

Genotypic Interaction Between DRD4 and DAT1 Loci Is a High Risk Factor for Attention-Deficit/Hyperactivity Disorder in Chilean Families

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Attention-deficit/hyperactivity disorder, ADHD [MIM 126452], is a common, highly heritable neurobiological disorder of childhood onset, characterized by hyperactivity, impulsiveness, and/or inattentiveness. As part of an ongoing study of ADHD, we carried out a family-based discordant sib-pair analysis to detect possible associations between dopamine receptor D4 (DRD4) and dopamine transporter 1 (DAT1) polymorphisms and ADHD in Chilean families. Both loci individually classified as homozygotes or heterozygotes for the DRD4 7-repeat and DAT1 10-repeat alleles, did not exhibit genotype frequency differences between affected children and their healthy siblings (Fisher's exact test $P > 0.25$ in both cases). However, the simultaneous presence of both DRD4 7-repeat heterozygosity and DAT1 10 allele homozygosity were significantly higher (34.6%) in cases (26), compared with their unaffected siblings (25) (4%; Fisher's exact test $P = 0.0096$; odds-ratio, OR = 12.71). Increased density of dopamine transporter in ADHD brains, along with abundance of 7-repeat D4 receptors in prefrontal cortex, which is impaired in ADHD patients, make the observed gene-gene interaction worthy of further incisive studies.

KEY WORDS: DRD4; DAT1; genotypic interaction; ADHD; Association with (?)

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) [MIM 126452] is one of the most common neurobiological pathologies affecting ~5% of children and adolescents and ~3% of adults in the United States [Wolraich et al., 1996; Goldman et al., 1998;

Swanson et al., 1998; Scahill and Schwab-Stone, 2000]. Recently published epidemiological and clinical data seem to indicate similar prevalence rates of ADHD across diverse geographic and cultural settings [Baumgaertel et al., 1995; Wolraich et al., 1996; Gomez et al., 1999; Rohde et al., 1999; Tahir et al., 2000; Wilens et al., 2002].

The age of onset of the disorder is 7 years and it is more frequently diagnosed in boys, with male:female ratios being around 4:1 [Cantwell, 1996; Swanson et al., 1998]. Under criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, DSM-IV, American Psychiatric Association, 1994, three subtypes are recognized: inattentive, hyperactive-impulsive, and combined. Comorbidity with oppositional disorders, mood disorders, anxiety, and learning disabilities is common [August and Garfinkel, 1989; Pelham et al., 1992; Biederman et al., 1996; Wolraich et al., 1998; Brown et al., 2001; Wilens et al., 2002].

ADHD has a strong genetic determination as supported by clinical [Biederman et al., 1992; Faraone and Biederman, 1994], twin [Levy et al., 1997; Faraone and Doyle, 2001], and adoption studies [Morrison and Stewart, 1973; Cantwell, 1975; van den Oord et al., 1994].

Molecular genetic investigations have selected candidate genes involved in functions associated with the frontal-cortex and frontal-striatal networks as well as the treatment efficacy of stimulants [Barkley and Biederman, 1997; Yamasaki et al., 2002]. The results from candidate gene studies are, nevertheless, equivocal, and the effect of susceptibility alleles barely significant [Palmer et al., 1999; Comings et al., 2000; McCracken et al., 2000; Barr et al., 2001; Curran et al., 2001; Payton et al., 2001]. Dopamine D4 receptor gene (DRD4) and/or dopamine transporter (DAT-1) polymorphisms have shown to be associated in several studies [Faraone et al., 2001; Mill et al., 2001; Bobb et al., 2005], estimated genotype relative risks being modest.

SUBJECTS AND METHODS

As part of an ongoing study on genetic, electrophysiological, imageological, and cognitive aspects of ADHD, we consecutively approached the parents of 51 children from Chilean ADHD families in the greater Santiago area through hospitals and clinics in order to conduct a family-based case control study to detect possible associations with DRD4 and DAT1 polymorphisms. Clinical histories and blood samples were obtained after signature of an informed consent form approved by the Ethics Committee of the Faculty of Medicine of the University of Chile.

