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Genetic Analyses of Dopamine Related Genes in Adult ADHD Patients Suggest an Association With the DRD5-Microsatellite Repeat, But Not With DRD4 or SLC6A3 VNTRs

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Attention deficit hyperactivity disorder (ADHD) is a common and highly heritable psychiatric disorder in children and adults. Recent meta-analyses have indicated an association between genes involved in dopaminergic signaling and childhood ADHD, but little is known about their possible role in adult ADHD. In this study of adults with ADHD, we evaluated the three most commonly studied ADHD candidate genetic polymorphisms; the dopamine receptor D4 (DRD4) exon 3 VNTR repeat, a microsatellite repeat 18.5 kb upstream of the DRD5 locus and the 3′UTR dopamine transporter SLC6A3 (DAT 1) VNTR. We examined 358 clinically diagnosed adult Norwegian ADHD patients (51% males) and 340 ethnically matched controls. We found a nominally significant overall association with adult ADHD for the DRD5 microsatellite marker ($P = 0.04$), and a trend toward increased risk associated with the 148-bp allele consistent with recent meta-analyses. The strongest overall association ($P = 0.02$) and increased risk for the 148-bp allele [odds ratio (OR) = 1.27 (95% CI: 1.00–1.61)] were seen in the inattentive and combined inattentive/hyperactive group as previously reported for childhood ADHD. No association was found for the DRD4 or SLC6A3 polymorphisms in this patient sample. In conclusion, our results among adults with a clinical diagnosis of ADHD support an association between ADHD and the DRD5 locus, but not the DRD4 or SLC6A3 loci. It is possible that the latter polymorphisms are associated with a transient form of ADHD with better long-term clinical outcome.

KEY WORDS: attention deficit hyperactivity disorder (ADHD); adult ADHD; genetic association; dopamine system

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) has been reported to affect between 2% and 12% of children world wide and it has been estimated that approximately 65% continue to show symptoms of ADHD in adulthood [Biederman and Faraone, 2005; Faraone et al., 2006]. A recent study indicated that the prevalence of ADHD among young American adults is approximately 4%, with the majority being undiagnosed and untreated [Kessler et al., 2006].

ADHD is considered a complex disorder with a substantial genetic component, as shown by several twin and adoption studies [Thapar et al., 1999; Biederman and Faraone, 2005]. Despite the strong heritability, no major gene effects have been discovered; rather it is likely that several genetic variants, each with small effects, together influence an individual's risk of developing ADHD. To date, genes involved in the dopaminergic, serotonergic, and noradrenergic systems have been most extensively studied, based on their plausible functional properties [Thapar et al., 2005; Faraone and Khan, 2006]. In particular, the dopamine system has received much attention, as it has been shown that stimulant medications such as methylphenidate and amphetamine

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Abbreviations: ADHD, attention deficit hyperactivity disorder; OR, odds ratio; CI, confidence interval; VNTR, variable number of tandem repeat; SLC6A3, dopamine transporter 1; DRD4, dopamine receptor D4; DRD5, dopamine receptor D5.

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block the dopamine transporter encoded by the *SLC6A3* (*Dat1*) gene [Krause et al., 2000]. Historically, three genetic variants in dopamine genes have been most intensely tested for association with ADHD [Thapar et al., 2005; Faraone and Khan, 2006]; (1) a variable number of tandem repeat (VNTR) polymorphism in the 3′UTR of SLC6A3 (DAT 1), which has been suggested to regulate expression of the gene [Fuke et al., 2001], (2) the dopamine receptor D4 (*DRD4*) VNTR in the third exon, which encodes 32–176 amino acids of the protein, and (3) a microsatellite marker with no known function located 18.5 kb upstream the dopamine receptor D5 gene (*DRD5*). Despite somewhat conflicting results across studies, a recent meta-analysis of genetic association studies found the strongest evidence for increased risk associated with the DRD4 7-repeat allele and the DRD5 148-bp allele [Li et al., 2006]. However, the meta-analysis did not support a role for the SLC6A3 polymorphism [Li et al., 2006].

