PERSPECTIVES: GENETICS

Rethinking Behavior Genetics

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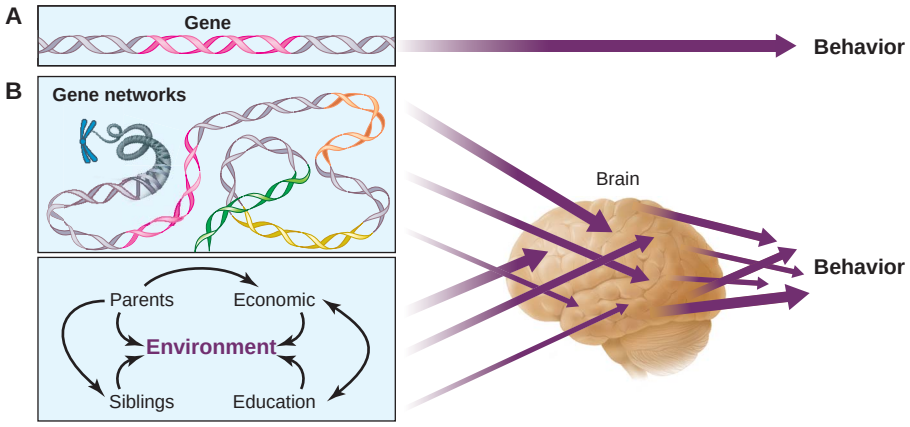
The first 100 years spent studying the genetics of behavior were straightforward. The aim was to determine the extent to which individual differences in the way people think, feel, and behave are due to variations in their genetic makeup. The basic approaches, first described by Sir Francis Galton in the late 1800s, were to compare identical and fraternal twins, other family members, and adoptees that had been raised together or apart.

The results were consistently striking, albeit slow to be accepted. Genes were shown to influence virtually every aspect of human personality, temperament, cognitive style, and psychiatric disorder. The effects of heredity were substantial, typically representing 30 to 70% of total variation, and highly replicable across societies and cultures. The long reach of genes extended from a friendly disposition to xenophobia, from bipolar disease to bedwetting, from getting married to keeping a job. About the only characteristics that seemed not to be at least partially heritable were purely learned traits such as the particular language one spoke or the religion one believed in (*1*).

The second century of behavior genetics has gotten off to a less satisfying start. The current aim is to identify the specific genes that contribute to individual differences and determine what they do in the brain. The approach is to search for DNA sequence variations that correlate with behavioral and personality traits, either by tracking anonymous markers close to the genes of interest in family members (linkage analysis) or by directly comparing the coding and regulatory sequences of candidate genes (association analysis).

The results have been disappointing and inconsistent. Large and well-funded linkage studies of the major psychiatric disorders including schizophrenia, alcoholism, Tourette syndrome, and bipolar disorder have come up empty-handed; not a single new gene has been conclusively identified. Most candidate gene findings have failed consistent replication, and even those that have been verified account for only a small fraction of total variation. Meanwhile, the statisticians who are supposed to be guiding and evaluating the research are unable to agree on how to design experiments or to interpret the results; their advice has proven as faddish (and useful) as the Hula-Hoop.

What's the problem? It's not the basic premise of linkage and candidate gene analysis; these approaches have identified dozens of genes involved in inherited diseases. Nor is it the lack of DNA sequence information; virtually the entire code of the human genome is now known. The real culprit is the assumption that the rich complexity of human thought and emotion can be reduced to a simple, linear relation between individual genes and behaviors (see the figure). This oversimplified model, which underlies most current research in behavior genetics, ignores the critical importance of the brain, the environment, and gene expression networks.



Two views of behavior genetics. (**A**) A simplified model underlying much behavior genetics research envisages a direct linear relationship between individual genes and behaviors. (**B**) The reality is likely to be far more complex with gene networks and multiple environmental factors impacting brain development and function, which in turn will influence behavior.

Three recent publications in *Science* show how measuring brain activity, environmental variables, and subtle alterations in gene expression can strengthen behavior genetics research. Hariri *et al*. (*2*) examined the influence of the serotonin transporter gene in the response of the amygdala to a fearful stimulus. There is a frequent DNA sequence variation in the control region of the human serotonin transporter gene that influences the expression levels of this protein and thereby the amount of synaptic serotonin, a potent modulator of emotional responses. When the polymorphism was discovered 6 years ago, it was found to be associated with abnormal levels of anxiety as assessed by self-report questionnaires (*3*). Although this finding has been replicated in numerous subsequent studies and verified in mice lacking the serotonin transporter gene, the effect of this gene on subjective measures of personality is modest, typically accounting for only a few percent of total variance (*4*).

Hariri and colleagues predicted that the gene would have a larger effect on directly measured brain activity. To test this idea, they performed functional nuclear magnetic resonance imaging on normal subjects as they performed either an emotional task—matching the affect of angry or afraid faces to a target face—or a sensorimotor control task. As expected, subjects with the poorly transcribed, high-anxiety serotonin transporter genotype showed a larger response of the amygdala to the emotional task than did the subjects with the highly transcribed, low-anxiety genotype; there was no difference between the two genotypes on the control task. Importantly, the difference between the two genotype groups was nearly fivefold, accounting for 20% of total variance—an effect size nearly 10-fold higher than in typical experiments using subjective behavioral or personality measures as the outcome. This is precisely as expected from viewing the brain as the obligatory intermediate between genotype and behavior (see the figure).

Technical advances in noninvasive functional neuroimaging will rapidly make this type of analysis both more routine and more powerful (*5*, *6*). Besides increasing signal size and thereby decreasing statistical noise, the main advantage of directly studying the brain will be to focus attention on those behaviors that have a dedicated brain circuit to begin with. It should be obvious that the heritability of some complex traits, like sexual orientation (*7*) and language acquisition (*8*), is probably the direct result of evolutionarily selected genetic programs whereas others, like getting divorced or cigarette smoking, are more likely to involve an unrelated set of

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characteristics that happen to be amalgamated by culture. All too often, though, the decision of what to study is driven by socio-medical politics rather than biological logic.

