



NEWS

Parsing the Genetics of Behavior

It takes more than one gene, or even a few genes, to make a personality trait. But which ones?

SOME YEARS AGO, A SCIENTIST-EDUCATOR told *Science* she would never be convinced of a biological basis for sex differences in math performance until someone showed her a “math gene.” The comment rests on a commonly held misconception: that simple one-to-one links exist between a gene and each facet of our personalities. Headlines such as “‘Ruthlessness’ Gene Discovered” or “‘Divorce Gene’ Linked to Relationship Troubles” feed that impression.

For some of us, it’s satisfying to attribute social awkwardness to anxiety genes or to think that the driver who cuts off other cars as he zips across lanes is pumped up by the “warrior” gene. Was it a bad dopamine receptor gene that made author Ernest Hemingway prone to depression? Can variations in a vasopressin receptor gene—a key to monogamy in voles—help explain adulterous behavior?

But as scientists are discovering, nailing down the genes that underlie our unique personalities has proven exceedingly difficult. That genes strongly influence how we act is beyond question. Several decades of twin, family, and adoption studies have demonstrated that roughly half of the variation in most behavioral traits can be chalked up to genetics. But identifying the causal chain in single-gene disorders such as Huntington’s disease is child’s play compared with the challenges of tracking genes contributing to, say, verbal fluency, outgoingness, or spiritual leanings. In fact, says Wendy Johnson, a psychologist at the University of Edinburgh, U.K., understanding genetic mechanisms for personality traits “is one of the biggest mysteries facing the behavioral sciences.”

All we really know so far is that behavioral genes are not solo players; it takes many to

orchestrate each trait. Complicating matters further, any single gene may play a role in several seemingly disparate functions. For example, the same gene may influence propensities toward depression, overeating, and impulsive behavior, making it difficult to tease out underlying mechanisms.

Each gene comes in a variety of flavors, or alleles, with varying degrees of sequence variation. One allele might contribute to a winning personality whereas another may raise the risk of mental illness. Environment plays a strong hand, bringing out, neutralizing, or even negating a gene’s influence. And genes interact with one another in unpredictable ways.

Science took a look at a few genes that have been in the news, with an eye toward understanding just what we do—and can—know about genes behind individual variation in temperament and personality.

Loves me, loves me not ...

A genetic screen for marital success? It sounds like a *Saturday Night Live* skit, but one Canadian company is actually offering just that sort of test. For \$99, Genesis Biolabs in St. John's, Newfoundland, will examine your—or your partner's—*vasopressin 1a receptor (AVPR1a)* gene, which this year grabbed headlines once as the “ruthlessness gene” and again as a “divorce gene.” But is the test really any more predictive than pulling petals off a daisy?

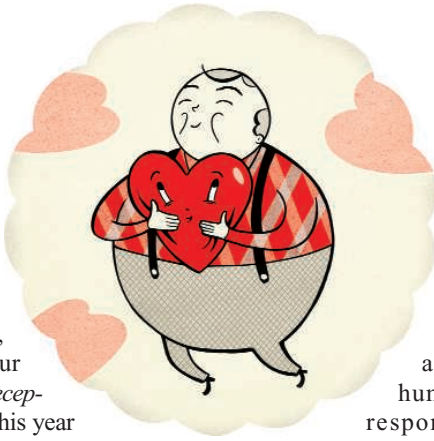
Vasopressin is a hormone involved in attachment to mates and offspring. Among voles, prairie voles are true to their mates. Meadow and montane voles prefer to play the field. Prairie voles have a few extra bases in the DNA in front of this gene, which influences how much and where vasopressin is released in the brain. This difference matters: Extra *AVPR1a* in the brain makes promiscuous meadow voles act more like monogamous prairie voles, spending more time with partners and grooming offspring (see p. 900).

Subsequent research has disproved any simple relationship between this gene and animal mating patterns. Nonetheless, scientists have now observed hints that variation in the human *AVPR1a* gene may influence the far more complex arena of human behavior.

