

Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD)

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Molecular genetic investigations of attention deficit hyperactivity disorder (ADHD) have found associations with a variable number of tandem repeat (VNTR) situated in the 3'-untranslated region of dopamine transporter gene (*DAT1*), a VNTR in exon 3 of dopamine receptor 4 gene (*DRD4*) and a microsatellite polymorphism located at 18.5 kb from the 5' end of dopamine receptor 5 gene (*DRD5*). A number of independent studies have attempted to replicate these findings but the results have been mixed, possibly reflecting inadequate statistical power and the use of different populations and methodologies. In an attempt to clarify this inconsistency, we have combined all the published studies of European and Asian populations up to October 2005 in a meta-analysis to give a comprehensive picture of the role of the three dopamine-related genes using multiple research methods and models. The *DRD4* 7-repeat (OR = 1.34, 95% CI 1.23–1.45, $P = 2 \times 10^{-12}$) and 5-repeat (OR = 1.68, 95% CI 1.17–2.41, $P = 0.005$) alleles as well as the *DRD5* 148-bp allele (OR = 1.34, 95% CI 1.21–1.49, $P = 8 \times 10^{-8}$) confer increased risk of ADHD, whereas the *DRD4* 4-repeat (OR = 0.90, 95% CI 0.84–0.97, $P = 0.004$) and *DRD5* 136-bp (OR = 0.57, 95% CI 0.34–0.96, $P = 0.022$) alleles have protective effects. In contrast, we found no compelling evidence for association with the 480-bp allele of *DAT* (OR = 1.04, 95% CI 0.98–1.11, $P = 0.20$). No significant publication bias was detected in current studies. In conclusion, there is a statistically significant association between ADHD and dopamine system genes, especially *DRD4* and *DRD5*. These findings strongly implicate the involvement of brain dopamine systems in the pathogenesis of ADHD.

INTRODUCTION

Evidence from family, twin and adoption data suggests that attention deficit hyperactivity disorder (ADHD) is familial and heritable (75–91%) (1–3). It is a common, highly disruptive, disabling neurodevelopmental disorder that affects up to 6% of children (3). Subjects with ADHD have, compared with controls, a higher frequency of course failures, fewer friends (4), greater risk of substance abuse (5) and more traffic citations including speeding, vehicular crashes and license suspensions (6).

At least 20 potential susceptibility genes have so far been studied in relation to ADHD (7). Evidence from pharmacological, neuroimaging and animal studies have suggested the involvement of specific neurotransmitter systems, notably dopaminergic pathways, in ADHD (3). Stimulant drugs, which for half-a-century have provided the primary pharmacological treatment for ADHD, have their site of action in the dopaminergic system (8). Thus, the genes encoding the dopamine transporter and receptors have been the most attractive candidate genes for ADHD. The most extensively studied have been the dopamine transporter gene (*DAT1*), the

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dopamine receptor 4 gene (*DRD4*) and the dopamine receptor 5 gene (*DRD5*).

The 52.6 kb human *DAT1* gene (*SLC6A3*) is located on chromosome 5p15.3 and codes for a transmembrane protein responsible for the presynaptic reuptake of dopamine (8). Using a family-based association study, Cook *et al.* (9) first reported an association between ADHD and the 480-bp allele of a variable number of tandem repeat (VNTR) polymorphism situated in the 3'-untranslated region. Subsequent findings have been mixed, but a meta-analysis (10) of family-based studies in 2001 showed a statistically significant effect, and a recent analysis (2) also found a small but significant association.

The *DRD4* gene of size 3400 bp, at chromosome 11p15.5, is one of the most variable human genes known. A VNTR polymorphism in exon III consists of a 48-bp repeat unit and codes for an amino-acid sequence located in the third intracellular cytoplasmic loop of the receptor. Ten alleles (2–11 repeats) have been identified in the global population, and allele frequencies vary considerably between populations. An early study (11) suggested that the 7-repeat allele conferred increased risk of ADHD, a finding which was confirmed by meta-analysis (12) in 2001.

