Multivariate Imaging Genetics Study of MRI Gray Matter Volume and SNPs Reveals Biological Pathways Correlated with Brain Structural Differences in Attention Deficit Hyperactivity Disorder

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Background:
Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder affecting children, adolescents, and adults. Its etiology is not well understood, but it is increasingly believed to result from diverse pathophysologies that affect the structure and function of specific brain circuits. Although one of the best-studied neurobiological abnormalities in ADHD is reduced fronto-striatal-cerebellar gray matter (GM) volume, its specific genetic correlates are largely unknown.

Methods:
In this study, T1-weighted MR images of brain structure were collected from 198 adolescents (63 ADHD-diagnosed). A multivariate parallel independent component analysis (Para-ICA) technique-identified imaging genetic relationships between regional GM volume and single nucleotide polymorphism data.

Results:
Para-ICA analyses extracted 14 components from genetic data and 9 from MR data. An iterative cross-validation using randomly chosen subsamples indicated acceptable stability of these ICA solutions. A series of partial correlation analyses controlling for age, sex, and ethnicity revealed two genotype–phenotype component pairs significantly differed between ADHD and non-ADHD groups, after a Bonferroni correction for multiple comparisons. The brain phenotype component not only included structures frequently found to have abnormally low volume in previous ADHD studies but was also significantly associated with ADHD differences in symptom severity and performance on cognitive tests frequently found to be impaired in patients diagnosed with the disorder. Pathway analysis of the genotype component identified several different biological pathways linked to these structural abnormalities in ADHD.

Conclusion:
Some of these pathways implicate well-known dopaminergic neurotransmission and neurodevelopment hypothesized to be abnormal in ADHD. Other more recently implicated pathways included glutamatergic and GABA-ergic physiological systems; others might reflect sources of shared liability to disturbances commonly found in ADHD, such as sleep abnormalities.