A team led by Hasse Walum of the Karolinska Institute in Stockholm looked at the DNA preceding the *AVPR1a* gene in about 500 pairs of adult same-sex Swedish twins, all of them married or cohabiting for at least 5 years, and their partners. One short variant of a stretch of DNA in this region—there are several variants—was associated with less stable relationships. Answers to questions such as “How often do you kiss your mate?” and “How often are you and your partner involved in common interests outside the family?” reflected slightly lower feelings of attachment on the part of men with this variant, researchers reported in the 16 September issue of the *Proceedings of the National Academy of Sciences*. These men were less likely to be married and, among those in relationships, more likely to have experienced recent marital strife.

A gene worth testing to be assured of marital bliss? Not quite. “This is a brand-new study for which replication has not been attempted,” Johnson points out.

Another paper published last spring



showed a different link between *AVPR1a* and how people treat others. Richard Ebstein and colleagues at Hebrew University in Jerusalem reported that the length of the variant predicted how human subjects would respond in the “dictator game,” a way to assess altruism.

The researchers divided 200 volunteers into groups “A” and “B.” The “A’s” received \$14 each and were told to share as much as they wished with a “B” whom they had never met. About 18% kept all the money, and 6% gave it all away, with the rest somewhere in the middle. The people who behaved more selfishly—or, as the headlines proclaimed, more ruthlessly—had the same variant as the people with the less stable relationships in the study mentioned earlier. Ebstein speculates that in these people, vasopressin receptors were distributed in such a way that they provided less of a sense of reward from the act of giving (or loving). He and other scientists suspect that short variants of this gene will be implicated in autism and related disorders, because a core feature of autism is the inability to make connections with other people.

Although such theories are intellectually appealing, there are few replicated studies to give them heft, notes psychologist Simon Easta of Australian National University in Canberra. Too often, the subjects assessed are too different—How does one compare adolescents with married couples?—and the effect of environment too difficult to control for. So, getting reliable replications of studies involving behavior is, he says, “much harder than for studies of medical conditions.”

A “bounce-back” gene

Some people are like Woody Allen characters who melt down in the face of the smallest obstacles. Others seem to have a thick hide against life’s slings and arrows. The roots of such resilience may lie in a gene for a protein that regulates serotonin, a brain messenger that has been associated with emotional ups and

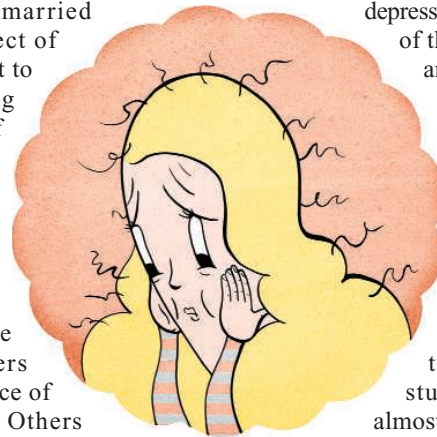
downs. The gene is called *SERT* for serotonin transporter.

In a classic paper published in *Science* in 1996, Klaus-Peter Lesch of the University of Würzburg, Germany, and colleagues at the U.S. National Institutes of Health reported that the length of the regulatory DNA at the beginning of *SERT* affected human behavior. Lesch’s team found that among 505 adults, those scoring high on various tests measuring “neuroticism”—depression and anxiety—tended to have one or two copies of a short variant whereas those who were more laid back had only the long form. The short version translates into more serotonin in the synapse, and too much serotonin leads to anxiety, in both animals and humans.

The short version accounted for up to 4% of the increase in anxiety and negative emotions in this group. Four percent doesn’t sound like much, but it’s huge for any personality trait, says psychologist Turhan Canli of Stony Brook University in New York state. In fact, he says, scientists have been able to find “no gene in the intervening years that has accounted for that much variability.”