Compared to childhood ADHD, there have been few molecular genetic studies on adult ADHD. Consequently, little is known about the contribution of genetic variation to the persistence of ADHD symptoms into adulthood. In our efforts to explore the etiology of ADHD we have therefore recruited adult individuals with a clinical diagnosis of ADHD from the genetically homogeneous Norwegian population. Here, we present the first genetic association study of this patient population and test for association between adult ADHD and the three most studied dopamine related genetic markers, the SLC6A3 (DAT1) 3′UTR VNTR, the DRD4 exon 3 VNTR, and the microsatellite marker located 18.5 kb upstream *DRD5*.

MATERIALS AND METHODS

Subjects

ADHD. The patients in this study were white adults (>18 years) of Norwegian ancestry with a clinical diagnosis of ADHD recruited from all parts of Norway. The reason for the recruitment strategy is derived from the Norwegian legislation regarding prescription of the stimulant drugs amphetamine and methylphenidate. Before 1997, the prescription of stimulant drugs for children with ADHD was allowed, but not for patients older than 18 years. However, the laws were revised in 1997. Thus, from October 1997 to May 2005, for Norwegian adults to be able to receive treatment with stimulant drugs case records had to be reviewed by one of three regional diagnostic committees (expert committees) before the diagnosis was finally confirmed and they were allowed to try stimulant drugs. Each of the diagnostic committees consisted of three to five clinicians (mainly psychiatrists and neuropsychologists), with experience from diagnosing ADHD in children and adults. During this period, nearly 5,000 Norwegian adult patients were referred to the committees, and for about 3,600 of them a diagnosis of ADHD was confirmed. From May 2005, treatment of adult ADHD has been considered a standard clinical procedure and the mandatory registration of patients has been abandoned.

Most patients included in our study were initially referred by their primary physician to out-patient psychiatric clinics where they were diagnosed by psychiatrists, or clinical psychologists using the ICD-10 research criteria [World Health Organization, 1993], with the aid of a written protocol provided by the expert committees. In this protocol the ICD-10 criteria were modified so that, similar to the criteria of DSM-IV [American Psychiatric Association, 2000] inattentive symptoms alone (six of nine symptoms) were sufficient for a diagnosis of hyperkinetic disorder. As the final diagnostic criteria were very similar to that used in the DSM-IV protocol, the term ADHD was considered most appropriate for this patient sample. A minority of the patients (6%) were similarly diagnosed at psychiatric hospitals, before the diagnoses were approved by one of the expert committees.

Using the patient address registry of the expert committees, approximately 2,000 patients with a confirmed ADHD diagnosis were invited by letter to join the project. The first 230 patients who responded positively to this invitation were included in the present study, together with 128 patients who were directly recruited by psychiatrists from out-patient clinics from June 2004 to September 2006, using the protocol described above. An informed consent form, checklists of current symptoms, including the World Health Organization Adult ADHD Self-report Scale (ASRS), were filled in by the patients, and a scheme containing information about diagnosis, current therapy and treatment response was filled in by their present psychiatrist or general practitioner. Saliva or venous blood samples were obtained at the time of inclusion in the project. Thus, the total sample consists of 358 ADHD patients (182 males and 176 females) recruited using this protocol. The project was approved by the Regional Committee for Medical Research Ethics of Western Norway.

Controls. A group of 340 (157 males and 183 females) ethnically matched healthy controls (198 blood donors and 142 healthy volunteers) were recruited for this study. No screen for ADHD was undertaken in this group. This might lead to reduced power. However, the prevalence of ADHD in this group is assumed to be no higher, possibly lower, than in the general population of adults, that is, <5%.

Methods

Phenotyping: Adult ADHD Self-Report Scale. ASRS is a short screening scale for use in the general population [Kessler et al., 2005]. The Norwegian version of the ASRS is a translation of the original scale and consists of 18 questions that follow the DSM-IV-TR criteria for ADHD [American Psychiatric Association, 2000]. Nine questions address the frequency of inattentive symptoms, and nine address the frequency of hyperactivity symptoms. The participants indicate how often symptoms occur by using a Likert scale of 0–4 (0 = never, 1 = seldom, 2 = sometimes, 3 = often, 4 = very often).

