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REVIEW ARTICLE

Candidate gene studies of ADHD: a meta-analytic review

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Abstract Quantitative genetic studies (i.e., twin and adoption studies) suggest that genetic influences contribute substantially to the development of attention deficit hyperactivity disorder (ADHD). Over the past 15 years, considerable efforts have been made to identify genes involved in the etiology of this disorder resulting in a large and often conflicting literature of candidate gene associations for ADHD. The first aim of the present study was to conduct a comprehensive meta-analytic review of this literature to determine which candidate genes show consistent evidence of association with childhood ADHD across studies. The second aim was to test for heterogeneity across studies in the effect sizes for each candidate gene as its presence might suggest moderating variables that could explain inconsistent results. Significant associations were identified for several candidate genes including *DAT1, DRD4, DRD5, 5HTT, HTR1B,* and *SNAP25.* Further, significant heterogeneity was observed for the associations between ADHD and *DAT1, DRD4, DRD5, DBH, ADRA2A, 5HTT, TPH2, MAOA,* and *SNAP25,* suggesting that future studies should explore potential moderators of these associations (e.g., ADHD subtype diagnoses, gender, exposure to environmental risk factors). We conclude with a discussion of these findings in relation to emerging themes relevant to future studies of the genetics of ADHD.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by persistent and pervasive symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association 2000). Approximately 3–7% of children are diagnosed with ADHD, making it one of the most prevalent childhood psychiatric disorders (American Psychiatric Association 2000). Twin and adoption studies of ADHD suggest that genetic influences contribute substantially to its etiology, with heritability estimates ranging from 60 to 90% (Waldman and Rhee 2002). Thus, molecular genetic studies attempting to identify the specific genes involved in the etiology of ADHD are being published at a rapid rate (Faraone and Khan 2006; Waldman and Gizer 2006).

Despite such efforts, the search for susceptibility genes for ADHD, like those for other complex traits (Ioannidis et al. 2001; Lohmueller et al. 2003), has yielded largely inconsistent results (Faraone et al. 2005; Waldman and Gizer 2006). For example, one of the first candidate gene studies of ADHD reported a significant association between the dopamine transporter gene (*DAT1*) and ADHD (Cook et al. 1995). This report was followed by studies attempting to replicate the original association that yielded approximately equal numbers of positive and negative results (Curran et al. 2001b; Swanson et al. 2000b; Todd et al. 2001a; Waldman et al. 1998). Notably, this pattern of results is not specific to candidate gene studies of ADHD, as similar findings have been reported for genetic association studies of most if not all complex traits that have been studied (Ioannidis 2003).

Geneticists typically refer to a 'complex trait' as a phenotype with a genetic etiology that is composed of a multitude of susceptibility genes, each contributing only a small magnitude of the overall risk for the disorder (Lander and Schork 1994). This polygenic etiology presents several challenges to identify genes that confer risk for a complex trait (Chakravarti 1999; Lander and Schork 1994; Risch and Merikangas 1996; Risch 2000). For example, there is likely to be genetic heterogeneity in the etiology of a complex trait, such that different genes can result in the same phenotype. Further, each susceptibility gene is likely to have low penetrance, thus not all carriers will develop the disorder. Specific environmental influences are also more likely to be important risk factors for complex disorders than for simple Mendelian diseases, and gene–environment interactions are more likely to be involved in the etiology of complex disorders.

Given these challenges, candidate gene studies require large samples to achieve adequate statistical power and replicable results (Ioannidis et al. 2003). Nonetheless, many published candidate gene studies have employed relatively small samples. It is thus difficult to interpret discrepant findings that are the norm across genetic association studies of complex traits as several competing explanations for the discrepant findings are possible. First, the initial reported association may simply represent a false positive result. Second, the initial reported association may reflect an upwardly biased estimate relative to the true effect size (Lohmueller et al. 2003), thus subsequent studies may be substantially underpowered to detect an association if this inflated estimate was used to determine an appropriate sample size. These two potential explanations are the direct consequence of using small samples to conduct tests of association between complex traits and candidate gene polymorphisms that likely confer only a small risk for the disorder.

A third potential explanation for the discrepant findings is the presence of unmeasured sources of heterogeneity that modify the association between the candidate gene and the disorder, thus contributing to the heterogenous findings across studies. For example, differences in the genetic backgrounds of the populations sampled, in the assessment or diagnostic methods used, or in unmeasured environmental risk factors could each contribute to difficulties in replicating genetic associations. By aggregating data across studies, meta-analyses provide a systematic method of evaluating discrepant association findings between a candidate gene and a disorder that can be used to determine whether a true association exists and estimate its magnitude. Further, meta-analysis can be used to determine whether true heterogeneity may be contributing to the lack of consistent results across studies.

In this paper, we present a series of meta-analyses of the more commonly studied candidate gene polymorphisms for childhood ADHD. For each candidate gene, the most frequently examined polymorphisms were identified and the extant literature meta-analyzed to answer two specific questions: (1) is there evidence of a significant association between this polymorphism and ADHD? and (2) is there significant and substantial heterogeneity in the effect sizes across studies that might explain the discrepant findings? Results are presented for each candidate gene, starting with genes involved predominately in dopaminergic function, followed by candidate genes in the other major neurotransmitter systems (e.g., adrenergic and serotonergic), and ending with genes involved in various aspects of brain and nervous system development outside of such neurotransmitter systems (see Table 1 for a summary of these findings).

Methods

Study sample identification and inclusion/exclusion criteria

We used a four-stage approach to identify relevant studies for meta-analysis. In the first stage, we conducted searches of three databases—PubMed, PsycInfo, and Google Scholar—to identify an initial set of articles. The search terms used to query the databases included "ADHD" and related terms such as "inattention" and "hyperactivity." Each of these terms was used to conduct searches with all relevant names of the candidate gene of interest and its protein product. For example, for *DAT1,* the terms "dopamine transporter gene," "*DAT1*," and "*SLC6A3*" were each used to query the database in conjunction with the terms "ADHD," "inattention," and "hyperactivity", resulting in a total of nine queries. In the second stage, we searched the reference sections of the most recently published studies identified in stage 1, as well as any recently published review articles, to identify studies that might have been missed in stage 1. In stage 3, we used the Web of Science Cited Reference Search® (http://www.thomsonreuters.com/products_services/scientific/Web_of_Science) to compile a list of publications citing the initial association studies for the candidate gene of interest. This list was then reviewed to identify any published studies that might have been missed in stages 1 and 2. Finally, in stage 4, we contacted researchers conducting genetic association studies of ADHD to collect any relevant unpublished data that could be included in the meta-analyses. Researchers were contacted through the Collaborative ADHD Genetics Consortium (PI-Dr. Stephen Faraone, R13MH59126-0641) and were asked to provide only summary statistics for each candidate gene polymorphism included in this review. For family-based TDT studies, this included the number of 'high-risk' alleles transmitted and non-transmitted to ADHD cases. For case-control studies, this included the

