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Review Article

A Meta-Analysis of Association Studies Between the 10-Repeat Allele of a VNTR Polymorphism in the 3′-UTR of Dopamine Transporter Gene and Attention Deficit Hyperactivity Disorder

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The association between the 10-repeat allele of the dopamine transporter gene (*DAT*) and attention deficit hyperactivity disorder (ADHD) is uncertain. This study aimed to conduct a meta-analysis of the association between the 10-repeat allele of a variable number tandem repeat (VNTR) polymorphism in the 3′-untranslated region (UTR) of the *DAT1* gene and ADHD. We pooled up 18 published transmission disequilibrium test (TDT) studies between the 40-base pair VNTR polymorphism in the3′-UTR of the *DAT1* gene and ADHD. It included a total of 1,373 informative meioses, 7 haplotype-based haplotype relative risk (HHRR) studies, and 6 case-control-based association studies. There were statistically significant evidences for heterogeneity of the odds ratio in TDT and HHRR studies ($P < 0.10$), but not in case-control studies. The results of random effects model showed small but significant association between ADHD and the *DAT1* gene in TDT studies (OR = 1.17, 95% CI = 1.05–1.30, chi-square = 8.11, df = 1, $P = 0.004$), but not in HHRR and case-control studies. The 10-repeat allele of a VNTR polymorphism in the 3′-UTR the *DAT1* gene has a small but significant role in the genetic susceptibility of ADHD. These meta-analysis findings support the involvement of the dopamine system genes in ADHD liability variation. However, more work is required to further identify the functional allelic variants/mutations that are responsible for this association.

KEY WORDS: ADHD; TDT; DAT

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders of childhood. Empirical data from clinical studies consistently support the polygenetic nature of ADHD. Its heritability ranges from 0.6 to 0.9 [Levy et al., 1997; Faraone and Biederman, 1998; Nadder et al., 1998; Tannock, 1998; Todd, 2000].

Dopamine system dysfunction plays an important role in the pathogenesis of ADHD [Levy, 1991; Xu et al., 1994; Giros et al., 1996; Tannock, 1998; Volkow et al., 1998; Ernst et al., 1999; Gatley et al., 1999; Faraone and Doyle, 2000; Granon et al., 2000; Cardinal et al., 2001; Castellanos and Arnsten, 2001; Todd and Botteron, 2001; Viggiano et al., 2002; Sorrentino et al., 2003]. Molecular genetic studies have focused on genes that regulate dopamine neurotransmission such as the dopamine D4 receptor (*DRD4*) and the dopamine transporter (*DAT1*) genes. The *DAT1* gene is of great interest as a candidate gene in ADHD. Some studies reported that patients with ADHD show increased DAT density in brains compared with controls [Dougherty et al., 1999; Dresel et al., 2000; Krause et al., 2000; Madras et al., 2002; Cheon et al., 2003]. Others [e.g., Dresel et al., 2000; Krause et al., 2000] showed that methylphenidate, which is widely used to ameliorate the symptoms of ADHD, is supposed to inhibit the function of this transporter by preventing presynaptic reuptake of dopamine reduces DAT density in functional neuroimaging studies. Data from animal studies showed that DAT knock-out mice also exhibited some behavioral and pharmacological characteristics of ADHD [Giros et al., 1996; Gainetdinov and Caron, 2001]. In particular, dopamine was found to remain 100 times longer in the extracellular medium of homozygous DAT KO mice than in heterozygous and wild-type animals. Finally, dopamine transport inhibitors indirectly activate dopamine receptor subtypes. D4 and D5 dopamine receptors are implicated in ADHD, and these dopamine receptor activity enhances attention and experiential salience and engenders stimulation. The evidence above implicated the dopamine transporter involved in the pathogenesis of ADHD.

The dopamine transporter is a member of a family of Na^+ and Cl^--dependent neurotransmitter transporters containing

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12 transmembraned domains, with consensus sites for glycosylation that function to regulate DAT trafficking and stability [Cragg and Rice, 2004; Li et al., 2004]). The human *DAT1* gene encodes for a dopamine transporter and regulates the re-uptake of released dopamine back into presynaptic terminals after its synaptic release. Located on chromosome 5p15.3, it contains a variable number tandem repeat (VNTR) in the 3′- untranslated region (UTR) due to repetition of a 40-bp core sequence, ranging from 3 to 13 times depending on the population studied [Giros et al., 1992; Vandenbergh et al., 1992]. The VNTR may change DAT1 function, since it has been suggested to regulate gene expression [Michaelhaugh et al., 2001; Mill et al., 2002]. The 10-R allele of the *DAT1* gene may be associated with a dopamine transporter that is abnormally efficient at the re-uptake process [Mill et al., 2002]. This in turn may produce underactivity in dopamine pathways—both the mesocorticolimbic pathway (which is rich in D4 dopamine receptors in the frontal lobes) and the nigrostriatal pathway (which is rich in D2 dopamine receptors).