Kessler et al. [2005] have shown that it is possible to divide adult ADHD patients into DSM-IV subtypes with high sensitivity and specificity using the ASRS, with a cut-off score of 21 points on both the inattentive and the hyperactive/impulsive subscales. If the score is below cut-off on both factors, the participant is classified as "sub-threshold." This method was used in the present study to determine the levels of ADHD symptoms during the past 6 months and to classify the patients according to DSM-IV subtypes.

Genotyping. Genomic DNA was extracted either from whole blood, or from saliva using the Oragene™ DNA Self-Collection Kit from DNA Genotek (DNA Genotek, Inc., Ontario, Canada) at the HUNT biobank (Levanger, Norway). DNA from cases and controls was diluted to a final concentration of 10 ng/μl before distributed to 96 well plates. Cases and controls were mixed with a minimum of two internal controls and two blank samples on each plate. A protocol for PCR amplification and fragment analysis is available upon request. In short, to reduce the risk of erroneous genotyping due to differential amplification of the repeats, all reverse primers were fluorescently labeled and PCR products were visualized on an ABI 3100 sequencer and automatically called using the GeneMapper software (Applied Biosystems, Foster City, CA). All genotype calls were also manually inspected by at least one person. Samples that failed initial genotyping criteria were subjected to a second round of PCR amplification and fragment analysis. A formal repeat genotyping test involving 100 duplicate samples for each marker showed one discrepancy

out of 300 genotypes (99.7% concordance rate). Final genotyping call rate was >0.99.

Statistical Analysis. Allele frequencies and the overall likelihood ratio test for each marker were calculated using the UNPHASED software [Dudbridge, 2006] which allows testing of multi-allelic markers. For the overall test, we set the rare allele frequency threshold to 5%. A simple 2×2 Chi-square test was used to compare the allelic odds between the "at-risk-allele" versus all other alleles at each marker. Power calculations were performed using the Power Calculator software [Purcell et al., 2003] at http://pngu.mgh.harvard.edu/~purcell/gpc/. Assuming a multiplicative effect we had approximately 63% power at the $\alpha = 0.05$ level to detect an allelic odds ratio (OR) = 1.34 for a disease allele frequency (f) = 0.2. No significant deviations from Hardy–Weinberg equilibrium were detected for any marker. *P* values are presented without correction for multiple testing.

RESULTS

Demographic Characteristics

Table I shows the clinical characteristics of the 358 case subjects. The gender distribution was almost 1:1 (49% females) and mean age at inclusion was similar across gender. Twenty percent of the patients reported that they had received an ADHD or hyperkinetic disorder diagnosis in childhood (men 27%, women 12%). Ninety-three percent of the patients reported that they had received treatment with central stimulant drugs, and 76% were still using stimulants at the time of inclusion. A high proportion (32–45%) of both sexes reported first-degree relatives with ADHD. However, an additional 34% of males and 36% of females answered "not known" on this question, raising the possibility that even more patients have family members with ADHD. All patients had been diagnosed with adult ADHD prior to the inclusion in our study. As some of the patients had been diagnosed up to 7 years prior to the inclusion in the study, we also examined their present symptom profile during 2005 or 2006 using the ASRS questionnaire. Eighteen percent of the female and 26% of the male patients obtained total scores below 21 on both ASRS subscales, possibly due to symptom fluctuation, spontaneous recovery or effective treatment. Although these patients were classified as "sub-threshold" they had previously received a formal diagnosis of adult ADHD and were included in the overall case group for the genotyping study. Furthermore, the ASRS allocated more women (62%) compared to men (44%) to the group with a combined subtype of ADHD.

