

Association between a SLC6A3 intron 8 VNTR functional polymorphism and ADHD in a Brazilian sample of adult patients
Associação entre um polimorfismo VNTR funcional no intron 8 do gene SLC6A3 e TDAH em uma amostra de adultos brasileiros

Table 1 - Distribution of genotypes and alleles of the SLC6A3 30-bp VNTR intron 8 polymorphism in cases and controls

Genotypes	Cases (%)	Controls (%)	χ^2	p value
5/5	5 (5.32)	38 (7.90)	8.49	0.038
5/6	32 (34.05)	230 (47.82)		
6/6	54 (57.45)	203 (42.20)		
Others	3 (3.18)	10 (2.08)		
Total	94 (100)	481 (100)		
Alleles			6.30	0.038
5	43 (22.87)	307 (31.91)		
6	142 (75.53)	645 (67.05)		
Others	3 (1.60)	10 (1.04)		
Total	188 (100)	962 (100)		

Allele 4 = 4 repeat 30 base pair (bp); allele 5 = 5 repeat 30bp; allele 6 = 6 repeat 30bp; allele 7 = 7 repeat 30bp; allele 10 = 10 repeat 30 bp

Dear Editors,

Attention deficit hyperactivity disorder (ADHD) affects about 5% of school-age children and from 1% to 6% of the adult population.¹ It is highly heritable and familial influences seem strongest for ADHD persisting into adulthood. However, most of the genetic research in ADHD has been carried out in children and adolescents with the disorder.

Findings from pharmacological, neuroimaging and animal studies have suggested the involvement of specific neurotransmitter systems, notably the dopaminergic pathway. Among the dopaminergic genes, the one that has received most attention in ADHD genetics is the SLC6A3/DAT1 encoding the dopamine transporter, a transmembrane protein responsible for the presynaptic reuptake of dopamine.² The 52.6 kb human SLC6A3 is located on chromosome 5p.15.3.²

Persistence into adulthood may represent a promising marker for studying the genetic background of ADHD. As well, SLC6A3 is an important candidate gene for molecular association studies. Therefore, we have performed an investigation of a six-copy 30-bp

variable-number tandem repeat (VNTR) functional polymorphism located in SLC6A3 intron 8³ in a Brazilian sample comprised by 94 adult patients with DSM-IV ADHD and 481 control subjects. Among the 94 ADHD patients, 58 (61.20%) were males and 36 (38.30%) were females, while in the control group, 323 (67.15%) were males and 158 (32.85%) were females. The mean ages of the ADHD and control groups were, respectively, 33.0 (sd = 9.21) and 32.5 (sd = 9.5). More information about the clinical sample can be found elsewhere.⁴ The study was previously approved by the Clinical Hospital Ethics Committee and all participants gave their written informed consent.

The statistical power of the sample was evaluated using the CaTS Program (<http://www.sph.umich.edu/csg/abecasis/CaTS/index.html>). Polymorphism frequency differences were investigated

by the Monte Carlo method using the Clump v1.9 with 10,000 simulations. To perform such analysis, we have collapsed columns with small values into one group to maximize the chi-square value and produce more conservative results. The Hardy-Weinberg equilibrium was tested using the HWE Program.

The genotypic distribution was in Hardy-Weinberg equilibrium (cases: $\chi^2 = 1.15$, $p = 0.99$ and controls: $\chi^2 = 8.65$, $p = 0.76$). The power of the sample, based on 94 patients and 481 controls, a estimated disorder prevalence in adults of 2.0%, average allelic frequency around 40%, multiplicative model with the genotype relative risk = 1.6, and significance level of 0.05, was 86%. The 6-repeat allele was statistically associated with ADHD ($\chi^2 = 6.30$, $p = 0.038$) - Table 1. Although there was a rejection of the null hypothesis of homogeneity between the groups of cases and controls at the 0.05 level concerning the polymorphism distribution, the p -values (allelic and genotypic) were very close to the level set for significance (Table 1). Therefore, the difference between groups was small. In other samples the present results could be different.

A possible limitation of the present investigation may be related to population stratification. Researches investigating different ethnical populations have shown significant variations in the allelic frequency among them. However the fact that in the present study the patients and controls are in Hardy-Weinberg equilibrium must

indicate that our sample may not have important problems of population stratification.⁵

The present study provides evidence for the association between the 6-repeat allele of the investigated polymorphism and ADHD in our Brazilian sample of adult patients. Recent investigation has also found in adults with ADHD the association replicated in the present study.² Research on gene and environment interaction has evidenced that the 6-repeat allele of the 30-bp VNTR polymorphism may moderate the impact of the SLC6A3/DAT1 on ADHD symptoms, suggesting that DAT1 would affect only those individuals exposed to psychosocial adversity.⁶

A previous study that investigated the same polymorphism in a Brazilian sample compounded by children with ADHD observed no preferential transmission from parents to probands of any allele at the 3' region of the gene, including the VNTR of intron 8.⁷ If confirmed by longitudinal studies, this differential association of genes with ADHD, in children and in adults, might imply that SLC6A3 plays a role in modulating the ADHD phenotype, rather than causing the disorder.²

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Disclosures

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* Modest

** Significant

*** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

Note: IPq-FM-USP = Instituto de Psiquiatria do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo; USP = Universidade de São Paulo; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico.

For more information, see Instructions for authors.

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