Table 1 Meta-analytic results for associations between candidate gene polymorphisms and childhood ADHD

Gene	Location	Polymorphism	Risk allele	# Studies (TDT/CC or HHRR)	Meta-analysis model (fixed/random)	Results		Q statistic	
						OR (95% CI)	χ^2 (*P* value)	χ^2 (*P* value)	I^2
DAT1	3′**UTR**	**VNTR**	**10 repeat**	**34 (15/19)**	**Random**	**1.12 (1.00–1.27)**	**3.66 (0.028)**	**92.97 (<0.000001)**	**65**
	Intron 8	**VNTR**	**3 repeat**	**5 (4/1)**	**Random**	**1.25 (0.98–1.58)**	**3.35 (0.034)**	**11.22 (0.012)**	**64**
	Exon 8	rs6347	Unknown	6 (3/3)	Random	1.08 (0.94–1.22)	1.21 (0.272)*	5.81 (0.325)	14
	3′**UTR**	**rs27072**	**'G' allele**	**7 (5/2)**	**Random**	**1.20 (1.04–1.38)**	**6.32 (0.006)**	8.29 (0.217)	28
	Intron 13	rs40184	'G' allele	4 (2/2)	Random	1.06 (0.90–1.24)	0.46 (0.249)	5.47 (0.141)	45
DRD4	**Exon 3**	**VNTR**	**7-repeat**	**26 (10/16)**	**Random**	**1.33 (1.15–1.54)**	**14.51 (0.00007)**	**54.32 (0.0006)**	**54**
	Promoter	In/Del	Unknown	8 (6/2)	Random	1.05 (0.86–1.31)	0.29 (0.590)*	**15.16 (0.033)**	**54**
	Promoter	**rs1800955**	**'T' allele**	**5 (3/2)**	**Fixed**	**1.21 (1.04–1.41)**	**6.01 (0.007)**	3.54 (0.472)	0
DRD2	3′ Flank	TaqI	Unknown	6 (3/3)	Random	1.65 (0.89–3.06)	2.56 (0.110)*	**55.01 (<0.000001)**	**91**
DRD5	**5′ Flank**	**Dinucleotide repeat**	**148-bp allele**	**9 (6/3)**	**Random**	**1.23 (1.06–1.43)**	**7.73 (0.0027)**	***14.80 (0.063)***	***46***
DRD3	Exon 1	rs6280	Unknown	6 (4/2)	Fixed	1.07 (0.95–1.21)	1.23 (0.268)*	1.12 (0.952)	0
COMT	Exon 4	rs4680	Val allele	16 (8/8)	Random	0.99 (0.91–1.08)	0.04 (0.575)	17.55 (0.287)	15
DBH	Intron 5	TaqI (rs2519152)	'A2' allele	6 (1/5)	Random	1.12 (0.80–1.55)	0.43 (0.206)	**17.54 (0.004)**	**71**
	5′ Flank	rs1611115	Unknown	4 (1/3)	Random	1.05 (0.83–1.33)	0.16 (0.692)*	4.77 (0.189)	37
	Exon 2	rs1108580	'A' allele	5 (1/4)	Random	1.09 (0.93–1.28)	1.12 (0.145)	5.04 (0.284)	20
SLC6A2	Exon 9	rs5569	Unknown	5 (3/2)	Fixed	1.06 (0.95–1.18)	1.17 (0.279)*	0.27 (0.992)	0
	Intron 13	rs2242447	Unknown	4 (2/2)	Random	1.04 (0.91–1.19)	0.29 (0.589)*	3.51 (0.319)	14
ADRA2A	5′ Flank	rs1800544	'G' allele	11 (5/6)	Random	0.99 (0.89–1.11)	0.01 (0.542)	12.20 (0.272)	18
	5′UTR	rs1800545	Unknown	4 (3/1)	Fixed	0.99 (0.81–1.21)	0.01 (0.914)*	1.55 (0.670)	0
	3′UTR	rs553668	'T' allele	4 (3/1)	Random	0.94 (0.66–1.34)	0.12 (0.638)	**8.09 (0.044)**	**63**
5HTT	**Promoter**	***5HTTLPR***	**Long allele**	**19 (10/9)**	**Random**	**1.17 (1.02–1.33)**	**5.40 (0.010)**	**52.80 (0.00003)**	**66**
	Intron 2	STin2	10-repeat	9 (2/7)	Fixed	1.01 (0.92–1.10)	0.03 (0.428)	4.08 (0.850)	0
	3′ UTR	rs3813034	'T' allele	5 (2/3)	Random	1.05 (0.87–1.26)	0.26 (0.304)	5.71 (0.222)	30
HTR1B	**Exon 1**	**rs6296**	**'G' allele**	**9 (4/5)**	**Fixed**	**1.11 (1.02–1.20)**	**5.45 (0.010)**	7.92 (0.441)	0
HTR2A	Exon 3	rs6314	'T' allele	6 (2/4)	Random	1.05 (0.82–1.34)	0.16 (0.343)	8.71 (0.121)	42
	Exon 1	rs6313	Unknown	6 (3/3)	Fixed	0.96 (0.86–1.06)	0.77 (0.379)*	3.36 (0.644)	0
	5′ Flank	rs6311	Unknown	6 (2/4)	Fixed	1.04 (0.94–1.14)	0.57 (0.449)*	2.97 (0.705)	0
TPH1	Intron 6	rs1800532	Unknown	4 (2/2)	Random	0.97 (0.83–1.12)	0.19 (0.662)*	5.10 (0.164)	41
TPH2	Intron 5	rs1843809	'T' allele	4 (4/0)	Random	1.15 (0.73–1.82)	0.35 (0.276)	**19.46 (0.0002)**	**84**
	Intron 5	rs1386493	'T' allele	4 (4/0)	Random	1.04 (0.77–1.40)	0.06 (0.400)	**9.76 (0.021)**	**69**
MAOA	Promoter	VNTR	Hi-activity alleles	6 (3/3)	Random	1.02 (0.72–1.43)	0.01 (0.464)	**15.28 (0.009)**	**67**
CHRNA4	***Exon 2***	***rs2273506***	***'T' allele***	***4 (2/2)***	***Fixed***	***1.19 (0.92–1.54)***	***1.82 (0.089)***	2.34 (0.504)	0
	Intron 2	***rs6090384***	***'T' allele***	***4 (2/2)***	***Random***	***1.28 (0.89–1.84)***	***1.76 (0.093)***	3.91 (0.271)	23
SNAP25	Intron 4	rs362987	'A' allele	5 (4/1)	Random	1.00 (0.84–1.18)	0.00 (0.488)	***7.80 (0.099)***	***49***
	Intron 6	rs363006	'G' allele	7 (5/2)	Random	0.99 (0.86–1.15)	0.01 (0.547)	6.94 (0.326)	14
	3′ **UTR**	**rs3746544**	**Unknown**	**7 (4/3)**	**Fixed**	**1.15 (1.01–1.31)**	**4.71 (0.030)***	2.69 (0.847)	0
	3′ UTR	rs1051312	'T' allele	6 (4/2)	Random	1.06 (0.86–1.31)	0.30 (0.298)	***9.70 (0.084)***	***48***
BDNF	Promoter	rs6265	'G' allele	8 (4/4)	Fixed	1.01 (0.91–1.12)	0.02 (0.406)	6.31 (0.504)	0

