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ADHD genes found, known to play roles in neurodevelopment

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Pediatric researchers have identified hundreds of gene variations that occur more frequently in children with attention-deficit hyperactivity disorder (ADHD) than in children without ADHD. Many of those genes were already known to be important for learning, behavior, brain function and neurodevelopment, but had not been previously associated with ADHD.

"Because the gene alterations we found are involved in the development of the nervous system, they may eventually guide researchers to better targets in designing early intervention for children with ADHD," said lead author Josephine Elia, M.D., a psychiatrist and ADHD expert at The Children's Hospital of Philadelphia.

The study appeared online today in the journal *Molecular Psychiatry*.

Unlike changes to single DNA bases, called SNPs or "snips," the alterations examined in the current study are broader changes in structure. Called copy number variations (CNVs), they are missing or repeated stretches of DNA. CNVs have recently been found to play significant roles in many diseases, including autism and schizophrenia Everyone has CNVs in their DNA, but not all of the variations occur in locations that affect the function of a gene. The current study is the first to investigate the role of CNVs in ADHD.

Individually, each CNV may be rare, but taken together, a combination of changes in crucial regions may interact to raise an individual's risk for

a specific disease. "When we began this study in 2003, we expected to find a handful of genes that predispose a child to ADHD," said study co-leader Peter S. White, Ph.D., a molecular geneticist and director of the Center for Biomedical Informatics at Children's Hospital. "Instead, there may be hundreds of genes involved, only some of which are changed in each person. But if those genes act on similar pathways, you may end up with a similar result—ADHD. This may also help to explain why children with ADHD often present clinically with slightly different symptoms."

ADHD is the most common neuropsychiatric disorder in children, affecting an estimated 1 in 20 children worldwide. It may include hyperactive behavior, impulsivity and inattentive symptoms, with impaired skills in planning, organizing, and maintaining focus. Its cause is unknown, but it is known from family studies to be strongly influenced by genetics.

Drawing on DNA samples from the Children's Hospital pediatric network, the researchers analyzed genomes from 335 ADHD patients and their families, compared to more than 2,000 unrelated healthy children. The team used highly automated gene-analyzing technology at the Center for Applied Genomics at Children's Hospital, directed by Hakon Hakonarson, M.D., Ph.D., a co-leader of this study.

The study team found a similar quantity of CNVs in both groups. However, distinct patterns emerged. Among 222 inherited CNVs found in ADHD families but not in healthy subjects, a significant number were in genes previously identified in other neurodevelopmental disorders, including autism, schizophrenia and Tourette syndrome. The CNVs found in ADHD families also altered genes important in psychological and neurological functions such as learning, behavior, synaptic transmission and nervous system development.

"We took a systems biology approach, grouping genes into groups with common functions," said White. "We found that the sets of genes more likely to be changed in ADHD patients and families affected functions that made sense biologically." For instance, said White, the team found four deletions of DNA in a gene recently linked to restless legs syndrome, a type of sleep disorder common in adults with ADHD.

Another deletion occurred in a gene for a glutamate receptor. Glutamate is a neurotransmitter, a protein that carries signals in the brain. While ADHD medications act on dopamine and serotonin, which are also neurotransmitters, this new finding may suggest an important role for glutamate as well, at least for some ADHD patients.

"As we delve into the genetics of very complex diseases such as ADHD, we find many contributing genes, often differing from one family to another," added White. "Studying the functions of different genes allows us to identify biological pathways that may be involved in this neuropsychiatric disorder."

Some of the biological pathways involved in ADHD may also be common to other neurological conditions, say the researchers. Likewise, there is some overlap among the CNVs found in ADHD that also occur in autism, schizophrenia and other neurological disorders. This overlap was not surprising, said Elia, because ADHD patients frequently also have one of more of these disorders. However, as researchers learn more about specific genes in neurological conditions, the hope is that researchers might in the future personalize treatments to a patient's own genetic profile, to achieve more targeted, specific therapies.

Elia and White stressed that much further work must be done before genetic findings lead to ADHD treatments.

More information: Elia et al, "Rare Structural Variants Found in

Attention-Deficit Hyperactivity Disorder Are Preferentially Associated with Neurodevelopmental Genes," *Molecular Psychiatry,* published online, June 23, 2009.

Source: Children's Hospital of Philadelphia (news : web)