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Twenty-six subjects (24 males and 2 females) from 9 to 14 years of age, were diagnosed as ADHD combined subtype, according to DSM-IV criteria of the American Psychiatric Association, 1994, by a specialized pediatric neurologist (XC). The social and familial behavior of parents and healthy sibs were assessed through interviews conducted by a clinical psychologist (PR). All patients were applied the Wechsler Intelligence Scale Revised Edition WISC-R for children in order to evaluate their IQ's and to obtain a qualitative appraisal of their behavior.

To study the association of DRD4 and DAT1 polymorphisms with ADHD, we compared the 26 affected children with their healthy sibs. This method has the advantage of comparing cases and controls belonging to the same ethnic group and socioeconomic level and sharing most psychosocial and familial factors, which may interact with a potential genetic predisposition. Other methods, as for example the extended transmission disequilibrium test (ETDT) [Shain, 1999] could, at this stage, not be applied because of a lack of collaboration of many parents (specially the fathers of the children who manifested little interest in visiting the laboratory to donate blood samples). Genomic DNA was isolated from lymphocytes and amplified by PCR to identify the VNTR's of the DRD4 and DAT1 loci using the protocol described by Nanko et al. [1993].

For statistical analyses of the observed genotype data at both loci, genotypes at the DRD4 locus (a variable number of tandem repeat [VNTR] polymorphism of 48 base pair motif sequence) were grouped as +/- (for subjects who were heterozygotes for the 7-repeat allele), and -/- (for subjects who carried no copy of the 7-repeat allele). No 7-repeat homozygosity was observed in our sample of cases and controls. Likewise, for the DAT1 locus, the VNTR polymorphism of a 40 base pair repeat motif (ranging from 3 to 11 copies) was summarized as genotypes ++ (for subjects that were homozygous for the 10-repeat allele at the locus), and +/- (heterozygous for the 10-repeat allele). No individual was found who lacked the 10-repeat allele totally (i.e., there was no -/- genotype at this locus).

The rationale of such summarization of multi-allelic polymorphism stemmed from the fact that all previous studies on implication of involvement of *DRD4* and *DAT1* (alias *SLC6A3*) genes in the pathogenesis of ADHD refer to association with the 7-repeat allele of DRD4 and the 10-repeat allele of DAT1 [Hawi et al., 2003; reviewed also in Di Maio et al. [2003] and Bobb et al. [2005]; Kent, 2004].

The two-locus (DRD4 and DAT1, considered simultaneously) genotypes were summarized as heterozygosity for the 7-repeat allele for DRD4, together with homozygosity of the 10-repeat allele at DAT 1; versus all other genotypes grouped together.

The pooling algorithms of genotypes resulted in 2×2 contingency table contrast of genotype frequencies between cases (children with ADHD) and controls (their unaffected siblings). The significance of genotype frequencies was tested for each of the contrasts (each locus considered individually, and both loci considered together) by Fisher's exact tests. When significant frequency difference was found (as in the two-locus analysis), odds ratio (OR) and its 95% confidence interval were estimated by the traditional method as described in Woolf [1955] and Haldane [1956].

RESULTS

Genotype frequencies, defined by grouping of alleles at both loci (DRD4 and DAT1) as described in the earlier section, for cases (affected children) and controls (their discordant unaffected siblings, one per family) are shown in Table I. At a single locus level, heterozygosity for the 7-repeat allele was observed in 10 out of the 26 affected children (38.5%), not significantly different (Fisher's exact test $P = 0.5621$) from that (7 out of 25;

TABLE I. DRD4 and DAT1 Genotype Frequencies in Cases and Controls

Genotypes		Frequency in		
DRD4 ^a	DAT1 ^b	Cases	Controls	Total
+/-	+/+	9	1	10
	+/-	1	6	7
-/-	+/+	7	10	17
	+/-	9	8	17
Total		26	25	51

^a+/- denotes heterozygotes for the DRD4 7-repeat allele and -/- are genotypes not carrying the 7-repeat allele; no individual was homozygous for the 7-repeat allele in cases or controls.

^b+/+ denotes homozygosity for the 10-repeat allele at the DAT1 locus and +/- for individuals with one copy of the 10-repeat allele; all individuals in the sample of cases and controls carried at least one 10-repeat allele in their genotypes.

