From Rare Copy Number Variants to Biological Processes in ADHD

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Abstract

Objective: Attention deficit hyperactivity disorder (ADHD) is a highly heritable psychiatric disorder. The objective of this study was to define ADHD-associated candidate genes and their associated molecular modules and biological themes, based on the analysis of rare genetic variants.

Methods: The authors combined data from **11 published copy number variation studies** in 6,176 individuals with ADHD and 25,026 control subjects and prioritized genes by applying an integrative strategy based on criteria including recurrence in individuals with ADHD, absence in control subjects, complete coverage in copy number gains, and presence in the minimal region common to overlapping copy number variants (CNVs), as well as on protein-protein interactions and information from cross-species genotype-phenotype annotation.

Results: The authors localized 2,241 eligible genes in the 1,532 reported CNVs, of which they classified 432 as high-priority ADHD candidate genes. The high-priority ADHD candidate genes were significantly coexpressed in the brain. A network of 66 genes was supported by ADHD-relevant phenotypes in the cross-species database. Four significantly interconnected protein modules were found among the high-priority ADHD genes. A total of 26 genes were observed across all applied bioinformatic methods. Lookup in the latest genome-wide association study for ADHD showed that among those 26 genes, *POLR3C* and *RBFOX1* were also supported by common genetic variants.

Conclusions: Integration of a stringent filtering procedure in CNV studies with suitable bioinformatics approaches can identify ADHD candidate genes at increased levels of credibility. The authors' analytic pipeline provides additional insight into the molecular mechanisms underlying ADHD and allows prioritization of genes for functional validation in validated model organisms.