The *DRD5* gene, of size 2031 bp, maps to chromosome 4p15.1-p15.3. Daly *et al.* (13) first reported a risk effect of the 148-bp allele of a microsatellite polymorphism (CT/GT/GA)_n located 18.5 kb from the 5' end of the gene. A meta-analysis (14) of five studies and a joint analysis (15) of 14 groups also showed association with the 148-bp allele. Haplotype analysis (16) has also revealed a significant association. The polymorphism was also reported to be associated with oppositional defiant disorder, which was diagnosed in more than half of the children clinically referred with ADHD (17).

The positive findings with each of the three candidate genes have been independently replicated by other groups using either case-control or family-based association designs. However, a proportion of subsequent studies have produced contrary results. The association data has increased sharply in recent years in both European and, more particularly, Asian populations. To reconcile the conflicting findings and elucidate the genetic architecture of ADHD, the current meta-analysis combines results from all case-control and family-based association studies published up to October 2005.

RESULTS

The combined search yielded 885 references. Among these 36, 50 and 13 studies were found to be association studies on the *DAT1*, *DRD4* and *DRD5* genes, respectively. These references were then filtered to ensure conformity with the inclusion criteria. Some studies were excluded although we tried to contact authors in cases where there were queries regarding their studies. For the *DAT1* gene, one study (18) was discarded because of insufficient data; two studies (19,20) because the identity of the risk allele was uncertain [although we tried to contact the authors to query the data (18–20)]; one haplotype relative risk (HRR) (21) because the risk alleles (440-, 480- and 520-bp) were combined; one (22) because the sample

overlapped with that of another study [case-control and transmission disequilibrium test (TDT)] (21); and one (23) because it is used as a trait measure design. For the *DRD4* gene, one study (24) was discarded because of insufficient data; one (20) because the identity of the risk allele was uncertain; two (25,26) because the risk alleles (2–7-repeat) were combined; two (27,28) for overlapping samples with other studies (29,30), respectively; one (23) for trait measure design; and one (case-control) (31) for using non-healthy subjects as controls. For the *DRD5* gene, two studies (15,32) were discarded because of insufficient data and one (19) because the identity of the risk allele was uncertain. As a result, 26, 38 and 9 studies were included for the *DAT1*, *DRD4* and *DRD5* genes, respectively. These studies included 2576 cases, 3453 controls and 6592 parent-offspring trios.

DAT1 VNTR polymorphism

The included studies comprised eight case-control (21,33–39), two HRR (36,40), three haplotype-based haplotype relative risk (HHRR) (9,13,16) and 13 TDT studies (21,33,41–50). The 480-bp allele was the most common allele, having higher frequency in Asians than in Europeans, and the frequency differences between cases and controls varied among different populations. Overall, the results for all three putative risk alleles (480, 520 and 440-bp) were either very weak or non-significant (Table 1). However, there was evidence of heterogeneity in all combined studies for the 480-bp allele, because of greater evidence for positive association results from the family-based studies and European studies than from the case-control studies and Asian studies, respectively (Tables 2 and 3).

DRD4 VNTR polymorphism

The selected studies comprised 15 case-control (11,21,29,33–36,38,51–57), three HRR (31,36,58), two HHRR (29,54) and 18 TDT studies (21,29,30,33,44–46,52,55,59–66). For the 7-repeat allele, the frequency varied widely across normal populations, being abundant in Europeans (9.1–25.6%), but undetectable in Asians (21,38). In the 12 European case-control studies, 10 studies showed higher frequency in cases than in controls. In the 21 European family-based studies, 19 showed preferential transmission. The combined European studies produced a significant *P*-value of 2×10^{-12} , with only weak evidence for heterogeneity between studies (*P* = 0.03) (Table 1). No evidence for publication bias was found. The overall OR was 1.34 (1.23, 1.45). The significant results were consistent between case-control and family-based studies although heterogeneity was found between design types (*P* = 0.002), with a larger odds ratio estimate in case-control than in family-based studies (Table 2).