In another landmark study published in 2003, researchers showed that the effect of the gene depends on life experiences. In Dunedin, New Zealand, researchers led by Avshalom Caspi of the Institute of Psychiatry in London tracked 847 people over more than 20 years from the age of 3. The researchers counted stressful life events occurring between the ages of 21 and 26 and asked subjects if they had been depressed in the past year.

Among people who had not reported any major life stresses, the probability of depression was low regardless of their *SERT* alleles. But among people who had been through four or more stressful experiences, 43% of those with two short alleles reported a major depressive episode—more than double the proportion of subjects with two long alleles. The study also showed that almost two-thirds of people with a history of abuse as children experienced major depression as adults if they had two short alleles. But child abuse didn’t raise the risk of adult depression in people with two long alleles.



Wanted: Math Gene

Last year, researchers at Washington University in St. Louis, Missouri, reported in the journal *Behavior Genetics* that certain aspects of IQ seemed to be related to *CHRM2* (*cholinergic muscarinic 2 receptor*), a gene whose protein is involved in pathways related to learning, memory, and problem-solving.

There, a team led by psychiatric geneticist Danielle Dick analyzed DNA and IQ test results from members of 200 families, 2150 individuals in all, as part of the Collaborative Study on the Genetics of Alcoholism. The team found a modest correlation between spatial and logical reasoning skills and certain variations in this gene.

But this study is one of very few to find any connection between genes and IQ—and it has yet to be replicated. This situation reflects a major paradox. Cognitive abilities are among the most genetically influenced of human behavioral traits: In studies over the years, scientists have estimated that somewhere between 40% to 80% of the variation in individual IQ scores in a given population is attributable to individual genetic differences. This is comparable to the genetic influence on height. Yet IQ genes have so far been impossible to nail down.

Unfortunately, however, the picture is still unclear. Psychologists at the University of Bristol in the United Kingdom published a meta-analysis of studies of this gene in July in *Biological Psychiatry*. They concluded that the published studies weren't based on large enough samples and that the interaction effect between the gene and stressful life events is probably "negligible."

The more researchers look into this gene, the more widespread its associations appear to be, adding to the confusion. "The serotonin transporter is implicated in everything from heart disease to sleep disorders and irritable bowel syndrome [as well as] schizophrenia, depression, attention deficit hyperactivity disorder, autism, and sensation-seeking, to name just a few," says Johnson. With such a broad scope, its effects on behavior must be "extremely general," she notes. So to call it a resilience gene doesn't really fit.

Warrior gene

In 2006, a New Zealand researcher, Rod Lea, stirred up a political storm when he reported that a variant of a gene for monoamine oxidase-A (MAO-A)—which breaks down neurotransmitters—could be behind risk-taking and aggressive behavior in Māori, the indigenous



Psychologist Robert Plomin of the Institute of Psychiatry in London has spent years scouring genomes for signs of loci associated with high IQ. The largest study yet was a genome-wide scan of DNA from 6000 children using 500,000 markers that could help pinpoint relevant DNA. The study compared groups of low-IQ children with groups of high-IQ children in hopes of teasing out markers linked to intelligence.

A handful of markers had a significant association with the aspects of IQ deemed most heritable, such as verbal ability. But none accounted for more than 0.4% of the variance. In other words, if the IQs of the population in question ranged from 80 to 130 points, the biggest gene effect the researchers could find would account for less than one-quarter of an IQ point.

It seems to be much easier to identify genes for disabilities than for abilities. "The only genes we have identified so far for cognitive ability are for mental retardation, and there are about 300 of them," some of which have quite severe repercussions, says Wendy Johnson of the University of Edinburgh, U.K. Many are also associated with other types of disabilities. But corresponding genius-type alleles, particularly for specific skills such as math ability, don't seem to exist.

—C.H.

people of New Zealand. The Māori have a warlike heritage, and a large proportion of this ethnic group carry a version of the gene shown in animal studies to be connected to aggressive behavior. Lea, a genetic epidemiologist at the Institute of Environmental Science and Research in Wellington, suggested that the gene could help explain Māori social and health problems such as fighting, gambling, and addictions. Although it's true that 60% of Asians (including Māori) carry the "warrior" variant (compared with 40% of Caucasians), Lea's critics quickly pointed out that it was too big a leap to ascribe Māori social problems to a single gene.

