BEHAVIORAL GENETICS

Getting the Short End of the Allele

Some people are much more vulnerable to emotional stresses than others. Ophelia, for example, couldn't handle Hamlet's abuse and drowned herself. But others get through painful breakups without a lot of melodrama. Now scientists claim they've identified a version of a common gene that plays a small but significant role in whether or not people get depressed in response to life stresses.

A team headed by Avshalom Caspi at the U.K. Medical Research Council's psychiatry research center at King's College, London, has nailed down the association through an unusual longitudinal study of New Zealanders. The ongoing project is designed to uncover genes activated by environmental circumstances—in this case, adverse life events.

Image not available for online use.

Outrageous fortune. A gene helps determine whether suffering leads to depression.

It's "absolutely spectacular" work, says psychiatrist Daniel Weinberger of the National Institute of Mental Health in Bethesda, Maryland, who says this is the biggest genetic fish yet netted for psychiatry. The study, he says, provides hard data for a principle clinicians and epidemiologists have known for a long time: Many genes related to psychiatric ills don't "make you sick in a vacuum [but help determine] how one deals with the environment."

The gene in question is for a chemical transporter called 5-HTT that fine-tunes transmission of serotonin, the neurotransmitter affected by the antidepressant Prozac and others of its ilk. The gene comes in two common versions: the long (l) allele and the short (s) allele. Animal studies have shown that in stressful conditions, those with two l's cope better. Mice with one or two copies of the s allele show more fearful reactions to stresses such as loud sounds. And monkeys with the s allele that are raised in stressful conditions have impaired serotonin transmission.

The new study, reported on page 386, is based on a cohort of 847 members of the Dunedin Multidisciplinary Health and Development Study, who have undergone a variety of assessments over more than 2 decades, starting at the age of 3. The researchers counted stressful life events, such as romantic disasters, bereavements, illnesses, and job crises, occurring between the ages of 21 and 26. Subjects were also assessed for whether, at age 26, they had been depressed in the past year. The researchers double-checked mood ratings by asking close friends about the subjects' depression symptoms.

Overall, 17% of the study participants reported a major depressive episode in the prior year and 3% reported having felt suicidal. Among people who had not reported any major stresses, the probability of depression was the same regardless of their 5-HTT alleles. But the negative effects of adverse experiences were stronger among people with one s allele and stronger still for those with two s alleles. For people with two s alleles (17% of the group), the probability of a major depressive episode rose to 43% among those who had been through four or more stressful experiences. That was more than double the risk for the subjects with two l's (who made up 31% of the group) who had been similarly buffeted by life's vicissitudes. The average score on a depression symptom inventory was likewise more than twice as high for stressed people with two s alleles as for those with two l versions.

Looking back on their records of childhood abuse for the cohort, the researchers found an additional link between 5-HTT gene variants and depression: Abuse as a child predicted depression after the age of 18 only in people carrying at least one s allele. Among the 11% who had experienced severe maltreatment, the double s–allele subjects ran a 63% risk of a major depressive episode. The l-allele participants averaged a 30% risk, regardless of whether they had been abused as children.

The researchers say they ruled out the possibility that an s allele could somehow predispose a person to getting tangled up in stressful events. There was no significant difference among the three genotype groups in the number of bad experiences they reported.

Weinberger says the study fits with other research showing that people with the short 5-HTT allele show more intense brain reactions to fearful stimuli than do those without this version (*Science*, 19 July 2002, p. 400). "The s alleles take things too seriously," he says, whereas the people with l's seem to be more resilient.

Harvard cognitive scientist Steven Pinker praises the study as a successful documentation of the elusive phenomena known as "gene-environment interactions," which, ▶

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ScienceScope

NCI Moves Ahead With National Tissue Bank

The National Cancer Institute (NCI) is launching a national bank of cancer tissue samples, NCI Director Andrew von Eschenbach announced at the annual meeting of the American Association for Cancer Research in Washington, D.C., last week.

Named the National Biospecimen Network, the bank is being set up by NCI officials and others as part of the National Dialogue on Cancer, a private entity von Eschenbach helped create (*Science*, 24 May 2002, p. 1395). It's still unclear where samples will be stored, what cancers will be included, and how the venture will be funded.

Not everyone believes that a national bank is the right approach. "I'm wary, as budgets get tighter, in investing a lot of money in something that may not get used," says Harold Varmus, president of the Memorial Sloan-Kettering Cancer Center in New York City. —JENNIFER COUZIN

State Sets Phosphorus Levels For Everglades

After nearly a decade of debate, a Florida environmental agency has agreed on a new standard for phosphorus levels that is intended to preserve the Everglades. But environmental advocates are critical of the rule, saying that it relies on calculations that make phosphorus levels appear deceptively low.

Roughly 80 tons of phosphorus get dumped into the Florida Everglades every year by way of runoff from sugar-cane farms and other agricultural industries, badly damaging parts of the 970,000-hectare ecosystem. Last week, the state's Environmental Regulation Commission voted to limit phosphorus to 10 parts per billion (ppb), a level that is one-fifth of the previous standard.