Bold text indicates significant result at $P < 0.05$. Italics indicate a trend towards significance at $P < 0.10$. All reported *P* values are one-tailed unless followed by an * indicating that it is two-tailed. I^2 describes the proportion of total variation in study effect sizes due to heterogeneity

allele counts of the 'high-risk' and 'low-risk' alleles in both the ADHD cases and non-disordered controls.

After all relevant studies were identified, a series of inclusion and exclusion criteria were applied to determine which studies would be included in the meta-analysis for a given polymorphism. First, each study had to be published prior to December 2008 unless an online version of the study had been released prior to this date. Second, each study was reviewed to ensure that the necessary aforementioned data for meta-analysis were presented in the publication. Third, each study was required to report data from an independent sample. When multiple publications from a particular research group reported data for overlapping samples, results for the study that presented the largest dataset were included. This typically occurred when a more recent study was published using an expanded dataset from

an earlier publication. Fourth, only studies that used child samples were included. Differences may exist between the etiology, operationalization, and assessment of childhood and adult ADHD, thus studies using adult samples were excluded from the present review. Fifth, only studies were included in which ADHD diagnoses were made by best-estimate diagnosis or symptom checklists that correspond to DSM-IV symptoms. As a result, studies that approximated diagnoses using measures such as the Child Behavior Checklist (CBCL) (Achenbach and Edelbrock 1979) that do not provide comprehensive assessments of DSM ADHD symptomatology were excluded. Sixth, studies that selected samples based on a disorder other than ADHD (e.g., Tourette's syndrome, reading disability, or substance abuse) were excluded. Following the application of these inclusion/exclusion criteria, meta-analyses were performed for all polymorphisms for which usable data were reported in at least four published studies.

Meta-analytic methods

Meta-analyses of TDT and Case-Control/HHRR studies were performed using the catmap package (version 1.6) (Nicodemus 2008) in R (version 2.7.0; http://www.r-project.org). The catmap package was specifically designed to conduct meta-analyses of combined data from both TDT and Case-Control/HHRR studies (Kazeem and Farrall 2005). For TDT studies, odds ratios were estimated from the number of transmissions versus non-transmissions of the designated 'high-risk' allele to ADHD cases from heterozygous parents. For case-control studies, odds ratios were estimated by contrasting the ratio of counts of the 'high-risk' versus 'low-risk' alleles in ADHD cases versus non-disordered controls. Odds ratios for HHRR studies were estimated using a similar approach, in which the number of transmissions of the 'high-risk' and 'low-risk' alleles from both homozygous and heterozygous parents to ADHD cases was contrasted with the number of non-transmissions of the 'high-risk' and 'low-risk' alleles.

The catmap package analyzes these data to generate both fixed- and random-effect estimates of pooled odds ratios and their significance tests, tests of heterogeneity thereof, cumulative meta-analytic and sensitivity analysis results, and forest and funnel plots. Heterogeneity in effect sizes across studies was tested using the Q-statistic and its magnitude was quantified using I^2, which is an index that describes the proportion of total variation in study effect size estimates that is due to heterogeneity and that is independent of the number of studies included in the meta-analysis and the metric of effect sizes (Higgins and Thompson 2002). Note that random effects meta-analyses were not performed in the absence of heterogeneity among study effect sizes, as in such cases, the random effect estimates are identical to the fixed effect estimates.

For those polymorphisms in which the previous literature provided an indication of the risk-inducing allele, one-tailed *P* values were reported. In the absence of such prior data, two-tailed *P* values were reported and were indicated as such in the text. It should also be noted that some studies reported data for both TDT and case-control analyses. A recent review of candidate gene studies using both designs suggested that, in aggregate, estimates of association were equivalent across methods with observed differences most likely due to uncertainty in the estimates resulting from small sample sizes (Evangelou et al. 2006). Given this result and the larger sample sizes provided by case-control studies, when a study reported results from both case-control and TDT analyses, data from the case-control analysis were included in the meta-analysis.

Results

Dopaminergic pathway

Dopamine transporter gene (DAT1)

The dopamine transporter gene (*DAT1, SLC6A3*) has been mapped to chromosome 5p15 (Vandenbergh et al. 1992). It codes for a solute carrier protein responsible for the reuptake of dopamine from the synaptic cleft back to the presynaptic neuron. This protein is densely distributed in the striatum and nucleus accumbens and represents the primary mechanism of dopamine regulation in these brain regions (Ciliax et al. 1999). Several lines of research justify *DAT1* as a candidate gene for ADHD. For example, stimulant medications such as methylphenidate, which are the most widely prescribed and among the most effective treatments available for ADHD symptoms, have been shown to inhibit the function of the dopamine transporter and thereby increase the levels of available dopamine in the synapse (Ritz et al. 1987; Volkow et al. 1995). Further, mice that were bred lacking both copies of the *DAT1* gene (i.e., *DAT1* "knockout" mice) exhibited behaviors analogous to ADHD such as greater motor activity, compared to "wild-type" controls and mice bred with a single intact copy of the gene (Giros et al. 1996).

The most widely studied *DAT1* polymorphism is a variable number of tandem repeats (VNTR) sequence in the 3′ untranslated region (UTR) that is 40 base pairs (bp) in length (Vandenbergh et al. 1992). The most common alleles are the 10 (480-bp) (71.9%) and 9 (440-bp) (23.4%) repeats (Doucette-Stamm et al. 1995). There is some evidence suggesting that this polymorphism is functional, with

studies using single photon emission computed tomography (SPECT) showing that dopamine transporter availability (Heinz et al. 2000) and binding potential (Jacobsen et al. 2000) are influenced by genotype at this VNTR, and additional studies suggesting that *DAT1* messenger RNA (mRNA) levels in post-mortem brain tissue are also influenced by genotype at this VNTR (Brookes et al. 2007; Mill et al. 2002).