Positive association with the 10-repeat allele of a VNTR of DAT1 has been independently replicated in a number of studies [Cook et al., 1995; Gill et al., 1997; Waldman et al., 1998; Daly et al., 1999; Barr et al., 2001; Curran et al., 2001; Chen et al., 2003]. However, other groups have failed to find support for this finding [Asherson et al., 1998; Palmer et al., 1999; Holmes et al., 2000; Swanson et al., 2000; Curran et al., 2001; Todd et al., 2001; Muglia et al., 2002]. The conflicting results may be due to different statistical power, sample bias, diverse design methodologies, operational definition, and heterogeneity of ADHD. Meta-analysis provides a quantitative approach for combining the results of various studies on the same topic, and for estimating and explaining their diversity [Mosteller and Colditz, 1996; Rice, 1997]. A few studies have reviewed the association between *DAT1* gene and ADHD [Maher et al., 2002; DiMaio et al., 2003; Faraone et al., 2005; Purper-Ouakila et al., 2005]. DiMaio et al. [2003] qualitatively concluded the implication of DAT1 in ADHD. Maher et al. [2002] reported a non-significant pooled odds ratio without heterogeneity between studies, Faraone et al. [2005] reported a small but significant association, and Purper-Ouakil et al. [2005] reported no significant association with an important between-samples heterogeneity. Taking account of empirical data, possible role of dopamine in the pathogenesis of ADHD, and several additional studies published since the meta-analysis by Purper-Ouakila et al. [2005], we performed an up-to-date meta-analysis examining preferential transmission of the 10-repeat allele of the *DAT* gene to children with ADHD.

METHODS AND MATERIALS

Literature Search

To identify studies eligible for this meta-analysis, we conducted a computerized search (Medline, Embase, PsycINFO, BiosisPreview) using the following key words: "DAT gene OR SLC6A3" and "ADHD" from 1995 up to February 2006. We also used reference lists from identified articles and reviews to find additional articles not indexed by Medline. In-press articles in psychiatric journals were also examined.

Inclusion Criteria

Only those studies examining the 40-bp VNTR polymorphism in 3′-UTR of *DAT1* gene were included in the current meta-analysis. Furthermore, studies had to meet all the following criteria: (1) used a family-based (transmission disequilibrium test (TDT) or haplotype-based haplotype relative risk (HHRR)) or case-control design; (2) were written in English or Chinese; (3) presented original data, and provided enough data to calculate an effect size; (4) were independent from other studies (i.e., studies that included and re-analyzed a previously published data set were not regarded as independent; in this case, only the study composed of a larger sample size was included in the meta-analysis).

Meta-Analytic Methods

We performed three meta-analyses, two for the family-based studies (TDT and HHRR) and one for the case-control studies. For the TDT study, each study provided the two-by-two transmission disequilibrium table, which classifies heterozygous parental alleles (informative meioses) by transmission status (10-repeat allele transmitted to the ADHD child or not) and data type (the number of observed transmission vs. the number of theoretic transmission). For the HHRR studies, each study provided the two-by-two HHRR table, which classifies parental alleles by type of allele (10-repeat or not) and transmission status (transmitted to the ADHD child or not). For the case-control data, each study provided the two-by-two table classifying subjects by diagnosis (ADHD or not) and DAT1 10-repeat allele status (present or not). We summarized the strength of association in these two-by-two tables by using the odds ratio (OR).

For each meta-analysis, a Cochran Q test for heterogeneity was first performed. In addition, the I^2 test was used to attempt at quantifying any apparent inconsistency and was interpreted as approximately the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. An I^2 value greater than 50% may be considered substantial heterogeneity and not appropriate to perform a meta-analysis. A fixed effect model was chosen given the lack of heterogeneity, otherwise a random effect model was chosen under the condition that the value of $I^2 < 50\%$. Fixed effect models assume that all studies aim at evaluating a common truth and results differ by chance alone. Random effect models anticipate that the studies may have genuine differences in their results [Cooper and Hedges, 1994]; thus, they also incorporate a between-study variance in their estimates. Pooled calculations of odds ratios were obtained and compared using test statistic z and 95% confidence intervals (CI).

