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Meta-Analysis of the Heterogeneity in Association of DRD4 7-Repeat Allele and AD/HD: Stronger Association With AD/HD Combined Type

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The purpose of this meta-analysis was to examine whether association studies between attention deficit/hyperactivity disorder (AD/HD) and the dopamine receptor 4 gene 7-repeat (DRD4 7R) allele vary systematically based on study characteristics. A total of 27 empirical studies with 28 distinct samples using either case–control or family-based association analyses were included. Consistent with previous meta-analytic work [Gizer et al. (2009), Hum Genet 126:51–90], the DRD4 7R allele was associated with AD/HD across studies (OR = 1.33; 95% CI = 1.16–1.53, z = 4.04, $P = 0.00005$) and there was significant systematic variability among studies ($Q = 54.24$; $P = 0.001$; $I^2 = 50.22$). To account for the variability among studies, sample and study level covariates were examined. No differences in overall effect size emerged between family-based and case–control studies. However, the risk allele frequency in the control population accounted for a significant portion of the variance in overall effect size within case–control studies. In addition, evidence for the association between the DRD4 7R allele and distinct AD/HD subtypes emerged across family-based and case–control studies. The proportion of AD/HD, combined type individuals within the AD/HD sample was associated with a significant increase in the magnitude of association between the DRD4 7R allele and AD/HD. Conversely, an increase in the proportion of AD/HD, predominantly inattentive type individuals within the AD/HD sample was associated with a decrease in study effect size. Implications regarding AD/HD etiological and phenotypic heterogeneity are discussed.

Key words: attention; hyperactivity; dopamine; genetics; meta-regression

INTRODUCTION

Attention deficit/hyperactivity disorder (AD/HD) is characterized by persistent, pervasive and developmentally inappropriate levels of inattention, hyperactivity–impulsivity, or both that lead to clinically significant impairment. The AD/HD phenotype is highly heterogeneous and there has been much debate on how to appropriately reduce phenotypic heterogeneity by creating diagnostic subtypes or separate disorders [e.g., Milich et al., 2001]. According to the DSM-IV, individuals are sub-grouped into AD/HD combined type (AD/HD-C) if they exhibit high levels of both inattention and hyperactive-impulsive symptoms; AD/HD predominantly inattentive type (AD/HD-I) if they display excessive inattention only; and AD/HD predominantly hyperactive-impulsive type (AD/HD-HI) if they show excessive hyperactive-impulsive symptoms only. AD/HD-I is the most prevalent subtype in community samples [e.g., Gaub and Carlson, 1997; DuPaul et al., 1998]. In contrast, AD/HD-C tends to be the most prevalent subtype in clinical populations, outnumbering AD/HD-I by 2:1 and AD/HD-HI by 3:1 [Lahey et al., 1994]. Given that AD/HD-HI is the least prevalent subtype and lacks temporal stability [Lahey et al., 2005], this subtype will not be further discussed in detail.

Although the specific etiology is not completely understood, several factors associated with the development of AD/HD have been identified. Evidence from family, twin, and adoption studies suggest that genetic factors substantially contribute to the development of AD/HD [heritability estimate = 0.76; Faraone et al., 2005]. Molecular genetics research has attempted to identify genes that increase susceptibility for the disorder. Consistent with the dopamine deficit hypothesis of AD/HD etiology [Levy, 1991], genes associated with the dopamine system (e.g., DAT1 and DRD4) have been major foci of study. The dopamine receptor 4 gene 7 repeat (DRD4 7R) allele has been widely studied and is one of the most strongly associated alleles with AD/HD [OR = 1.33; Gizer et al., 2009].

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The DRD4 gene is a 48-bp VNTR on exon 3, located on chromosome 11p15.5 [Gelernter et al., 1992; Petronis et al., 1993]. Allele variants produce structural differences in the 3rd intracellular loop of the D4 receptor, which belongs to the D_2 receptor family, and couples to pre- and post-synaptic G-protein effectors. D_4 receptors are found at high densities in the frontal cortex, amygdala, hippocampus, hypothalamus, and mesencephalon [Van Tol et al., 1991; O'Malley et al., 1992], and the 7R allele may be associated with a sub-sensitive post-synaptic D_4 receptor or hypofunctioning of mesolimbic and mesocortical dopamine branches [Missale et al., 1998]. Ten alleles (2R-11R) have been identified in the global population [Seeman and Van Tol, 1994] with the 2R, 4R and 7R alleles being the most common variants. DRD4 allele frequency varies substantially between ethnic groups [Chang et al., 1996]. Generally, the 7R allele is relatively most prevalent in Central and South American populations, less prevalent in European Ancestry populations, and least prevalent in Asian populations [Van Tol et al., 1991; Chang et al., 1996].

Despite an overall association between the DRD4 7R allele and AD/HD, a recent meta-analysis [Gizer et al., 2009] found that the magnitude of the association varies substantially across studies. Though many different potential sources of heterogeneity exist, researchers have focused primarily on AD/HD subtype and, to a lesser extent, study methodology.