The first study to test for association between the VNTR in the *DAT1* 3′UTR and ADHD was conducted by Cook et al. (1995) using a sample of 57 children diagnosed with ADHD. They reported a significant association between *DAT1* and ADHD using an HHRR analysis, and found that the 10-repeat allele was preferentially transmitted to ADHD probands. Since this initial report, more than 100 studies have been published examining the relations between *DAT1* polymorphisms and ADHD and ADHD-related phenotypes. In the present review, we meta-analyzed the association between childhood ADHD and 5 markers in *DAT1*, including the VNTR in the 3′UTR, a VNTR in intron 8, and 3 SNPs.

For the 3′UTR VNTR, independent data were available from 15 TDT (Asherson et al. 2007; Brookes et al. 2006b; Curran et al. 2001b; Feng et al. 2005b; Galili-Weisstub and Segman 2003; Hebebrand et al. 2006; Kim et al. 2005b; Kustanovich et al. 2004; Lim et al. 2006; Maher et al. 2002; Mick et al. unpublished data; Todd et al. 2001a; Waldman et al. 1998) and 19 Case-Control/HHRR studies (Bakker et al. 2005; Banoei et al. 2008; Bobb et al. 2005; Carrasco et al. 2004; Cheuk et al. 2006b; Cook et al. 1995; Cornish et al. 2005; Das and Mukhopadhyay 2007; Genro et al. 2007; Hawi et al. 2003; Jiang et al. 1999; Kim et al. 2006b; Kopeckova et al. 2008; Langley et al. 2005; Qian et al. 2004; Simsek et al. 2005; Smith et al. 2003; Swanson et al. 2000b; Wang et al. 2008), with the 480-bp (or 10-repeat) allele designated as the "risk" allele. Results of this meta-analysis, shown in Fig. 1, indicated a significant but modest association between ADHD and the 480-bp allele (fixed effects: OR = 1.10, 95% CI = 1.03–1.17, $\chi^2 = 8.70$, $P = 0.002$; random effects: OR = 1.12, 95% CI = 1.00–1.27, $\chi^2 = 3.66$, $P = 0.028$) with substantial heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 92.97$, $P < 0.000001$; $I^2 = 65$). Sensitivity analyses for this polymorphism, as well as similar analyses conducted for each of the polymorphisms described below, indicated that the pooled estimates of effect size and their significance did not depend on any particular study, as these remained very similar with the exclusion of each study in turn, including the first study and the studies with the highest and lowest odds ratios.

More recently, studies have begun to genotype additional markers in and around *DAT1* to conduct more comprehensive tests of association. For example, a VNTR in intron 8 of *DAT1* has been genotyped in several recent

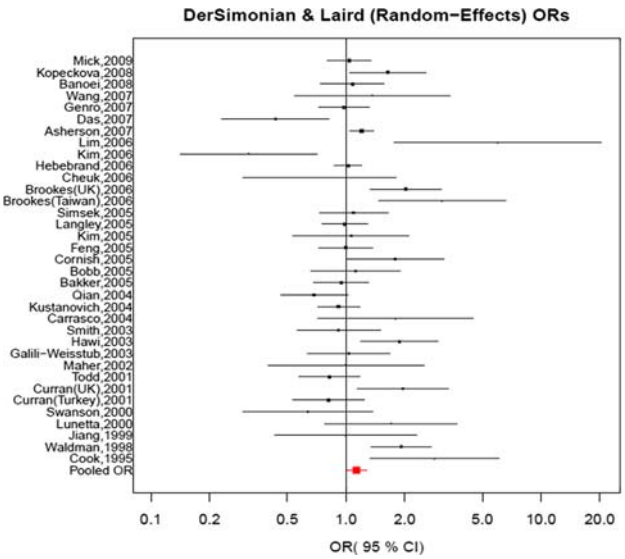

Fig. 1 Odds ratios (ORs) from random effects meta-analysis of ADHD and the *DAT1* 3′UTR VNTR

studies. This VNTR is a 30-bp repeat sequence with two common alleles of 5- and 6-repeats, and there is some evidence that it is functional with an increasing number of repeats associated, with increased *DAT1* mRNA levels (Brookes et al. 2007) and reduced expression in response to cocaine exposure (Guindalini et al. 2006). Four TDT studies (Asherson et al. 2007; Brookes et al. 2006b; Mick et al. unpublished data) and one Case-Control/HHRR study (Genro et al. 2008) were identified that tested for association between this polymorphism and childhood ADHD that were appropriate for meta-analysis. Based on the initial association report (Brookes et al. 2006b), the 6-repeat allele was designated as the "risk" allele. Results of the meta-analysis, shown in Fig. 2a, indicated a significant but modest association between ADHD and the 6-repeat allele of this polymorphism (fixed effects: OR = 1.19, 95% CI = 1.05–1.34, $\chi^2 = 8.10$, $P = 0.002$; random effects: OR = 1.25, 95% CI = 0.98–1.58, $\chi^2 = 3.35$, $P = 0.034$). Substantial heterogeneity in effect sizes was again observed across studies (Q-statistic $\chi^2 = 11.22$, $P = 0.012$; $I^2 = 64$) suggesting that future studies are needed to identify the sources of this variation.

In addition to these VNTRs, three SNPs in *DAT1* were identified that had been tested for association with childhood ADHD in sufficient numbers to allow for meta-analysis. Data for the first SNP, rs6347 located in exon 8, were available from three TDT (Brookes et al. 2006a; Feng et al. 2005b; Friedel et al. 2007) and three Case-Control/HHRR (Bobb et al. 2005; Genro et al. 2008; Guan et al. 2008) studies. Because rs6347 has not shown evidence of an association with ADHD in the extant literature, a 'risk' allele

