NKPD1 gene variant increases depression risk

April 4 2017

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A study of people from an isolated village in the Netherlands reveals a link between rare variants in the gene NKPD1 and depressive symptoms. The findings are published in the current issue of *Biological Psychiatry*. The study, led by co-first authors Najaf Amin, PhD, of Erasmus University Medical Center in the Netherlands and Nadezhda Belonogova of the Russian Academy of Sciences in Novosibirsk, Russia, helps

researchers understand the molecular pathology of the disease, which could eventually improve how depression is diagnosed and treated.

Genetics play a strong role in risk for depression, but the identification of specific genes contributing to the disorder has eluded researchers. "By sequencing all of the DNA that codes for mRNA and ultimately, proteins, Dr. Amin and colleagues found a single gene that may account for as much as 4% of the heritable risk for depression," said Doctor John Krystal, Editor of Biological Psychiatry.

To identify the gene, the researchers assessed data from the Erasmus Rucphen Family study, which was composed of a collection of families and their descendents living in social isolation until the past few decades. In a population like this, genetic isolation leads to an amplification of rarely occurring variants with little other genetic variation, providing a more powerful cohort for the discovery of rare variants. Nearly 2,000 people who had been assessed for depressive symptoms were included in the analysis.

Using whole-exome sequencing to examine portions of DNA containing genetic code to produce proteins, Amin and colleagues found that several variants of NKPD1 were associated with higher depressive symptom scores. The association between depressive symptoms and NKPD1 were also replicated in an independent sample of people from the general population, although the replication sample highlighted different variants within NKPD1.

"The involvement of NKPD1 in the synthesis of sphingolipids and eventually of ceramides is interesting," said Dr. Amin, referring to the predicted role of NKPD1 in the body. Altered sphingolipid levels in blood have been associated with depression and have been proposed as a therapeutic target for major depressive disorder.

"We are the first to show a possible genetic connection in this respect," said Dr. Amin, adding that this implies that such a therapy might be beneficial for patients carrying risk variants in the NKPD1 gene.

As with other psychiatric disorders, depression lacks genetic or biochemical markers to aid diagnosis and treatment of the disorder. According to Dr. Amin, moving depression treatment into the era of precision and personalized medicine will require a transition to objective and unbiased measurements where patients are stratified based on the molecular pathology of the disease. "NKPD1 may be one such molecular mechanism," she said.

More information: Najaf Amin et al. Nonsynonymous Variation inNKPD1Increases Depressive Symptoms in European Populations, *Biological Psychiatry* (2017). DOI: 10.1016/j.biopsych.2016.08.008

Provided by Elsevier

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