Family-based association of the brain-derived neurotrophic factor gene in attention-deficit hyperactivity disorder

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Attention-deficit hyperactivity disorder (ADHD), a highly heritable neurodevelopmental disorder, is characterized by inattention and hyperactivity. The brain-derived neurotrophic factor (BDNF), a member of the neurotrophic factor family, is important for normal neuronal development. It has been proposed that BDNF may play a role in the therapeutic action and pathogenesis of ADHD (Tsai, 2003). A common single-nucleotide polymorphism (SNP) consisting of a missense change (G196A) that produces a nonconservative amino acid change (valine to methionine) has been identified in the coding exon of the BDNF gene at position 66 (Val66Met, rs6265). The replacement of Val66 by Met66 disrupts cellular processing, trafficking, and activity-dependent secretion of BDNF (Egan et al., 2003). Several association studies have tested the possible involvement of this BDNF Val66Met polymorphism in ADHD, although the results are controversial (Forero et al., 2010). The Val66Met polymorphism has been associated with ADHD in Taiwanese families, using transmission disequilibrium analysis.

Our sample comprised 285 Chinese families who had at least one child diagnosed with ADHD according to DSM-IV criteria by senior board-certified child psychiatrists. Patients were excluded if there was no evidence of conduct disorder, mood disorder, anxiety disorder, Tourette’s syndrome, mental retardation (IQ < 70), pervasive developmental disorder, or neurological conditions. The study was approved by the Ethics Committee of the Taiwan Adventist Hospital. A written informed consent was obtained from all patients. Saliva was taken from the patients for genotyping. We selected five SNPs in the BDNF gene (NM_170731.4): rs1519480 (5’-flanking region), rs6265 (exon 1), rs7940188 (intron 1), rs7103411 (intron 1), and rs7103873 (intron 1). These polymorphisms are the tagging SNPs that capture other SNPs with minor allele frequencies greater than 10% in the BDNF gene among Han Chinese. Haploview 4.2 was used to examine the Hardy–Weinberg equilibrium for genotype distribution of the studied SNPs. Single-marker and haplotype-based transmission disequilibrium tests functioning in PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/) were also used for the ADHD trios samples.

Of the total 312 probands in 285 families, 257 (82.4%) were boys and 55 (17.6%) were girls, and the sample has been reported in our previous study (Hsu et al., 2013). Their ages ranged from 6 to 24 years, with a mean age of 13.0±2.9 (SD) years. Analysis of the transmission disequilibrium test in the ADHD parent–proband trios demonstrated no significant differences in the frequency between the transmitted and nontransmitted minor alleles for the three polymorphisms (rs1519480-T: T/NT = 108/103, P = 0.731; rs6265-A: T/NT = 148/140, P = 0.637; rs7940188-G: T/NT = 87/82, P = 0.701; rs7103411-T: T/NT = 150/137, P = 0.443; rs7103873-G: T/NT = 145/152, P = 0.685; T = transmitted; NT = nontransmitted). The genetic association with ADHD was further analyzed by investigating the haplotypes. However, no association was found between ADHD and any haplotype constructed by the five studied SNPs (data not shown).

Because of its influence on neurodevelopment, variants of the BDNF gene have been widely investigated in ADHD. Several previous studies report an association between SNPs located in BDNF and ADHD; however, the findings are inconsistent (Forero et al., 2009; Sánchez-Mora et al., 2010). The BDNF Val66Met polymorphism has been shown to have a major influence on cellular processing, trafficking, and activity-dependent secretion of BDNF, with the Val66-allele being associated with ADHD (Sánchez-Mora et al., 2010). We tested this potential association of Val66Met polymorphism in a Taiwanese family-based ADHD sample. There was no evidence for an overtransmission of the risk allele. We also evaluated the associations between four other BDNF genetic variants and ADHD. The transmissions of these polymorphisms were not significantly associated with ADHD.
We conclude that the markers examined thus far in BDNF are not associated with ADHD, although BDNF remains an interesting candidate gene in ADHD, especially for the treatment response.

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Conflicts of interest
There are no conflicts of interest.

References


