

Glutamate neurotransmission system may be involved with depression risk

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Researchers using a new approach to identifying genes associated with depression have found that variants in a group of genes involved in transmission of signals by the neurotransmitter glutamate appear to increase the risk of depression. The report published in the journal *Translational Psychiatry* suggests that drugs targeting the glutamate system may help improve the limited success of treatment with current antidepressant drugs.

"Instead of looking at DNA variations one at a time, we looked at grouping of genes in the same biological pathways and found that a set of genes involved in glutamatergic transmission was associated with the risk of depression," says Jordan Smoller, MD, ScD, director of the Psychiatric and Neurodevelopmental Genetics Unit in the Massachusetts General Hospital (MGH) Department of Psychiatry, senior author of the study. "Our findings are particularly interesting in light of recent studies showing that drugs affecting glutamate transmission can have rapid antidepressant effects."

While the risk of depression clearly runs in families, the genome-wide association studies typically used to identify gene variants that increase disease risk have been unable to find strongly associated genes. The research team – which includes investigators from the Broad Institute of MIT and Harvard and other research centers in the U.S., Australia and the Netherlands – adopted a strategy called gene set pathway analysis.

Starting with a set of genes that previous studies had implicated in

depression, they used an analysis process called [text mining](#) to scan the [medical literature](#) for information on the [biological function](#) of these genes. Based on those findings, they identified 178 biological pathways that included these genes. Only one of those pathways – the one involved in transmission of [neural signals](#) carried by glutamate – was significantly associated with the risk for depression.

"Glutamate is the excitatory transmitter most widely used by the central nervous system, and several studies in animals and humans have suggested that it may play a role in depression," explains Smoller, an associate professor of Psychiatry at Harvard Medical School. "Most intriguingly, recent studies have found that ketamine – a drug known to block one glutamate receptor – appears to have antidepressant effects that are much faster than those of traditional antidepressants, which can take several weeks to become effective. Now additional research needs to confirm these findings and investigate exactly how variation in glutamate function affects brain systems involved in depression."

Provided by Massachusetts General Hospital

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