For the 4-repeat allele, in the 13 case-control studies, 11 showed lower frequency in cases. In the 14 family-based studies, nine showed reduced transmission to affected offspring. The 4-repeat allele was the most prevalent allele, ranging from 60.8–77% across normal populations, and appears to confer a protective effect. All studies together showed a significant *P*-value of 0.004 [OR = 0.90 (0.84, 0.97)] without evidence

Table 1. Results of all combined studies

Genes/Alleles	Overall OR (95% CI)	<i>P</i> (<i>Z</i>)	<i>P</i> (<i>Q</i>)	<i>P</i> (<i>T</i>)
<i>DATI</i> 440-bp (11) ^a	1.02 (0.93, 1.13)	0.6418	0.7829	0.309
<i>DATI</i> 480-bp (26)	1.04 (0.98, 1.11)	0.1955	1×10^{-6}	0.065
<i>DATI</i> 520-bp (7)	1.48 (1, 2.18)	0.050	0.9236	0.729
<i>DRD4</i> 2-repeat (28)	0.97 (0.86, 1.09)	0.6059	0.2157	0.204
<i>DRD4</i> 3-repeat (24)	0.99 (0.8, 1.23)	0.9507	0.3767	0.891
<i>DRD4</i> 4-repeat (27)	0.90 (0.84, 0.97)	0.0042	0.0513	0.070
<i>DRD4</i> 5-repeat (21)	1.68 (1.17, 2.41)	0.0053	0.2067	0.290
<i>DRD4</i> 7-repeat (33)	1.34 (1.23, 1.45)	2×10^{-12}	0.0314	0.062
<i>DRD5</i> 148-bp (9)	1.34 (1.21, 1.5)	8×10^{-8}	0.0008	0.011
<i>DRD5</i> 136-bp (3)	0.57 (0.34, 0.96)	0.0223	0.6247	0.202
<i>DRD5</i> 146-bp (3)	0.84 (0.6, 1.15)	0.2252	0.2118	0.593

P(*Z*): *Z* test used to determine the significance of the overall OR.

P(*Q*): Cochran's χ^2 -based *Q* statistic test used to assess the heterogeneity.

P(*T*): *T* test used to evaluate the significance of publication bias.

For Tables 1–3, data in columns *P*(*Z*), *P*(*Q*) and *P*(*T*) are the *P*-values for the corresponding tests.

^aThe number of studies included are indicated in parentheses.

Table 2. Heterogeneity analyses by design types

Alleles/Types	Overall OR (95% CI)	<i>P</i> (<i>Z</i>)	<i>P</i> (<i>Q</i>)	<i>P</i> (<i>Q</i>) ^a
<i>DATI</i> 440-bp				0.4536
Case-control (6)	1.14 (0.91, 1.43)	0.3600	0.7583	
Family-based (5)	1 (0.89, 1.12)	0.9726	0.5260	
<i>DATI</i> 480-bp				0.1759
Case-control (8)	0.91 (0.76, 1.09)	0.4169	0.1966	
Family-based (18)	1.06 (0.99, 1.14)	0.0862	0.000001	
<i>DATI</i> 520-bp				0.2926
Case-control (4)	1.81 (1.06, 3.08)	0.0288	0.9614	
Family-based (3)	1.18 (0.67, 2.09)	0.5690	0.7568	
<i>DRD4</i> 2-repeat				0.9574
Case-control (14)	0.97 (0.82, 1.15)	0.2797	0.1294	
Family-based (14)	0.97 (0.82, 1.14)	0.6888	0.8369	
<i>DRD4</i> 3-repeat				0.5912
Case-control (11)	1.07 (0.79, 1.44)	0.6826	0.0962	
Family-based (13)	0.95 (0.7, 1.28)	0.7260	0.7782	
<i>DRD4</i> 4-repeat				0.01
Case-control (13)	0.8 (0.71, 0.9)	0.0002	0.1680	
Family-based (14)	0.97 (0.89, 1.05)	0.4138	0.2717	
<i>DRD4</i> 5-repeat				0.2958
Case-control (10)	1.92 (1.21, 3.03)	0.0055	0.2949	
Family-based (11)	1.32 (0.75, 2.35)	0.3373	0.4327	
<i>DRD4</i> 7-repeat				0.0017
Case-control (12)	1.65 (1.41, 1.92)	2×10^{-10}	0.0792	
Family-based (21)	1.23 (1.12, 1.36)	0.00002	0.4249	

Family-based = HRR + HHRR + TDT.

