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

S. Johansson,1,2 H. Halleland,3 A. Halmøy,1 K.K. Jacobsen,1,2 E.T. Landaaas,1,2 M. Dramsdahl,1 O.B. Fasmer,4,5 P. Bergsholm,5 A.J. Lundervold,3 C. Gillberg,6 K. Hugdahl,3,4 P.M. Knappskog,2,7 and J. Haavik1,4*

1Department of Biomedicine, University of Bergen, Bergen, Norway
2Center of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway
3Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway
4Division of Psychiatry, Haukeland University Hospital, Bergen, Norway
5Department of Clinical Medicine, Section for Psychiatry, University of Bergen, Bergen, Norway
6Department of Child and Adolescent Psychiatry, Göteborg University, Göteborg, Sweden
7Department of Clinical Medicine, University of Bergen, Bergen, Norway

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 \( \text{OR} = 1.27 \) (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.

© 2007 Wiley-Liss, Inc.

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


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 dopaminergic system has received much attention, as it has been shown that stimulant medications such as methylphenidate and amphetamine...
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 (DAT1), 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 five 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 OrageneTM 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 α = 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 additional 34% of males and 36% of females answered “not known” on this question. Although these patients were classified as “sub-threshold” they had previously received a recovery or effective treatment. Furthermore, the subscales, possibly due to symptom fluctuation, spontaneous present symptom profile during 2005 or 2006 using the ASRS prior to the inclusion in the study, we also examined their 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 (Poverall) 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)].

**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>
<thead>
<tr>
<th>TABLE I. Demographic and Clinical Characteristics of the 358 Norwegian Adults With a Clinically Defined ADHD Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males (n = 182)</strong></td>
</tr>
<tr>
<td>Mean age, years (range)</td>
</tr>
<tr>
<td>ADHD subtype based on ASRS self report, % (n)</td>
</tr>
<tr>
<td>Sub-threshold</td>
</tr>
<tr>
<td>Predominantly inattentive</td>
</tr>
<tr>
<td>Predominantly hyperactive</td>
</tr>
<tr>
<td>Combined</td>
</tr>
<tr>
<td>First degree relative with ADHD*</td>
</tr>
<tr>
<td>Diagnosed in childhood</td>
</tr>
</tbody>
</table>

*An additional 34% of males and 36% of females answered “not known” on this question.
ADHD has withstood the test of time according to recent meta
individuals to ADHD as suggested by some studies [Brookes
cannot rule out that other variants in the region predispose
phenotype \(P_{\text{overall}} = 0.02, 148\)-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 show-
ed a (non-significant) tendency toward stronger association
than women, despite equally sized groups. However, to formal-
ly 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, espe-
cially 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,
A Developmental Perspective
Our study supports a common genetic risk locus for child-
hood 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

\[\text{TABLE II. Comparison of Allele Frequencies in Three Candidate Polymorphisms Among 358 Adult Norwegian ADHD Patients and 340 Controls} \]

<table>
<thead>
<tr>
<th>Gene</th>
<th>Marker</th>
<th>(P_{\text{overall}})</th>
<th>Risk allele(^a)</th>
<th>Cases (n = 358)</th>
<th>Controls (n = 340)</th>
<th>OR</th>
<th>(P_{\text{allelic}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRD5</td>
<td>VNTR 18.5 kb 5-prime</td>
<td>0.04</td>
<td>148</td>
<td>0.54</td>
<td>0.49</td>
<td>1.20 (0.97–1.48)</td>
<td>0.09</td>
</tr>
<tr>
<td>SLC6A3</td>
<td>VNTR 3’UTR</td>
<td>0.48</td>
<td>10</td>
<td>0.71</td>
<td>0.73</td>
<td>0.94 (0.74–1.19)</td>
<td>0.59</td>
</tr>
<tr>
<td>DRD4</td>
<td>VNTR exon 3</td>
<td>0.31</td>
<td>7</td>
<td>0.22</td>
<td>0.24</td>
<td>0.90 (0.70–1.15)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

\(^a\)Risk allele based on previous meta-analysis studies in ADHD.

\[\text{TABLE III. DRD5 Allele Distribution in Different ASRS Sub Groups Compared to Controls} \]

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

\(^a\)Overall \(P\)-values of likelihood test (only alleles above 5% frequency).
\(^b\)OR from the \(2 \times 2\) 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). 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. 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). 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.

ACKNOWLEDGMENTS

Michael Lensing, Ullevål University Hospital, is thanked for helpful advice and for assistance during patient recruitment. Heidi Wagningen, Vivica Næss, and Ragnhild Nordenborg are also thanked for assistance during patient recruitment and Sigrid Erdal is thanked for technical assistance. This project was supported by the Research Council of Norway and Helse Vest.

REFERENCES


Dudbridge F. 2006. UNPHASED user guide. Cambridge, UK: MRC Biostatistics Unit.


Purcell S, Cherny SS, Sham PC. 2003. Genetic power calculator: Design of linkage and association genetic mapping studies of complex traits. Bioinformatics 19:149–150.