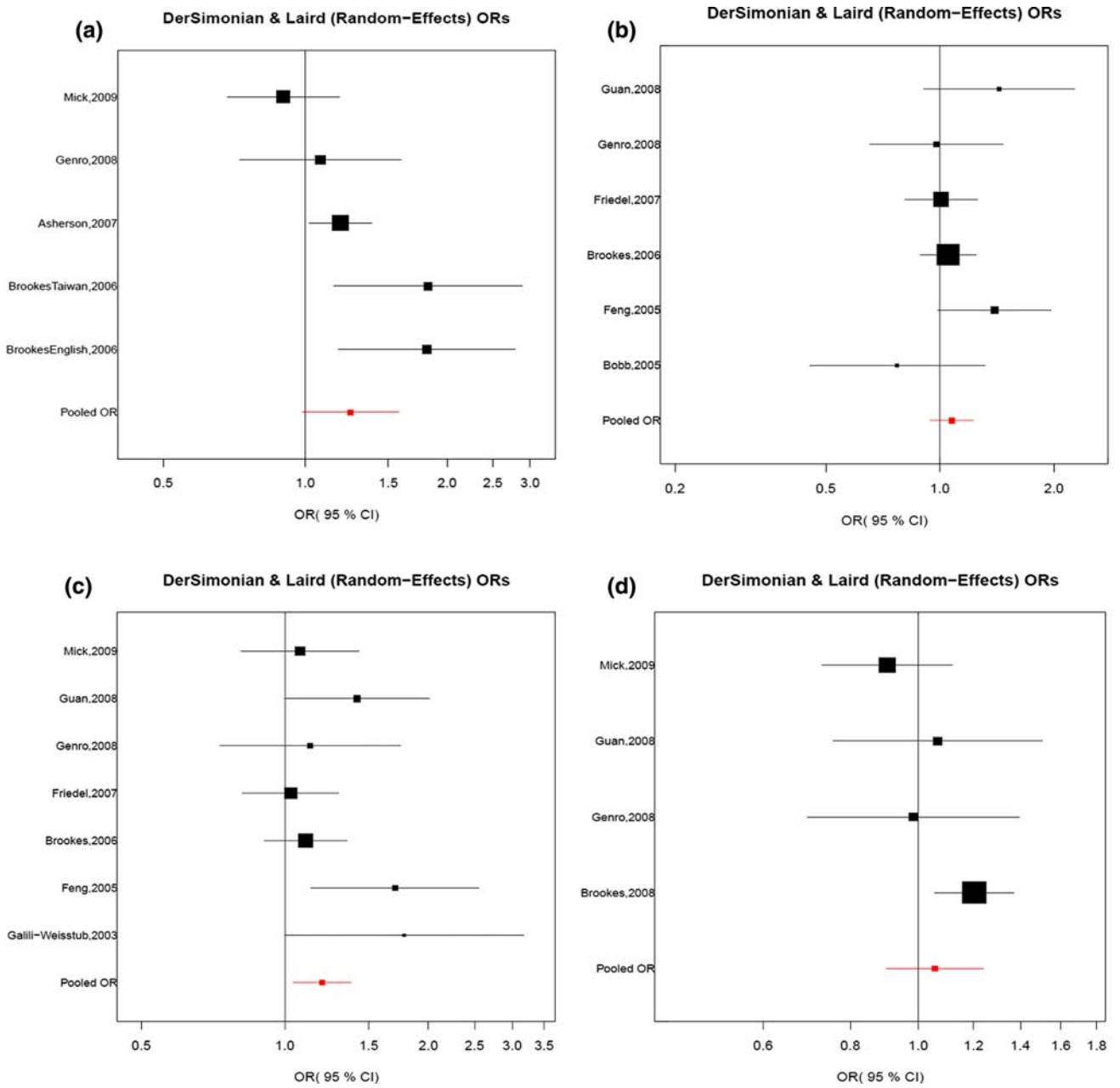

Fig. 2 Odds ratios (ORs) from random effects meta-analysis of ADHD and additional *DAT1* polymorphisms. **a** The single study and pooled ORs for the association between ADHD and the intron 8 VNTR. **b** The single study and pooled ORs for the association between ADHD and rs6347. **c** The single study and pooled ORs for the association between ADHD and rs27072. **d** The single study and pooled ORs for the association between ADHD and rs40184

was not designated. Results of the meta-analysis did not support an association between ADHD and rs6347 as shown in Fig. 2b (fixed effects: OR = 1.07, 95% CI = 0.96–1.20, $\chi^2 = 1.39$, two-tailed $P = 0.238$; random effects: OR = 1.08, 95% CI = 0.94–1.22, $\chi^2 = 1.21$, two-tailed $P = 0.272$), with minimal heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 5.81$, $P = 0.325$; $I^2 = 14$). Thus, there was no evidence to suggest an association between this SNP and ADHD.

The two remaining SNPs that were meta-analyzed (rs27072 and rs40184) were located in the 3′ UTR of *DAT1*. For rs27072, data were available from five TDT (Brookes et al. 2006a; Feng et al. 2005b; Friedel et al. 2007; Galili-Weisstub and Segman 2003; Mick et al. unpublished data) and two Case-Control/HHRR (Genro et al. 2008; Guan et al. 2008) studies. Based on the initial association study (Galili-Weisstub and Segman 2003), the "G" allele of this polymorphism was designated as the

"risk" allele. The results of this meta-analysis, shown in Fig. 2c, indicated a significant and modest association between ADHD and the "G" allele (fixed effects: OR = 1.17, 95% CI = 1.05–1.31, $\chi^2 = 7.49$, $P = 0.003$; random effects: OR = 1.20, 95% CI = 1.04–1.38, $\chi^2 = 6.32$, $P = 0.006$) with modest but non-significant heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 8.29$, $P = 0.217$; $I^2 = 28$).

Data were available from two TDT (Brookes et al. 2008; Mick et al. unpublished data) and two Case-Control/HHRR (Genro et al. 2008; Guan et al. 2008) studies that tested for association between rs40184 and ADHD. The 'G' allele was designated as the 'risk' allele for this analysis based on the initial association report (Brookes et al. 2006a). The fixed effects meta-analysis of these studies (Fig. 2d) indicated a trend towards a modest association between this allele and ADHD (OR = 1.10, 95% CI = 0.99–1.21, $\chi^2 = 3.25$, $P = 0.036$), but random effects meta-analysis yielded a nonsignificant result (OR = 1.06, 95% CI = 0.90–1.24, $\chi^2 = 0.46$, $P = 0.249$). Notably, moderate but non-significant heterogeneity in effect sizes across studies was observed (Q-statistic $\chi^2 = 5.47$, $P = 0.141$; $I^2 = 45$). An important caveat to these findings is that the results are based on only 4 studies, thus further studies are needed to better establish the nature and magnitude of association of this SNP with ADHD.

As noted above, several of the meta-analyzed polymorphisms in *DAT1* exhibited significant or suggestive evidence of heterogeneity in effect sizes across studies, and there are several potential sources, which might contribute to this heterogeneity. First, differences in study sample characteristics could contribute. For example, previous studies have suggested that *DAT1* is more strongly associated with the hyperactive–impulsive symptoms of ADHD and similarly the Combined ADHD subtype than with the inattentive symptoms or Inattentive ADHD subtype (Mill et al. 2005; Waldman et al. 1998). Second, there may be important environmental variables that moderate the association between *DAT1* polymorphisms and ADHD. Several studies have now tested for gene-environment interactions using variables such as maternal smoking and/or alcohol use during pregnancy (Becker et al. 2008; Brookes et al. 2006b; Kahn et al. 2003; Langley et al. 2008; Neuman et al. 2007) and psychosocial adversity (Laucht et al. 2007) to examine the association between *DAT1* and ADHD, though the results have been mixed.