^aHeterogeneity test between design types (case-control versus family-based).

for heterogeneity or for publication bias ($P > 0.05$) (Table 1). However, there was weak evidence for heterogeneity between design types ($P = 0.01$).

The 5-repeat allele also appears to confer an increased risk. Combining all studies showed a significant *P*-value of 0.005 [OR = 1.68 (1.17, 2.41)], without evidence for heterogeneity or for publication bias (Table 1). Also there was no heterogeneity between design types and sample ethnicities (Tables 2 and 3).

Table 3. Heterogeneity analyses by sample ethnicities

Alleles/Ethnicities	Overall OR (95% CI)	<i>P</i> (<i>Z</i>)	<i>P</i> (<i>Q</i>)	<i>P</i> (<i>Q</i>) ^a
<i>DATI</i> 440-bp				0.0749
European (8)	1 (0.9, 1.11)	0.9960	0.8914	
Asian (3)	1.45 (0.98, 2.15)	0.0657	0.8727	
<i>DATI</i> 480-bp				0.0792
European (21)	1.07 (1, 1.15)	0.0513	0.00002	
Asian (5)	0.93 (0.81, 1.07)	0.3275	0.0163	
<i>DATI</i> 520-bp				0.5349
European (4)	1.15 (0.47, 2.78)	0.7596	0.9037	
Asian (3)	1.57 (1.02, 2.42)	0.0421	0.6053	
<i>DRD4</i> 2-repeat				0.8673
European (23)	0.96 (0.83, 1.11)	0.6028	0.3403	
Asian (5)	0.98 (0.8, 1.21)	0.8784	0.0814	
<i>DRD4</i> 3-repeat				0.5213
European (20)	0.98 (0.78, 1.23)	0.8642	0.4320	
Asian (4)	1.23 (0.64, 2.37)	0.5357	0.1956	
<i>DRD4</i> 4-repeat				0.1345
European (23)	0.88 (0.81, 0.95)	0.0012	0.0367	
Asian (4)	1 (0.86, 1.15)	0.9637	0.7298	
<i>DRD4</i> 5-repeat				0.9445
European (17)	1.7 (1.06, 2.71)	0.0276	0.4031	
Asian (4)	1.65 (0.93, 2.93)	0.0864	0.4101	

The *DRD4* 7-repeat allele was not detected in Asian populations.

^aHeterogeneity test between sample ethnicities (European versus Asian).

For the 3- and 2-repeat alleles, the results were non-significant.

Figures 1 and 2 show the forest plots and funnel plots for the 7-repeat allele. The forest/funnel plots for other alleles are shown as supplements.

DRD5 polymorphism

The selected studies comprised two HHRR (13,16) and seven TDT studies (44–46,64,67–69), all of European origin. For the 148-bp risk allele, combining all studies showed a significant *P*-value of 8×10^{-8} [OR = 1.34 (1.21, 1.5)] with evidence of heterogeneity ($P = 0.0008$) and weak evidence for publication bias ($P = 0.01$) (Table 1). For the 136-bp allele, the results were weak [$P = 0.02$, OR = 0.57 (0.34, 0.96), respectively] without evidence of heterogeneity or publication bias. The 148-bp allele has a risk effect on ADHD, whereas the 136-bp allele has a protective effect. For the 146-bp allele, no preferential transmission was found (Table 1).

