

## Brief Research Communication

# Association of the Dopamine Receptor D4 (*DRD4*) Gene 7-Repeat Allele With Children With Attention-Deficit/Hyperactivity Disorder (ADHD): An Update

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Polymorphisms of the dopamine receptor D4 gene *DRD4*, 11p15.5, have previously been associated with attention-deficit/hyperactivity disorder (ADHD) [Bobb et al., 2005; Am J Med Genet B Neuropsychiatr Genet 132:109–125; Faraone et al., 2005; Biol Psychiatry 57:1313–1323; Thapar et al., 2005; Hum Mol Genet 14 Spec No. 2:R275–R282]. As a follow up to a pilot study [see Castellanos et al., 1998; Mol Psychiatry 3:431–434] consisting of 41 probands and 56 controls which found no significant association between the *DRD4* 7-repeat allele in exon 3 and ADHD, a greatly expanded study sample (cases  $n = 166$  and controls  $n = 282$ ) and long term follow-up ( $n = 107$ , baseline mean age  $n = 9$ , follow-up mean age of  $n = 15$ ) prompted reexamination of this gene. The *DRD4* 7-repeat allele was significantly more frequent in ADHD cases than controls ( $OR = 1.2$ ;  $P = 0.028$ ). Further, within the ADHD group, the 7-repeat allele was associated with better cognitive performance (measured by the WISC-III) ( $P = 0.013–0.07$ ) as well as a trend for association with better long-term outcome. This provides further evidence of the role of the *DRD4* 7-repeat allele in the etiology of ADHD and suggests that this allele may be associated with a more benign form of the disorder. © 2006 Wiley-Liss, Inc.

**KEY WORDS:** genetic association; transmission disequilibrium test; quantitative TDT

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## INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common, highly heritable childhood disorder defined by chronic inattention, hyperactivity, and impulsivity based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [American Psychiatric Association, 1994]. Family, twin and adoption studies, as well as linkage and association studies, have shown strong genetic contributions to the etiology of ADHD [Faraone and Biederman, 1998; Fisher et al., 2002; Ogdie et al., 2003; Arcos-Burgos et al., 2004]. The most consistently replicated candidate gene in ADHD genetics is the association with the dopamine receptor D4 gene (*DRD4*) [LaHoste et al., 1996; Smalley et al., 1998; Swanson et al., 1998; Comings et al., 1999; Faraone et al., 1999; Holmes et al., 2000; Muglia et al., 2000; Tahir et al., 2000; Curran et al., 2001; Mill et al., 2001; Roman et al., 2001; Bhaduri et al., 2006]. The majority of these studies have reported on a variable number tandem repeat (VNTR) polymorphism in exon 3 of the *DRD4* gene. Despite a few inconsistencies in reported associations of this VNTR and ADHD [Eisenberg et al., 2000; Hawi et al., 2000; Sunohara et al., 2000; Marino et al., 2003; Purper-Ouakil et al., 2005] the majority of reports and several meta-analyses have found positive support for the association [LaHoste et al., 1996; Smalley et al., 1998; Comings et al., 1999; Curran et al., 2001; Mill et al., 2001; Roman et al., 2001; Holmes et al., 2002; Bobb et al., 2005; Faraone et al., 2005; Bhaduri et al., 2006].

In the present study, we used both case-control and family-based designs to test the association between ADHD and the *DRD4* 7-repeat allele using an expanded sample from a previous pilot study [Castellanos et al., 1998] of ADHD patients recruited as part of a day treatment program at the NIMH.

## MATERIALS AND METHODS

### ADHD Subjects

Children and adolescents ( $n = 166$ ) meeting criteria for Diagnostic Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [American Psychiatric Association, 1994] ADHD were recruited locally for this study. Exclusion criteria included a full-scale WISC-III IQ less than 80, significant medical or neurological disorders, or other primary axis I psychiatric disorder. Comorbidity for learning disability, oppositional defiant disorder, and anxiety were permitted. Patients meeting DSM-IV diagnosis of ADHD were administered a Diagnostic Interview for Children and Adolescents (DICA)-Child, Adolescent and Parent versions [Reich, 2000]. Other measures included the Conners Parent and Teacher Rating Scales [Goyette et al., 1978; Werry et al., 1975], Child

