# New gene study of ADHD points to defects in brain signaling pathways

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Pediatric researchers analyzing genetic influences in attention-deficit/hyperactivity disorder (ADHD) have found alterations in specific genes involved in important brain signaling pathways. The study raises the possibility that drugs acting on those pathways might offer a new treatment option for patients with ADHD who have those gene variants—potentially, half a million U.S. children.

"At least 10 percent of the ADHD patients in our sample have these particular genetic variants," said study leader Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia. "The genes involved affect neurotransmitter systems in the brain that have been implicated in ADHD, and we now have a genetic explanation for this link that applies to a subset of children with the disorder."

The study appears online in *Nature Genetics*.

ADHD is a common but complex neuropsychiatric disorder, estimated to occur in as many as 7 percent of school-age children and in a smaller percentage of adults. There are different subtypes of ADHD, with symptoms such as short attention span, impulsive behavior and excessive activity. Its causes are unknown, but it tends to run in families and is thought to be influenced by many interacting genes. Drug treatment is not always effective, particularly in severe cases.

The study team did whole-genome analyses of 1,000 children with

ADHD recruited at The Children's Hospital of Philadelphia, compared to 4,100 children without ADHD. The researchers searched for copy number variations (CNVs), which are deletions or duplications of DNA sequences. They then evaluated these initial findings in multiple independent cohorts that included nearly 2,500 cases with ADHD and 9,200 control subjects. All the study subjects were children of European ancestry.

Among those cohorts, the research team identified four genes with a significantly higher number of CNVs in children with ADHD. All the genes were members of the glutamate receptor gene family, with the strongest result in the gene GMR5. Glutamate is a neurotransmitter, a protein that transmits signals between neurons in the brain. "Members of the GMR gene family, along with genes they interact with, affect nerve transmission, the formation of neurons, and interconnections in the brain, so the fact that children with ADHD are more likely to have alterations in these genes reinforces previous evidence that the GRM pathway is important in ADHD," said Hakonarson. "Our findings get to the cause of the ADHD symptoms in a subset of children with the disease."

"ADHD is a highly heterogeneous disorder, and separating out the different subgroups of genetic mutations that these children have is very important," said co-first author Josephine Elia, M.D., a child psychiatrist at Children's Hospital and an ADHD expert. She added that thousands of genes may contribute to the risk of ADHD, but that identifying a gene family responsible for 10 percent of cases is a robust finding in a common neuropsychiatric disorder such as ADHD. Overall, according to the CDC, 5.2 million U.S. children aged 3 to 17 have been diagnosed with ADHD.

Elia said the fact that their study identified gene variants involved in glutamate signaling is consistent with studies in animal models,

pharmacology and brain imaging showing that these pathways are crucial in a subset of ADHD cases. She added, "This research will allow new therapies to be developed that are tailored to treating underlying causes of ADHD. This is another step toward individualizing treatment to a child's genetic profile."

Hakonarson expects this study will set the stage for further discoveries of ADHD-related genes along GMR signaling pathways. Moreover, the current research strongly suggests that selective GRM agonists could be tested in clinical trials as a potential therapy for ADHD in patients harboring particular CNVs. He added that further preclinical studies must first be done to evaluate candidate drugs.

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