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# Report on Gene for Depression Is Now Faulted

**By BENEDICT CAREY**

One of the most celebrated findings in modern psychiatry — that a single gene helps determine one's risk of depression in response to a divorce, a lost job or another serious reversal — has not held up to scientific scrutiny, researchers reported Tuesday.

The original finding, published in 2003, created a sensation among scientists and the public because it offered the first specific, plausible explanation of why some people bounce back after a stressful life event while others plunge into lasting despair.

The new report, by several of the most prominent researchers in the field, does not imply that interactions between genes and life experience are trivial; they are almost certainly fundamental, experts agree.

But it does suggest that nailing down those factors in a precise way is far more difficult than scientists believed even a few years ago, and that the original finding could have been due to chance. The new report is likely to inflame a debate over the direction of the field itself, which has found that the genetics of illnesses like schizophrenia and bipolar disorder remain elusive.

"This gene/life experience paradigm has been very influential in psychiatry, both in the studies people have done and the way data has been interpreted," said Dr. Kenneth S. Kendler, a professor of psychiatry and human genetics at Virginia Commonwealth University, "and I think this paper really takes the wind out of its sails."

Others said the new analysis was unjustifiably dismissive. "What is needed is not less research into gene-environment interaction," Avshalom Caspi, a neuroscientist at Duke University and lead author of the original paper, wrote in an e-mail message, "but more research of better quality."

The original study was so compelling because it explained how nature and nurture could collude to produce a complex mood problem. It followed 847 people from birth to age 26 and found that those most likely to sink into depression after a stressful event — job loss, sexual abuse, bankruptcy — had a particular variant of a gene involved in the regulation of serotonin, a brain messenger that affects mood. Those in the study with another variant of the gene were significantly more resilient.

"I think what happened is that people who'd been working in this field for so long were desperate to have any solid finding," Kathleen R. Merikangas, chief of the genetic epidemiology research branch of the National Institute of Mental Health and senior author of the new analysis, said in a phone interview. "It was exciting, and some people thought it was the finding in psychiatry, a major advance."

The excitement spread quickly. Newspapers and magazines reported the finding. Columnists, commentators and op-ed writers emphasized its importance. The study provided some despairing patients

with comfort, and an excuse — “Well, it is in my genes.” It reassured some doctors that they were medicating an organic disorder, and stirred interest in genetic testing for depression risk.

Since then, researchers have tried to replicate the gene finding in more than a dozen studies. Some found similar results; others did not. In the new study, being published Wednesday in The Journal of the American Medical Association, Neil Risch of the University of California, San Francisco, and Dr. Merikangas led a coalition of researchers who identified 14 studies that gathered the same kinds of data as the original study. The authors reanalyzed the data and found “no evidence of an association between the serotonin gene and the risk of depression,” no matter what people’s life experience was, Dr. Merikangas said.

By contrast, she said, a major stressful event, like divorce, in itself raised the risk of depression by 40 percent.

The authors conclude that the widespread acceptance of the original findings was premature, writing that “it is critical that health practitioners and scientists in other disciplines recognize the importance of replication of such findings before they can serve as valid indicators of disease risk” or otherwise change practice.

Dr. Caspi and other psychiatric researchers said it would be equally premature to abandon research into gene-environment interaction, when brain imaging and other kinds of evidence have linked the serotonin gene to stress sensitivity.

“This is an excellent review paper, no one is questioning that,” said Myrna Weissman, a professor of epidemiology and psychiatry at Columbia. “But it ignored extensive evidence from humans and animals linking excessive sensitivity to stress” to the serotonin gene.

Dr. Merikangas said she and her co-authors deliberately confined themselves to studies that could be directly compared to the original. “We were looking for replication,” she said.