Behavior Checklist [Achenbach and Edelbrock, 1981], Teacher Report Form [Achenbach et al., 1991], Full Scale Wechsler Intelligence Scale for Children, Third Edition (WISC-III), a computerized response inhibition task [Casey et al., 1993], and an anatomic brain MRI scan [see Castellanos et al., 2002 for details]. Ninety-four percent of the patients were diagnosed with ADHD combined type and the remaining 6% were diagnosed with primary inattentive type. Whole blood was drawn from all probands and immediate family members. For the family-based analyses, 87 trios and 26 dyads were available. Forty-one of the original probands from the previously reported genetics study were included in the analysis [see Castellanos et al., 1998]. The current sample was 53% male and the majority was Caucasian (75% Caucasian, 12% African American, 10% Hispanic, 2% Asian and 1% other) with a mean age of  $9.02 \pm 2.22$  years.

### Healthy Subjects

Healthy subjects ( $n = 282$ ; average age  $15.99 \pm 8.13$  years) were recruited from the local community and nationally with no personal or family history of psychiatric or neurological disorders. All subjects were given age-appropriate versions of the WISC, and comprised 82% Caucasian, 10% African American, 3% Hispanic, 3% Asian, and 2% mixed or other ethnicities. Either whole blood ( $n = 149$ ) or saliva samples ( $n = 133$ ) were collected for DNA isolation. There were no significant differences in allele frequencies or data quality between the different DNA sources. To assess genotype quality, 20 samples were randomly selected for repeat genotyping, and all genotypes were consistent.

### Nucleic Acid Purification and PCR

DNA was available for 161 ADHD subjects and 282 normal controls. Genomic DNA was extracted from immortalized lymphoblastoid cells using the QIAamp DNA Extraction Kit (Qiagen, Inc., Valencia, CA) and saliva samples using PUREGENE<sup>®</sup> (www.gentra.com). The VNTR polymorphic site in exon 3 of the dopamine receptor D4 gene was amplified using primers D4-F-GCGACTACGTGGTCTACTCG and D4-R-AGGACCCTCATGGCCTTG. Reactions were performed in a 96-well format in a total reaction volume of 25  $\mu$ l containing 2.6  $\mu$ l of 10  $\mu$ g/ $\mu$ l DNA, 1  $\mu$ l of each 10  $\mu$ M primer, 2.5  $\mu$ l of PCR buffer, 0.5  $\mu$ l  $MgCl_2$ , 5  $\mu$ l of GC rich buffer, 2  $\mu$ l of 7-deaza-2'Deoxy GTP dNTP mix, 0.2  $\mu$ l of Fast Start Taq DNA polymerase and 2.6  $\mu$ l of  $H_2O$  (Roche, <https://shop.ibuybiochem.com/rasstoreus/rasstoreus.html>). PCR was performed using 1 cycle of denaturation for 3 min at 95°C, 45 cycles of annealing for 30 sec at 95°C, 30 sec at 62°C, and 45 sec at 72°C, followed by 1 cycle of extension for 5 min at 72°C. PCR products were run out on a 3% agarose gel at 100 V for 100 min.

### Statistical Analysis

COCAPHASE was used to compare allele frequencies in cases and controls [Dudbridge, 2003]. TDTPHASE was used for family-based TDT analyses. QTPHASE was used to examine genetic associations with quantitative phenotypes among the ADHD probands (<http://www.hgmp.mrc.ac.uk/~fdudbrid/software/unphased/>). One-tailed asymptotic *P*-values are reported for alleles that were previously reported to be associated in other studies.

## RESULTS

The allele frequencies of the VNTR alleles in cases and controls are shown in Table I. ADHD patients had a higher frequency of the 7-repeat allele as compared to controls, 23% versus 17% respectively ( $P = 0.028$ ). Conversely, the controls

TABLE I. Case Control Results

Allele	Case frequency	Control frequency	Odds ratio	<i>P</i> -value
2	0.10	0.09	1.00	0.632
3	0.04	0.04	0.81	0.758
4	0.62	0.68	0.82	0.040
5	0.00	0.01	0.21	0.108
6	0.01	0.00	na	0.048
7	0.23	0.17	1.19	0.028
8	0.00	0.00	na	0.163

had a higher frequency of the 4-repeat allele (62% in cases and 68% in controls,  $P = 0.04$ ), consistent with previous reports. This association was not confirmed in the TDT analyses, which assesses transmissions from parents to affected offspring (see Table II; global  $P = 0.79$ ).