Publication bias was assessed by funnel plot (showing a symmetrical inverted funnel without the publication bias), Begg and Mazumdar's rank correlation test and linear regression analysis [Egger et al., 1997; Vilar et al., 1997], in which the standard normal deviate of the OR is regressed on the precision of the OR (the inverse of the standard error of the OR). When there is no publication bias, the regression line should pass through the origin, and the expected value of intercept will be zero. An examination of publication bias is a test of the null hypothesis that intercept is equal to zero, as determined by the t test. The meta-analysis was conducted by Comprehensive Meta-analysis Version 2 [Borenstein et al., 2005].

RESULTS

The application of foregoing criteria yielded 30 studies [Cook et al., 1995; Gill et al., 1997; Waldman et al., 1998; Daly et al., 1999; Jiang et al., 1999; Palmer et al., 1999, in Chinese; Holmes et al., 2000; Lunetta et al., 2000; Swanson et al., 2000; Barr et al., 2001; Curran et al., 2001; Roman et al., 2001; Todd et al., 2001; Kirley et al., 2002; CEDAR from Maher et al., 2002; Muglia et al., 2002; Chen et al., 2003; Qian et al., 2003, in Chinese; Hawi et al., 2003; Kustanovich et al., 2004; Wang et al., 2004; Qian et al., 2004; Bakker et al., 2005; Bobb et al., 2005; Feng et al., 2005; Kim et al., 2005; Langley et al., 2005;

TABLE I. Descriptive Characteristics of Individual Articles Include in Meta-Analysis

Study	Diagnostic criteria	Sample ascertainment	Diagnostic assessment	Number of probands	Age group	Sample IQ	Clinical subtypes (%)	Comorbidity	Ethnic Origin	10-R allele proportion in probands (%)	Methods
Waldman et al. [1998]	DSM-IV	Psychiatry clinics (children with behavioral and learning problems)	Diagnosis based on emory diagnostic rating scale	117	9.26 ± 2.75				Caucasian	69	TDT
Swanson et al. [2000]	DSM-IV	Recruited for a stimulant medication trial for ADHD	Structured interview (DISC)	80	7–12	>85	CT 100	Without serious comorbidity	U.S.A		TDT, HHRR
Lunetta et al. [2000]	DSM-IV			42					U.S.A		TDT
Holmes et al. [2000]	DSM-III-R/DSM-IV and ICD-10	District psychiatry clinics	Semi-structured diagnostic interview (CAPA)	137	9.17 ± 1.33	91.2 ± 13.1			British descent	74	TDT
Todd et al. [2001]	DSM-IV	Psychiatry clinics	Structured diagnostic interview (MAGIC)	219	7–19		PI 56.6, HI 7.8, CT 35.6		Missouri	75	TDT
Curran et al. [2001]	DSM-IV	University clinics		66			PI 1.9, HI 9.1,CT 89	3% affective disorder	Caucasian		TDT
Curran et al. [2001]	DSM-IV	University clinics	Consensus diagnosis based on structured-interview and clinical information (K-SADS)	111			CT 100	34% Tic, 8% anxiety/ depression disorder	Caucasian		TDT
Kirley et al. [2002]	DSM-IV	District psychiatric clinics school, ADHD support group	Consensus diagnoses based on clinical information and rating scales	118	4–14		PI 7.5, HI 2.5, CT 90.0	CD/ODD 72, LD 20, 18% mood disorder, 22% anxiety disorder	Irish	71	TDT
CEDAR [Maher et al., 2002 review]	DSM-III-R	Clinic	Consensus diagnosis based on semi-structured diagnostic interview and clinical information	33					Caucasian		TDT
Chen et al. [2003]	DSM-IV			110	5–15		PI 22, CT 78	ODD 4, Tic 4	Taiwanese	94.5	TDT,HH-RR
Qian et al. [2004]	DSM-IV	University psychiatric clinic	Consensus diagnoses based on Structured diagnostic interviewer (CDIS)	340	10.4 ± 2.6	100.6 ± 13.6	PI 51.8, HI 6.2, CT 42.1, LD 39.1	CD 7.1, ODD 41.8, 15.6% emotional Disorder, 14.4% Tic, 10.3% affective disorder	Chinese	87	TDT,Case-control
Kustanovich et al. [2004]	DSM-IV	District clinics, school and responses to advertisement	Structured interview (K-SADS-PL, SADS-LA-IV) and rating scales	535	11 ± 4	105 ± 15	PI 43, HI 7, CT 50		Caucasian	70.8	TDT
Wang et al. [2004]	DSM-IV	University child behavior clinic		54	9.37 ± 2.16	98.85 ± 12.79	PI 22.2, HI 9.3, CT 68.5		Chinese	92.6	TDT, HHRR
Kim et al. [2005]	DSM-IV	University psychiatric clinics	Structured diagnostic interview (K-SADS-PL-K)	126	8.3 ± 1.8	104 ± 16	PI 27.8, HI 7.9, CT 28.6 (NOS 35.7)	4.8% depressive disorder, 3.2% anxiety, 13% MR, 6% PDD	Korea	91.2	TDT