A third potential source of heterogeneity could be the presence of allelic heterogeneity if multiple polymorphisms within *DAT1* were providing unique contributions to the genetic risk underlying ADHD, either directly or indirectly through linked, causal polymorphisms. For example, the *DAT1* polymorphisms that were meta-analyzed in the present review are located in the middle to 3′ end of the gene, but it is notable that several studies have also reported significant associations with polymorphisms at the 5′ end of the gene. For example, two SNPs (rs2550946 and rs11564750) located in the promoter region of *DAT1* have shown evidence of association with ADHD in the International Multi-site ADHD Genetics (IMAGE) (Faraone and Asherson 2005) sample (Brookes et al. 2006a; Brookes et al. 2008), and although they tested for association using different sets of SNPs, two additional studies have reported significant associations with SNPs in the 5′ region (Friedel et al. 2007; Genro et al. 2007). Given that there is little evidence of linkage disequilibrium between polymorphisms at the 5′ and 3′ ends of *DAT1* (Greenwood et al. 2002), these results, in addition to those of the present review, suggest that there may be multiple functional variants within *DAT1* that confer risk for ADHD. If so, it may be that different polymorphisms within *DAT1* are contributing to the genetic risk across studies, which could explain a portion of the heterogeneity in effect sizes observed across studies (Brookes et al. 2008). Relatively few studies investigating potential sources of heterogeneity such as those described have been conducted to date, thus it should be stressed that identifying potential moderating variables that can explain the heterogeneity in the association between *DAT1* polymorphisms and ADHD represents an important priority for future research.

Dopamine D4 receptor gene (DRD4)

The dopamine D4 receptor is a G protein-coupled receptor belonging to the dopamine D2-like receptor family, which act to inhibit adenylyl cyclase (Oldenhof et al. 1998). The dopamine D4 receptor gene (*DRD4*) has been mapped to chromosome 11p15.5 (Gelernter et al. 1992; Petronis et al. 1993). Given that abnormalities in the dopamine neurotransmitter system have been hypothesized to underlie ADHD (Levy 1991), the genes that code for the dopamine receptors have been identified as candidate loci for ADHD. More specifically, *DRD4* is predominantly expressed in frontal lobe regions, such as the orbitofrontal cortex and anterior cingulate, and these brain regions are thought to be involved in the etiology of the disorder (Floresco and Tse 2007; Noain et al. 2006). Additional interest in *DRD4* as a candidate gene for ADHD was sparked by association studies that linked the gene to the personality trait of novelty seeking (Benjamin et al. 1996; Ebstein et al. 1996), which has been compared to the high levels of impulsivity and excitability often seen in ADHD (Faraone et al. 1999). Further, the *DRD4* "knockout" mouse has been shown to exhibit a heightened response to cocaine and methamphetamine relative to controls, as indicated by increases in locomotor behavior (Rubinstein et al. 1997).

The most widely studied *DRD4* polymorphism in association studies of ADHD has been the 48-bp VNTR in exon 3.

The most common alleles of this polymorphism are the 2-, 4-, and 7-repeat alleles, though allele frequencies have been shown to vary significantly across ethnic groups (Chang et al. 1996; Van Tol et al. 1992). There is some evidence that this VNTR is functional with studies suggesting that the 7-repeat allele differs, albeit slightly, from the 2- and 4-repeat alleles in secondary messenger (i.e., cAMP) activity and possibly also in response to the antipsychotic medication clozapine (Asghari et al. 1995; Asghari et al. 1994). The initial study to test for an association between the *DRD4* exon 3 VNTR and ADHD was a case-control study that included 39 cases and 39 ethnically matched controls (LaHoste et al. 1996). The authors reported increased prevalence of the 7-repeat allele and the 7/7 genotype in cases (i.e., 29 and 49%, respectively) compared to controls (i.e., 12 and 21%, respectively). A number of replication studies have investigated this association, but the results across studies have been mixed. Thus, it is noteworthy that several meta-analyses have demonstrated a significant *DRD4*–ADHD association (Faraone et al. 2001, 2005; Li et al. 2006a).

Since the publication of the last meta-analysis (Li et al. 2006a), several additional studies have been published examining the association between the exon 3 VNTR and ADHD. The present meta-analysis included independent data available from 10 TDT (Arcos-Burgos et al. 2004a; Brookes et al. 2006a; Kustanovich et al. 2004; Lunetta et al. 2000; Maher et al. 2002; Mick et al. unpublished data; Sunohara et al. 2000; Tahir et al. 2000b; Todd et al. 2001b) and 16 Case-Control/HHRR (Bakker et al. 2005; Bhaduri et al. 2006; Carrasco et al. 2006; Curran et al. 2001a; El-Faddagh et al. 2004; Frank et al. 2004; Gornick et al. 2007; Hawi et al. 2000a; Holmes et al. 2000; Kotler et al. 2000; LaHoste et al. 1996; Mill et al. 2001; Roman et al. 2001; Rowe et al. 1998; Smith et al. 2003; Swanson et al. 1998) studies, with the 7-repeat considered the "high-risk" allele. Two studies in Asian populations could not be included in the meta-analysis, given insufficient frequencies of the 7-repeat allele (Cheuk et al. 2006a; Kim et al. 2005b). Results of this meta-analysis, shown in Fig. 3, indicated a significant, moderate association between ADHD and the 7-repeat allele (fixed effects: OR = 1.27, 95% CI = 1.16–1.39, $\chi^2 = 28.01$, $P < 0.00001$; random effects: OR = 1.33, 95% CI = 1.15–1.54, $\chi^2 = 14.51$, $P = 0.00007$), thus replicating the findings of previous meta-analytic reviews (Faraone et al. 2001, 2005; Li et al. 2006a). Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study, as these remained very similar with the exclusion of each study in turn, including the first study and the studies with the highest and lowest odds ratios. It is noteworthy, however, that substantial heterogeneity in effect sizes across studies was observed (Q-statistic $\chi^2 = 54.32$, $P = 0.0006$; $I^2 = 54$).