The significant case control findings led to exploration of potential genetic associations with other phenotypic measures. There was evidence for significant association with three subscales of the WISC and the 7-repeat allele within the ADHD group. Specifically, probands with a 7-repeat allele had higher scores on the information ( $P = 0.01$ ), and vocabulary ( $P = 0.01$ ), and a trend for association with the similarities ( $P = 0.07$ ), subscales of the WISC. In addition, we had follow-up information on a large proportion of the ADHD sample ( $n = 107$ ) and had DNA on 69 of these 107. We categorized the follow-up sample as having "good" or "poor" outcome based on a median split of scores at follow-up on the Children's Global Assessment Scale (CGAS) [Shaffer et al., 1983; Shaw et al., 2006]. There was a higher frequency of the 7-repeat allele in the good outcome group as compared to the poor outcome group (28% vs. 18%, respectively), though this difference did not reach statistical significance, likely due to the small sample size ( $P = 0.11$ ).

## DISCUSSION

The current study confirms previous reports of an association between ADHD and the 7-repeat allele of the *DRD4* gene. This study represents an expanded sample of cases and controls collected at the NIMH, which originally reported no association [Castellanos et al., 1998], most likely due to a lack of power given the observation that the allele frequencies in that report were similar to those in the current expanded sample. Several case control studies from other research groups also found comparable allele frequencies of the 7-repeat polymorphism in their samples [LaHoste et al., 1996; Swanson et al., 1998; Holmes et al., 2000; Muglia et al., 2000; Tahir et al., 2000; Curran et al., 2001; Mill et al., 2001; Roman et al., 2001]. This study is notable as we report not only a trend for better clinical outcome among carriers of the *DRD4* 7-repeat allele, but also better cognitive abilities. These findings, along with previous reports in the literature, suggest that the 7-repeat allele may identify a subgroup with behavioral but not the

TABLE II. TDT Results

Allele	Transmitted	Not transmitted	<i>P</i> -value
2	22	19	0.622
3	6	9	0.429
4	135	138	0.758
5	1	1	1.000
6	0	1	0.239
7	45	41	0.628

cognitive components of ADHD in carriers of this allele [Swanson et al., 2000].

There is considerable debate about the nature of the phenotype associated with the 7-repeat allele. Swanson et al. [2000] reported that 7-repeat carriers showed intact performance on tests of selective and executive attention, with normal reaction times and variability of response. By contrast, children with ADHD without the 7-repeat showed the neuropsychological profile that is thought to characterize the disorder of slow and variable reaction times. They proposed that the 7-repeat thus delineates a subtype of ADHD characterized by behavioral but not cognitive components of ADHD. This was essentially replicated by Manor et al. [2002], who showed that children with the 7-repeat had a more accurate response style on a variant of the continuous performance test. Our finding of better cognitive performance in those with the 7-repeat is also congruent with the concept of an intact cognitive profile, and is of particular interest given evidence that the 7-repeat may have arisen as a relatively new variant which is under positive selection [Ding et al., 2002].

However there are several conflicting findings. Firstly, Langley et al. [2004] found that ADHD children with the 7-repeat had a *more* inaccurate and impulsive response style. Also Mill et al. [2001] found that a lower IQ in ADHD subjects with the 7-repeat in two epidemiological cohorts. The discrepancies may partially relate to developmental factors. For example, the Langley report of a deleterious cognitive style in 7-repeat carriers studied a younger group (mean age of 9.2 years) than the subjects in Swanson's report of intact attention (this group had a mean 11.9 years). Comparisons between the studies is also complicated by the variety of experimental paradigms used, highlighting the need for a common neuropsychological battery for assessing the disorder.

Some limitations deserve mention. First, we observed a positive association only in the case control sample, not in the family sample utilizing the TDT test. This discrepancy is not completely accounted for by the slightly smaller sample size in the family-based analyses. The case-control finding also held when the allele frequency data was analyzed with Caucasians only (22% vs. 17%) indicating that the positive case-control association was not simply due to population stratification. Second, all *P*-values are nominal and would not survive a multiple comparison correction. Therefore, the current findings need to be confirmed in independently collected samples.

In summary, we confirm the association of the *DRD4* 7-repeat allele with ADHD and delineate a possible phenotype. Additional studies utilizing such phenotypes may help reduce diagnostic heterogeneity within ADHD and help to better understand the underlying genetic influences [Castellanos and Tannock, 2002; Gottesman and Gould, 2003].

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