(*Continued*)

TABLE I. (*Continued*)

Study	Diagnostic criteria	Sample ascertainment	Diagnostic assessment	Number of probands	Age group	Sample IQ	Clinical subtypes (%)	Comorbidity	Ethnic Origin	10-R allele proportion in probands (%)	Methods
Feng et al. [2005]	DSM-IV	District clinics (children with behavioral and learning problems)	Semi-structured interviews (PICS-IV) based on clinical in formation and rating scales	178	6-17	>80		PI 24, HI 19, CT 57	Canada	71.1	TDT
Bobb et al. [2005]	DSM-IV	Recruited locally and nationally	Semi-structured diagnostic interview (DICA) and rating scales	163	9.02 ± 2.22	109 ± 15	PI 6, CT 94		Caucasian		TDT,Case-control
Brookes et al. [2006]	DSM-IV		Semi-structured interview (HYPECHEME)	180	10.41 ± 2.34	>70	CT 100		European Caucasian	73	TDT
Brookes et al. [2006]	DSM-IV	District child psychiatric clinics	Semi-structured interview and rating scales	216	8.96 ± 2.60	13% 50–69, 87%>69	PI 22, CT 78	CD/ODD 1.9	Taiwanese	90	TDT
Cook et al. [1995]	DSM-III-R	University clinic	Consensus diagnosis based on clinical information and rating scales	57	4–17	97.6 ± 13.0		CD 10.2, ODD 33.3	Caucasian	76.2	HHRR
Jiang et al. [1999]	DSM-III-R	Special education school		74	10.3 ± 0.8	96.8 ± 16.3			Chinese	92	HHRR
Roman et al. [2001]	DSM-IV	Child and adolescent psychiatric clinic	Semi-structured interview (KSADS-E)	81	10.1 ± 3.23	90.9 ± 14.34	PI 16.1, HI 7.4, CT 76.5	CD 13.6, ODD 43.2	Brazilian	74	HHRR, Case-control
Hawi et al. [2003]	DSM-IV	District psychiatric clinics school, ADHD support group	Consensus diagnoses based on clinical information and rating scales	118	4–14		PI 7.5, HI 2.5, CT 90	CD/ODD 72, LD 20	Irish	71	HHRR
Simsek et al. [2005]	DSM-IV	University psychiatry clinic Case-control	Diagnosis based on questionnaire	92					Omani	62	Case-control
Langley et al. [2005]	DSM-III-R or DSM-IV and ICD-10	District psychiatry clinics	Semi-structured diagnostic interview (CAPA)	263	9.17 ± 1.33	91.2 ± 13.1			British	74	Case-control
Cheuk et al. [2006]	DSM-IV	University clinic	Structured diagnostic interview	64	<18		PI 25, HI 7.7,CT 67.3		Hong Kong	90.6	Case-control

Simseka et al., 2005; Brookes et al., 2006; Cheuk et al., 2006] and 25 studies were included in current meta-analysis (18 for TDT, 7 for HHRR, and 6 for case-control studies), as listed in Table I. A few studies were initially identified but later excluded because they did not meet inclusion criteria. Studies by Langley et al. [2005], Bakker et al. [2005], and Cheuk et al. [2006] were excluded in TDT studies because there were inconsistence between TDT method and the results and our inquires received no replies. For TDT, studies by Barr et al. [2001], Qian et al. [2003, in Chinese], and Palmer et al. [1999] were excluded because they were not independent from the studies by Feng et al. [2005], Qian et al. [2004], and Kustanovich et al. [2004], respectively. For HHRR, studies by Kirley et al. [2002], Gill et al. [1997], and Daly et al. [1999] were excluded without being independent from study by Hawi et al. [2003]. Muglia et al. [2002] was excluded because categorical data were not reported. Studies of Curran et al. [2001] and Brookes et al. [2006] involved two samples so they were included as two independent studies, respectively.

