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Susceptibility genes for a trait measure of attention deficit hyperactivity disorder: a pilot study in a non-clinical sample of twins

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a highly heritable disorder, and molecular genetic studies are underway, with most researchers focusing on identifying susceptibility genes in clinical samples with ADHD. An alternative approach is to search for quantitative trait loci underlying the trait measure of ADHD in non-clinical samples. Positive findings of association of the dopamine transporter DAT1 480 bp allele (allele 10) and the DRD4 7 repeat allele with clinical ADHD have been previously reported. In this pilot study, we examined these polymorphisms in a selected population-based sample of twins (50 high scoring pairs, 42 low scoring pairs). There was a trend for an increase in the frequency of the dopamine receptor DRD4 7 repeat allele in the high-scoring concordant monozygotic twins (odds ratio = 1.4). Although this result was not statistically significant, the frequency of the 7 repeat allele was similar to that reported for our clinic sample of ADHD patients drawn from the same geographical area. There was a non-significant trend for an increased frequency of the DAT1 allele 10 (odds ratio = 1.3). These results suggest that a molecular genetic study based on a questionnaire-derived measure of ADHD in a non-clinical sample is feasible and the results appear to be comparable with those from studies of clinical cases. However, sample size and power are key issues to consider when using this approach.

Keywords: Attention deficit hyperactivity disorder; Molecular genetics; DRD4; DAT1; Twins

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1. Introduction

There is much evidence that attention deficit hyperactivity disorder (ADHD) is influenced by genetic factors, and molecular genetic studies of the clinical disorder are underway. An alternative approach to examining the genetic basis of ADHD is to search for quantitative trait loci (QTL) for ADHD defined as a quantitative trait rather than as a clinical disorder. There is much empirical support for viewing ADHD as a continuum. Twin studies of ADHD have consistently shown that ADHD defined as a continuum is highly heritable (Thapar et al., 1999) and that the genetic aetiology of extreme scores is similar to the contribution of genetic influences on normal variation (Levy et al., 1997). Moreover, ADHD also appears to act as a dimension in terms of its associated risk effects (Rutter et al., 1998).

There has been increasing interest in methods aimed at identifying genes of small effect for quantitative traits (quantitative trait loci; QTL), in particular QTL linkage mapping strategies using sib pairs (Sham, 1998). Although extremely large sample sizes are required to detect QTL linkage, power can be greatly enhanced by selecting extreme concordant and discordant sib pairs (Risch and Zhang, 1996; Sham, 1998). There is much less information on strategies for optimising statistical power using QTL association methods, although again sampling extremes is likely to increase the power to detect genes of small effect. However, a key question is, are the results of such studies that are based on non-clinical samples relevant to clinic patients with a rigorously defined disorder?

In this pilot study we explored the feasibility of identifying susceptibility genes for ADHD defined as a trait measure in a sample selected from the general population. We examined the association of polymorphisms in the dopamine transporter DAT1 gene and the dopamine receptor DRD4 gene with ADHD symptom scores in a selected sample of twins. These two candidate genes were chosen on the grounds that positive association findings for DAT1 and DRD4 in clinic-derived samples of children who fulfil diagnostic criteria for ADHD have been frequently reported (Collier et al., 2000). This would allow us to compare findings for a trait measure of ADHD in a non-clinical sample with results from traditional clinic and diagnosis-based association studies.

Findings for DAT1 (Cook et al., 1995) have been independently replicated (Daly et al., 1999; Waldman et al., 1998; Curran et al., 2001), although there have also been a number of negative reports (Palmer et al., 1999; Swanson et al., 1998; Holmes et al., 2000). Results for DRD4 have been more promising, with many positive findings reported (Barr et al., 2000; Smalley et al., 1999; Swanson et al., 1998; Faraone et al., 1999; Comings et al., 1999; Muglia et al., 2000; Sunohara et al., 2000; Tahir et al., 2000). Some positive results have been reported with case control analysis but negative family-based findings (Rowe et al., 1998; Holmes et al., 2000; Mill et al., 2001), but others have failed to detect any effects (Castellanos et al., 1998; Eisenberg et al., 2000; Hawi et al., 2000; Kotler et al., 2000). A recent meta-analysis suggests that there is an association between the DRD4 7 repeat allele and clinical ADHD, but the size effect appears to be small (Faraone et al., 2001).

2. Methods

2.1. Subjects

The Greater Manchester Twin Register was established in 1996 and contains a population-based sample of 2846 twin pairs aged between 5 and 17 years. A package of questionnaires was posted to these families and following two postal and one telephone reminder, an overall response rate of 73% (2082/2846) was achieved (Thapar et al., 2000). The characteristics of the original sample have been described previously (Thapar et al., 2000). Parent ratings of ADHD symptoms for each twin were obtained using a modified version of the DuPaul ADHD rating scale (DuPaul, 1981). Zygosity was assigned using parent responses on the twin similarity questionnaire (Cohen et al., 1975) and further checked in the laboratory for the selected sample.