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Interaction between gene variants may alter brain function in schizophrenia

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A collaborative study led by investigators from Massachusetts General Hospital (MGH) is giving what may be the first look at how interactions between genes underlie a key symptom of schizophrenia, impaired working memory. Functional imaging studies reveal how a combination of common variants in two genes is associated with reduced activity of important brain structures in schizophrenia patients but not in normal controls. The report has been released online in the Early Edition of the *Proceedings of the National Academy of Sciences*.

"Schizophrenia is a highly genetic disorder, but we are learning that its genetics are not straightforward. In most cases potential risk genes appear to have very small effects on symptoms, making it difficult to attribute clinical findings to particular genes," says Joshua Roffman, MD, of the MGH Department of Psychiatry, the study's lead author. "To amplify some of these subtle effects, we and others are looking how the genes affect brain function, rather than just behavior."

The team – which included investigators from the University of New Mexico, University of Iowa and University of Minnesota through the MIND Clinical Imaging Consortium – used functional MRI to scan an area of the prefrontal cortex known to be critical to working memory in 79 schizophrenia patients and 75 healthy controls as they completed a memory task. Levels of cortical activity were then analyzed for any association with common variants in two genes: MTHFR, which regulates folate metabolism and has been associated with schizophrenia risk, and COMT, which is involved with dopamine processing during

working memory.

Although the schizophrenia-associated variant of MTHFR was found in both patients and controls, when the working memory task become more difficult, weaker cortical function associated with that variant was seen only in the schizophrenia patients, not in controls. While variations in COMT did not influence cortical activation patterns on their own, the combined effects of both genes did make a difference. The reduction in cortical function seen in patients with the schizophrenia-associated MTHFR variant was even more pronounced in patients who also had a COMT variant previously associated with less efficient working-memory-related brain activity.

"Based on the known effects of these alleles on brain biochemistry, it is likely that our results reflect cumulative impacts of the gene variants on dopamine signaling, particularly in the prefrontal cortex. These findings may help us to identify patients more likely to benefit from new treatments targeting the dopamine and folate systems," Roffman says. "We are hopeful that this approach will catalyze the development of individualized treatment regimens, since it will allow us to examine the effects of treatment-related genes on brain function using a much smaller groups of study participants."

Source: Massachusetts General Hospital