Sensitivity and retrospective analyses

The results of the *DRD4* 7-repeat allele and the *DRD5* 148-bp allele were consistent, and were not changed substantially by the removal of any data set. For the 7-repeat allele, the *P*-values were never $> 2 \times 10^{-10}$; for the 148-bp allele, the largest *P*-value was 6×10^{-6} . For the 5-repeat allele, which has a low frequency (0–8%), the *P*-value became non-significant ($P > 0.05$) after study by Comings (51) was removed. This study accounted for more than one-third of the total sample size.

Analysis in retrospect based on the publication year (70), showed that the cumulative results tended to be stable after 2001 for the *DRD4* long alleles, but not for the *DRD5* gene,

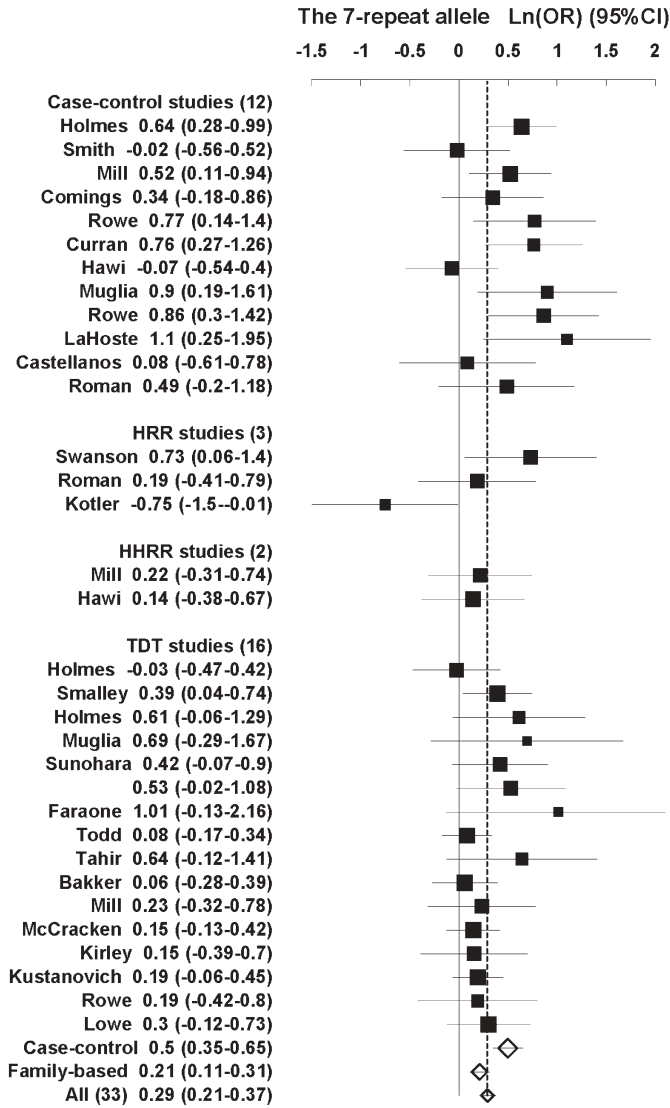


Figure 1. Forest plots of Ln(OR) and overall Ln(OR) with 95% CI for the *DRD4* 7-repeat allele. Black squares indicate the Ln(OR), with the size of the square inversely proportional to its variance, and horizontal lines represent the 95% CIs. The overall Ln(OR) are indicated by the unshaded black diamond.

for which the rough asymptote line suggested that more studies are needed (Fig. 3).

Sensitivity analyses and other meta-data/figures of each individual study are available on request.

DISCUSSION

Compelling evidence for the involvement of dopamine systems in ADHD derives from the fact that dopamine enhancers such as amphetamine and methylphenidate improve behavioral symptoms of most children with ADHD (71). This has resulted in dopamine system genes being considered as candidate genes for the well established heritability of ADHD (72). *DATI* initially was considered as a candidate because stimulant medications are known to block the dopamine transporter

