

A Genetic Investigation of Sex Bias in the Prevalence of Attention-Deficit/Hyperactivity Disorder.

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Biol Psychiatry. 2017 Dec 2. pii: S0006-3223(17)32245-X.
doi: 10.1016/j.biopsych.2017.11.026.

Abstract

BACKGROUND:

Attention-deficit/hyperactivity disorder (ADHD) shows substantial heritability and is two to seven times more common in male individuals than in female individuals. We examined two putative genetic mechanisms underlying this sex bias: sex-specific heterogeneity and higher burden of risk in female cases.

METHODS:

We analyzed genome-wide autosomal common variants from the Psychiatric Genomics Consortium and iPSYCH Project ($n = 20,183$ cases, $n = 35,191$ controls) and Swedish population register data ($n = 77,905$ cases, $n = 1,874,637$ population controls).

RESULTS:

Genetic correlation analyses using two methods suggested near complete sharing of common variant effects across sexes, with r_g estimates close to 1. Analyses of population data, however, indicated that female individuals with ADHD may be at especially high risk for certain comorbid developmental conditions (i.e., autism spectrum disorder and congenital malformations), potentially indicating some clinical and etiological heterogeneity. Polygenic risk score analysis did not support a higher burden of ADHD common risk variants in female cases (odds ratio [confidence interval] = 1.02 [0.98-1.06], $p = .28$). In contrast, epidemiological sibling analyses revealed that the siblings of female individuals with ADHD are at higher familial risk for ADHD than the siblings of affected male individuals (odds ratio [confidence interval] = 1.14 [1.11-1.18], $p = 1.5E-15$).

CONCLUSIONS:

Overall, this study supports a greater familial burden of risk in female individuals with ADHD and some clinical and etiological heterogeneity, based on epidemiological analyses. However, molecular genetic analyses suggest that autosomal common variants largely do not explain the sex bias in ADHD prevalence.