

## NEUROSCIENCE: Mutant Gene Tied to Poor Serotonin Production and Depression

Researchers are closely scrutinizing a gene that could explain why some people are depressed--and also why they don't respond to antidepressant drugs that act on the neurotransmitter serotonin. A team headed by cell biologist Marc Caron of Duke University in Durham, North Carolina, has found that a group of severely depressed people were 10 times as likely as nondepressed controls to have a gene variant that reduces the expression of serotonin in the brain.

It's "a very exciting finding, as it represents the first functional [variant] in the key enzyme that synthesizes brain serotonin," says neuroscientist Huda Akil of the University of Michigan, Ann Arbor. "This is exactly what the 'serotonin hypothesis' of depression would have predicted." The study "suggests that we can begin to break major depression into subgroups," adds psychiatrist Thomas Insel, head of the National Institute of Mental Health.

The focus of the new study is the gene for tryptophan hydroxylase-2 (Tph2), an enzyme that controls serotonin production in the brain. The researchers had established in earlier mouse studies that there is a direct connection between Tph2 variation and the rate of serotonin synthesis (*Science*, 9 July, p. [217](#)). More recently, they found that human cells expressing one mutant form of the enzyme produced 80% less serotonin than is made by cells expressing the more common form. In the current study, reported online in *Neuron* on 9 December, Caron's group reveals that in a group of 87 elderly patients with a history of major depression, nine carried the mutated gene variant encoding the poor producer of serotonin, compared with just three in a control group of 219 individuals.



**Running low.** A mutant gene that decreases serotonin production may spur depression and stymie antidepressants.

Moreover, even though they weren't diagnosed with depression, the three control subjects with the Tph2 mutation still had problems, such as generalized anxiety, mild depression, or family histories of alcohol abuse or mental illness. The mutation, which changes the enzyme by a single amino acid, appears to be specific to unipolar depression--no one in a group of 60 patients with manic depression, or bipolar disorder, had it.

This is the first gene linked to unipolar depression that has a documented functional effect in brain chemistry, according to Caron. Last year a team headed by Avshalom Caspi of King's College, London, tied vulnerability to depression to a mutant version of a transporter gene that fine-tunes transmission of serotonin. However, says Caron, that was

an association study and not one in which the mutation was clearly shown to affect serotonin in the brain. "That's the exciting thing about our mutation," explains Caron. "We have been able to document in a biochemical way that it does affect function."

Caron and his colleagues suggest that the mutation could help predict who will be helped by selective serotonin reuptake inhibitors (SSRIs) such as Prozac. Seven of the depressed subjects with the mutant Tph2 allele failed to respond to SSRIs, and the other two required extremely high doses. Apparently, patients with the mutation put out so little serotonin that SSRIs, which cause the chemical to linger in a synapse, make little difference.

What's more, citing unpublished mouse studies, Caron hints that the mutation could play a role in some of the problems associated with SSRI use, including extreme agitation, psychosis, and suicidal behavior. Such reactions have caused both the United Kingdom and the United States to issue warnings about prescribing SSRIs to children and adolescents.

Depression is likely influenced by many different genes, but if future, larger studies support the importance of Tph2 variants, says Akil, "it would represent a real breakthrough" that could help clinicians detect susceptibility to depression as well as tailor drug treatment to a patient's genetic profile. Says Insel: "This is just the first paragraph in what will be a long and fascinating new chapter about serotonin and depression."