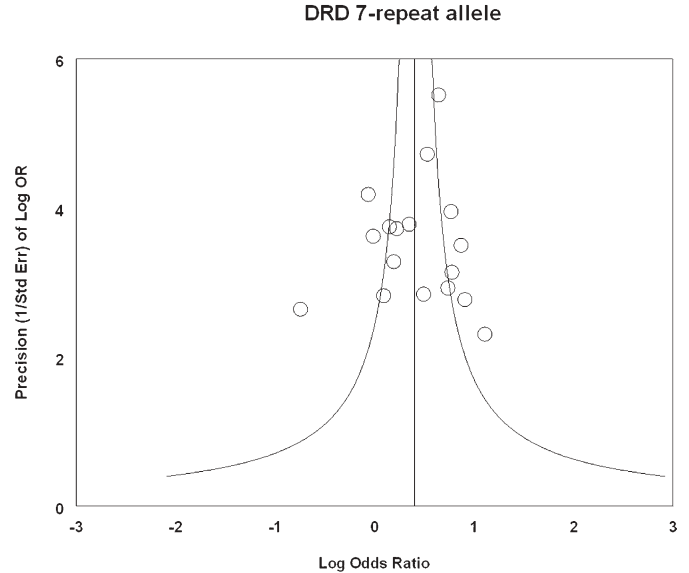


Figure 2. Egger's funnel plots of the combined studies (case-control + HRR + HHRR) for the *DRD4* 7-repeat allele. The larger deviation from funnel curve of each study means the more pronounced asymmetry. Results from small studies will scatter widely at the bottom of the graph, with the spread narrowing among larger studies. The significance of the intercept was evaluated using the *t*-test. Plots for other alleles were shown as supplements.

in achieving their therapeutic effects (73). In the present study the results overall were weak or non-significant. However, a negative result is only conclusive if the entire gene has been adequately tagged by SNPs and/or microsatellite polymorphisms and that there is sufficient power and uniformity in the studies. Indeed, there is evidence in the literature for *DATI* haplotypes that include the 480-bp allele, being associated with ADHD (16,41,74,75). It is therefore possible that the 480-bp allele is in linkage disequilibrium with a risk allele or alleles elsewhere in *DATI* or that susceptibility to ADHD depends upon interaction between the 480-bp allele and another *DATI* variant. This could explain the lack of significant association but significant heterogeneity that was observed in family-based studies and European-based studies. Evidence for heterogeneity with the 480-bp allele could in principle also reflect subtle differences in ascertainment, diagnostic criteria, or other methodological differences, or the result from the fact that the 480-bp allele confers risk by means of an interaction with another locus or with an environmental factor. With regard to the latter suggestion, it is of interest that a recent study (75) provided evidence that a haplotype involving the 480-bp allele might interact with maternal use of alcohol during pregnancy to increase risk of ADHD.

In contrast to the weak effects observed for *DATI*, strong evidence ($P = 2 \times 10^{-12}$) was obtained that the 7-repeat allele of *DRD4* confers increased risk, with evidence also obtained that the 5-repeat allele confers increased risk ($P = 0.005$) and that the 4-repeat is protective ($P = 0.004$). Weak evidence for heterogeneity was found in the effects of the 7-repeat allele ($P = 0.03$) and the 4-repeat allele in European populations ($P = 0.04$). Furthermore, for the two alleles, heterogeneity was found between design types ($P = 0.002$ and 0.01 , respectively),