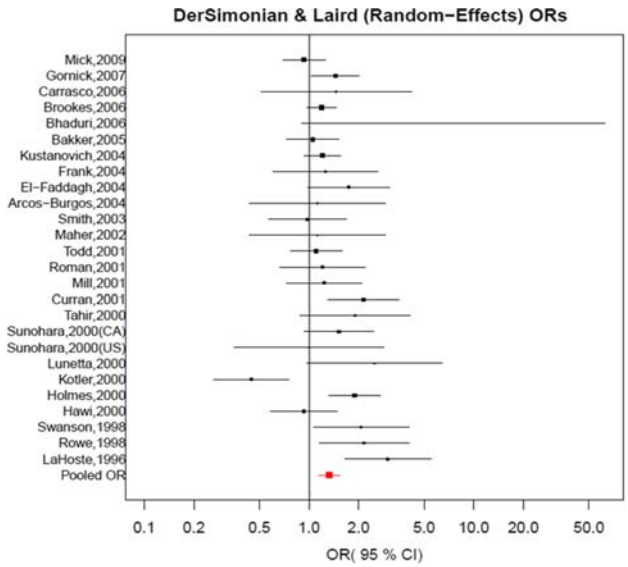

Fig. 3 Odds ratios (ORs) from random effects meta-analysis of ADHD and the *DRD4* exon 3 VNTR

After the exon 3 VNTR, the two most widely studied *DRD4* polymorphisms in association studies of ADHD are found in the promoter region of the gene. The first is an 120-bp duplication located 1.2 kilobases upstream of the transcription start site consisting of 2 common alleles of 120- and 240-bps (Seaman et al. 1999). There is some data suggesting that this polymorphism influences transcription with the 120-bp allele exhibiting higher transcriptional activity in transfected cell lines relative to the 240-bp allele (D'Souza et al. 2004; Kereszturi et al. 2007). The first study to investigate this polymorphism in relation to ADHD reported an over-representation of the 240-bp allele among children diagnosed with ADHD relative to controls (McCracken et al. 2000), and this finding was later replicated in an expanded sample (Kustanovich et al. 2004). Nonetheless, there have also been several failures to replicate (Barr et al. 2001; Todd et al. 2001b) as well as reported associations with the 120-bp rather than the 240-bp allele (Kereszturi et al. 2007).

The meta-analysis of association between childhood ADHD and the *DRD4* Promoter Insertion/Deletion included data from six TDT (Arcos-Burgos et al. 2004a; Barr et al. 2001; Brookes et al. 2005; Kustanovich et al. 2004; Lowe et al. 2004b; Todd et al. 2001b) and two Case-Control/HHRR (Bhaduri et al. 2006; Kereszturi et al. 2007) studies. Given the conflicting reports regarding which allele is associated with increased risk for ADHD, a 'risk' allele was not designated for meta-analysis. The results, shown in Fig. 4a, suggested no association between ADHD and either allele (fixed effects: OR = 1.00, 95% CI = 0.87–1.14, $\chi^2 = 0.00$, two-tailed $P = 0.998$; random effects: OR = 1.05, 95% CI = 0.86–1.31, $\chi^2 = 0.29$, two-tailed $P = 0.590$), but

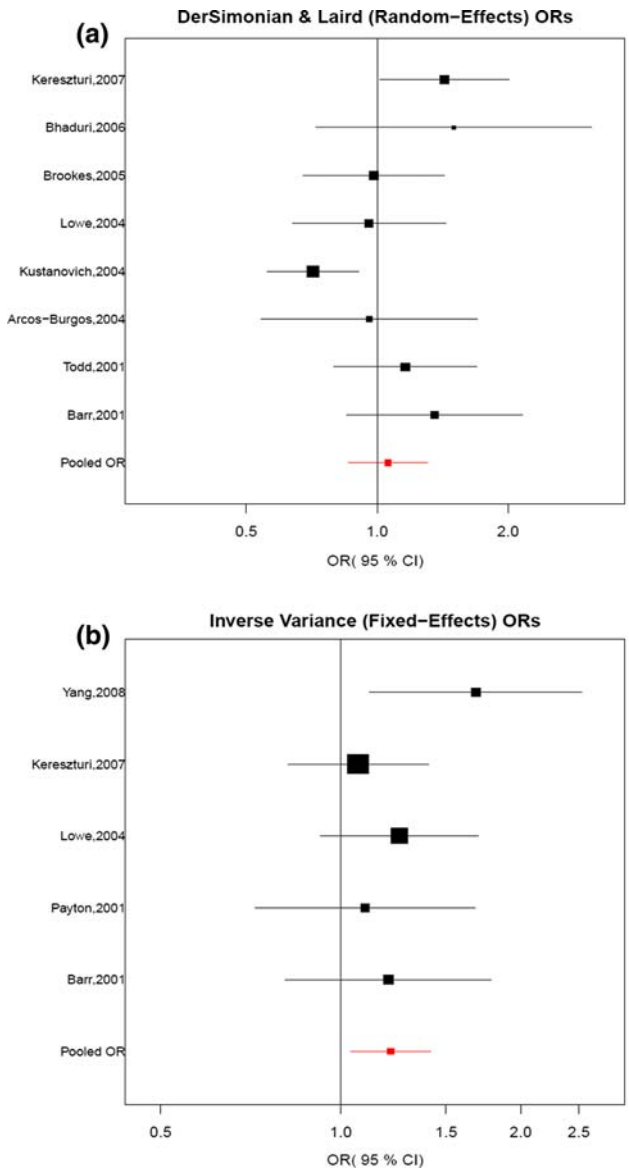

Fig. 4 Odds ratios (ORs) from meta-analysis of ADHD and additional *DRD4* polymorphisms. **a** The single study and pooled ORs for the random effects meta-analysis of the association between ADHD and the *DRD4* Promoter Insertion/Deletion. **b** The single study and pooled ORs for the fixed effects meta-analysis of the association between ADHD and rs1800955

substantial heterogeneity was observed in effect sizes across studies (Q-statistic $\chi^2 = 15.16$, $P = 0.033$; $I^2 = 54$). Based on these results, a clear priority for future research is investigating the sources of the heterogeneity in effect sizes across studies.

The second frequently studied polymorphism studied in the *DRD4* promoter region is a SNP located 521 bp upstream of the transcription start site (−521 C/T; rs1800955). This SNP is thought to influence promoter activity with the "T" allele exhibiting a 40% reduction in promoter activity relative to the "C" allele in transfected cells (Okuyama et al. 1999). Three TDT (Barr et al. 2001; Lowe et al. 2004b; Payton et al. 2001) and two Case-Control/HHRR (Kereszturi et al. 2007; Yang et al. 2008) studies were identified for the meta-analysis of association between childhood ADHD and the *DRD4* −521 C/T SNP (rs1800955). Based on previous studies (Barr et al. 2001; Lowe et al. 2004b), the "T" allele was considered the "risk" allele. Results of this meta-analysis, shown in Fig. 4b, indicated a significant, modest association between ADHD and the T allele (fixed effects: OR = 1.21, 95% CI = 1.04–1.41, $\chi^2 = 6.01$, $P = 0.007$) with no evidence for heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 3.54$, $P = 0.472$; $I^2 = 0$). Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study.

