Sequencing of sporadic Attention-Deficit Hyperactivity Disorder (ADHD) identifies novel and potentially pathogenic de novo variants and excludes overlap with genes associated with autism spectrum disorder.


Abstract

Attention-Deficit Hyperactivity Disorder (ADHD) has high heritability; however, studies of common variation account for <5% of ADHD variance. Using data from affected participants without a family history of ADHD, we sought to identify de novo variants that could account for sporadic ADHD. Considering a total of 128 families, two analyses were conducted in parallel: first, in 11 unaffected parent/affected proband trios (or quads with the addition of an unaffected sibling) we completed exome sequencing. Six de novo missense variants at highly conserved bases were identified and validated from four of the 11 families: the brain-expressed genes TBC1D9, DAGLA, QARS, CSMD2, TRPM2, and WDR83. Separately, in 117 unrelated probands with sporadic ADHD, we sequenced a panel of 26 genes implicated in intellectual disability (ID) and autism spectrum disorder (ASD) to evaluate whether variation in ASD/ID-associated genes was also present in participants with ADHD. Only one putative deleterious variant (Gln600STOP) in CHD1L was identified; this was found in a single proband. Notably, no other nonsense, splice, frameshift, or highly conserved missense variants in the 26 gene panel were identified and validated. These data suggest that de novo variant analysis in families with independently adjudicated sporadic ADHD diagnosis can identify novel genes implicated in ADHD pathogenesis. Moreover, that only one of the 128 cases (0.8%, 11 exome, and 117 MIP sequenced participants) had putative deleterious variants within our data in 26 genes related to ID and ASD suggests significant independence in the genetic pathogenesis of ADHD as compared to ASD and ID phenotypes.