Factors Accounting for Heterogeneity in the Association of DRD4 7R Allele With AD/HD

AD/HD subtype. According to Sagvolden et al. [2005], hypofunctioning in the mesolimbic dopaminergic pathway is related to hyperactivity–impulsivity, and hypofunctioning in the mesocortical dopaminergic pathway is related to poor executive functioning and attentional processes. Given that the DRD4 7R allele is implicated in the hypofunctioning of both dopaminergic pathways [Missale et al., 1998], it is likely that the DRD4 7R allele would give rise to both inattention and hyperactivity–impulsivity symptoms. Therefore, the DRD4 7R allele may be more strongly associated with individuals with AD/HD-C compared to AD/HD-I. Furthermore, youth with AD/HD and the 7R allele tend to have a quicker response time [Manor et al., 2002; Langley et al., 2004] and a more consistent reaction time to target stimuli than AD/HD youth without the 7R allele [Swanson et al., 2000; Manor et al., 2002; Bellgrove et al., 2005]. Therefore, it is unlikely that the DRD4 7R allele is associated with AD/HD-I, as a subset of individuals with AD/HD-I has a slowed reaction time to target stimuli [e.g., Derefinko et al., 2008]. However, findings from studies that have examined the differential association between the DRD4 7R allele and AD/HD subtypes and AD/HD symptom dimensions have been inconsistent [Rowe et al., 1998, 2001; McCracken et al., 2000; Todd et al., 2001; Frank et al., 2004]. Similarly, findings on the association between single nucleotide polymorphisms in the DRD4 promoter region and AD/HD symptom dimensions have also been inconsistent [Lasky-Su et al., 2007, 2008].

A few researchers have examined the association of the DRD4 7R allele and AD/HD with the presence or absence of oppositional defiant disorder (ODD) and found that the DRD4 7R allele tends to be more strongly associated with AD/HD when comorbid with ODD [Holmes et al., 2002; Kirley et al., 2004].

Such inconsistent findings may be related to the small sample sizes and limited stability of the DSM-IV AD/HD subtypes overtime [Lahey et al., 2005]; thus, this question may be better addressed in the context of a mega-sample or meta-analysis [Faraone, 2008]. For example, by combining 14 independent samples, Lowe et al. [2004] demonstrated that the DRD5 148 bp allele was associated with AD/HD-C and AD/HD-I but not AD/HD-HI. Similarly, I.D. Waldman (personal communication, September 8, 2009) used summary statistics between studies and found evidence for a stronger relationship between DAT1 and 5HTTLPR risk alleles and AD/HD-C compared to AD/HD-I.

Study methodology. Others have taken a between-studies approach and explored whether study methodology moderates the magnitude of effect size. Li et al. [2006] explored the heterogeneity in effect sizes between association studies using study design (case–control vs. family-based) as a moderating variable and found that case–control studies had a significantly higher mean effect size than family-based studies. The authors suggest that such differences may be the result of population stratification [Cardon and Bell, 2001] or differences between subjects ascertained from case–control and family-based study designs [West et al., 2002].

Summary and Hypotheses

Given the differences in samples, assessment methodology and study design, systematic variation in observed effect sizes [Gizer et al., 2009] is likely to result from a combination of sample and study characteristics. Building from previous meta-analyses that have found significant variation in the association between AD/HD and the DRD4 7R allele [Li et al., 2006; Gizer et al., 2009], the purpose of this study was to examine how certain sample and study variables may moderate the association between DRD4 7R allele and AD/HD. Of particular interest is the distribution of AD/HD subtypes in identified samples. Thus, based on AD/HD etiological theory [Sagvolden et al., 2005], the following hypothesis was made:

An increase in the proportion of individuals with AD/HD-C in the AD/HD sample would be associated with an increase in magnitude of association between AD/HD and the DRD4 7R allele. Conversely, an increase in the proportion of AD/HD-I in the AD/HD sample will be associated with a decrease in magnitude of association between AD/HD and the DRD4 7R allele.

In addition, several exploratory moderators of the relationship between DRD4 7R allele and AD/HD were examined. Given that additional studies have been published since Li et al. [2006], the moderator of study design (case–control and family-based) was re-examined. The allele frequency in cases and controls, the mean age of the AD/HD sample, the proportion of males in the AD/HD sample, diagnostic classification system, and sample ethnicity were also examined as potential moderators to the relationship between DRD4 7R and AD/HD.

MATERIALS AND METHODS

Literature Search

First, computer searches were conducted using the PubMed and PsycInfo search engines. Keywords associated with AD/HD phenotype (ADHD, inattention and hyperactivity) were crossed with words associated with the DRD4 7R allele (DRD4, D4DR, dopamine receptor) to identify relevant studies that were published between January 1990 and July 2009. The author reviewed abstracts and if the study included an AD/HD or related sample (e.g., hyperkinetic disorder) and had genotyped DRD4 then the full-text article were retrieved. Next, the reference section of each full text-article, including previous meta-analyses [Faraone et al., 2001, 2005; Maher et al., 2002; Li et al., 2006; Gizer et al., 2009], were reviewed to find additional studies that were not identified in the computer search. All together, this approach yielded 44 studies that provided data on the association between AD/HD and DRD4 7R allele. Using a developed protocol (available upon request), data from each study was extracted on two separate occasions by this study's author. Next, the separate protocols for each study were compared, and the corresponding author(s) for each identified study were sent the protocol, asked to clarify any discrepancies, and asked to provide supplementary information including raw data to compute the effect size and values for moderating variables of interest. No additional studies were identified in correspondence with corresponding authors.

