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Working out the genetic risk for ADHD

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Genetics play a strong part in the development of attention-deficit/hyperactivity disorder (ADHD), but the path from a gene to risk for the disorder has remained a black box to researchers.. A new study in *Biological Psychiatry* suggests how the risk gene ADGRL3 (LPHN3) might work. ADGRL3 encodes the protein latrophilin 3, which regulates communication between brain cells. According to the study, a common variation of the gene associated with ADHD disrupts its ability to regulate gene transcription - the formation of mRNA from DNA that leads to expression of the gene.

Evidence for ADGRL3 in ADHD risk had already been stacked against it - common variants of the gene predispose people to ADHD and predict severity of the disorder. The study, led by Dr. Maximilian Muenke of the National Human Genome Research Institute in Bethesda, Maryland, brings scientists closer to understanding how ADGRL3 contributes to risk by providing functional evidence that implicates a transcription factor in the pathology of the disorder.

According to first author Dr. Ariel Martinez, the study is an effort to address limitations of existing ADHD medications that don't work for all patients, and develop new medication targeting the protein encoded by the ADGRL3 gene.

"In this new era of genomics and precision medicine, the key to success lies in dissecting genetic contributions and involving some level of patient stratification," Martinez said.

The researchers analyzed the ADGRL3 genomic region in 838 people, 372 of whom were diagnosed with ADHD. Variants in one particular segment within the gene, the transcriptional enhancer ECR47, showed the highest association with ADHD and with other disorders that commonly occur alongside ADHD, such as disruptive behaviors and substance use disorder.

ECR47 functions as a transcriptional enhancer to boost gene expression in the brain. However, the researchers found that a variation of ECR47 associated with ADHD disrupted ECR47's ability to bind an important neurodevelopmental transcription factor, YY1 - an indication that the risk variant interferes with gene transcription.

In an analysis of postmortem human brain tissue from 137 control subjects, they also found an association between the ECR47 risk variant and reduced ADGRL3 expression in the thalamus, a key brain region for coordinating sensory processing in the brain. The findings link the gene to a potential mechanism for ADHD pathophysiology.

"The brain is extraordinarily complex. Yet we are starting to pull on the threads of that complex biology that reveal mechanisms through which disorders like ADHD might develop," said Professor John Krystal, Editor of Biological Psychiatry. "In this case, Martinez and colleagues help us to understand how variation in the ADGRL3 gene might contribute to thalamic dysfunction in ADHD."

More information: Ariel F. Martinez et al. An Ultraconserved Brain-Specific Enhancer Within ADGRL3 (LPHN3) Underpins Attention-Deficit/Hyperactivity Disorder Susceptibility, *Biological Psychiatry* (2016). DOI: 10.1016/j.biopsych.2016.06.026

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