Genetic influences on ADHD symptom dimensions: Examination of a priori candidates, gene-based tests, genome-wide variation, and SNP heritability.

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Abstract

Although the heritability of ADHD is estimated to be high, identifying specific genetic markers remains challenging. Most studies to date have examined the genetic basis of ADHD by employing dichotomous diagnostic phenotypes, but, as ADHD symptoms tend to be phenotypically dimensional, an alternative and potentially informative approach are to examine continuous indices of inattention and hyperactivity-impulsivity symptoms. The current study aimed to identify genetic effects on dimensionally-focused adult ADHD-related phenotypes in 990 individuals of European ancestry with intentionally low levels of substance misuse to avoid confounding. The study used four complementary approaches: (1) analysis of a priori candidate loci identified in prior meta-analytic work; (2) gene-based analysis; (3) hypothesis-free genome-wide association testing; and (4) single nucleotide polymorphism (SNP) heritability via genomic-relatedness-matrix restricted maximum likelihood analysis (GREML). The GREML analysis included a bivariate model to test whether the ADHD symptom dimensions index the same genetic liability. The results revealed significant differential associations between two a priori loci and ADHD phenotypes, rs6296 in HTR1B with inattention and rs3746544 in SNAP-25 with hyperactivity-impulsivity. No significant gene-based or genome-wide associations were detected, but SNP heritability revealed that a large portion of genetic variance was accounted for by common SNPs (44%, 55%, and 59% for inattention, hyperactivity-impulsivity, and total ADHD, respectively) and substantial shared genetic variance across inattention and hyperactivity-impulsivity (86%). These findings reveal both unique and common patterns of genetic influences across dimensional ADHD-related phenotypes. More broadly, these findings reveal the value in using multiple methods to understand the genetic aetiology of ADHD.