Table II gives the odds ratios and their 95% CIs for the 18 TDT studies. There was statistically significant evidence for heterogeneity of the OR among these studies ($Q = 26.475$, $df = 17$, $P = 0.066 < 0.10$, $I^2 = 35.8\%$) and the random effect model was chosen. Although 10 of these studies showed a positive association between ADHD and the DAT1 10-repeat allele, only three showed a statistically significant effect. The combined estimate was small but statistically significant (OR = 1.17, 95% CI = 1.05–1.30, chi-square = 8.11, df=1, $P = 0.004$).

The studies distribution of the funnel plot was substantially symmetrical about the combined effect size (Fig. 1). The Egger's regression intercept and Begg's rank correlation were not significant (Intercept = 1.259, t = 1.669, df = 16, $P = 0.115$; Kendall' tau = 0.216, $P = 0.225$, respectively), suggesting no publication bias for TDT studies.

For TDT studies, we further grouped the studies according to the ethnic origin, and the results showed no significantly preferential transmission of the 10-repeat allele of the *DAT* gene either in Asian children with ADHD ($Q = 6.06$, $P = 0.19$; OR = 1.42, 95%CI = 1.00–2.01 for fixed effect model) or in western children ($Q = 19.00$, $df = 12$, $P = 0.09$, $I^2 = 36.8\%$; OR = 1.19, 95%CI = 0.96–1.48 for random effect model).

For seven HHRR studies, there was statistically significant evidence for heterogeneity of the OR ($Q = 14.88$, $df = 6$, $P = 0.021$) and the random effect model was chosen. The combined estimate was not statistically significant (OR = 1.50, 95% CI = 0.97–2.33, $z = 1.81$, $P = 0.07$) (Table III).

For six case-control studies, there was no statistically significant evidence for heterogeneity of the OR ($Q = 4.04$, $df = 5$, $P = 0.54$) and the fixed effect model was chosen. The combined estimate was not statistically significant (OR = 0.95, 95% CI = 0.80–1.12, $z = -0.61$, $P = 0.54$) (Table IV).

DISCUSSION

Our meta-analysis showed a small but statistically significant association between the 10-repeat allele of a VNTR polymorphism in 3′-UTRof *DAT1* gene and ADHD in TDT studies but not in HHRR and case-control studies. Based on the detection of unequal transmission of particular alleles by heterozygous parents to affected children, the TDT has certain advantages over HHRR and case-control methods [Schaid and Sommer, 1994]. These advantages include greater statistical power, robustness against artifacts induced by population stratification, the provision of a test of linkage in the presence of association. The number of studies included in TDT was much more than those in HHRR and case-control studies. In this part, we would mainly discuss the result of TDT method.

There was significant heterogeneity among studies within TDT study given the wide range of clinical methods used (Table I). A random-effects model may be used to incorporate heterogeneity among trials (Cochrane reviewer's handbook 4.2.2). This model is particularly germane for this study because substantial between-study differences are expected due to genetic heterogeneity, diagnostic differences, diverse

TABLE II. Meta-Analysis of TDT Studies of Association Between ADHD and 10-Repeat Allele of *DAT1* Gene

