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ORIGINAL RESEARCH ARTICLE

Attention deficit hyperactivity disorder (ADHD) and the dopamine D4 receptor gene: evidence of association but no linkage in a UK sample

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Recent studies report association and linkage between attention deficit hyperactivity disorder (ADHD) and the 7-repeat allele of a 48 base-pair repeat in the dopamine D4 receptor gene (DRD4).[1] We examined the frequency of this allele in a sample of probands with DSM-IV ADHD using a case-control design, as well as the transmission disequilibrium test (TDT) and haplotype-based haplotype relative risk (HHRR) in the subset of probands with DNA available from both parents. One hundred and thirty-two ADHD probands were compared with 189 controls ($\chi^2 = 6.17$, 1 df, $P = 0.01$, OR = 1.73, 95% CI = 1.11–2.71). A total of 85 complete trios were available for within-family tests of association and linkage. Fifty-two heterozygous parents carrying one copy of the 7-repeat were informative for the TDT (29 transmitted *vs* 23 non-transmitted, $\chi^2 = 0.69$). Analysis of the entire sample of 132 probands using TRANSMIT[2] provided no additional evidence for excess transmission of the 7-repeat allele (58 transmitted *vs* 54 non-transmitted). HHRR gave similar results. We conclude that the case-control findings are likely to be falsely positive, resulting from genetic stratification. However we can not rule out alternative explanations of low statistical power and gene–environment correlation. *Molecular Psychiatry* (2001) **6,** 440–444.

Genetic studies aimed at the identification of susceptibility loci for ADHD have focused on genes involved in the regulation of dopamine neurotransmission. The most robust finding to date is the association and linkage between the 7-repeat allele in DRD4 and ADHD. Nine published studies have shown association or association and linkage between the 7-repeat and ADHD,[3–11] whereas four have found no association.[12–15] A recent meta-analysis of published and unpublished data suggests a respectable but modest odds ratio (OR) of 1.9 (95% CI 1.4–2.2, $P = 0.00000008$) from seven case-control studies and 1.4 (95% CI 1.1–1.6, $P = 0.02$) from 14 family-based studies.[16] Here we describe new data on the association between the 7-repeat allele and ADHD in two samples from the South of England, using both case-control and within-family forms of analysis.

In total, 132 probands with DSM-IV ADHD, were genotyped and compared with two sets of controls (Table 1). It was found that the frequency of the 7-repeat allele among probands was increased compared to a sample of UK Caucasian children unselected for phenotype (TEDS sample) ($\chi^2 = 5.27$, 1 df, $P = 0.02$) and a sample of UK Caucasian children selected for low maternal ratings of hyperactivity (CHIP sample) ($\chi^2 = 3.07$, 1 df, $P = 0.08$). Since frequencies of the major alleles are similar for the two control samples we can combine these to compare all cases with all controls ($\chi^2 = 6.17$, 1 df, $P = 0.01$, OR = 1.73, 95% CI = 1.11–2.71). All the cases in this sample had the combined subtype (7-repeat frequency = 21.7%), apart from nine cases with the hyperactive/impulsive subtype (7-repeat frequency = 11.1%) and three cases with the inattentive subtype (7-repeat frequency = 33.3%). Within the ADHD sample, 7-repeat allele frequencies were similar among nine cases with Axis I comorbidity (22.2%) and eleven cases with a questionnaire rating suggestive (but no clinical diagnosis) of pervasive development disorder (21.74%). Removal of these cases to define a refined phenotype under DSM-IV of the combined subtype with no Axis I comorbidity gave similar results to the sample overall ($\chi^2 = 6.80$, 1 df, $P = 0.01$).

A total of 85 complete trios were available for within-family tests of association and linkage (Table 2). Among these there were 52 heterozygous parents carrying one copy of the 7-repeat allele, informative for the TDT (29 transmitted *vs* 23 non-transmitted, $\chi^2 = 0.69$). Analysis of the entire sample of 162 probands using TRANSMIT,[2] which estimates probabilities for missing parental genotypes provided no additional evidence for excess transmission of the 7-repeat (58 transmitted *vs* 54 non-transmitted). We also carried out HHRR by examining frequencies of transmitted vs non-transmitted parental alleles from the 85 trios. Comparable with the TDT, we found no evidence for the association with the 7-repeat ($\chi^2 = 0.64$) and found that non-transmitted 7-repeat frequencies were more similar to our cases (18.8% *vs* 21.1%) than our controls (18.8% *vs* 13.8%). Furthermore, we observed a 7-repeat frequency of 21% in the parents of the complete trios and

