. Consequently, dominant genes are typically represented by capital letters—in the case of a dominant gene for brown eyes, "B." Nondominant genes, called recessive genes, are typically represented by lowercase letters—in the case of a recessive gene for blue eyes, "b." And because you get one set of genes from your father and one from your mother, a given person's genes for eye color can be represented as either BB (a brown-eyed person,

because both their maternally contributed and their paternally contributed eye-color genes are for brown eyes), bb (a blue-eyed person, because both their maternally contributed and their paternally contributed eye-color genes are for blue eyes), or Bb (a brown-eyed person, because a gene for brown eyes was received from one parent, and a gene for blue eyes was received from the other parent, a combination that yields brown-eyed offspring because the gene for brown eyes is dominant over the gene for blue eyes). Interestingly, the standard story is that a brown-eyed person characterized by Bb genes can have eyes every bit as brown as a person characterized by BB genes. And it is because a fully brown-eyed person of the Bb type can have a blue-eyed child (provided that person's mate is either bb or Bb) that Mendel's conceptualization has been, over the past 100 years, able to completely sweep the older notion of blending inheritance from biologists' theories.

Mendel's conceptualization has been so successful at explaining observed phenomena that it is generally regarded as correct. It is at the core of many genetic analyses, and it is taught to schoolchildren no differently than we teach them that one plus one equals two. The only trouble with this situation is that on a concrete level, Mendel's conceptualization turned out to be simply wrong; in fact, there really are no such things as single genes that determine human eye colors.

As it happens, there have been geneticists who understood this from the start. As early as 1915, Alfred H. Sturtevant, discussing the red and white eye colors that are characteristic of fruit flies, wrote:

> Although there is little that we can say as to the nature of Mendelian genes, we do know that they are not "determinants." . . . Red is a very complex color, requiring the interaction of at least five (and probably of very many more) different genes for its production. . . . We can then, in no sense identify a given gene with the red color of the eye. . . . All that we mean when we speak of a gene for pink eyes is, a gene which differentiates a pink eyed fly from a normal one—not a gene which produces pink eyes per se, for the character pink eyes is dependent upon the action of many other genes.[5]

Likewise, modern genetic research has confirmed a similar understanding for human eye colors. As Sturm and Frudakis note,

> What is still commonly taught in schools today as a beginners guide to genetics [is] that brown eye colour is always dominant to blue, with two blue-eyed parents always producing a blue-eyed child, never one with brown eyes. Unfortunately, as with many physical traits, this simplistic model does not convey the complexities of real life and the fact is that eye colour is inherited as a polygenic not as a monogenic trait. Although not common, two blue-eyed parents can produce children with brown eyes.[6]

These researchers concluded that "the use of eye colour as a paradigm for 'complete' recessive and dominant gene action should be avoided in the teaching of genetics to the layperson, which is often their first encounter with the science of human heredity."[7] But it turns out that the Mendelian conception of genes not only fails to capture accurately what determines our eye colors; it actually fails to represent accurately how genes contribute to the development of *any* of our traits. In fact, it is no longer even clear that there really are such things as Mendelian genes contained in our DNA that determine the final forms of our biological or psychological traits.

It is well known that nearly a century after Mendel published his findings, Watson and Crick correctly deduced the structure of DNA, ushering in the modern age of genetics in the 1950s. At last it became possible to begin studying how molecules that could be passed from parents to their children could influence the children's characteristics. What is less well known is how exactly the "genes" that have since been identified in DNA are related to the "genes" Mendel effectively identified in the middle of the nineteenth century. Because both entities share the same name, it is generally assumed that they refer to the same things. But there is good reason to think otherwise.

First, segments of DNA—which are the kinds of genes that we typically hear about these days on the evening news—most definitely contribute to the observed characteristics of all living things.[8] However, unlike Mendelian genes—which to this day remain strictly theoretical—they do not *determine* those characteristics. Instead, biologists have learned that our characteristics always emerge following the process of development, which always entails interactions between DNA and environmental factors.[9] These factors include both the environment outside our bodies and nongenetic factors (such as hormones, for example) that are inside our bodies (and many of these nongenetic factors in our bodies can be influenced by the environment outside our bodies). Thus, although our traits are always influenced by genetic factors, they are always influenced by nongenetic factors, too; genes do not determine our characteristics, as Mendelian theory implies.[10]