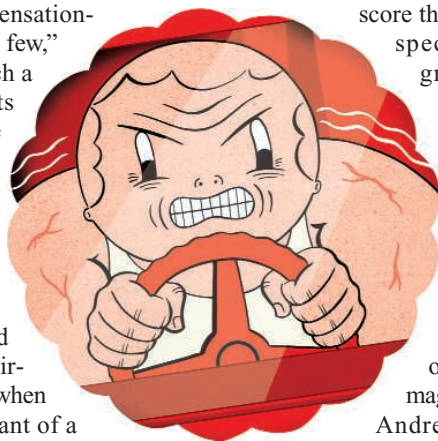
Yet brain-imaging studies "underscore the role of MAO-A [quite] specifically" in male aggressiveness, says neuroscientist Nelly Alia-Klein of Brookhaven National Laboratory in Upton, New York: Researchers have not detected connections between brain MAO-A and any other personality trait, she notes. In one study using functional magnetic resonance imaging,

Andreas Meyer-Lindenberg and colleagues at the National Institute of Mental Health (NIMH) in Bethesda, Maryland, presented normal subjects with neutral or "emotionally aversive" images such

as fearful faces. Monitoring activity in key brain regions such as the amygdala, the seat of fear, they found that the amygdalas of subjects with the "warrior" variant were hyper-responsive to such images. This sensitivity suggests that these individuals had problems regulating their emotions, which would also make them more likely to act on aggressive impulses, Meyer-Lindenberg reported.

But the gene variant isn't all that matters. Caspi's Dunedin study has shown that the environment—in the form of traumatic life events—plays a critical role in how this gene is expressed. Caspi's group reported in 2002 that the warrior *MAOA* variant is associated with violent and antisocial behavior but only in people with a history of abuse as children. These men were 2.8 times as likely as nonabused males with this genotype to develop behavioral problems that are often the precursor to a life of crime and drug abuse. Children with a different variant were less likely to develop antisocial problems in response to maltreatment (*Science*, 2 August 2002, p. 851).

Earlier this year, researchers drew similar conclusions based on the University of North Carolina's (UNC's) long-running National Longitudinal Study of Adolescent Health (NLSAH). Guang Guo of UNC Chapel Hill and colleagues analyzed genetic and social data from 1100 males and found that the undesirable effects from the "warrior" allele were only manifested when "social controls"—the steadying influence of a healthy



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family and social environment—were absent. They reported these results in the August 2008 issue of the *American Sociological Review*.

Testosterone seems to add toxicity to the mix. Rickard Sjöberg of Uppsala University in Sweden and David Goldman of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in Bethesda compared the genes and testosterone levels of 95 male alcoholics who have criminal records with those of 45 nonalcoholic, law-abiding controls. They reported that the combination of low MAO-A and high testosterone spells antisocial behavior, as revealed by answers on an aggression scale. If these findings are replicated, Goldman says, they might help clear up the relationship of testosterone to aggression: Maybe the hormone causes trouble only in males who also have this gene variant, he says.

The warrior gene as the root of social ills may be dead, but it still has a fighting chance as a gene important to behavior.

Can't get no satisfaction

What do Janis Joplin, Amy Winehouse, and Jimi Hendrix have in common? If you want to find examples of people whose brain reward circuits have gone haywire, the world of rock stars is probably a good place to look. But is a dopamine receptor gene at the heart of these musicians' addictions?

Scientists have proposed that deficiencies in the brain messenger dopamine lead to various unhealthy forms of sensation-seeking to compensate for the failure to get a charge out of things that give most people pleasure. For years, they've been trying to nail down the role of dopamine receptors, in particular one called the D2 dopamine receptor, in addictions to alcohol, drugs, smoking, or gambling, as well as eating disorders and obesity.