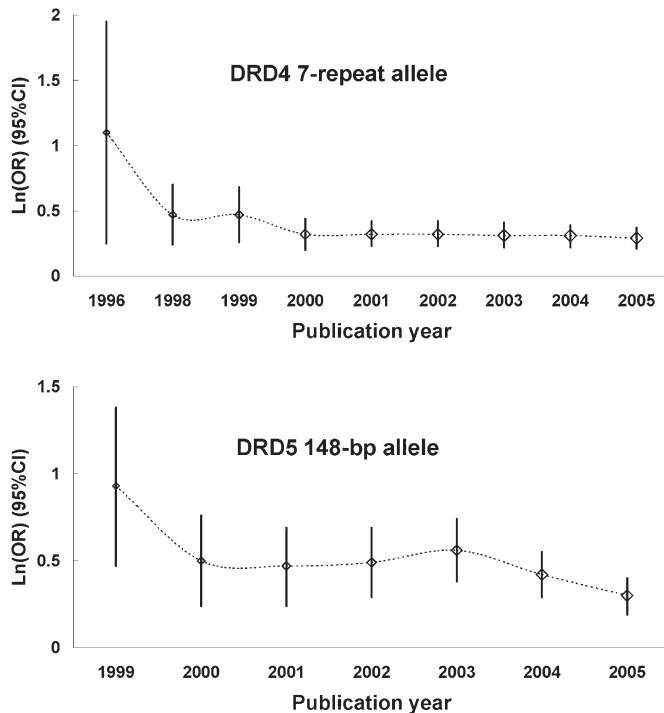


Figure 3. Cumulative syntheses of studies for the *DRD4* 7-repeat allele and the *DRD5* 148-bp alleles shown by overall $\ln(\text{OR})$, the 4-, 5-repeat alleles and *DAT1* 480-bp allele (data not shown) were similar with the 7-repeat allele.

with case-control studies having higher ORs. This could reflect stratification in the case-control design. This is consistent with an inflation of significance in case-control studies because of population stratification (76), but we suspect that this is unlikely because of the large number of case-control studies and the lack of significant evidence for heterogeneity of OR among the case-control studies. A more likely explanation is that there are quantitative or qualitative phenotypic differences between the cases of ADHD in case-control and in family-based samples, and that these have different levels of association with *DRD4* alleles. Indeed, there is preliminary evidence that cases of ADHD from completely ascertained trios have a more severe phenotype and are more likely to have symptoms of conduct disorder than cases where one parent is not available for genotyping (77).

We have pooled OR estimates from different designs to obtain an overall OR for the association between an allele and ADHD. The purpose of this is to obtain a single summary of the overall level of evidence for an association. However, we do appreciate that different designs may capture subjects with different characteristics, and may be subject to different biases, and the combination of ORs across different study designs may obtain an average that is not very meaningful. The tests of heterogeneity between ORs from different study designs are to some extent helpful for revealing important differences between designs.

The *DRD5* 148-bp allele confers increased risk ($P = 8 \times 10^{-8}$) and heterogeneity was found ($P = 0.0008$) possibly because of differences in the diagnostic criteria,

subtype ascertainment and demographic characteristics. The 136-bp risk allele is protective ($P = 0.02$).

In this study, we accessed as much of the literature as possible, in order to achieve a complete and unbiased representation of the relevant studies. Those studies with insufficient or ambiguous data were excluded. This effort to take a comprehensive and even-handed approach to the literature inclusion may have strengthened the robustness of the findings while it avoided publication bias and minimized heterogeneity (78). Compared with previous studies (12,14,15,79), the current meta-analysis pooled larger sample sizes, analyzed them both combined and separately, generated even more significant results with systematic design types and analysis approaches and included tests of heterogeneity by study design and ethnicity, as well as sensitivity analyses. [The two previous meta-analyses (12,14) of the *DRD4* gene included only 9 and 11 studies, respectively (Supplementary Material, Table S1).] The current results demonstrate the robustness of the association between the 7-repeat allele of *DRD4* and ADHD, which was significant in multiple studies, and in both case-control and family-based studies.

In order to improve the scope and validity of subsequent meta-analyses, there are two important issues that individual studies should address. First, there needs to be clear description of ascertainment and selection of cases and controls. Second, raw genotype counts in the different groups, preferably stratified by ethnicity and other potential confounding variables, should be presented. Indeed, the presentation of only allele counts in some studies has restricted the meta-analysis to an allele-wise analysis with the limitations that the assumptions of Hardy-Weinberg equilibrium and multiplicative risks have to be made.

ADHD, which is polygenic, is caused by the combined actions of many factors. For greater insight into its genetic component, more work is required to confirm the role of other genes that may have a small effect, and to identify new genetic risk factors. The large samples required will necessitate multi-site projects and meta-analyses on the basis of national and international collaboration.