Inclusion Criteria

A study was included in the meta-analysis if it met all of the following criteria: (1) presented an association analysis between the DRD4 7R allele and AD/HD using either case–control or family-based methods; (2) included (or the author provided) sufficient data to calculate an odds ratio (OR) and variance for the association between AD/HD and the DRD4 7R allele; (3) reported data from an independent sample or was the largest dataset in a set of studies with overlapping samples; and (4) case–control studies employed healthy individuals for their control sample. For studies that used both case–control and family-based methods, results from case–control analyses were reported. Finally, for moderating analyses, the study needed to provide a value for the relevant moderating variable. For non-independent samples, the largest sample that provided a value for the moderating variable was included.

Identified Studies

Of the 44 identified studies, a total of 17 studies were excluded from the primary analysis. Five studies conducted with Asian populations were excluded due to the absence of 7R alleles [Qian et al., 2004; Brookes et al., 2005; Kim et al., 2005; Leung et al., 2005; Cheuk et al., 2006]. Four studies were excluded because the OR corresponding to the association between the 7R allele and AD/HD could not be computed [Manor et al., 2002; Bhaduri et al., 2006; Brookes et al., 2006; Monuteaux et al., 2008]. Seven studies were excluded due to partially overlapping samples with larger samples [Smalley et al., 1998; Faraone et al., 1999; McCracken et al., 2000; Holmes et al., 2002; Kirley et al., 2002; Grady et al., 2003; Johnson et al., 2008]. Lowe et al. [2004] was also excluded from the primary analysis but included in a moderating analysis as the proportion of AD/HD subtypes could not be calculated in Hawi et al. [2000]. One study was excluded because the control sample did not consist of healthy individuals [Ballon et al., 2007]. Note that a number of included case–control studies reported family-based association ORs [Hawi et al., 2000; Holmes et al., 2000; Mill et al., 2001; Roman et al., 2001; Gornick et al., 2007]. In these studies, only the data from the case–control association analyses were reported as they were associated with more precise sample information, included more participants, and are comparable to family-based results [Evangelou et al., 2006].

A total of 27 studies and 28 samples were included in the overall meta-analysis. Sixteen case–control and 12 family-based samples were included (see Tables IA and IB). AD/HD was diagnosed according to DSM-IV criteria in the majority of studies. Smith et al. [2003] did not use a formal diagnostic classification system but their sample approximated DSM-IV criteria for AD/HD-C or ADHD-HI. Curran et al. [2001] used developmentally deviant scores on a brief behavioral questionnaire. DSM-III criteria were employed in three studies [Comings et al., 1999; Maher et al., 2002; El-Faddagh et al., 2004]. Johansson et al. [2008] used the ICD-10 and made DSM-IV modifications allowing the sample to meet for AD/HD-I. Swanson et al. [1998] required participants to meet both DSM-IV and ICD-10 criteria.

Some studies applied additional inclusion criteria including: (1) meeting criteria for DSM-IV AD/HD-C [LaHoste et al., 1996; Tahir et al., 2000; Carrasco et al., 2006]; (2) a therapeutic response to stimulant medication [Swanson et al., 1998; Sunohara et al., 2000 Irvine Sample]; (3) absence of comorbid psychiatric disorders excluding ODD [Swanson et al., 1998; Muglia et al., 2000; Sunohara et al., 2000 both Samples]; and (4) male gender [Swanson et al., 1998]. Common exclusionary criteria included low IQ or the presence of pervasive developmental disorder or neurological disorder.

The majority of AD/HD samples were clinic-referred; three samples were community-based [Curran et al., 2001; Todd et al., 2001; El-Faddagh et al., 2004]. In addition, most samples were child-based; two adult samples were included [Muglia et al., 2000; Johansson et al., 2008]. In case–control studies, control samples were selected using a variety of different methods including healthy blood donors, healthy siblings, paternity testing services and matched controls from epidemiological studies. In several studies, AD/HD was not formally assessed in the control sample; thus, some control subjects may have met diagnostic criteria for the disorder.