Second, several recent discoveries have cast serious doubt on the idea that there are coherent entities in our DNA that can unambiguously be called "genes."[11] Perhaps the most important of these discoveries is related to a phenomenon known as RNA splicing. It turns out that genetic information is scattered among segments of DNA that do not have any currently understood purpose.[12] To illustrate, imagine for a moment that information in DNA represents an instruction for the development

of a characteristic (but please note that this is an imaginary scenario; in reality, the situation is quite a bit more complex than this, and many theorists would now argue that DNA is best not thought of as containing instructions).[13] If the instruction we are imagining is "begin to grow an arm here," it would ordinarily appear in the DNA scattered among purposeless information, like this: "do baryell note beginner to red dog rowing ckjswnrt bell tag an arm legitimate shopping ampere." (In case the instruction in question appears to be completely absent in that stream of information, let me use italics to help bring it out: "do baryell note *begin*ner *to* red dog *row*ing ckjswnrt bell tag *an arm* legitimate s*h*opping amp*ere.*") Obviously, to serve any useful function, the meaningless information—for instance, the "opping amp" segment separating the "h" from the "ere"—needs to be cut out of the sequence, and the meaningful portions must be spliced together to produce the functional instruction "here." Crazy, right? But we now understand that this is how the system works.[14]

Perhaps even more incredible is the phenomenon known as "alternative splicing," in which a single segment of DNA can be spliced in many different ways, producing many different kinds of "instructions."[15] For example, the seemingly gibberish-filled sentence above could be spliced to produce the instructions "begin growing a leg here," "grow a leg there," or even "do not grow arms here" (if you look back at the sentence, you should be able to make out each of these sentences buried deep in the gibberish). Clearly, a single segment of DNA—a gene—can have a variety of different effects depending on how it is interpreted, and remarkably, the interpretation favored in any given situation is typically a matter of context. Given this reality, the "genes" that molecular biologists are discovering every day are very different sorts of things from those Mendel's followers were imagining. We now know that DNA cannot be thought of as containing a code that specifies particular predetermined (or context-independent) outcomes.[16] In fact, what this means is that the same segment of DNA can do two entirely different things in different bodies (because different bodies can provide different contexts for their genes). So as unlikely as it sounds, it is possible that a particular gene in John Lennon might have done something different than that same exact gene would have done in J. Edgar Hoover. Indeed, a large team of biologists recently concluded that the various protein products coded for by "individual mammalian genes . . . may have related, distinct, or even opposing functions."[17]

Of course, if alternative splicing were a relatively rare event, one could still maintain that Mendelian genes are the rule and alternative splicing

the exception. But it has become clear that it is the other way around. In the late 1990s scientists were estimating that approximately 33 percent of our genes were subjected to alternative splicing, but by 2003 that number was up to 74 percent.[18] Now we know that alternative splicing is virtually universal, influencing the transcription of between 92 and 95 percent of our genes.[19] And alternative splicing is not the only phenomenon that has cast a large shadow over the Mendelian concept of the gene. Among other recently discovered phenomena that call this conceptualization into question is the finding that some gene products can function both as molecules used in protein production and as molecules that perform entirely different cellular functions.[20]

One consequence of this strange state of affairs is that there is currently debate among theorists about whether Mendel's gene concept has any applicability to DNA segments at all. Evelyn Fox Keller wrote in her book *The Century of the Gene* that "the concept of the gene [is on] the verge of collapse," and to date, there is still no agreed-on definition of the word "gene" in biological writings.[21] The fact of the matter is that in spite of the frequency with which the word is used these days, it does not actually refer to any one thing—or class of things—in particular.

What is clear is that the genes most of us envision inside us, calling the shots and determining our characteristics, are myths. There are no coherent entities in our cells that deterministically dictate how our bodies or our minds will develop. Instead, unprocessed, ambiguous lengths of DNA—which are not themselves single genes for specific traits—are cut up and combined in a variety of ways (depending on the context) to produce other molecules that then merely *contribute* to the construction of our traits.[22] Of course, DNA sequences can be altered as a result of exposure to, for example, radiation, and such mutations can contribute to the development of various disease states. But these mutated segments of DNA do not themselves produce diseases single-handedly, any more than a gene that is necessary for the development of blue eyes can single-handedly cause a person's irises to appear blue.[23] Even the symptoms of diseases like phenylketonuria, cystic fibrosis, and sickle-cell anemia—all of which are conditions that were once thought of as being directly caused by the actions of single genes—are now recognized as phenotypes caused by a variety of factors that interact in complex ways during development.[24]