Table 1 Case-control analysis. Allele counts and frequencies for DRD4 in IOP, UB and control samples

No. of repeats	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*Total*
IOP								
Total	23 (11.27%)	10 (4.90%)	121 (59.31%)	5 (2.45%)	1 (0.49%)	44 (21.57%)	0 (0%)	204
Combined subtype	21 (11.05%)	10 (5.26%)	113 (59.47%)	4 (2.11%)	1 (0.53%)	41 (21.58%)	0 (0%)	190
Birmingham								
Total	5 (8.33%)	2 (3.33%)	40 (66.67%)	1 (1.67%)	0 (0%)	12 (20.0%)	0 (0%)	60
Combined subtype	3 (6.0%)	1 (2.0%)	34 (68.0%)	1 (2.0%)	0 (0%)	11 (22.0%)	0 (0%)	50
IOP + Birmingham								
Total	28 (10.61%)	12 (4.55%)	161 (60.98%)	6 (2.27%)	1 (0.38%)	56 (21.21%)	0 (0%)	264
Combined subtype	24 (10.0%)	11 (4.58%)	147 (61.25%)	5 (2.08%)	1 (0.42%)	52 (21.67%)	0 (0%)	240
Controls								
CHIP low SDQ	20 (11.2%)	6 (3.4%)	119 (66.9%)	4 (2.2%)	0 (0%)	26 (14.6%)	3 (1.7%)	178
TEDS	18 (9.00%)	18 (9.00%)	137 (68.5%)	0 (0%)	1 (0.5%)	26 (13%)	0 (0%)	200
Combined	38 (10.00%)	24 (6.34%)	256 (67.7%)	4 (1.1%)	1 (0.3%)	52 (13.8%)	3 (0.8%)	378

Table 2 Haplotype-based haplotype relative risk. Transmitted and untransmitted parental alleles for 85 complete trios

No. of repeats	*Not 7*	*7*	*Total*
Transmitted alleles	132 (77.6%)	38 (22.4%)	170
Non-transmitted alleles	138 (81.2%)	32 (18.8%)	170

20% if we include 33 additional single parents, both significantly different from the two control samples (CHIP and TEDS) used in this study ($\chi^2 = 5.92$, 1 df, $P = 0.015$ and $\chi^2 = 7.00$, 1 df, $P = 0.008$ respectively).

The results of the case-control analysis are consistent with previous reports of a positive association between the 7-repeat and ADHD. This was expected since we had 95% power at an alpha level of 0.05 to confirm the association, assuming an OR of 1.9. We attempted to exclude the possibility of stratification by genotyping control samples drawn from two independent sources of English Caucasian children; one unselected for phenotype (TEDS sample) and the other selected for low maternal hyperactivity ratings (CHIP sample). Furthermore, the frequency of the 7-repeat in published reports of UK Caucasians shows a high level of consistency with our data (Table 3). On the other hand, within-family tests of association and linkage performed on the sub-set of 85 trios did not reach statistical significance and showed only a very weak trend in the expected direction. In this study, the power of the TDT and HHRR tests are lower than the power of the case-control analysis, since we analysed only 85 complete trios out of a total of 132 ADHD probands. To overcome this problem we used TRANSMIT,[2] which estimates transmission ratios from the entire dataset by assigning probabilities to parental genotypes where data are missing from one or both parents and makes use of sibling genotypes. This is a useful strategy in our sample in which we have genotypes from 89 siblings. Although TRANSMIT requires the estimation of allele frequencies for the population and is no longer robust to genetic stratification, we might expect a result close to our case-control findings if non-replication was simply a matter of power. In fact, this was not what we found since the transmission ratio estimate from TRANSMIT showed an extremely weak and non-significant trend in the expected direction (58 T *vs* 54 NT). The most obvious conclusion from these data is therefore, that the case-control findings are false positive results, arising from a population stratification artefact.

