BEHAVIORAL GENETICS:  
Getting the Short End of the Allele  
Constance Holden

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.

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 HYPERLINK "http://www.sciencemag.org/cgi/content/short/301/5631/386"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. HYPERLINK "http://www.sciencemag.org/cgi/content/short/297/5580/400"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, 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."