Effect Size and Within Study Variance

In case–control studies the OR is the ratio of the odds of having the DRD4 7R allele to non-7R alleles in the ADHD group compared to controls. Similarly, the OR for haplotype-based haplotype relative risk (HHRR) studies was the ratio of the odds of parents transmitting the 7R allele to non-7R allele transmissions to AD/HD cases, compared to the non-transmission of the DRD4 7R and non-7R alleles. For transmission disequilibrium test (TDT) studies the method reported by Lohmueller et al. [2003] was followed. Specifically, to compute the OR for TDT studies, the frequency that a heterozygous parent passed on the DRD4 7R allele to their affected

TABLE IA. Effect Size and Sample Characteristics for Case–Control Association Studies of the DRD4 7R Allele and AD/HD

References	Country	ADHD N	Control N	Age	Male	CT	IT	DRD4 7R frequency (ADHD)	DRD4 7R frequency (control)	OR (95% CI)
LaHoste et al. [1996]	US	39	39	—	—	1.00	0.00	0.28	0.12	3.01 (1.29–7.05)
Rowe et al. [1998]	US	107	58	9.4	0.70	0.65	0.35	0.24	0.13	2.16 (1.16–4.04)
Comings et al. [1999]	US	52	737	—	—	—	—	0.18	0.14	1.41 (0.84–2.37)
Hawi et al. [2000]	Ireland	99	88	—	0.86	—	—	0.24	0.26	0.93 (0.58–1.49)
Holmes et al. [2000]	UK	129	442	—	—	0.76	0.08	0.22	0.13	1.89 (1.33–2.70)
Muglia et al. [2000]	Canada	66	66	34.3	0.56	—	—	0.21	0.10	2.46 (1.21–5.00)
Curran et al. [2001]	UK	133	91	—	—	—	—	0.26	0.14	2.14 (1.30–3.52)
Mill et al. [2001]	UK	132	189	10.4	—	0.91	0.02	0.21	0.14	1.69 (1.11–2.56)
Roman et al. [2001]	Brazil	66	100	10.1	0.86	0.77	0.16	0.25	0.17	1.63 (.95–2.79)
Smith et al. [2003]	US	105	68	—	—	—	—	0.20	0.20	0.98 (0.57–1.68)
El-Faddagh et al. [2004]	Germany	24	231	4.5	0.71	—	—	0.33	0.19	2.19 (1.15–4.16)
Frank et al. [2004]	US	81	24	—	0.80	—	0.38	0.30	0.25	1.26 (0.61–2.63)
Carrasco et al. [2006]	Chile	26	25	—	0.92	1.00	0.00	0.19	0.14	1.46 (0.51–4.20)
Gornick et al. [2007]	US	166	282	9.0	0.53	0.94	0.06	0.23	0.17	1.45 (1.03–2.03)
Johansson et al. [2008]	Norway	358	340	33.9	0.51	0.21	0.17	0.22	0.24	0.90 (0.70–1.15)
Martinez-Levy et al. [2009]	Mexico	105	84	14.3	—	—	—	0.30	0.35	0.77 (0.50–1.20)

Age = mean age of the AD/HD sample; Male = proportion of males in the AD/HD sample; CT = proportion of individuals with ADHD-C in the AD/HD sample; IT = proportion of individuals with AD/HD-I in the AD/HD sample.

TABLE IB. Effect Size and Sample Characteristics for Family-Based Association Studies of the DRD4 7R Allele and AD/HD

References	Method	Country	ADHD N	Triads	Dyads	Age	Male	CT	IT	OR (95% CI)
Swanson et al. [1998]	HHRR	US	52	52	0	—	1.00	—	—	2.08 (1.06–4.06)
Kotler et al. [2000]	HHRR	Isreal	47	—	—	9.89	—	0.87	0.13	0.47 (0.22–.99)
Lunetta et al. [2000]	TDT	US	17	4	13	—	—	—	—	1.50 (0.58–3.87)
Sunohara et al. [2000], Irvine	TDT	US	59	21	38	—	—	—	—	1.00 (0.57–1.74)
Sunohara et al. [2000], Toronto	TDT	Canada	88	75	13	—	—	—	—	1.52 (0.03–2.47)
Tahir et al. [2000]	TDT	Turkey	29	26	3	—	—	1.00	0.00	1.90 (0.88–4.09)
Todd et al. [2001]	TDT	US	201	201	0	—	0.56	0.36	0.58	1.11 (0.77–1.59)
Maher et al. [2002]	TDT	US	33	33	0	—	—	—	—	1.13 (0.43–2.92)
Arcos-Burgos et al. [2004]	TDT	Colombia	—	—	—	—	—	—	—	1.13 (0.43–2.92)
Kustanovich et al. [2004]	TDT	US	535	535	0	11.0	.74	0.50	0.43	1.21 (0.94–1.56)
Lowe et al. [2004]	TDT	Ireland	178	—	—	—	—	0.63	0.12	1.35 (0.88–2.07)
Bakker et al. [2005]	TDT	Netherlands	236	231	5	—	—	—	—	1.06 (0.76–1.48)
Niederhofer et al. [2008]	TDT	Germany	49	36	13	8.4	0.88	0.59	0.33	0.92 (0.40–2.08)

Age = mean age of the AD/HD sample; Male = proportion of males in the AD/HD sample; CT = proportion of individuals with AD/HD-C in the sample; IT = proportion of individuals with AD/HD-I in the sample.

offspring was divided by the frequency that the allele was not passed to their affected offspring. Such a method is considered asymptotically equivalent to calculating an OR in a case–control study, as in a large population of control participants the expected transmission ratio would approach 50:50 [Lohmueller et al., 2003]. The ORs for both study types were then converted to log ORs and the log OR variance within case–control and HHRR studies was calculated by summing the reciprocals of the 7R allele and non-7R allele frequencies in cases and controls and for transmitted and non-transmitted alleles, respectively. The variance in TDT studies was calculated assuming a large control sample. Thus, the sum of the reciprocals for the frequency of the transmitted risk allele and non-transmission of the risk allele were considered asymptotically equivalent to the sum of the reciprocal from each cell of a case–control study [Lohmueller et al., 2003].