The question then remains: why is Mendel's conceptualization still regularly taught in schools? The answer is that his 140-year-old approach still works to a reasonable extent when we are trying to predict

the characteristics of offspring produced when particular plants or animals mate. This is very useful, of course: breeders looking to maximize a characteristic in an animal—say, the amount of milk produced by a cow—can use Mendel's conceptualization to help them do that. But just because a particular methodology can help generate relatively accurate predictions does not mean that the conceptualizations of the people using the methodology accurately reflect reality. Five thousand years ago in Neolithic Ireland, a temple was constructed at Newgrange in such a way as to allow people to predict the coming of the longer days of springtime, but this was centuries before Stonehenge or Egypt's great pyramids were built, and long before anyone had an accurate conceptualization of how the earth's revolution around the sun—coupled with its tilted axis of rotation—produces our seasons. The predictions were accurate even though no one at the time had any real understanding of how or why the system was working as it was. Similarly, although what we learn about genetics in school has some heuristic value—that is, it can serve as an occasionally useful mental shortcut that leads to accurate predictions in some cases—we must not make the mistake of thinking that our genes work as Mendel hypothesized, namely, in a deterministic if-you-have-the-gene-you-are-doomed-to-have-the-trait kind of way. Because genetic factors always interact with nongenetic factors in the construction of our traits, the experiences and environments we encounter as we develop always matter, even if developmental science is still so much in its infancy that we currently do not understand much about *how* these nongenetic factors contribute to the construction of our traits.

In 2003 Lenny Moss wrote a book titled *What Genes Can't Do*. As a man with doctorates in both biochemistry and philosophy, Moss is exceptionally well situated to analyze critically the concepts used by biologists. One of the conclusions he reaches in his book is that we must begin to distinguish between two very different types of "genes," specifically, the segments of DNA that actually influence the development of our traits, and the hypothetical entities posited by Mendel that geneticists find useful in spite of the fact that they appear not to really exist. Moss calls the former "Genes-D" because they can be thought of as resources that organisms use during development, when our eyes, personalities, and bodies actually take on their characteristics. He calls the latter "Genes-P" because they are imagined to determine our traits preformationistically, that is, before development. Thus, although geneticists might find it useful (for the purposes of prediction) to imagine the existence of a Gene-P for blue eyes—the recessive little "b"—it is now quite

clear that there is no such thing as a DNA sequence (a Gene-D) that causes the development of blue eyes. As Moss puts it:

> The condition for having a gene for blue eyes or a gene for cystic fibrosis does not entail having a specific nucleic acid (DNA) sequence but rather an ability to predict, within certain contextual limits, the likelihood of some phenotypic trait. . . . Blue eyes are not made according to the directions of the Gene-P for blue eyes [because no such physical entity actually exists]. . . . Reference to the gene for blue eyes serves as a kind of instrumental short hand with some predictive utility.[25]

Griffiths and Stotz are among the other theorists who have joined Moss in his efforts to distinguish different possible meanings of the word "gene."[26]

Thus, although Genes-P are not actually physical things in our bodies at all, Mendel's notion can still facilitate prediction in certain well-controlled contexts (e.g., in greenhouses, scientific laboratories, and livestock-breeding facilities). In contrast, Genes-D actually are the real, material genes we inherit from our parents, but they do not determine our characteristics independently of the contexts in which we develop. In the real world of Genes-D, it is simply not the case that the presence of particular genes allows us to make unerring predictions about the characteristics an individual will ultimately develop. In this sense, then, there are no such things as genes for blue eyes, breast cancer, obesity, alcoholism, or anything else, including the ability to get away with fewer than eight hours of sleep each night. Although the DNA we inherit from our parents contributes to the development of all our characteristics, it determines none of them.[27] The environments in which we develop always matter too. So the next time you hear a news story about the discovery of a new gene for a particular disease, talent, or vice, be excited and curious, but be skeptical as well; the new discovery will most likely contribute to our understanding of the disease, talent, or vice in the long run, but when the complete story is finally told, there will be more to it than the gene alone.

Elle est la norme par excellence et, par suite, ne saurait rien contenir d'anormal." Durkheim, *Les règles de la méthode sociologique,* 4.

8. E.g., Canguilhem writes, "We think with Goldstein that the norm concerning pathology is above all an individual norm." Georges Canguilhem, *Essai sur quelques problèmes concernant le normal et le pathologique,* Publications de la Faculté des Lettres de l'Université de Strasbourg (Clermont-Ferrand: Imprimerie "La Montagne," 1943), 72. See also his essay "Le concept et la vie" [1966], in *Etudes d'histoire et de philosophie des sciences,* 3rd ed. (Paris: Vrin. 1975), 364.
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10. This is not to suggest that maintaining such a diet is an easy task, or that the almost inevitable relapses are not without dire risks. Probably the best discussions of the history and politics of PKU, as well as of risks associated with its treatment, are to be found in Diane B. Paul, "The History of Newborn Phenylketonuria Screening in the U.S.," in *Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing,* ed. N. A. Holtzman and M. S. Watson (Baltimore: Johns Hopkins University Press, 1998), 137–160; Diane B. Paul, "A Double-Edged Sword," *Nature* 405 (2000): 515; and Diane B. Paul and Paul J. Edelson, "The Struggle over Metabolic Screening," in *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s–1970s,* ed. S. de Chadarevian and H. Kamminga (Amsterdam: Harwood Academic Publishers, 1998), 203–220.
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4. Big B, Little b

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