Family-based association study of tryptophan hydroxylase 2 and serotonin 1A receptor genes in attention deficit hyperactivity disorder
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Attention deficit hyperactivity disorder (ADHD) is a complex genetic disorder that is caused by multiple heritable and environmental factors. Serotonergic system-related genes are likely to be involved in the mechanisms underlying ADHD, because serotonin dysregulation has been related to impulsive and aggressive behavior in children, and has thus been hypothesized to play a causal role in ADHD. The firing rate of the dorsal raphe serotonergic neurons is modulated by somatodendritic 5-hydroxytryptamine 1A (5-HT1A) auto-receptors. The human 5-HT1A receptor gene (HTR1A) transcription is modulated by a functional C-1019G promoter polymorphism (rs6295). In a case–control association study with 78 Korean ADHD patients and 107 normal controls, Shim et al. (2010) found a significant difference in the genotype distributions and allele frequencies of HTR1A C-1019G between the ADHD group and the control group (P = 0.044 and 0.017, respectively). Tryptophan hydroxylase 2 (TPH2) is a rate-limiting enzyme in the biosynthesis of serotonin and is expressed exclusively in the brain. In 103 German families with 225 ADHD children, Walitza et al. (2005) reported a preferential transmission for two polymorphisms in TPH2’s regulatory region (rs4570625, P = 0.049; rs11178997, P = 0.034).

In the present study, we sought to replicate these findings in a Taiwanese sample by carrying out a family-based association study. Our sample included 282 Taiwanese families who had at least one child diagnosed with ADHD, and the sample has been reported in our previous study (Hsu et al., 2012). Each patient was diagnosed with ADHD according to the DSM-IV criteria by a senior board-certified child psychiatrist. Patients were excluded if there was any 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. Written informed consent was obtained from all participants. We genotyped these three polymorphisms (rs6295, rs4570625, and rs11178997) using high-throughput MALDI-TOF mass spectrometry (Sequenom Inc., San Diego, California, USA).

Transmission disequilibrium test analyses for the three polymorphisms in the ADHD trios were carried out using PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/index.shtml).

Of the total 312 probands in 282 families, 257 (82.4%) were boys and 55 (17.6%) were girls. Their ages ranged from 6 to 24 years, with a mean age of 13.0 ± 2.9 (SD) years. The genotype frequencies of the three polymorphisms in the probands, fathers, and mothers were rs6295 (GG/GT/TT): 187/104/18, 163/95/21, and 163/101/20; rs4570625 (GG/GT/TT): 63/150/97, 61/142/76, and 61/148/73; and rs11178997 (TT/TA/AA): 217/86/8, 194/79/7, and 200/75/8. Analysis of the transmission disequilibrium test in the ADHD parent–proband trios showed no significant differences in the frequency between transmitted (T) and nontransmitted (NT) minor alleles for the three polymorphisms (rs6295: G: T/NT = 94/188, P = 0.099; rs4570629: G: T/NT = 150/162, P = 0.500; rs11178997: A: T/NT = 80/84, P = 0.755).

Our family-based study found no association between the HTR1A (rs6295), TPH2 (rs4570625 and rs11178997) polymorphisms and ADHD, and, therefore, does not support the earlier reports that described a significant association (Walitza et al., 2005; Shim et al., 2010).

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Conflicts of interest
There are no conflicts of interest.

References
Hsu CD, Tzang RF, Loh EW, Liou YJ, Hong CJ, Tsai SJ (2012). Family-based association study of cocaine- and amphetamine-regulated transcript (CARTPT) and protein interaction with C-kinase-1 (PICK1) genes in attention-deficit hyperactivity disorder. Psychiatry Res [Epub ahead of print].