Statistical Analysis

Meta-analysis of case–control, HHRR and TDT studies was conducted using Comprehensive Meta-Analysis (Version 2.0, BIOSTAT, Englewood, NJ). Given that the samples and methods employed between studies are variable, it is assumed that the effect size from each study is a sample from a distribution of true effects [Borenstein et al., 2009]. Thus, a random effects model was used to estimate the mean of all relevant true effects [Borenstein et al., 2009] and the mean effect of moderator variables. Compared to a fixed effects model, a random effects model allows inferences about population parameters including the effect size and regression coefficients. The presence of heterogeneity in effect sizes between studies was tested using the χ^2-based *Q*-statistic. Heterogeneity was also measured with T^2 and t which are estimates of the variance and standard deviation of true effects using the DerSimonian and Laird [1986] method. The amount of heterogeneity was quantified using I^2, which measures the proportion of total variation that reflects real differences in the variability between studies in observed effect size [Borenstein et al., 2009].

Subgroup analysis and meta-regression analyses were utilized to examine the influence of categorical and continuous moderating variables on observed effect size. Subgroup analyses utilized a mixed-effects model, where T^2 was calculated separately using a random effects model within subgroups and using a fixed effects model between subgroups [Borenstein et al., 2009]. If a subgroup had fewer than five studies, then T^2 was pooled across subgroups using a random-effects model, consistent with the recommendation from Borenstein et al. [2009]. A *Q*-test was used to test for heterogeneity across subgroups.

A method of moments meta-regression was used to calculate the following model. Following notation by Raudenbush and Bryk [2002]:$d_j = \gamma_0 + \gamma_1 W_{1j} + u_j + e_j$where d_j is the odds ratio of study j, γ_0 and γ_1 are regression coefficients; W_{1j} is a study characteristic predicting effect sizes (e.g., proportion of AD/HD-C individuals in a sample); and u_j is the between studies random error which is not predicted by the study characteristic for which we assume $u_j \sim N(0, \tau^2)$ and τ^2 is the between studies variance and e_j is sampling error associated with the estimate (i.e., d_j) of the population effect size δ, for study j, for which we assume $e_j \sim N(0, V_j)$. Here V_j is considered "known" and is the sampling variance for d_j. In this model, γ_0 represents the estimated effect size when W_{1j} is equal to zero, and γ_1 indicates the amount of change in the effect size for a one-unit increase in W_{1j} [Feinn et al., 2005]. Two-tailed z-tests were used to assess the impact of the moderating variables on effect size. An analogous index for proportion of variance explained was calculated; ($R^2_{analog} = T^2_{explained}/T^2_{Total}$) to describe the proportion of systematic, between studies variance that is explained by the presence of the moderating variable [Borenstein et al., 2009]. Alpha was set to 0.05 for hypothesized analyses and reduced to 0.007 for exploratory meta-regression and sub-group analyses using a Bonferonni adjustment.

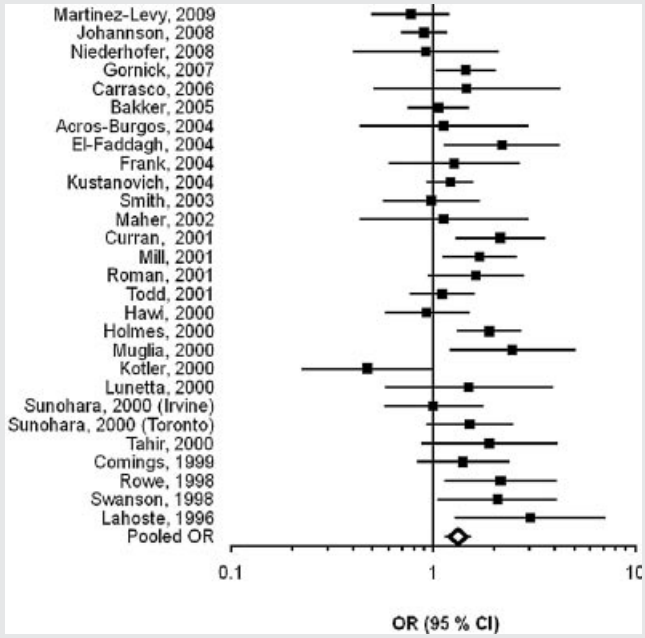

FIG. 1. Forest plot of OR and pooled OR for association studies between AD/HD and the DRD4 7R allele.

RESULTS

See Tables IA and IB for a summary of included studies. Twenty-eight independent samples met inclusion criteria to estimate the mean effect size for the association between the DRD4 7R allele and AD/HD. A total of 1,688 identified AD/HD cases and 2,864 control subjects drawn from case–control studies were included in the meta-analysis. In family-based studies, approximately 1,346[1] affected individuals participated. Fewer individuals in each sample were included in TDT analyses as they require a parent to be heterozygous for the allele of interest.