To conclude, the 4-, 5- and 7-repeat alleles of the *DRD4* gene and 148-bp and 136-bp alleles of the *DRD5* gene show strongly consistent associations with ADHD, in which the *DRD4* 7- and 5-repeat alleles and the *DRD5* 148-bp allele have risk effects, whereas the *DRD4* 4-repeat and the *DRD5* 136-bp alleles have protective effects. In contrast, *DAT1* shows at best only weak evidence for association. The meta-analysis strongly suggests the involvement of the brain dopamine system genes, especially *DRD4* and *DRD5*, in the pathogenesis of ADHD, which may have potentially important scientific and public health implications.

MATERIALS AND METHODS

Literature search

The publications included in the analysis were selected from PubMed and from www.cnki.net/index.htm with keywords 'attention deficit hyperactivity disorder', 'ADHD', 'dopamine transporter', 'dopamine 4 receptor', 'dopamine 5 receptor', 'association' and the specific names and abbreviations of each gene (e.g. 'dopamine receptor 4' and '*DRD4*'). All references

cited in these studies and in published reviews were examined in order to identify additional works not indexed by MEDLINE. The analyzed data cover all English and Chinese publications from April 1995 to October 2005.

Inclusion criteria

Eligible studies had to meet all of the following criteria (1): published in peer-reviewed journal (2), contained independent data (3), presented sufficient data to calculate the OR with CI and *P*-value (4), were association studies investigating one or more of the three polymorphisms using either case-control or family-based approaches (5), described the genotyping primers, machines and protocols or provided reference of them (6), diagnosed ADHD patients according to the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD), American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) or Chinese classification of mental disorders (CCMD) systems and (7) used healthy individuals as controls in case-control studies.

Statistical analyses

Studies were classified according to design into case-control and family-based, and the latter further subdivided according to statistical methodology into HRR, HHRR and TDT. Studies were also subdivided between those dealing with European ethnic populations and those dealing with Asian ethnic populations. A study that contained data from both ethnic populations was considered effectively as two studies.

Data from the case-control, HRR and HHRR studies were summarized by two-by-two tables (meta-analysis was conducted based on allele data, i.e. HHRR methodology, for studies that originally used HRR or HHRR for analysis) and TDT studies were summarized by two-by-one tables. The two types of studies were statistically combined by the method used by Lohmueller *et al.* (80), Cho *et al.* (81) and Li *et al.* (82) to join case-control and family-based studies into a single meta-analysis. From each table, a log-odds ratio and its sampling variance were calculated (81). Cochran's χ^2 -based *Q* statistic test (83–85) was performed in order to assess possible heterogeneity of OR between the individual studies. Heterogeneity *Q* tests (83,84) were also performed for differences in OR between design types (case-control versus family-based), and between sample ethnicities (European versus Asian). A test for funnel plot asymmetry, described by Egger *et al.* (86), was used to assess evidence for publication bias. ORs were pooled using the method of DerSimonian and Laird (87) and 95% CIs were constructed using Woolf's method (88). The significance of the overall OR was determined by the *Z*-test. For the sensitivity analysis, each study was removed in turn from the total, and the remaining was re-analyzed. This procedure was used to ensure that no individual study was entirely responsible for a finding. The analysis was conducted by Comprehensive Meta Analysis software (Version 1.0.23, BIOSTAT, Englewood, NJ, USA). The type I error rate was set at 0.05. *P*-values were two-tailed.

ELECTRONIC-DATABASE INFORMATION.

Accession numbers and URLs for data presented herein are as follows: Genotype data, <http://www.hapmap.org/> for *DAT1*, *DRD4* and *DRD5*; GenBank, <http://www.ncbi.nlm.nih.gov/> for genomic structure of *DAT1*, *DRD4* and *DRD5*; Genome data, <http://genome.ucsc.edu/> for *DAT1*, *DRD4* and *DRD5*; Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> for *DAT1*, *DRD4* and *DRD5*.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG Online.

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Conflict of Interest statement. No conflicts of interest.

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