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## Serotonin Gene, Even When Combined With Life Events, Has No Effect on Depression

Barbara Boughton

June 17, 2009 — A gene variation that has long been thought to increase the risk for depression in combination with stressful life events may have no effect after all, according to a new meta-analysis published in the June 17 issue of the *Journal of the American Medical Association*.

The serotonin-transporter gene has been the focus of genetics research on depression for years, because it results in decreased transport of serotonin into cells. While a 2003 study by Caspi et al, hailed as a breakthrough at the time, showed that a genetic variation in the promoter region of the gene increased risk for depression among those who had stressful life events over a 5-year period (Caspi A et al. *Science*. 2003;301:386-389), the new meta-analysis failed to find any association.

"The findings remind us that if we strictly look for genes involved in mental illness, without appreciating how complex the pathways are to these disorders, we may not have something at the end of the road that we can translate into prevention or treatment for illnesses such as depression," said Kathleen Ries Merikangas, PhD, senior investigator and chief of the genetic epidemiology research branch at the National Institute of Mental Health (NIMH).

Dr. Merikangas noted that this meta-analysis was performed by world-renowned experts in statistics, epidemiology, and genetics and rigorously examined data from 14 studies published from 2003 to 2009, but the research team was unable to replicate the findings of the previous study.

### Replication "Crucial"

The meta-analysis was the result of a workshop held by the NIMH after it began receiving thousands of applications to try to replicate the Caspi study and apply its approach to a range of other disorders, Dr. Merikangas said. While many studies had failed to find a link between the serotonin-transporter gene variation and depression, the Caspi study was the first to find it had an effect when stressful life events were also considered.

Yet since 2003, the scientific literature had failed to clearly validate these findings. While some studies supported the gene-environment interaction and its relationship to depression, others could not replicate the results. Since considerable resources were being devoted to studies on the serotonin-transporter gene, and some researchers had proposed marketing a test for it to the public, the question of whether the Caspi findings could be verified was crucial, Dr. Merikangas said.

In the meta-analysis, the researchers analyzed data on 14,250 participants in 14 studies. From among these, the researchers also reanalyzed original data on 10,943 participants in 10 studies.

The researchers did find an association between stressful life events and depression (odds ratio, 1.41; 95% CI, 1.25–1.57). However, they found no association between the serotonin-transporter gene variation (*5-HTTLPR*) and the mental disorder (OR, 1.05; 95% CI, 0.98–1.13) or any increased risk for depression when the genetic polymorphism and stressful life events were combined (OR, 1.01; 95% CI, 0.94–1.10).

Further, no link between the serotonin-transporter gene variation, stressful life events, and depression was found when data were analyzed for women, men, or both sexes combined.

"The strength of the meta-analysis is that it was very inclusive — we considered studies whether they claimed they had replicated the original findings of the Caspi study or not. We also went back and got the original data and reanalyzed them in exactly the same fashion as the Caspi study was done," said Neil Risch, PhD, lead author and director of the Institute for Human Genetics at the University of California, San Francisco. The meta-analysis applied the same definitions of study variables and used the same data-analysis methods used in the Caspi study, he added.

The research team did note that the meta-analysis had some limitations. Recoding of the data according to the methods used in the Caspi study may have led to findings different from those originally reported, they write. They were also able to obtain original data on only 10 of the studies. However, they note that data from the remaining studies would not have changed the report's conclusions, since the participants made up only 10% of the population studied.

While the study does seem to disprove theories about the serotonin-transporter gene, stressful life events, and depression, it confirms the importance of verifying genetic findings about mental disorders, Dr. Risch said. "It is critical that health practitioners and scientists in other disciplines recognize the importance of replicating such [genetic] findings before they can serve as valid indicators of disease risk or have utility for translation into clinical and public-health practice," the researchers write.

Dr. Risch also noted that studying candidate genes that may enhance risk for medical disorders, including psychiatric disorders, may not be as promising an approach as whole genomewide analysis, in which many genes with modest effects on an illness may be unearthed. "The technology for this analysis has really come down in price and is so much more efficient now. Most studies in the future will concentrate on this approach," he said.

### Doors Left Open

Still, whatever methods are used to study the interactions among genes, environment, and depression, the debate about the serotonin-transporter gene may still continue. While the new meta-analysis and its conclusions are significant, it probably will not settle questions about the effects of the serotonin-transporter gene variation and its interactions with life events in increasing risk for depression, according to Steven Hamilton, MD, PhD, a researcher in the genetics of psychiatric disorders and associate professor of psychiatry at the University of California, San Francisco.

"It's not the definitive answer, and there were some doors left open," he said. For instance, while the largest studies considered in the meta-analysis did not support the original Caspi findings, the smaller studies did verify its conclusions. "Some might argue that there's something different about these small studies that can't be picked up in a meta-analysis. Some studies were also performed more rigorously than others, and that wasn't taken into account," he said.

"There's still much that people can argue about on this issue," Dr. Hamilton noted. However, he added that the study does show that it is crucial for genetic studies, particularly those that study the interaction between genes and environmental factors, to be as consistent with one another and as rigorous as possible. "Gene-environment interaction studies require a heightened level of consensus in the field," he said.

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