In the absence of a moderating variable, the unconditional model produced a log OR of 0.29 for γ_0. This corresponds to an OR of 1.33 (95% CI = 1.16–1.53, $z = 4.04$, $P = 0.00005$; Fig. 1). Neither visual inspection of a funnel plot nor Egger's funnel plot statistic

[1]The number 1,346 reflects the combined sample size from family-based studies with the exception of Arcos-Burgos et al. 2004 as the number of individuals with AD/HD from this study was not reported.

TABLE II. Study Characteristics Examined as Potential Moderating Variables of Effect Size

Moderator	γ_1	SE	z	$df_{residual}$	*P*
Transformed[a] proportion of AD/HD-C in AD/HD sample	1.47	0.55	2.67	13	0.008
Proportion of AD/HD-C in AD/HD sample	0.85	0.28	3.02	13	0.003
Transformed[b] proportion of AD/HD-I in AD/HD sample	−0.88	0.38	−2.28	13	0.023
Proportion of AD/HD-I in AD/HD sample	−0.90	0.43	−2.09	13	0.037
DRD4 7R allele frequency in AD/HD sample	0.99	2.72	0.37	14	0.715
7R Allele frequency in control sample	−5.02	0.92	−5.48	14	0.000
Proportion of AD/HD males in AD/HD sample	0.52	0.81	0.64	8	0.523
Log mean AD/HD age	−0.18	0.21	−0.85	10	0.396

The intercept for each analysis is not presented as the unconditional model demonstrated an overall association between the risk allele and the disorder, and the intercept for all moderating analyses varied substantially. In addition, given that the coverage of some covariates near the intercept were lacking, estimates of the intercept were considered extrapolations beyond available data.[a] $1/(2-X)$. [b] $\sqrt{X}$.

[$P = 0.062$; Egger et al., 1997] indicated the presence of publication bias. In addition, Rosenthal's fail-safe N suggests that 227 additional studies with a mean OR of 1.0 would need to be added to the analysis before the effect would be no longer significant. ORs ranged from 1.30 to 1.36 and remained statistically significant when each study was removed from the analysis, one at time, indicating that no one study produced the significant overall effect. In the unconditional model, the variability in observed effect size between studies was greater than would be expected if each study shared a common effect ($Q = 54.24$; $P = 0.001$). Furthermore, $I^2 = 50.22$ suggests that approximately half of the observed variability in effect size was systematic in nature. This indicates that moderating variables, such as AD/HD subtype, may account for the heterogeneity in effect sizes between studies. In order to test for this, the unconditional model was expanded to include moderating variables. Table II displays a summary of the results from these analyses.

To test the primary hypothesis that the DRD4 7R allele is more strongly associated with AD/HD-C compared to other AD/HD subtypes, the proportion of AD/HD-C individuals within the AD/HD sample was entered into the equation as a moderating variable. Given the proportional nature of this variable and that multiple studies included only AD/HD-C individuals, the proportion of AD/HD-C individuals within reporting studies was negatively skewed, thus the reciprocal of $2 - X$ was applied to normalize the distribution.[2] Increases in the transformed proportion of AD/HD-C individuals in the AD/HD sample predicted increases in the observed log OR (see Fig. 2). The transformed proportion of AD/HD-C individuals in the AD/HD sample accounted for 95% of the systematic variability in the observed ORs between studies. This was consistent with the untransformed proportion of AD/HD-C. These findings were mirrored by the proportion of AD/HD-I individuals in the AD/HD sample. The distribution of the proportion of the AD/HD-I variable was positively skewed and a square root transformation was applied to normalize the distribution.[3] Increases in the square root transformation of the proportion of AD/HD-I individuals in the AD/HD sample was associated with a decreased log OR (see Fig. 3). This finding was consistent with the effect of the non-transformed proportion of the AD/HD-I variable on observed log OR.

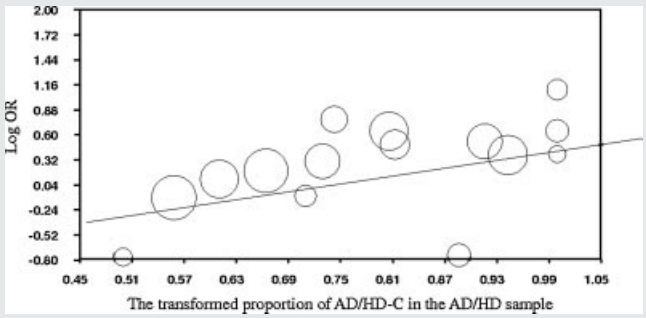

FIG. 2. Random-effects meta-regression analysis of study log OR on the transformed proportion AD/HD-C individuals in the AD/HD sample. The size of each data point reflects the relative weight of each study.

