A Great Gene Environment Depression Story Fades Into the Sunset

Andrew A. Nierenberg, MD

It was a great story. Caspi et al.[1] made a big splash with their 2003 article that looked at the Dunedin Multidisciplinary Health and Development Study, which observed 1,037 children starting at age 3 years until they were age 26 years. They showed quite convincingly that those who were homozygous for the short arm of the serotonin transporter gene *5-HTTLPR* (serotonin-transporter-linked polymorphic region), repeat polymorphism in *SLC6A4* (solute carrier family 6 member 4) (ss) were more likely to develop depressive symptoms and major depressive episodes under conditions of negative life events compared to those with the long arm (l/s or l/l). Furthermore, the more negative life events and the more certainty of maltreatment, the greater the risk of depression. Of those with at least four stressful life events, almost twice as many (33%) with an s allele became depressed compared to those who were homozygous for l/l (17%).[1]

These findings fit in with the narrative that those who are susceptible to the negative effects of stress are more likely to develop depression than those who are less genetically susceptible. According to Google Scholar, other researchers have cited the Caspi et al.[1] article 8,635 times. The article was conducted at a time when researchers used a candidate gene strategy, in part, because genotyping was so expensive. They would pick out a candidate gene and then see if it had any relationship to the genes of interest. But as science progresses, methods evolve and cherished beliefs crumble.

In 2019 along comes one of the largest genome wide association studies of depression ever done.[2] In this study, Border et al.[2] analyzed data from between 62,138 and 443,264 people to assess 18 previous candidate genes and gene/environment interactions, including *SLC6A4*. No associations were found. As the authors state, "The genetic underpinnings of common complex traits such as depression appear to be far more complicated than originally hoped." The great story appears to have been a false positive and confirms that we should be humble and cautious when a story just seems too good to be true.

Andrew A. Nierenberg, MD, is the Thomas P. Hackett, MD, Endowed Chair in Psychiatry, the Director of the Dauten Family Center for Bipolar Treatment Innovation, and the Co-Director, Center for Clinical Research Education, Massachusetts General Hospital; and a Professor of Psychiatry, Harvard Medical School.

Address correspondence to Andrew A. Nierenberg, MD, via email: psyann@Healio.com.

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