The study by Caspi *et al*. (*9*) also analyzed a promoter region polymorphism, in this case for the gene encoding monoamine oxidase A (MAOA), an enzyme that breaks down the neurotransmitters serotonin, dopamine, and norepinephrine. Although the MAOA gene had previously been implicated in aggression and impulse control in both humans and rodents (*10*), this transcriptional variant had not been associated with personality traits (*11*). Caspi *et al*. hypothesized that the effect of the gene would be more readily revealed if the environment were explicitly taken into account.

Their study group was a large birth cohort, representative of the male population of New Zealand, whose development had been carefully followed for 26 years. The environmental variable of interest was childhood maltreatment, and the outcome was a composite measure of antisocial behavior. Although the MAOA genotype by itself failed to predict antisocial behavior, there was a significant interaction with childhood history; individuals with both a low-activity genotype and previous maltreatment were by far the most likely to have committed a violent crime and to be diagnosed with conduct disorder. Over 85% of the males who had both "bad genes" and a "bad environment" developed some form of antisocial behavior by the time they were 26. It will now be crucial to repeat this intriguing finding on other populations with documented developmental histories.

The serotonin transporter and MAOA stories nicely illustrate how changes in regulatory rather than coding sequences can influence brain function and behavior. Such variations in gene expression probably play a predominant role in many types of individual differences, but this has been difficult to prove in humans because we are so genetically outbred. Yan and colleagues (*12*) devised an elegant solution to this problem. They measured the expression of different alleles in a single person who was heterozygous for the locus in question, thus avoiding the problems of extraneous differences in genetic background or other factors. Remarkably, even though most of the variations they studied were random single-nucleotide substitutions far from the promoter region, almost half of them were associated with detectable changes in messenger RNA levels. A few of the genes they studied are expressed in the brain, and many more will soon follow.

Although the Hariri, Caspi, and Yan reports provide tantalizing glimpses of how the study of complex traits can be improved, they are still at the primitive stage of examining single genes. This isn't how the brain works. Human behaviors, and the brain circuits that produce them, are undoubtedly the product of intricate networks involving hundreds to thousands of genes working in concert with multiple developmental and environmental events. Further advances in the field will require the development of techniques, such as microarray analysis, that measure the activity of many different genes simultaneously. Only then will the gene hunters have a shot at achieving the promises held out by the past century of classical behavior genetics research.

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PERSPECTIVES: COSMOLOGY

The Cosmic Web of Baryons

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About 80% of the mass in the universe is composed of "dark matter," which can only be detected through its effects on gravity. The nature of this material is entirely unknown. The remaining 20% is the kind of matter that we are all familiar with. Known as baryons, this matter forms the stars and galaxies in the local universe. But all the stars contain less than a tenth of the baryons that existed when the universe was young (*1*, *2*). Four recent papers shed light on the whereabouts of the missing baryons.

A few minutes after the big bang, the first elements—helium, deuterium, and trace amounts of other light elements—were produced. The relative amounts of these isotopes and elements are sensitive to Ω_b, the ratio of the baryon density to the critical density of the universe (*3*). Abundance measurements of primordial deuterium and other isotopes show that $\Omega_b = 0.04$.

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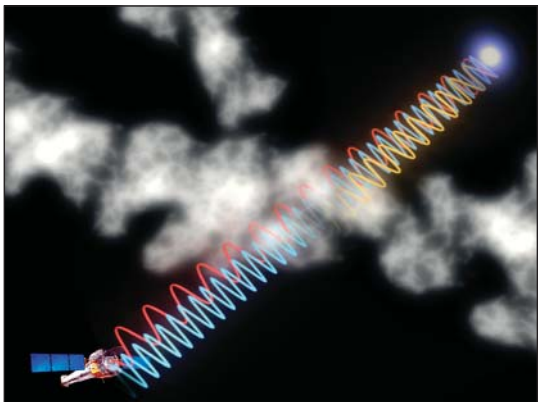
A few billion years later, when the universe was about one-quarter of its current age, active galactic nuclei (enormously luminous objects powered by massive black holes in the centers of galaxies) formed. In their spectra, we see absorption lines from very distant gas distributed across the universe. This gas is either neutral or moderately ionized, with a temperature below ~20,000 K. A veritable forest of absorption lines from hydrogen, the most common element, tells us that at this time, $\Omega_b = 0.04$, the same as shortly after the big bang.



Absorption by intergalactic gas. This artist's impression shows how x-ray emission from a distant active galactic nucleus reaches the Chandra x-ray observatory. Some x-rays are absorbed by gas filaments in the intergalactic space. See chandra.harvard.edu/photo/2002/igm/index.html.

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In the present-day universe, this "forest" of gas absorption lines has nearly vanished. At first, the gas was believed to have been incorporated into the galaxies and stars that we see today. However, a mass census of the local universe shows that the baryons in galaxies and cool gas amount to only $\Omega_b = 0.004$. Hence, 90% of the baryons must be located elsewhere.

Gas is still found between galaxies. For example, galaxy-clusters contain a stable hot atmosphere of gas with temperatures of up to 10^8 K and masses as great as, or greater than, those of the galaxies. Yet even including the gas in these clusters (and in less massive groups of galaxies), most of the baryons are still missing.

Theoretical calculations suggest a solution that features "filaments" of matter formed by gravitational collapse. The filaments, which are much larger than galaxy clusters and not nearly as dense, connect the many galaxy clusters and groups in a cosmic