The A1 allele of this gene yields receptors that don't work as well, and that translates into less dopamine firing up the reward circuits. Some scientists think this can lead to a tendency to abuse drugs and engage in impulsive, sensation-seeking, or antisocial behavior—including problems forming relationships.

Scientists led by anthropologist Dan Eisenberg of Northwestern University in Evanston, Illinois, reported last year in *Evolutionary Psychology* that in a group of 195 student subjects at Binghamton University in New York state, those with A1 alleles were more likely to engage in early sexual activity but were less inclined to develop steady relationships. This putative role in attachment

has attracted the attention of political scientists looking for possible biological foundations for political behavior (see p. 912).

James Fowler and colleagues at the University of California, San Diego, picked up on reports such as this, as well as on animal research suggesting a connection between low dopamine receptor binding and low social bonding. They hypothesized that people with more efficient receptors—that is, with one or more A2 alleles—would be more trusting and therefore more likely to join a political party. After delving into NLSAH, they reported that, indeed, people with two A2 alleles (and no A1) were 8% more likely to form political attachments. Fowler called it “the first gene ever associated with partisan attachment.”

But that's only the latest in the long and contradiction-riddled history of research on the D2 dopamine receptor gene. Guo looked for a link between social behavior and this gene by assessing delinquency rates in teenagers. What he found was that boys with one A1 allele tended to have higher delinquency rates than those with two copies of the A2 allele. But the rates were also higher than in those boys with two A1 copies, suggesting that there is not a simple relationship between the amount of dopamine and behavior. Warns Goldman: “There is still more heat than light with this gene.”

Titrating anxiety

Scientists aren't doing much better at understanding the biological role of another player in the dopamine circuit. Dozens of studies have tried to figure out the gene for catechol *O*-methyltransferase (COMT), an enzyme that breaks down dopamine in the prefrontal cortex, the seat of higher cognitive functions such as planning and reasoning.

The two major variants of the gene code for enzymes that differ by one amino acid: The substitution of a valine for a methionine revs up the protein's activity fourfold. Both the high- and low-activity versions of the gene have their costs and benefits. Mice with the high-activity *COMT*—meaning less dopamine in the synapses—have poor memories and reduced sensitivity to pain.

With the gene knocked out, and thus higher dopamine activity, mice show increased startle and anxiety responses.

In humans as well, different versions of the gene have been implicated in cognitive and emotional dysfunction, says Goldman. In several studies, people with two low-activity *COMT* genes have tested high for fear, anxiety, and negative thinking. A study at Yale University in 2005, for example, gave 497 undergraduates personality tests and found that those with low-activity *COMT* genes were more neurotic and less extraverted.

In research getting closer to the interface between biology and behavior, published in the August issue of *Behavioral Neuroscience*, researchers reported a difference in a simple test that has come to be recognized as a reliable indicator for anxiety:

the startle reflex, as manifested in involuntary eye blinking in response to a sudden noise or unpleasant pictures. Among 96 female psychology students, individuals with two copies of the low-activity *COMT* had the most exaggerated startle responses, says Christian Montag of the University of Bonn in Germany.

Yet other work evaluating how well individuals organize their thoughts found low-activity *COMT* to be an asset. Psychiatrist Daniel Weinberger and colleagues at NIMH think they know why. Brain-imaging studies of 100 normal adults found that those with the low-activity *COMT* have denser nerve connections. Weinberger and others speculate that the elevated dopamine in the prefrontal cortex may bolster temporary connections, leading to better concentration but reduced ability to shift focus and more behavioral rigidity. As a result, a person may dwell excessively on stressful thoughts. So the gene seems to come with a tradeoff—better cognitive function but more anxiety—the scientists conclude.

The trouble with a lot of research on *COMT*, however, is that some studies find significant linkages only in women, and others don't find any at all. “*COMT* leaves a trail of intriguing hints,” says Edinburgh's Johnson, “but nothing that solidly replicates.”

—CONSTANCE HOLDEN

