# Gene Influences Antidepressant Response

***Ed. Note:*** *The following is a press release from the National Institute Of Mental Health.*

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Whether depressed patients will respond to an antidepressant depends, in part, on which version of a gene they inherit, a study led by scientists at the National Institutes of Health (NIH) has discovered. Having two copies of one version of a gene that codes for a component of the brain's mood-regulating system increased the odds of a favorable response to an antidepressant by up to 18 percent, compared to having two copies of the other, more common version.

Since the less common version was over 6 times more prevalent in white than in black patients - and fewer blacks responded - the researchers suggest that the gene may help to explain racial differences in the outcome of antidepressant treatment. The findings also add to evidence that the component, a receptor for the chemical messenger serotonin, plays a pivotal role in the mechanism of antidepressant action.

The study, authored by National Institute of Mental Health (NIMH) researchers Francis J. McMahon, M.D., Silvia Buervenich, Ph.D., and Husseini Manji, M.D., along with collaborators at several other institutions, was posted online March 8 and will appear in the May, 2006 *American Journal of Human Genetics*.

"This discovery brings us closer to the day when clinicians will be able to offer treatment options and medications that are tailored and personalized to be optimally effective for individual patients," said NIH Director Elias A. Zerhouni, M.D.

However, the findings cannot yet guide treatment decisions.

"To our knowledge, this is the first demonstration of significant, replicated association between genetic variation and outcome of antidepressant treatment," added Manji, director of the NIMH's Mood and Anxiety Disorders Program.

In the initial phase of the NIMH-funded STAR*D (Sequenced Treatment Alternatives for Depression) trial, about 47 percent of the 2,876 participants experienced some improvement with the serotonin selective reuptake inhibitor (SSRI) citalopram (Celexa). The NIH scientists set out to find genetic factors that might help to explain why some patients fared better than others.

They screened genetic material from 1,953 of the STAR*D patients, a sample with a higher percentage of responders (69 percent), in part because patients who were doing well tended to stay in contact longer and were more likely to allow a blood sample to be drawn. The researchers looked for associations between treatment response and 768 known sites of variability in 68 suspect genes - sites where letters in the genetic code vary across individuals.

They found the strongest connection in the gene that codes for the serotonin 2A receptor, one of several proteins to which serotonin binds when brain cells communicate.

Located on cells in the brain's thinking center (cortex), the serotonin 2A receptor regulates circuits implicated in depression. Antidepressants, including citalopram, reduce the number of serotonin 2A receptors in animal cortex over the course of a few weeks - the same time-frame required for the drugs to work in humans - suggesting that the receptors are important in the drugs' mechanism of action.

Everyone inherits two copies of the serotonin 2A receptor gene, one from each parent. A tiny glitch in the gene's chemical sequence results in some people having an adenine (A) at the same point that other people have a guanine (G). So an individual can have gene types AA, AG or GG. Overall, the prevalence of the A version was 38 percent, compared to 62 percent for the G version in this sample. Fourteen percent had AA gene type, 43 percent AG and 43 percent GG. Since the site of variation is located in a stretch of genetic material with no known function, the researchers suspect that it may be just a marker for a still-undiscovered functional variation nearby in the gene.

Based on scores on a depression rating scale, close to 80 percent of patients who had AA responded to the antidepressant, compared to about 62 percent of those with GG. Thus, patients with the AA gene type were 16-18 percent more likely to benefit from the medication. Even patients with AG showed some increased benefit.

But this only applied to white patients, in whom the A version was more than six times more frequent than in black patients. There was no significant association between gene type and treatment outcome in black patients, who tended to fare less well in the trial overall.

"We now have to consider genetic factors as well as psychosocial issues in our attempts to explain why antidepressants do not help our black patients as much as they should," McMahon said. "The new findings help make a compelling case for a key role of the serotonin 2A receptor in the mechanism of antidepressant action."

Also participating in the study were: A. John Rush and Madhukar Trivedi, University of Texas Southwestern Medical Center; Gonzalo Laje, NIMH; Dennis Charney, Mount Sinai Hospital; Robert Lipsky, National Institute on Alcohol Abuse and Alcoholism (NIAAA); Alexander Wilson, Alexa Sorant, and George Papanicolaou, National Human Genome Research Institute (NHGRI); Maurizio Fava, Massachusetts General Hospital; and Stephen Wisniewski, University of Pittsburgh.

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