No association between MspI allele of the ADRA2A polymorphism and ADHD: meta-analysis of family-based studies

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There is evidence for a genetic contribution to attention-deficit hyperactivity disorder (ADHD), although no candidate genes have attained genome-wide significance to date. Given that the noradrenergic system has been implicated in ADHD, the gene for the \( \alpha_2 \)-adrenergic receptor (\textit{ADRA2A}) has been hypothesized to contribute to the pathogenesis of ADHD. The present investigation reports results from a meta-analysis of family-based studies that did not find a significant association between the MspI polymorphism of the \textit{ADRA2A} gene and ADHD. \textit{Psychiatr Genet} 23:174–175 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

To identify studies eligible for meta-analysis, MEDLINE citations were surveyed using PubMed and PsychINFO online search engines with ‘ADHD’ and ‘ADRA2A’ as keywords. Only those studies examining the \textit{ADRA2A} MspI polymorphism were included in the meta-analysis. Further, studies had to meet all of the following inclusion criteria: (i) be published in a peer-reviewed journal between 2005 and 2012, (ii) present original data collected from participants aged 18 years or younger, and (iii) provide enough data to calculate an effect size. Of the studies that were retrieved through the literature search and retained by virtue of examining the correct polymorphism, none was excluded on the basis of these conditions. Of the 13 studies eligible for meta-analysis, 11 used a family-based strategy (\textit{Xu et al.}, 2001; \textit{Roman et al.}, 2003; \textit{Park et al.}, 2005; \textit{Bobb et al.}, 2005; \textit{Stevenson et al.}, 2005; \textit{Brookes et al.}, 2006; \textit{Deupree et al.}, 2006; \textit{Schmitz et al.}, 2006; \textit{Wang et al.}, 2006; \textit{Polanczyk et al.}, 2007; \textit{Cho et al.}, 2008; Table 1) and two had a case–control design (\textit{Comings et al.}, 1999; \textit{Guan et al.}, 2009). Five of these studies were then excluded from our analysis. Although both \textit{Comings et al.} (1999) and \textit{Guan et al.} (2009) examined the association between \textit{ADRA2A} and ADHD, neither of their studies provided allele transmission data. The studies by \textit{Roman et al.} (2003), \textit{Schmitz et al.} (2006), and \textit{Polanczyk et al.} (2007) used the haplotype-based haplotype relative risk (HHRR) test, rather than the transmission disequilibrium test (TDT) used by the other authors. Although the HHRR test uses families, it differs from the TDT in that, for the HHRR, the transmission of all alleles to the affected offspring is counted and not just those from heterozygous parents. We report the pooled estimate using a random-effects meta-analysis for the eight published family-based studies using TDT. No significant association of the MspI C allele with ADHD risk was observed with the random-effects model [odds ratio (OR) = 1.077, 95% confidence interval = 0.78–1.48, \( \chi^2(1) = 0.20, P = 0.65 \)]. A test for heterogeneity within the dataset was significant (\( \chi^2 = 44.72, I^2 = 82.1, P < 0.001 \)), suggesting that the effect of the \textit{MspI} C allele was not uniform across samples. The pooled ORs calculated after the sequential removal and replacement of each study ranged from 1.00 to 1.46, with 95% confidence intervals that always encompassed a value of 1.0, suggesting that no single study had excessive influence on the nonsignificance of the pooled OR. The potential moderators that were uniformly reported across all studies (age, sex, and ethnicity) were examined using a linear regression analysis, and the effect sizes were weighted by the inverse of the variance of the odds ratio.
The odds ratio derived from each study was unrelated to the age ($\beta = -0.60$, $P = 0.21$), sex ($\beta = 0.62$, $P = 0.19$), ethnicity ($\beta = -0.13$, $P = 0.77$), or proportion of children diagnosed with combined ADHD ($\beta = -0.14$, $P = 0.74$) in the sample.

These results are highly complementary to those of a recent meta-analysis (Gizer et al., 2009). Further, these results also elaborate upon previous results by Gizer and colleagues in two important ways. First, we report significant heterogeneity that warrants important consideration. This wide variability in findings suggests that further exploration of the relationship between the ADRD2A gene and ADHD may be needed, including examination of potential gene–environment or gene–gene interactions. Second, our study examined TDT data from three studies that were not included in the TDT analysis of the meta-analysis by Gizer et al. (2009). Instead, in their meta-analysis, HHRR or case–control data from the studies by Bobb et al. (2005), Stevenson et al. (2005), and Cho et al. (2008) was included. As we chose to only include peer-reviewed published data, it is possible that unpublished data may support an association between ADHD and the MspI variant of ADRD2A. However, as publication favors positive results, it is likely that any unpublished data support the conclusion of our meta-analysis demonstrating no significant association between the MspI variant of ADRD2A and ADHD.

Although more family-based studies are needed to more thoroughly evaluate the hypothesized relationship, our results do not support the hypothesis that the MspI variant of ADRD2A influences susceptibility to ADHD; however, our work does not preclude the possibility that other variants of the gene are influential or that the MspI variant might influence ADHD in a small fraction of cases.

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Conflicts of interest

There are no conflicts of interest.

References