The extent to which population stratification influences our findings may be estimated using procedures described by Pritchard and colleagues,[19] although the data required for such an analysis do not exist at this time. Nevertheless, in the light of reports from other studies, it is worth considering alternative explanations for these data. In a recent publication, Holmes and colleagues, using UK Caucasian samples,[11] reported a similar pattern of 7-repeat frequencies among ADHD probands ($n = 129$), parents of probands ($n = 210$) and unrelated controls ($n = 425$) to those seen in this study. In both studies, the size of the gene effect estimated from analysis of the case-control data was larger compared to the estimate from within-family data. Similar findings were reported in a recent meta-

Table 3 Published 7-repeat allele frequencies among UK Caucasian controls

Study	*Region of ascertainment*	*Source of controls*	*n alleles*	*n 7-repeat alleles*	*Allele-7 freq.*
Lim *et al*[17]	London, England	Non-psychiatric out-patients	118	16	13.6%
Daniels *et al*[18]	Cardiff, Wales	Relatives of cases with non-psychiatric disorders	238	45	18.9%
Holmes *et al*[11]	East Anglia & Manchester, England	General practice register & non-psychiatric out-patients	884	113	13.00%
CHIP-LOW SDQ (this study)	England	General practice register	178	26	14.61%
TEDS CONTROL (this study)	England	Epidemiological twin sample	200	26	13.00%
Combined total			1618	226	13.9%

analysis reported by Steve Faraone and colleagues.[16] The analysis of 1266 cases and 3068 Caucasian controls gave rise to an estimated odds ratio of 1.9 with a significance level of 8×10^{-8}, which meets Lander and Kruglyak's[20] stringent criteria assuming a genome-wide screen for association. In contrast an estimated odds ratio of 1.4 came from the HHRR analysis of 1665 trios with a lower level of significance ($P = 0.02$). If we speculate that the observed difference in odds ratios is a true difference, one of the consequences would be considerably more power to replicate case-control findings than within-family tests. For HHRR analysis, we have estimated that a sample size around 150 is needed to detect the 7-repeat association assuming an odds ratio of 1.9, whereas around 500 is required for an odds ratio of 1.4, assuming 80% power and alpha level of 0.05. But is there any feasible explanation for such a difference in odds ratios?

Holmes *et al* were the first to suggest this may indicate gene–environment correlation.[11] The 7-repeat association may be primarily with the parents of ADHD probands rather than with the ADHD probands themselves. In this scenario, the parental phenotype resulting from possession of 7-repeat would give rise to environmental risk factors for ADHD acting on offspring who do not carry copies of the 7-repeat, as well as those that do: for example, hostile parenting and poor parenting styles, or increased risk to the foetus from higher rates of smoking, alcohol and other toxins during pregnancy.

Is it possible that the increased rate of the 7-repeat among parents of ADHD probands, compared to population controls, is the result of assortative mating? We have considered the effect of this on the TDT and HHRR. For the TDT, estimates of odds ratio are robust to changes in allele frequency and Hardy–Weinberg Equilibrium (HWE) among parents, while for the HHRR odds ratio is robust to changes in allele frequency but decreases rapidly with departures from HWE (Sham, unpublished observations). In our sample, both fathers and mothers have an increased frequency of 7-repeats compared to controls (18% and 23%, respectively), but neither show any departure from HWE (data not shown). We therefore conclude that assortative mating is not expected to reduce the power of either analysis.

Finally, it has been frequently stated that the DRD4 exon 3 repeat polymorphism is functionally significant. Asghari *et al*[21] concluded that different repeat lengths conferred different pharmacological properties to the D4 receptor, with the 7-repeat acting to dull the response of cells to dopamine. Such findings, however, are not ubiquitous and more recent findings do not suggest an important functional role for the repeat region. Kazmi *et al*[22] found no quantitative differences in G-protein coupling when comparing constructs of the 2-, 4- and 7-repeat alleles. In another study of 2-, 4- and 7-repeats, Watts *et al*[23] concluded that the potency and efficacy of dopamine for sensitisation of cyclic-AMP accumulation was comparable. Jovanovic *et al*[24] compared 2- and 10-repeats and found no major differences in pharmacological or functional profiles for the two receptors. It is therefore possible that the 7-repeat is in linkage disequilibrium (LD) with a functional variant, such as the DRD4 promotor polymorphism, reported by Okuyama *et al*[25] to reduce transcriptional efficiency by around 40%. Variation in LD relationships found in different populations may confound association studies with the 7-repeat allele, leading to discrepant findings.

