Testing for the mediating role of endophenotypes using molecular genetic data in a twin study of ADHD traits.

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Abstract

Family and twin studies have identified endophenotypes that capture familial and genetic risk in attention-deficit/hyperactivity disorder (ADHD), but it remains unclear if they lie on the causal pathway. Here, we illustrate a stepwise approach to identifying intermediate phenotypes. First, we use previous quantitative genetic findings to delineate the expected pattern of genetically correlated phenotypes. Second, we identify overlapping genetic associations with ADHD-related quantitative traits. Finally, we test for the mediating role of associated endophenotypes. We applied this approach to a sample of 1,312 twins aged 7-10. Based on previous twin model-fitting analyses, we selected hyperactivity-impulsivity, inattention, reading difficulties (RD), reaction time variability (RTV) and commission errors (CE), and tested for association with selected ADHD risk alleles. For nominally significant associations with both a symptom and a cognitive variable, matching the expected pattern based on previous genetic correlations, we performed mediation analysis to distinguish pleiotropic from mediating effects. The strongest association was observed for the rs7984966 SNP in the serotonin receptor gene (HTR2A), and RTV (P = 0.007; unadjusted for multiple testing). Mediation analysis suggested that CE (38%) and RTV (44%) substantially mediated the association between inattention and the T-allele of SNP rs3785157 in the norepinephrine transporter gene (SLC6A2) and the T-allele of SNP rs7984966 in HTR2A, respectively. The SNPs tag risk-haplotypes but are not thought to be functionally significant. While these exploratory findings are preliminary, requiring replication, this study demonstrates the value of this approach that can be adapted to the investigation of multiple genetic markers and polygenic risk scores.