Next, to explore whether study design accounted for variability in effect size, studies were dichotomized into either case–control or family-based design. Though effect sizes between studies were not significantly different ($Q = 2.76$; $P = 0.097$), case–control studies had a larger mean effect size and a larger proportion of variability in observed effects (OR = 1.46; 95% CI = 1.19–1.79; z = 3.66; $P = 0.0002$; $I^2 = 62.04$) compared to family-based analyses (OR = 1.17; 95% CI = 1.00–1.38; z = 1.94; $P = 0.052$; $I^2 = 13.04$). Exploratory meta-regression analyses examined variability in case–control studies. Allele frequency in the AD/HD sample did not predict observed log OR, whereas increases in the allele frequency in the control sample was associated with decreases in the observed log OR (see Fig. 4). Within case–control studies, the allele frequency in the control sample accounted for approximately 100%[4] of the systematic variability in observed effect size between

[2]Where X is the proportion of individuals diagnosed with AD/HD-C. When X = 1 the proportion was revised to $X_1 = 2v - 1/2v$; where v is the AD/HD sample size.

[3]When the proportion of individuals with AD/HD-I was zero, the proportion was revised to 1/2v; where v is the AD/HD sample size.

[4]The R^2_{analog} theoretically ranges from 0 to 1 in the population; however, sampling error may cause the index to fall outside this range. In the present study, $R^2_{analog} = 1.30$, the value was set to 1.0 [Borenstein et al., 2009].

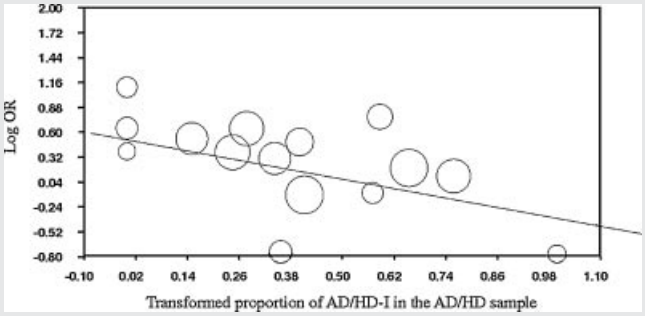

FIG. 3. Random-effects meta-regression analysis of study log OR on the transformed proportion of AD/HD-I individuals in the AD/HD sample. The size of each data point reflects the relative weight of each study.

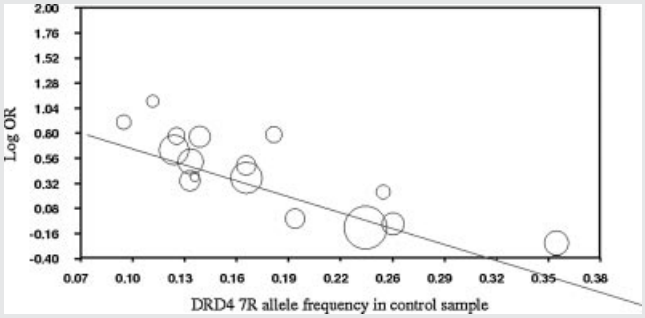

FIG. 4. Random-effects meta-regression analysis of case–control study log OR on the proportion of the DRD4 7R allele frequency in the control sample. The size of each data point reflects the relative weight of each study.

studies, whereas separately, the allele frequency in the AD/HD population only accounted for 19%.

Exploratory analyses were also conducted to examine if other variables were associated with the variability in effect sizes between studies. In subgroup analyses, studies drawing from Mexico, Brazil, Chile and Colombia were not significantly different from other studies ($Q = 0.07$; $P = 0.407$). In addition, studies using DSM-IV were not significantly different than studies using other diagnostic approaches ($Q = 0.88$; $P = 0.348$). In meta-regression, neither the proportion of males nor the log of the mean age of the AD/HD sample[5] predicted variability in observed effect size between studies.

DISCUSSION

The present meta-analysis examined the association of the DRD4 7R allele with AD/HD by combining 16 case–control and 12 family-based samples, which together included over 3,000 AD/HD cases and over 2,800 controls. The overall mean OR between the DRD4 7R allele and AD/HD was 1.33. This indicates that the DRD4 7R allele increases the odds that an individual is diagnosed with AD/HD by 33%. This is in line with recent meta-analyses on the same topic that used slightly different inclusion criteria [Faraone et al., 2005; Li et al., 2006; Gizer et al., 2009].

Consistent with recent meta-analyses [Li et al., 2006; Gizer et al., 2009], the magnitude of association varied significantly between studies. In an extension of previous topical meta-analyses and consistent with this study's primary hypothesis, increases in the proportion of AD/HD-C individuals within the AD/HD sample were associated with an increase in the magnitude of association between the DRD4 7R allele and AD/HD. Findings suggest that including only AD/HD-C individuals in an analysis would increase the OR from 1.22 to 1.79, assuming 55% of the AD/HD sample met criteria for AD/HD-C [Lahey et al., 1994]. Conversely, as the proportion of AD/HD-I individuals in the AD/HD sample increased, the observed OR decreased. Taken together, results were consistent with the hypothesis that the DRD4 7R allele is more strongly associated with AD/HD-C compared to AD/HD-I. The relative proportion of the two predominant AD/HD subtypes in the AD/HD sample accounted for the majority of systematic variability between reporting studies. Together, findings suggest that hypofunctioning in mesocortical and mesolimbic dopaminergic pathways may better characterize the etiology of AD/HD-C compared to AD/HD-I [Sagvolden et al., 2005]. This is in line with findings that the DAT1 10-repeat allele is more strongly associated with AD/HD-C than AD/HD-I [e.g., Waldman et al., 1998]. Furthermore, this meta-analysis suggests that reducing the AD/HD phenotypic heterogeneity may lead to the discovery of AD/HD etiological subtypes or possibly distinct disorders [e.g., Milich et al., 2001]. No other sample characteristics accounted for a significant proportion of true between studies variance.

