

Success or Failure of Antidepressant Citalopram Predicted by Gene Variation

Bethesda, Md., Aug. 1, 2007 – A variation in a gene called GRIK4 appears to make people with depression more likely to respond to the medication citalopram (Celexa) than are people without the variation, a study by the National Institute of Mental Health (NIMH), part of the National Institutes of Health, has found. The increased likelihood was small, but when people had both this variation and one in a different gene shown to have a similarly small effect in an earlier study, they were 23 percent more likely to respond to citalopram than were people with neither variation.

The finding addresses a key issue in mental health research: the differences in people's responses to antidepressant medications, thought to be based partly on differences in their genes. Some patients respond to the first antidepressant they attempt, but many don't. Each medication takes weeks to exert its full effects, and patients' depression may worsen while they search for a medication that helps. Genetic studies, such as the one described here, may lead to a better understanding of which treatments are likely to work for each patient.

Results of the study are in the August issue of *The American Journal of Psychiatry*, reported by lead researcher Francis J. McMahon, M.D., Silvia Paddock, Ph.D., of NIMH, and colleagues. Scientists from the National Human Genome Research Institute, the National Institute on Alcohol Abuse and Alcoholism, Mount Sinai School of Medicine, and University of Texas Southwestern Medical Center also contributed to the research.

"We're moving steadily closer to being able to personalize treatments based on patients' genetic variations. This is a crucial need for the millions of Americans who suffer from depression," said NIMH Director Thomas R. Insel, M.D. "New techniques have led to advances that would have been inconceivable a few years ago and are making individualized treatment an achievable goal."

The researchers studied DNA provided earlier by patients participating in a recently completed NIMH clinical trial, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. The trial showed that depressed patients who don't benefit from the first medication they try have a fair chance of being helped by others.

After the trial, researchers spelled out the DNA codes contained in 68 genes suspected of being involved in depression, collected from 1,297 of the patients who had participated in STAR*D. The genetic material included the occasional variations that

occur from person to person. Comparing the DNA codes of those who had responded to citalopram and those who hadn't, the scientists found that responders were more likely to have a variation in a gene called HTR2A. Results of that study were published in May 2006.

In the newest study, researchers examined the genetic material of more of the patients who had participated in STAR*D, for a total of 1,816 samples, and repeated the comparison of DNA from citalopram responders and nonresponders. They discovered that people with the variation in the GRIK4 gene had a higher likelihood of response, and again found that the variation in the HTR2A gene also made people more likely to respond. The results were reproduced, strengthening their validity.

The protein produced by HTR2A acts as a receptor on brain cells for the chemical messenger serotonin, one of several neurotransmitters that enable the cells to communicate with each other. The discovery that a variation in a serotonin-related gene could affect response to citalopram was not entirely surprising, since the serotonin system is known to be involved in depression. Citalopram targets this system.

But GRIK4 makes a protein that acts as a receptor in a different neurotransmitter system, the glutamate system. Recent studies suggest that the glutamate system also is involved in depression, an assertion supported by the new finding.

"We know that a number of biological mechanisms underlie depression and affect treatment. Findings like this one are building a picture of what they are and how they interact, and can reveal potential molecular targets for faster-acting and more effective medications," said McMahon.

Both of the genes consist of two copies each. The 23 percent increase in likelihood of response to citalopram occurred in people who carried the favorable variations in both copies of both of the genes. People with fewer of the favorable variations didn't have as high a response rate, but still were more likely to respond than were people with none of the favorable variations.

By using a recent technique called "SNP tags," the researchers used fewer resources, in less time, than usually required for these kinds of studies. SNP tags eliminated the need to compare all of the millions of structural units that comprise even a tiny segment of DNA - a resource- and time-intensive process - by organizing the units into more manageable blocks of information.

The National Institute of Mental Health (NIMH) mission is to reduce the burden of mental and behavioral disorders through research on mind, brain, and behavior. More information is available at the NIMH website: www.nimh.nih.gov. Source: National Institutes of Health