Genetic Analyses of Candidate Markers

Allele frequencies of the three candidate markers at the DRD5, SLC6A3, and DRD4 loci for the entire case control-group are presented in Supplementary Table I. The results of the overall likelihood ratio test at each marker are shown in Table II ($P_{overall}$) together with the individual allelic ORs for the previously suggested ADHD at-risk alleles for the DRD5 (148-bp), SLC6A3 (10 repeat), and DRD4 (7 repeat) loci. There was no evidence of association between ADHD and the previously reported SLC6A3- and DRD4 at-risk-alleles, nor for the overall test. However, there was a nominally significant association for the DRD5 microsatellite repeat (overall $P = 0.04$). Furthermore, the 148-bp allele was enriched among the patients [OR = 1.20 (95% CI: 0.97–1.49)], in agreement with previous meta-analyses on ADHD children. These studies have also suggested that the DRD5 association is mainly restricted to the inattentive and combined inattentive/hyperactive patients [Lowe et al., 2004]. We therefore stratified the analysis to include only the ADHD cases classified with current symptoms of the inattentive or combined inattentive/hyperactive subtypes (Table I) and compared them to the all-control group. As shown in Table III, these patients showed a stronger overall association with the DRD5 polymorphisms ($P = 0.02$) than the ADHD group as a whole, with a particular increased 148-bp allele risk [OR = 1.27 (95% CI: 1.00–1.61)]. In contrast, there was no evidence of DRD5 association with the ASRS-hyperactive/impulsive and/or sub-threshold groups.

Including gender as a modifier in the overall logistic regression test decreased the evidence for association ($P = 0.21$). We therefore stratified the analysis based on sex and found a tendency toward stronger association among male patients for the 148-bp allele, OR = 1.32 (95% CI: 1.02–1.70) (Table III) versus OR = 1.09 (95% CI: 0.84–1.41) for females. Among women with ADHD, only the inattentive subgroup displayed elevated frequency of the 148-bp allele (53%) while allele frequencies among men were similar in all DSM-IV-subclasses (data not shown). Explorative analysis of rare DRD5-alleles showed no trend toward association for the previously suggested weakly protective 136-bp allele, while the shortest allele in our population was more frequent among patients [OR = 3.48 (95% CI: 1.67–7.25)].

Stratification by gender and ASRS scores yielded no tendency toward association for the SLC6A3 and DRD4 variants for either sex.

DISCUSSION

We found a trend for association between adult ADHD and a microsatellite marker located 18.5 kb upstream of DRD5 in a sample of 358 adult Norwegian subjects with a clinical ADHD diagnosis. Although the association is only nominally significant and needs to be tested in other adult ADHD samples, the result is in agreement with previous studies in children [Daly et al., 1999; Lowe et al., 2004; Li et al., 2006], which consistently have shown an association with the 148-bp allele. Furthermore, the strongest effect was seen among individuals with the inattentive and combined inattentive/hyperactive

TABLE I. Demographic and Clinical Characteristics of the 358 Norwegian Adults With a Clinically Defined ADHD Diagnosis

	Males (n = 182)	Females (n = 176)
Mean age, years (range)	33.9 (18–67)	34.9 (18–71)
ADHD subtype based on ASRS self report, % (n)		
Sub-threshold	26% (45)	18% (31)
Predominantly inattentive	20% (35)	15% (26)
Predominantly hyperactive	9% (16)	5% (9)
Combined	44% (75)	62% (106)
First degree relative with ADHD[a]	32%	45%
Diagnosed in childhood	27%	12%

[a]An additional 34% of males and 36% of females answered "not known" on this question.

TABLE II. Comparison of Allele Frequencies in Three Candidate Polymorphisms Among 358 Adult Norwegian ADHD Patients and 340 Controls

Gene	Marker	$P_{overall}$	Risk allele[a]	Cases (n = 358)	Controls (n = 340)	OR	$P_{allelic}$
DRD5	VNTR 18.5 kb 5-prime	0.04	148	0.54	0.49	1.20 (0.97–1.48)	0.09
SLC6A3	VNTR 3′UTR	0.48	10	0.71	0.73	0.94 (0.74–1.19)	0.59
DRD4	VNTR exon 3	0.31	7	0.22	0.24	0.90 (0.70–1.15)	0.27

[a]Risk allele based on previous meta-analysis studies in ADHD.

phenotype [$P_{overall} = 0.02$, 148-bp allele; OR = 1.27 (95% CI: 1.00–1.61)] again in agreement with an earlier meta analysis [Lowe et al., 2004]. The results might also suggest that the association could be gender specific, since male patients showed a (non-significant) tendency toward stronger association than women, despite equally sized groups. However, to formally test this hypothesis, much larger sample sizes are needed.