In addition to sample characteristics, the association between study methodology and magnitude of effect size was explored. In contrast to Li et al. [2006], case–control studies did not have a significantly larger effect size than family-based studies, but there was a trend in this direction. Given that results of case–control studies may be biased by population stratification [Cardon and Bell, 2001], the relationship between 7R allele frequencies in the AD/HD and control samples and OR was examined. The allele frequency in the AD/HD sample was not related to the observed OR whereas the allele frequency in the control population did predict observed OR and accounted for close to all of the systematic variability of observed ORs between case–control studies. Given that the DRD4 allele frequencies vary substantially across ethnic groups [e.g., Chang et al., 1996] and that the association between the 7R allele and AD/HD may be dynamic [Shaw et al., 2007], the appropriateness of the control sample in case–control studies is of critical importance. Failure to appropriately control for such characteristics may have influenced the variability in findings.

These findings provide guidance for further study. First, indicators for the quality of AD/HD phenotyping are underreported in the literature. Future studies would be enhanced by: including information related to the psychometric properties of their assessments; describing how assessments are combined to form a diagnosis; reporting how many cases and controls did not meet criteria for study inclusion; and by presenting descriptive sample statistics for both cases and controls. In terms of genotyping, few studies

[5]Mean age of the AD/HD sample was severely positively skewed. Thus a log transformation was applied to normalize the distribution.

adequately reported tests of Hardy–Weinberg equilibrium [Gizer et al., 2009]. Future studies should report such information as it may help to explain variability between study findings. Though this meta-analysis included a relatively large number of samples, values for covariates of interest were often unavailable. For instance, like AD/HD subtype, differences in the rates of Conduct Disorder within and between samples may account for heterogeneity in candidate gene association studies [Thapar et al., 2006]; however, too few studies presented the rate of conduct disorder within their sample to be examined in this meta-analysis. In addition, values of covariates for TDT studies were attained from summary statistics that were based on the sample at-large and not only individuals included in the TDT analysis. Future research should stratify results based on potential moderating variables [Li et al., 2006] from the sample or sub-sample for which the results are based.

These findings also need to be considered in light of the limitations inherent in meta-regression analysis and subgroup analysis [see Thompson and Higgins, 2002 for a review]. First, values for moderating variables were not randomly assigned to studies; thus, relationships may be related to confounding bias. Second, meta-regression analyses examining sample characteristics deal with sample averages between studies and not individual level data within studies, thus observed relationships between studies are not necessarily found within studies (e.g., ecological bias). For instance, though some evidence suggests that the relationship between AD/HD and the DRD4 7R allele may reduce with age [Shaw et al., 2007], limited between study variability may have masked this association, which may be present within studies. This limitation can be attenuated through large collaborative efforts or by data stratified by moderating variables of interest. Finally, a practical limitation of meta-analysis and especially meta-regression is that access to observed effect size, its variance, and values for covariates are necessary.

Despite these limitations, such findings support the argument [e.g., Milich et al., 2001] that AD/HD-C and AD/HD-I (with few to no hyperactive–impulsive symptoms) may result from distinct etiological pathways. Further delineating samples based on symptoms related to Sluggish Cognitive Tempo [e.g., McBurnett et al., 2001] may allow for greater specificity in identifying shared and distinct pathways to distinct behavioral phenotypes. These findings also suggest that reducing the phenotypic variability within AD/HD may help to increase statistical power to detect candidate genes in molecular genetic studies.

By pooling summary data from a relatively large number of association studies, evidence suggests that the DRD4 7R allele is more strongly related to AD/HD-C compared to AD/HD-I. These findings suggest that etiological theories of AD/HD, which are primarily based on AD/HD-C individuals, may fall short in identifying appropriate candidate susceptibility genes for AD/HD-I. Additionally, given that the majority of genetic studies of AD/HD are conducted on clinical samples, which are disproportionally diagnosed with AD/HD-C [Lahey et al., 1994], such investigations may lack sufficient power to identify unique vulnerability genes associated with AD/HD-I. Therefore, exploratory genome wide association studies may have the potential to identify genes that are more replicable and have a stronger association [Gizer et al., 2009] for this group of individuals. To guide candidate gene studies, future research should look to elucidate the neurobiological underpinnings of severe inattentive symptomatology in the absence of hyperactivity–impulsivity so that the genetic underpinnings of this symptom presentation may be better understood. To the extent that AD/HD-C and AD/HD-I (with few or no hyperactivity–impulsivity symptoms) have unique etiological pathways, there would be sufficient evidence to categorize these AD/HD subtypes as separate disorders [e.g., Milich et al., 2001].

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