Study	Number of transmission	10-repeat allele		Expected distribution		OR	95% CI	*Z*-value	*P*-value
		T	NT	T	NT				
Waldman et al. [1998]	137	90	47	68.5	68.5	1.91	1.35–2.72	3.61	0.0003
Swanson et al. [2000]	26	10	16	13	13	0.63	0.28–1.38	−1.17	0.24
Lunetta et al. [2000]	27	17	10	13.5	13.5	1.70	0.78–3.71	1.33	0.18
Holmes et al. [2000]	85	40	45	42.5	42.5	0.89	0.58–1.36	−0.54	0.59
Todd et al. [2001]	122	55	67	61	61	0.82	0.57–1.17	−1.08	0.28
Curran et al. [2001]	59	39	20	29.5	29.5	1.95	1.14–3.34	2.43	0.02
Curran et al. [2001]	87	39	48	43.5	43.5	0.81	0.53–1.24	−0.96	0.34
Kirley et al. [2002]	79	49	30	39.5	39.5	1.63	1.04–2.57	2.12	0.03
CEDAR [2002]	18	9	9	9	9	1	0.40–2.52	0	1
Chen et al. [2003]	21	16	5	10.5	10.5	3.2	1.17–8.74	2.27	0.02
Qian et al. [2004]	92	43	49	46	46	0.88	0.58–1.32	−0.63	0.53
Kustanovich et al. [2004]	249	119	130	124.5	124.5	0.92	0.71–1.17	−0.70	0.49
Wang et al. [2004]	20	13	7	10	10	1.86	0.74–4.65	1.32	0.19
Kim et al. [2005]	33	17	16	16.5	16.5	1.06	0.54–2.10	0.17	0.86
Feng et al. [2005]	152	76	76	76	76	1	0.73–1.37	0	1
Bobb et al. [2005]	32	20	12	16	16	1.67	0.81–3.41	1.40	0.16
Brookes et al. [2006]	97	65	32	48.5	48.5	2.03	1.33–3.10	3.28	0.001
Brookes et al. [2006]	37	28	9	18.5	18.5	3.11	1.47–6.59	2.96	0.003
Combined	1373	745	628	686.5	686.5	1.17	1.05–1.30	8.11*	0.004*

T, transmitted (number of times the allele is transmitted from heterozygous parents to the proband); NT, not transmitted.
*Chi-square *P*-value, df = 1.

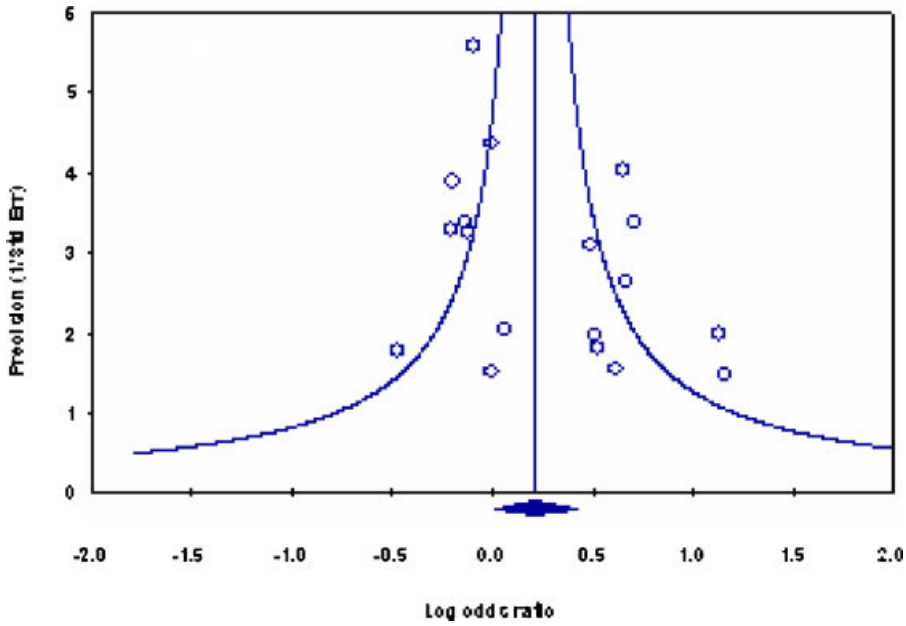

Fig. 1. Funnel plot of study precision by log odds ratio.

clinical subtypes, and differing ascertainment schemes between the studies. Thus, because it will generally yield a wider confidence interval, it is more conservative than a fixed-effects model [Berlin et al., 1989].

In light of the careful selection of included studies, we pooled the data of 1,373 informative meioses. Compared with 885 informative meioses in study by Purper-Ouakila et al. [2005], our data are more powerful to detect small effect size of minor gene in polygenic disorder such as ADHD. There is increasing evidence that small-sample-size association studies lack statistical power and have resulted in apparently contradicting findings. The use of meta-analysis is an important step in reconciling previously conducted studies with inconsistent results. One limitation of meta-analysis is publication bias, because the likelihood of publishing a study could be related to the positive results of the study [Egger et al., 1997]. In the current study, the funnel plot is quite symmetrical, showing no evidence of publication bias. The Egger's regression intercept and Begg's rank correlation tests further confirm no publication bias in TDT studies.