Interestingly, we did not find any evidence for an association between an adult ADHD diagnosis and the SLC6A3 3′UTR VNTR and DRD4 exon 3 VNTR. Both polymorphisms have long been considered to be major candidate genes for childhood ADHD, although results have varied between studies, especially for the SLC6A3 repeat. However, our SLC6A3 results are in agreement with a recent meta analysis which could not confirm an association with the marker in children with ADHD [Li et al., 2006]. Hence, it seems unlikely that the SLC6A3 3′UTR VNTR directly affects ADHD risk, although we cannot rule out that other variants in the region predispose individuals to ADHD as suggested by some studies [Brookes et al., 2006b; Asherson et al., 2007].

In contrast to SLC6A3, the DRD4 7-repeat association with ADHD has withstood the test of time according to recent meta analyses [OR = 1.34 (95% CI: 1.23–1.45), $P = 10^{-12}$] [Li et al., 2006] and has been suggested to be causally involved in childhood ADHD. Despite relatively good power (63%) in our sample to detect an effect of this magnitude, we did not find evidence for this association. In fact, if anything, the 7-repeat allele showed a trend toward protection in our adult patient population [OR = 0.90 (95% CI: 0.70–1.15)]. Although the true risk conferred by the 7-repeat allele among ADHD children might be somewhat less than estimated previously [Li et al., 2006], the 95% CI of the OR in our adult sample does not include even the smaller effect seen in the recent and largest ADHD-genotyping study performed to date, the IMAGE study (OR = 1.18, $P = 0.09$ for the 7-repeat allele) [Brookes et al., 2006a]. This suggests a different effect in our adult ADHD patients, although we formally cannot refute the possibility that the conflicting results could be explained by varying LD patterns between the test marker and disease variant in different populations.

Our patient sample had a strong family history of childhood and adult ADHD and, as has been found in previous studies, had a high life-time prevalence of anxiety, depression, substance abuse, or bipolar spectrum disorders. Despite the increasing awareness of ADHD as a clinical diagnosis in adults, few molecular genetic studies have been performed on this patient population. To our knowledge, the present study is to date the largest clinical adult ADHD sample tested for genetic variations in the dopamine related genes SLC6A3 and DRD4. Moreover, we are not aware of any previous genetic association studies on adult ADHD and DRD5.

Previously, Muglia et al. [2000], found an association between the DRD4-7 repeat allele and adult ADHD in a combined sample of 66 cases, 66 controls and 44 families from Canada (N = 10, $P = 0.003$, one-sided test). Lynn et al. [2005], also reported some association with ADHD for the 7-repeat allele among 127 parents (of children with ADHD) with and without symptoms of ADHD. However, Smith et al. [2003] did not find any evidence of an association for the DRD4-VNTR 7-repeat among 105 adult cases and 68 controls from the Milwaukee area, similar to the results from a population based sample of adolescents from the US (N = 201 trios) [Todd et al., 2001]. In accordance with our results, neither Muglia et al. [2002] nor Smith et al. [2003] found any evidence for an association between the SLC6A3 10-repeat allele and ADHD in the Canadian and in US-samples of adult ADHD described above. Hence, previous studies on adult ADHD samples are small and the results are conflicting. Further well-powered studies are needed to determine the relationship between the DRD4 7-repeat and ADHD in adults.

