The etiology of attention deficit hyperactivity disorder (ADHD) is complex and multifactorial, with an important genetics load. Pharmacological, animal, and brain image studies provide significant evidence that monoamine genes are relevant (Gizer et al., 2009). We aimed to explore the possible association between Val158Met COMT, VNTR 3’ UTR SLC6A3, and LPR SLC6A4 candidate genes with ADHD and its subtypes.

Patients were participants from a general population survey of mental health in adolescents of Mexico City (for detailed information, see Benjet et al., 2009). Main diagnosis of ADHD was based on parent and child reports of the computer-assisted World Mental Health Composite International Diagnostic Interview for Adolescents, using the DSM-IV criteria. Genomic DNA from mouthwash samples was genotyped for the aforementioned polymorphisms in 252 ADHD cases and 370 controls who did not fulfill the criteria for any psychiatric disorder.

Association analyses of the aforementioned polymorphisms with ADHD (sex and subtype) were carried out with the SPSS v15.0 software. Adjustment for multiple tests was performed with the SISA online procedure (http://www.quantitativeskills.com/sisa/calculations/bonfer.htm), and results that remained significant after correction were only those with \( P \leq 0.01 \).

All genotypes frequencies were in Hardy Weinberg Equilibrium (HWE) (tested with http://ihg2.helmholtz-muenchen.de/cgi-bin/hzga/hweal.pl): SLC6A3 (10/10: 177; 10/9: 37; 9/9: 1; HWE: \( F = -0.04; P = 0.52 \)); SLC6A4 (SS: 85; SL: 112; LL: 30; HWE: \( F = -0.05; P = 0.46 \)); and COMT (Val/Val: 70; Val/Met: 102; Met/Met: 35; HWE: \( F = -0.01; P = 0.83 \)). No significant association was found for SLC6A3 and SLC6A4 genes, however, a logistic regression analysis showed that individuals with the COMT Met/Met genotype were more likely to belong to the hyperactive/impulsive-combined ADHD subgroup [odds ratio (OR): 2.1, confidence interval (CI) 95%: 1.2–3.4, \( P = 0.008 \)]; moreover, when an interaction with sex was tested, an association between the COMT Met/Met genotype \( \times \) males was observed (OR: 2.3, CI 95%: 1.1–4.6, \( P = 0.02 \)) and a protective effect of the COMT Val + genotype \( \times \) Females was also detected (OR: 0.5, CI 95%: 0.2–0.4, \( P = 0.006 \)). Nonetheless, the results that remained significant after correction for multiple testing were only those marked with bold letters (\( P \leq 0.01 \)).

Previous meta-analyses have not established any significant association between the COMT Val158Met polymorphism and ADHD or its subtypes (Cheuk and Wong, 2006; Gizer et al., 2009). Others have reported a similar association between this genetic variant and clinical hyperactive/impulsive-combined ADHD-related phenotypes such as the response to methylphenidate on oppositional symptoms (Salatino-Oliveira et al., 2011) or the increase in the severity of symptoms (Palmason et al., 2010). Moreover, in Cheuk and Wong’s (2006) paper, where the effect of sex was analyzed, men showed an increase in the Met allele of COMT that was almost significant (\( P = 0.054 \)). Furthermore, most studies have evaluated primarily Caucasian and Asian populations, whereas this report contributes data for Mexican Mestizos. However, replication in different or extended cohorts is necessary before drawing any definite conclusion. Moreover, the putative functional impact of the COMT genetic variation requires further investigation in terms of specific cognitive and behavioral aspects related to ADHD.

**Acknowledgements**

This study was supported by grants SEP-2004-CO1-46594, CB-2006-01-60678 and from the Research support fund 0196 of the National Institute of Psychiatry.
Conflicts of interest
There are no conflicts of interest.

References


