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Resurrecting the So-Called 'Depression Gene': New Evidence That Our Genes Play a Role in Our Response to Adversity

University of Michigan Health System researchers have found new evidence that our genes help determine our susceptibility to depression.

Their findings, published online in the Archives of General Psychiatry, challenge a 2009 study that called the genetic link into question and add new support to earlier research hailed as a medical breakthrough.

In the summer of 2003, scientists announced they had discovered a connection between a gene that regulates the neurotransmitter serotonin and an individual's ability to rebound from serious emotional trauma, such as childhood physical or sexual abuse.

The journal Science ranked the findings among the top discoveries of the year and the Director of the National Institute of Mental Health proclaimed, "It is a very important discovery and a real advance for the field."
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That excitement was dampened in 2009, however, after the research was called into question by a study published in the Journal of the American Medical Association. The New York Times reported that analysis, which examined results from 14 different studies, showed the initial findings had "not held up to scientific scrutiny."

Srijan Sen, M.D., Ph.D, an Assistant Professor of Psychiatry at the University of Michigan Medical School, and his colleagues are presenting a new, broader analysis of the follow-up studies to date. The U-M team examined 54 studies dating from 2001 to 2010 and encompassing nearly 41,000 participants -- making it the largest analysis of the serotonin gene's relationship to depression.

"When we included all the relevant studies, we found that an individual's genetic make-up does make a difference in how he or she responds to stress," says Sen.

serotonin gene had a harder time bouncing back from trauma than those with long alleles.

Rudolf Uher, Ph.D., a clinical lecturer at the Institute of Psychiatry in London, says the U-M research will help cut through the debate about the genetic connection and refocus the field on making new advances to help those affected by mental illness.

"The major strength of the analysis is that it is the first such work that included all studies that were available on the topic," Uher says. "And it gives a very clear answer: the 'short' variant of the serotonin transporter does make people more sensitive to the effects of adversity."

The authors of the initial study from 2003 were also excited by the U-M team's results.

"Their careful and systematic approach reveals why the JAMA meta-analysis got it wrong," says Terrie Moffitt, Ph.D., a Professor at Duke University and one of the authors of the 2003 study. "We hope that the same journalists who were so hasty to publish a simplistic claim in 2009 will cover this more thoughtful new analysis."

When the U-M team restricted their analysis to the 14 studies included in the 2009 JAMA paper, they also failed to find a genetic link, suggesting to Sen that the scope of the analysis, not the methodology, was responsible for the new findings.

The U-M analysis found robust support for the link between sensitivity to stress and a short allele in those who had been mistreated as children and in people suffering with specific, severe medical conditions. Only a marginal relationship was found in those who had undergone stressful life events.

But that's also common sense. Different stressful life events may have very different effects, Sen says. For instance, there is no reason to think that the effects of divorce, at a biological level, would be similar to the effects of losing your home or being physically assaulted.

Still, the study results don't mean that everyone should run out and get a genetic test; additional susceptibility from having a short allele is only one factor among many that determine how an individual responds to stress, Sen says.

Additional research will help to map an individual's genetic profile for depression.

"This brings us one step closer to being able to identify individuals who might benefit from early interventions or to tailor treatments to specific individuals," Sen says.

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