Most researchers agree that the new standard is reasonable. But measuring phosphorus concentration is tricky. Ronald Jones, an ecologist at Florida International University in Miami, says "they've used new math to create a 10 that really isn't 10" by relying heavily on geometric means. Ernie Barnett, director of ecosystem projects at the Department of Environmental Protection in Tallahassee, agrees that the calculations are "contentious" but denies that they would allow for levels higher than 10 ppb. —JENNIFER COUZIN he says, "are like the weather, according to Mark Twain: Everyone talks about them, nobody does anything about them—until now." Co-author Terrie Moffitt explains that one reason psychiatric epidemiologists have found the hunt for vulnerability genes so frustrating is that most studies haven't taken environmental exposure into account. She compares it to looking for genetic susceptibility to malaria in a sample that includes people who live in mosquito-free places.

Depression is likely influenced by many different genes in different people, so responses to various drugs and other treatments are unpredictable. This work, notes Steven Hollon, a psychologist at Vanderbilt University in Nashville, Tennessee, is the kind of study that will help scientists identify people most at risk of depression and potentially figure out "who will respond to what."

–CONSTANCE HOLDEN

ASTROPHYSICS

Western Europe Joins Gravitational-Wave Search

NAPLES, ITALY—For the past year, a pair of exquisitely sensitive detectors at opposite ends of the United States has been listening for ripples in spacetime known as gravitational waves. The detectors, together known as the Laser Interferometer Gravitational Wave Observatory (LIGO), have yet to detect a gravitational wave. Now a European dark horse is gearing up to give them some help—and competition. VIRGO, a smaller French-Italian detector, will be inaugurated at Cascina, near Pisa, next week. As LIGO researchers continue to tweak their detectors to get better sensitivity, there is a chance that VIRGO, which is better insulated against seismic noise, could snatch the prize first.

The $75 million VIRGO is a Michelson interferometer whose most visible components are two 3-kilometer-long perpendicular vacuum pipes. The instrument takes a laser beam, splits it in two, and sends one beam down each arm. Mirrors at the ends of both vacuum pipes bounce the beams up and down the arms 50 times before recombining them to produce an interference pattern. In theory, when a gravitational wave passes the interferometer, it will stretch and squash one of the arms with respect to the other, causing a measurable change in the interference pattern. That difference in length may be as small as one-millionth of the width of an atom. It will take a good deal of fine-tuning to hone VIRGO to that sort of sensitivity, according to Filippo Menzinger, director of the VIRGO observatory. "We hope to start taking data during spring next year," he says.

VIRGO researchers are hedging their bets, however, because these things can take time. More than 3 years after LIGO was commissioned, researchers there are still ironing out wrinkles due to diverse problems such as earthquake damage and noise from logging. But the second data run, which ended in April, showed that the sensitivity had improved 10-fold since the first run 6 months earlier, says David Shoemaker of the Massachusetts Institute of Technology, a member of the LIGO team. "Now the best interferometer is a factor of 10 away from the design specifications," he says.

Astrophysicists believe that only the most violent astronomical events will produce detectable gravitational waves. These include supernovae, spinning neutron stars, and binary systems containing pulsars or black holes. Such binary systems are expected to lose energy by shedding gravitational waves so furiously that their two components will get closer and closer and orbit each other faster and faster until they merge catastrophically, emitting a final powerful gravitational-wave burst. Gravitational-wave researchers look out for the characteristic waveforms these events produce among the noisy signal from their detectors. They expect that when their interferometers reach maximum sensitivity, they will be able to detect a few astronomical events per year.

Focal point. VIRGO is open for business, but achieving design sensitivity could take months or years.

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But with devices this sensitive, researchers' lives are a constant battle against vibrations and noise. These can come from a multitude of sources, including thermal vibrations from the experimental equipment itself, slight variations in the output of the laser, heating of the mirrors by the laser beam, and seismic noise from the ground. VIRGO and LIGO deal with most of these problems in comparable ways. "The technology at critical points is very similar, and the systems will work at quite comparable levels," says Shoemaker. "[VIRGO is] very nicely built."

The key difference has to do with how the instruments isolate their optics from external rumblings and noise. LIGO uses enormous masses and springs. That approach makes LIGO sensitive to higher frequency vibrations but prevents it from detecting signals below 60 hertz. VIRGO has fewer problems with seismic noise. It is built on a layer of soft sediment in the alluvial plain of the Arno River, a natural isolator from microseismicity. And its mirrors and other optical elements are suspended from six sets of coupled inverted pendulums that damp horizontal movements, combined with six sets of springs and weights that damp vertical movements—an arrangement that requires 10-meter-high towers to contain it. "We have checked the system, and it is working very well," says Adalberto Giazotto of Italy's National Institute for Nuclear Physics.

The seismic isolation should enable VIRGO to detect waves with lower frequencies, down to 10 Hz. It will be able to pick up the signal of a binary earlier in its death spiral and follow it longer, thus increasing the chance of detecting a binary before its catastrophic merger.

LIGO researchers aren't just looking on in envy at VIRGO's isolation system; they're working on an upgrade, dubbed Advanced LIGO, which will likely rely on advances made at GEO600, a smaller British-German detector near Hannover. These include an intricate method of suspending mirrors that reduces their motion due to thermal noise. "A lot of the technology used in GEO600 looks like the way of the future," says Shoemaker.

The full power of gravitational-wave astronomy will come when LIGO, VIRGO, and other detectors, such as GEO600, work together, looking for signals that are detected simultaneously by all of them. Triangulation by two observatories could localize the source of a wave only to a ring in the sky, whereas three can pinpoint the source to a small patch. And, says Shoemaker, the orientation of VIRGO in space will permit scientists to make a "range of measurements" regarding the waves' polarization that would be impossible with LIGO alone.

–ALEXANDER HELLEMANS AND CHARLES SEIFE

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