28%) among unaffected siblings. Likewise, genotype frequency of 10-repeat homozygotes (16 out of 26 in cases, and 11 out of 25 in unaffected) were also not significantly different (Fisher's exact test $P = 0.2673$). However, as shown in Table I, the frequency of the genotype combination of heterozygosity of the 7-repeat allele of DRD4 together with homozygosity of the 10-repeat allele of DAT1 was significantly higher (Fisher's one sided exact test $P = 0.0096$) (9 out of 26; i.e., 34.6%) in affected children, compared with that in their unaffected siblings (1 out of 25; i.e., 4%). This leads to an odds ratio of 12.71 (95% CI = 1.47–109.89) for the risk of ADHD for this two-locus genotype (7-repeat heterozygosity at DRD4, conjoint with 10-repeat homozygosity at DAT, 1). Altogether, our data suggest evidence of gene-gene interaction effects on the prevalence of ADHD in the Chilean population.

DISCUSSION

The results of our study suggest no association of the DRD4 7-repeat allele with ADHD in Chilean families. This finding is in apparent disagreement with recently published studies in which this association has been investigated [Faraone et al., 2001, Swanson et al., 2001, Grady et al., 2003]. However, it should be noted that a discordant sib-pair analysis (our study design) offers a more conservative test of disease-gene association than a traditional case-control analysis, and further, our sample size (specifically of unaffected siblings) is small.

Nonetheless, the strong interaction of DRD4 7-repeat alleles with DAT1 10-repeat homozygotes on ADHD, as well as the high odds ratio 12.71 associated to the simultaneous occurrence of both genotypes, are supportive of recent hypotheses of pathogenesis of ADHD [see e.g., Asherson [2004], Image Consortium].

We note that similar but less significant results were reported by Roman et al. [2001] in Brazilian families. To our knowledge, the Brazilian and our own studies are, so far, the only ones in the literature that have considered the possibility of an interaction between the DRD4 and DAT1 loci, and have established a statistically significant association between them.

Based on a recently proposed model [Volkow et al., 2004], we suggest in what follows a tentative mechanism of action of the gene products of DRD4 and DAT1 loci in the pathogenesis of ADHD. In fact, Volkow et al. [2004] propose that a decreased signal-to-noise ratio in dopaminergic signaling, and a decrease in stimulus-related dopamine release, are central to ADHD symptomatology and attentional impairment. Stimulants such as methylphenidate act by blocking the dopamine transporter [Seeman and Madras, 1998; Volkow et al., 1998], probably

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increasing the peak of dopamine release and the signal-to-noise ratio, thus improving sustained attention in ADHD patients and in normal subjects [Volkow et al., 2004]. In this context, the DRD4 7-repeat and the DAT1 10-repeat alleles might participate in these two aspects of dopaminergic malfunction. The DRD4 gene codes for a postsynaptic dopaminergic receptor that inhibits adenyl cyclase. The 7-repeat allele may be unable to efficiently lower cAMP levels, thus increasing postsynaptic background activity and decreasing signal-to-noise ratio in cells receiving dopaminergic input. This “suboptimal” response of the 7-repeat allele to dopamine was hypothesized to underlie its association with the personality trait of novelty seeking [Klugar et al., 2002] and with ADHD [Swanson et al., 2001]. It was suggested that the inhibitory neurons utilizing the DRD4 7-repeat receptor would require increased dopamine for “normal” function [Swanson et al., 2000]. Furthermore, the DAT1 10-repeat allele may contribute to this condition by decreasing the amount of stimulus-related intersynaptic dopamine, possibly due to an excessively efficient re-uptake mechanism in the presynaptic terminal [Fuke et al., 2001; Heinz et al., 2000; Mill et al., 2002]. Thus, evidence from these studies strongly suggests that variability in the length or sequence of the 3'UTR of the *DAT1* gene may influence levels of DAT in the brain. Consequently, individuals simultaneously homozygotes for DAT1/10-repeat and heterozygotes for DRD4 7-repeat probably present both a low level of dopamine owing to increased transporter activity and a reduced response of the DRD4 7-repeat receptor to dopamine, providing a functional explanation to the results presented in this report.

We have recently suggested that the duration of dopamine release is a factor in sustained attention tasks [López et al., 2004]. If this is correct, a short duration of release would also explain the increased performance in divided attentional tasks of ADHD [Koschack et al., 2003], due to their increased ability to switch attention. This model predicts that during stimulant medication, increasing duration of dopamine release would yield both an improvement in sustained attention tasks and a poorer performance in divided attention tasks.

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