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Much touted 'depression risk gene' may not add to risk after all

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Stressful life events are strongly associated with a person's risk for major depression, but a certain gene variation long thought to increase risk in conjunction with stressful life events actually may have no effect, according to researchers funded by the National Institute of Mental Health (NIMH), part of the National Institutes of Health. The study, published in the *Journal of the American Medical Association,* challenges a widely accepted approach to studying risk factors for depression.

"Rigorous re-evaluations of published studies provide the checks and balances necessary for scientific progress," said Thomas R. Insel, M.D., director of NIMH. "We are still in the early days of understanding how genes and environment interact to increase the risk for depression."

Most mental disorders are thought to be caused by a combination of many genetic risk factors interacting with environmental triggers. However, finding the exact combinations continues to present significant challenges to research.

Advances in scientific understanding and technologies during the past decade have led to powerful tools for studying how genetic and environmental factors can affect a person's risk for disease. Such advances allowed mental health researchers in 2003 to show that a gene involved in serotonin activity increased the risk of major depression in people who had a number of stressful life events over a five-year period (see "More About the Science" below for more information about this gene and serotonin). Coming at a time of heightened research interest in

these gene-environment interactions and the relative lack of progress in the field for mental disorders, this study received wide acclaim and had a far-reaching influence. Not only have considerable resources been invested in subsequent studies that built on this finding, but also some researchers have proposed marketing the gene test to the public, claiming to be able to predict a person's risk for depression.

However, efforts to replicate the 2003 study's findings—a key step in scientific progress that helps show whether a particular finding was a chance event—have had inconsistent results.

To examine whether the 2003 study's finding had been confirmed, a group of scientists from NIMH and six universities with expertise in epidemiology, biostatistics, genetics, and psychiatry reviewed the status of relevant replication studies. Led by Kathleen Merikangas, Ph.D., of the NIMH Intramural Research Program, the workgroup did a meta-analysis, re-analyzing data on 14,250 participants in 14 studies published from 2003 through March 2009. Of these, the researchers also re-analyzed original data, including unpublished information, on 10,943 participants from 10 studies published before 2008. The workgroup analyzed these original data to see whether there were gender differences in the associations between the serotonin genotype, stressful life events, and depression.

By applying the same definitions of study variables and data analysis methods used in the 2003 study, the workgroup found a strong association between the number of stressful life events and risk of depression across the studies. However, the presumed high-risk version of the serotonin transporter gene did not show a relationship to increased risk for major depression, alone or in interaction with stressful life events, in the analysis of the 14 studies. Their findings were the same in men and women alone in the analysis of original data from 10 studies.

The workgroup noted that their analysis had some limitations. Individual level data were available for only 10 of the 14 studies published before 2008. However, these limitations would have had little effect on the overall findings because the number of participants in the studies not included was only a small proportion of the total sample.

These findings may account for the difficulty many researchers have faced in attempting to replicate the 2003 study. This analysis confirms some earlier reviews that had also questioned the validity of the gene's effect on depression risk. However, the workgroup emphasized that the intent of its analysis was not to deter research on gene-environment interactions for mental disorders.

"Identifying gene-environment interactions is most successful when studies can focus on a single gene with a major effect, or when the environmental exposure has a strong effect," said lead author Neil Risch, Ph.D., University of California, San Francisco and Kaiser Permanente Northern California. "In the case of modest gene effects or environmental impacts, the statistical power to detect an interaction will be low, and thus weak positive results should be interpreted carefully."

The authors concluded that incorporating environmental exposures in candidate gene studies (those that study a particular gene) may be as likely to yield false positive findings as the candidate gene studies themselves. Therefore, the results of other studies using the same approach as the 2003 study also deserve thorough review and meta-analysis.

"Even though our re-analysis did not confirm an association between the serotonin gene and depression, the finding that the environmental factor was strongly associated with depression in several studies reminds us that environmental factors are also involved in the complex pathways leading to mental disorders," noted Merikangas. "Future progress will require

thoughtful integration of the tools of genetics, epidemiology, and clinical and behavioral sciences."

Source: NIH/National Institute of Mental Health