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Genetics in depression: What's known, what's next

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Even with modern genomewide analysis techniques, it has proven difficult to identify genetic factors affecting risk for depression, according to a topical review in the January issue of *Harvard Review of Psychiatry*.

"Given the established heritability of depression, there is every reason to expect that with larger studies we will be able to identify genetic loci," said Erin C. Dunn, ScD, MPH, of Massachusetts General Hospital and colleagues. "Identifying ways to generate these larger samples is one of the many challenges before us."

So Far, Limited Success in Identifying Genetic Factors in Depression

Dunn and coauthors review recent findings and future directions in research on the genetics of depression. Depression is one of the most common, disabling, and costly mental health conditions. Understanding its causes—including genetic and environmental factors and the interactions between them—has important implications for prevention and treatment.

Depression is known to run in families. Based on studies of twins, it's estimated that genetic factors account for about 40 percent of the variation in population risk of depression.

In recent years, techniques such as genome-wide association studies (GWAS) have accelerated efforts to identify the genetic factors underlying a wide range of diseases. But so far, GWAS of depression have found no associations. The limited success of GWAS in identifying depression-associated genetic variants is in contrast to the results for other psychiatric disorders. For example, studies have identified more than 100 genetic variants for schizophrenia and bipolar disorder.

What's more, genetic factors previously suggested as contributors to depression risk—such as genes affecting dopamine or serotonin neurotransmission—haven't been confirmed.

Possible Gene-Environment Effects?

Another issue is that GWAS have not as of yet accounted for the role of environment. Studies of gene-by-environment (GxE) look at how genes may modify the effect of environmental factors on depression risk (or vice versa).

A 2003 study suggested an interaction between a gene variant affecting serotonin and stressful life events—for example, childhood maltreatment. Thus far, studies have yielded conflicting results for GxE—while some studies supported this GxE effect, others showed no associations with the serotonin variant. However, other GxE studies have suggested more consistent associations for other genes, including genes involved in regulating the stress response.

Dunn thinks the combination of GWAS and GxE may help yield new insights. "Large-scale GxE studies may lead to new discoveries about the genetic basis of depression," she said.

The researchers discuss the reasons for the lack of success of GWAS and GxE studies, and the many challenges that lie ahead. Because of the

complex genetic architecture of depression, very large studies will be needed to detect the individually small contributions of multiple genes. Approaches to account for the multiple types of depression will be needed as well.

Meanwhile, Dunn and colleagues believe that research on the genetics of depression is at "at an exciting, yet challenging crossroad." Dunn added, "Although the search to identify genes associated with depression has proven challenging, many scientists worldwide are working hard to identify its genetic underpinnings. With this knowledge, we can ultimately help prevent the onset of the disorder and improve the lives of those who already suffer."

More information: "Genetic Determinants of Depression: Recent Findings and Future Directions." journals.lww.com/hrpjournal/Fu … sion___Recent.1.aspx

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