A Developmental Perspective

Our study supports a common genetic risk locus for childhood and adult ADHD marked by the DRD5 microsatellite marker, but not for the DRD4 or SLC6A3 VNTR markers. It is often assumed that the susceptibility genes for ADHD are similar in all age groups, but this has not been systematically tested. Although 80% of our adult ADHD cases were not formally diagnosed until adulthood which is in agreement with other adult studies [Kessler et al., 2006], the diagnosis require that they in retrospect met the criteria for childhood diagnosis. Our results suggest that some genetic variants are more important for the maintenance of ADHD symptoms into

TABLE III. DRD5 Allele Distribution in Different ASRS Sub Groups Compared to Controls

		148-bp allele		
	$P_{overall}$[a]	Freq (n/total)	OR[b] (95% CI)	$P_{allelic}$
ADHD	0.04	0.54 (382/710)	1.20 (0.97–1.48)	0.09
ASRS-hyperactive and sub-threshold	—	0.50 (100/200)	1.03 (0.75–1.41)	0.85
ASRS-inattentive and combined	0.02	0.55 (265/480)	1.27 (1.00–1.61)	0.05
Males	0.04	0.56 (203/362)	1.32 (1.02–1.70)	0.04
Females	0.37	0.51 (180/350)	1.09 (0.84–1.41)	0.51
Controls[c]	NA	0.49 (332/674)	NA	NA

[a]Overall *P*-values of likelihood test (only alleles above 5% frequency).
[b]OR from the 2 × 2 table comparing the 148-bp allele versus all other alleles for each subgroup versus controls.
[c]No significant gender differences was seen among controls ($P = 0.38$).

adulthood, while other might display a stronger effect only among children with ADHD [Thapar et al., 2007].

Several independent studies have indicated that the presence of the 7-repeat allele of DRD4 is associated with a high level of cognitive function and a favorable long-term clinical outcome among children with ADHD [Swanson et al., 2000; Manor et al., 2002; Gornick et al., 2007]. On the other hand, other studies have reported conflicting results [Langley et al., 2004; Barkley et al., 2006; Mill et al., 2006]. However, there are several methodological differences between the studies, hence it is difficult to directly compare these results.

If the DRD4 7-repeat allele is mainly found in ADHD children with good outcome, the lack of an association of this marker with adult ADHD should not be unexpected. Our sample might be enriched with patients having more severe and protracted symptoms, and worse long-term prognosis. The high percentage of our adult patients reporting having first degree relatives with ADHD supports the strong heritability of the symptoms, and an analysis of the occupational status of our patient sample confirmed the severe impairment of these patients; only 25% of the subjects reported being employed, compared to 70% of the general population in the same age group (data from last quarter of 2006, Norwegian Statistics http://ssb.no/emner/06/arbeid/). As it is becoming increasingly recognized that ADHD is not only a childhood condition, the possibility that different susceptibility genes may exist for childhood symptoms and for the persistence or worsening of these symptoms during development ought to be considered and longitudinal studies should be performed to test this hypothesis.

Limitations and Strengths of the Study

The apparently conflicting genetic results presented here may reflect a true difference among children and adults with ADHD, but other explanations for the discrepancies should also be considered. Although the Norwegian population is considered to be genetically homogeneous, we cannot completely refute the risk of undetected population stratification which can potentially inflate results in case control studies. Furthermore, different clinical ascertainment criteria between studies may have influenced the results. We have studied a clinical sample of adult ADHD patients that were diagnosed by many different clinicians from all parts of Norway. ICD-10 research criteria have been used to diagnose ADHD in the present sample, but the criteria have been modified, as described in the Materials and Methods Section, so that they more closely resemble DSM-IV criteria, allowing for a diagnosis of ADHD in patients with only inattentive symptoms. The strength of the study is the size of the Norwegian sample, the selection procedure and the almost 1:1 gender distribution. During 1997–2003, a total of 1862 men and 652 women with ADHD were considered for stimulant therapy in Norway (74% males). Although the relative proportion of females has recently increased, the gender distribution in our study may partly reflect a greater willingness among women to participate in the study. Our patient group is characterized by strong familiar clustering of ADHD and relatively strong impairments, which suggest that the sample is well suited for molecular genetic studies.

In conclusion, the results in our adult Norwegian clinical ADHD sample support a role for the DRD5 locus as a risk factor of an adult ADHD diagnosis, but not for the much studied VNTRs located in the 3′UTR of SLC6A3 and DRD4 exon 3. This suggests that adult ADHD patients may represent a subgroup of ADHD patients who share some, but not all, heritable risk components with ADHD in childhood. Our results illustrate the importance of genetic studies in all age groups of ADHD patients.

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