

Gene variant is associated with brain anatomy

A variant of the dopamine receptor gene may be associated with attention-deficit/hyperactivity disorder (ADHD) and with thinner tissue in areas of the brain that handle attention, but also appears associated with better clinical outcomes among individuals with the disorder, according to a report in the August issue of *Archives of General Psychiatry*, one of the JAMA/Archives journals.

ADHD is among the most heritable of neuropsychiatric disorders, according to background information in the article. Several genes have been identified as possibly associated with the condition. One of the most frequently cited is a polymorphism or different type of the dopamine D4 receptor gene (DRD4) known as the 7-repeat form. “Previous studies have suggested that carriers of the risk allele [alternate form of a gene] may also have a unique neuropsychological, clinical and pharmacological profile, although there remains considerable debate over the exact nature of this phenotype [characteristic],” the authors write.

Philip Shaw, M.D., Ph.D., of the National Institute of Mental Health, Bethesda, Md., and colleagues compared 105 children with ADHD (average age 10.1) to 103 healthy controls, using both magnetic resonance imaging (MRI) and DNA testing. Sixty-seven (64 percent) of the children with ADHD also had a follow-up clinical evaluation an average of six years later.

Among all participants, both with and without ADHD, having the 7-repeat form of DRD4 was associated with thinner tissue in areas of the brain known to control attention—the right orbitofrontal/inferior prefrontal and posterior parietal cortex. Similar regions were also generally thinner in participants with ADHD than those without. “As a result of the overlapping main effects of genotype and diagnosis, there was a stepwise increment in cortical thickness in these regions, with subjects with ADHD with the DRD4 7-repeat allele having the thinnest cortex, followed by subjects with ADHD lacking the 7-repeat allele, healthy 7-repeat allele carriers and finally by healthy non-carriers,” the authors write.

Analyses of the children who participated in the follow-up revealed that the differences between the brain anatomy of those with and without the DRD4 7-repeat allele were most pronounced in early development and disappeared by late adolescence. Individuals with ADHD who carried the DRD4 7-repeat allele had better clinical outcomes and regained thickness in their right parietal cortex—a sign previously linked to better outcomes and that parallels ADHD’s natural history of improvement with age.

“Cross-sectional studies have found regional increases in cortical thickness to correlate with cognitive function, including enhanced verbal declarative and extinction memory, and with ‘fluid’ intelligence in older, healthy subjects,” the authors write. “In children, gains in verbal knowledge are mirrored by change in the cortical thickness of speech areas. While our current study demonstrates changes in cortical thickness and symptoms occurring in tandem, a future goal is to refine further our appreciation of cortical thickness by examining the links between this neuroanatomical variable and putative cognitive endophenotypes [invisible but measurable components on a disease pathway] for ADHD, such as response inhibition and working memory.”

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