Methods

Clinical sample

Two clinical samples were used in this study collected at the Institute of Psychiatry (IOP) and the University of Birmingham (UB). Subjects were identified from child behavioural clinics in London, Horsham, Southampton and Birmingham. Cases were referred for assessment if they were thought by experienced clinicians to have a diagnosis of the combined subtype of ADHD under DSM-IV criteria, with no significant Axis I co-morbidity apart from oppositional defiant disorder (ODD) and conduct disorder (CD). Parents of referred cases were interviewed with an abbreviated version of the Child and Adolescent Psychiatric Assessment (CAPA).[26] Information on ADHD symptoms at school

were obtained using the Conners questionnaire.[27] Following the IOP assessments, HYPESCHEME data sheets were completed using data gathered from the research interview, questionnaire and where necessary review of case notes. HYPESCHEME is an operational criteria checklist for ADHD and hyperkinetic disorders, which summarises and applies DSM-IV and ICD-10 operational criteria.[28] HYPESCHEME diagnoses were checked against researcher applied DSM-IV criteria and discrepancies reviewed by two researchers (PA and SR). Where consensus could not be reached, cases were brought to case conference and final consensus agreement made with a senior clinical researcher (ET). In the UB, DSM-IV criteria were applied directly by the researcher (LK) and consensus diagnosis agreed at case conference.

All the subjects used in this study were free of neurological disease and damage, and did not have any congenital disorders known to cause hyperactivity. They were all Caucasian, aged between 5 and 15 (mean = 10.41, SD = 2.34) at the time of first assessment and had an IQ above 60 (mean = 98.8, SD = 18.6, range 60–139). Cases were included in this study if they had a diagnosis of ADHD under DSM-IV criteria. Out of 132 cases collected at the IOP, 120 had the combined subtype, nine had the hyperactive/impulsive subtype and three the inattentive subtype. Out of 30 cases at UB, 24 had the combined subtype, four the hyperactive/impulsive subtype and two the inattentive subtype. Axis 1 comorbidity consisted of seven cases with an affective disorder and two cases with Tourettes syndrome.

In addition, the IOP samples were screened for evidence of pervasive developmental disorders (PDD) using the Autism Screening Questionnaire (ASQ)[29] and the pro-social scale from the Strengths and Difficulties Questionnaire (SDQ).[30] In a pilot study, full Autism Diagnostic Interviews were performed on eight ADHD cases who scored high on these screening questionnaires and all of these were found to score above diagnostic cut-offs on the social communication domain and five on at least one additional pervasive developmental disorder (PDD) domain. Based on these data, we identified 11 cases as having a questionnaire-based diagnosis of PDD, defined as a score of 16 or greater on the ASQ and five or less on the SDQ pro-social scale.

Control samples

Two independent epidemiologically obtained and ethnically matched control samples were used in this study. Initial control data were generated from 100 children, aged 3–5 years who were part of the Twins Early Development Study (TEDS). A second control sample comprised children aged 5–15 years with low hyperactivity scores on a parent rating scale. The five-item hyperactivity scale from the SDQ was used with selected controls scoring 0 or 1 on a 10-point scale. In addition, we collected DNA from both parents whenever possible, for within-family tests of association and linkage. Complete trio data were available from all 30 of the UB cases and 55 of the IOP cases. At the IOP, DNA was also collected from 89 siblings of ADHD probands.

Amplification of DRD4 exon 3 VNTR

The exon 3 VNTR was amplified with an initial 9-min denaturing step at 95°C, followed by 35 cycles of 93°C for 1 min, 55°C for 1 min and 72°C for 1 min, and a final extension phase of 72°C for 10 min. Primers used were 5′-GGT CTG CGG TGG AGT CTG-3′ and 5′-GCG ACT ACG TGG TCT ACT-3′. Reactions were performed in 22-μl volumes and included 50 ng of genomic DNA, 1.5 mM $MgCl_2$, 0.2 mM dNTPs (incorporating a 50/50 deaza dGTP/dGTP mix), 10% DMSO, 10 mM GeneAmp 10× PCR Gold Buffer and 1 unit of AmpliTaq Gold (PE Applied Biosystems, Foster City, CA, USA). PCR products were run out on a 2% agarose gel stained with ethidium bromide and analysed under UV light. Homozygous genotypes were repeated if clear and strong bands were not observed. The ability of this protocol to detect the long 7-repeat allele in heterozygotes, which shows marked differential amplification with the common 2, 3 and 4 repeat alleles, has been examined in our laboratory by comparison with fluorescently tagged products visualised on an ABI 310 (PE Applied Biosystems) and found to be sufficiently sensitive.

Statistical analysis

Association of the 7-repeat with ADHD was investigated in the case-control data using the Pearson chi-square statistic. The transmission disequilibrium test (TDT) and haplotype-based haplotype relative risk (HHRR) were applied to the sub-set of probands with parental DNA available for genotyping. To maximise the power of this sample for within-family tests, we also applied TRANSMIT, a program which tests for association between genetic marker and disease by examining the transmission of markers from parents to affected offspring. TRANSMIT can deal with unknown parental genotypes and data from unaffected siblings may be used to narrow down the range of possible parental genotypes.

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