DAT1 alleles frequencies are different among diverse ethnic origin [Kang et al., 1999; Mitchell et al., 2000]. When we categorized studies into two groups according to the ethnicity, the number of studies including in the pooled meta-analysis was 13 and 5 for western children with ADHD and for Asian children, respectively (Table I); and the number of informative meioses reduced to 1,170 and 203, respectively. The heterogeneity among studies was significantly different in the former and not in the latter. The odds of having statistically significant heterogeneity between the studies in a meta-analysis is greater when more studies were carried out [Ioannidis et al., 2001]. Compared with the whole pooled meta-analysis, the I^2 increased from 35.8% to 36.8%, indicating very little influence of the ethnicity on the association of 10 repeat VNTR of *DAT1* gene and ADHD.

The DAT is expressed selectively in all dopamine neurons, including those originating in the substantia nigra and ventral tegmental area [Ciliax et al., 1995], with neuronal projections to the striatum, nucleus accumbens, prefrontal cortex, and hypothalamus. High densities of DAT-immunoreactive axons were also detected in posterior parietal cortex and dentate gyrus of the hippocampus [Lewis et al., 2001].

The mechanism by which DAT expression is regulated is not yet fully understood. The DAT limits the duration of synaptic activity and diffusion by sequestering dopamine into neurons [Cragg and Rice, 2004]. Accumulating evidence that the 3′-UTR influences the nuclear export, polyadenylation, subcellular targeting, and rates of transcription and degradation of mRNA [Conne et al., 2000] supports the possibility that a VNTR polymorphism in this region could exert a regulatory

TABLE III. Meta-Analysis of HHRR Studies of Association Between ADHD and 10-Repeat Allele of *DAT1* Gene

	Transmitted		Untransmitted					
Study	10-R allele	Other alleles	10-R allele	Other alleles	OR	95% CI	*Z*-value	*P*-value
Hawi et al. [2003]	145	42	121	66	1.88	1.19–2.97	2.72	0.007
Wang et al. [2004]	100	8	94	14	1.86	0.75–4.64	1.33	0.18
Swanson et al. [2000]	60	20	66	14	0.64	0.30–1.37	−1.15	0.25
Cook et al. [1995]	72	12	57	27	2.84	1.32–6.10	2.68	0.007
Jiang et al. [1999]	136	12	136	12	1.00	0.43–2.30	0	1.00
Roman et al. [2001]	105	30	106	29	0.96	0.54–1.71	−0.15	0.88
Chen et al. [2003]					4.5	1.3–16.4	2.37	0.02
Combined					1.50	0.97–2.33	1.81	0.07

Study by Chen et al. [2003] only reported the OR and 95% CI.

TABLE IV. Meta-Analysis of Case-Control Studies of Association Between ADHD and 10-Repeat Allele of *DAT1* Gene

	Case		Control					
Study	10-R allele	Other alleles	10-R allele	Other alleles	OR	95% CI	*Z*-value	*P*-value
Qian et al. [2004]	578	86	392	40	0.69	0.46–1.02	−1.87	0.06
Cheuk et al. [2006]	116	12	119	9	0.73	0.30–1.80	−0.68	0.50
Langley et al. [2005]	387	139	424	150	0.99	0.75–1.29	−0.11	0.91
Roman et al. [2001]	98	34	166	58	1.01	0.62–1.65	0.03	0.98
Simseka et al. [2005]	59	33	67	43	1.15	0.65–2.04	0.47	0.64
Bobb et al. [2005]	88	238	65	193	1.10	0.77–1.59	0.49	0.62
Combined	1,326	542	1,233	493	0.95	0.80–1.12	−0.61	0.54

influence on gene function. Recent studies suggest that DAT1 VNTR variants may increase DAT expression. Michaelhaugh et al. [2001] found that the 9-repeat DAT1 allele enhanced transcription in dopamine neurons in neonatal rat midbrain and in an immortalized dopaminergic cell line. Fuke et al. [2001] and VanNess et al. [2005] showed that the 10-repeat DAT1 allele increased gene expression in human DNA. Inoue-Murayama et al. [2002], who assessed the relative luciferase activities associated with the human 9-, 10-, and 11-repeat alleles in addition to several non-human primate DAT1 VNTRs, reported an inverse relationship between reporter gene activity and repeat number, an observation consistent with possible length-dependent reductions in transfection efficiency. Miller and Madras [2002] demonstrated that vectors containing the 3′-UTR region of the human 9-repeat *DAT1* gene resulted in higher levels of reporter gene expression than analogous vectors containing the 10-repeat DAT1 3′-UTR. However vectors containing human 3′-UTR 10-repeat segments that differed on the basis of a single nucleotide polymorphism (SNP) had different effects on reporter gene expression in vitro. Mill et al. [2002] demonstrated that DAT1 mRNA levels were higher in human brain and lymphocyte tissue in individuals with the 10-repeat DAT1 allele compared to those with the 9-repeat DAT1 allele. Thus evidence from these studies strongly suggest that variability in the length or sequence of the 3′-UTR of the *DAT1* gene may influence levels of DAT in the brain. This may be through transcriptional regulation as suggested in the study by Michaelhaugh et al. [2001]. Alternatively VNTR sequences can act as translational and functional regulators of mRNA or as structural modifiers of protein [Nakamura et al., 1998]. However, Mill et al. [2005], who recently published a well-controlled set of reporter gene analyses using both neuronal and non-neuronal cell lines, found no significant difference in reporter gene activity attributable to VNTR copy number.

In some studies, abnormal levels of the DAT have been detected in the brains of ADHD subjects [Cheon et al., 2003; Krause et al., 2003]. However, the number of tandem repeats in the 3′ URT of the *DAT1* gene is not clearly associated with DAT density. Two studies demonstrated a higher DAT density with the 10/10 repeat genotype [Heinz et al., 2000; Cheon et al., 2005]. However, another study found a lower density in the 10/10 than in the 9/10 repeat genotype [Jacobsen et al., 2000], while a third study found no difference in DAT density among different genotypes [Martinez et al., 2001]. Recent data suggested that a specific haplotype involving the 10-repeat allele is specifically associated with ADHD. The 3′ untranslated VNTR might not be the functional site itself but instead is acting as a tagging marker for a nearby functional site, or the VNTR sequence might be interacted with a second functional polymorphic site. In these cases, differences in the strength of association between the 3′ VNTR and an alternative DAT1 functional site, or differences in the frequency of interacting genetic variants could influence the size of main effects observed with the 10-repeat allele. Barr et al. [2001] reported significant evidence of increased transmission of a haplotype of the 10-repeat allele with SNP alleles in exon 9 and intron 9 and Galili-Weisstub et al. [2005] with an exon 15 SNP. Hawi et al. [2003] also reported haplotype associations involving the 10-repeat allele but in association with alleles of simple sequence repeat markers flanking the gene. These studies indicate that the 10-repeat allele is most likely acting as a tagging marker for an alternative functional site.

Besides ethnicity, other confounding factors or moderators affecting the association between DAT1 10 repeat allele and ADHD should also be noted. Based on phenomenology, the ADHD phenotype can be divided into various subtypes (e.g., the inattentive, hyperactive-impulsive, and combined subtypes described in DSM-IV), and it is not clear whether these subtypes share the same genetic risk factors [Crosbie and Schachar, 2001]. In addition, comorbidity may reflect common genetic influences [Comings et al., 1996; Vandenbergh et al., 2000; Willcutt et al., 2000; Loo et al., 2004] and cannot be studied in the current analysis because of the insufficient data of available studies. Although random effect models, anticipating the genuine differences in studies, incorporate a between-study variance in their estimates and are more conservative, further studies are needed to minimize the heterogeneity among pooled studies. The endophenotypes may serve as intermediates to reduce the influence of heterogeneity instead of the phenotype of this disorder in the genetic study.

In summary, we show evidence of a small but significantly positive association between the DAT1 10 repeat allele and ADHD. It is possible that the 3′ untranslated VNTR functions in the control of expression of the *DAT1* gene so that the number of repeats is directly related to the expression of the *DAT1* gene. However, it may be that this allele is in linkage disequilibrium with the functional DNA variants that contribute to the ADHD phenotype. Further analysis of the variants in *DAT1* gene is necessary to identify other possible sequence variants within the gene that contribute to the increased susceptibility to ADHD.

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