As noted, both the exon 3 VNTR and the insertion/deletion in the promoter region showed significant evidence of heterogeneity in the effect sizes across studies. Studies that have further explored the association between *DRD4* and ADHD have often relied on two approaches with the potential to explain a portion of this heterogeneity. The first approach has been to test for differences in association between the Inattentive and Combined ADHD subtypes or the inattentive or hyperactive–impulsive symptom dimensions that underlie ADHD. Though the findings from these studies have been mixed, several studies have suggested that *DRD4* is more strongly related to the inattentive than the hyperactive–impulsive symptoms of ADHD (Lasky-Su et al. 2007a; Lasky-Su et al. 2008; McCracken et al. 2000; Rowe et al. 1998) and is related to attention problems in the general population (Laucht et al. 2006; Schmidt et al. 2001). The second approach has been to use neuropsychological measures as alternative phenotypes for ADHD with the assumption that such measures more directly assess the underlying genetic liability to disorder than symptom ratings (see Kebir et al. 2009 for a detailed review). Results from these studies have been conflicting, with several studies reporting associations between the 7-repeat allele and *poor* performance on neuropsychological measures (Kieling et al. 2006; Langley et al. 2004; Waldman 2005), and other studies reporting associations between the 7-repeat allele and *improved* performance on these measures (Bellgrove et al. 2005; Manor et al. 2002a; Swanson et al. 2000a). Given such findings, it is difficult to draw further conclusions regarding the association between ADHD and *DRD4* from these studies. Thus, a priority for future studies should be to explore potential sources of heterogeneity in this association to further our understanding of how *DRD4* confers risk towards the development of ADHD.

Dopamine D2 receptor gene (DRD2)

The dopamine D2 receptor is a G protein-coupled receptor, which acts to inhibit adenyl cyclase (Andersen et al. 1990).

The dopamine D2 receptor gene (*DRD2*) has been mapped to chromosome 11q23.1 (Eubanks et al. 1992). It is expressed in several brain regions thought to be relevant to ADHD such as the basal ganglia and prefrontal cortex, and plays a key role in regulating the mesolimbic "reward" pathways (Usiello et al. 2000). Initial studies of *DRD2* focused on the relation of a TaqIA restriction site (rs1800497) to alcohol dependence phenotypes (Blum et al. 1990; Noble et al. 1991). Notably, more recent studies have shown this polymorphism lies more than 10 kb downstream from *DRD2* in an exon of a neighboring gene, *ANKK1* (Neville et al. 2004). Nonetheless, the TaqIA polymorphism remains an interesting polymorphism for studying *DRD2* associations given that it has been related to *DRD2* expression levels (Laakso et al. 2005; Thompson et al. 1997) and urinary levels of the dopamine metabolite homovanillic acid (Ponce et al. 2004).

The initial published studies reported significant evidence for association between ADHD and the A1 allele in a sample selected for Tourette's syndrome (Comings et al. 1991, 1996). More recent studies have been conducted in samples selected specifically for ADHD (Kirley et al. 2002; Rowe et al. 1999), and thus, were considered for inclusion in the present review. The meta-analysis of the association between childhood ADHD and the *Taq*I *DRD2* polymorphism included three TDT (Kirley et al. 2002; Kustanovich et al. 2004; Rowe et al. 1999) and three Case-Control/HHRR (Huang et al. 2003; Kopeckova et al. 2008; Sery et al. 2006) studies. Given the conflicting findings regarding which allele is associated with ADHD (Huang et al. 2003; Kirley et al. 2002; Rowe et al. 1999), a 'risk' allele was not designated. The results of the meta-analysis (shown in Fig. 5) were statistically mixed, with the fixed effects analysis indicating a significant association between ADHD and the 'A1' allele (OR = 1.54, 95% CI = 1.29–1.83, $\chi^2 = 23.36$, two-tailed $P < 0.001$) and the random effects analysis indicating a weak trend towards such an association (OR = 1.65, 95% CI = 0.89–3.06, $\chi^2 = 2.56$, two-tailed $P = 0.110$). These mixed results may have been due to the significant and substantial heterogeneity in the effect sizes across studies (Q-statistic $\chi^2 = 55.01$, $P < 0.001$; $I^2 = 91$). Further, sensitivity analyses indicated that the Kopeckova et al. (2008) study was an outlier in providing by far the largest contribution to the overall effect size and observed heterogeneity as removing this study reduced the Q-statistic to non-significance (Q-statistic $\chi^2 = 7.31$, $P = 0.120$; $I^2 = 45$), and appreciably weakened the evidence for association (fixed effects: OR = 1.21, 95% CI = 1.00–1.46, $\chi^2 = 4.05$, $P = 0.044$; random effects: OR = 1.23, 95% CI = 0.93–1.62, $\chi^2 = 2.16$, $P = 0.142$). Nonetheless, due to the magnitude of the observed heterogeneity, it is difficult to draw definitive conclusions regarding the association between childhood ADHD and *DRD2*, and further studies are needed to explore this relation.

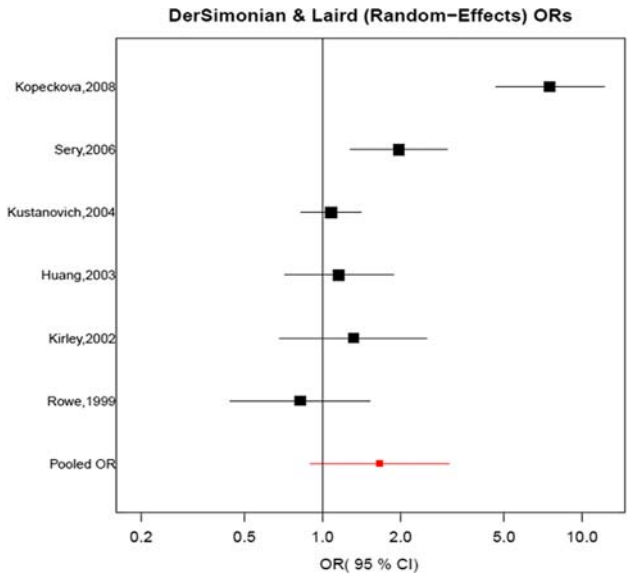

Fig. 5 Odds ratios (ORs) from random effects meta-analysis of ADHD and the *Taq*I (rs1800497) *DRD2* SNP

Dopamine D5 receptor gene (DRD5)

The dopamine D5 receptor is a G protein-coupled receptor that belongs to the D1 class of dopamine receptors and serves to stimulate adenyl cyclase activity (Sunahara et al. 1991). The dopamine D5 receptor gene (*DRD5*) has been mapped to chromosome 4p15.3 (Sherrington et al. 1993). *DRD5* is highly expressed in the hippocampus and related structures (Beischlag et al. 1995), and is thought to be involved in the induction of long-term potentiation related to novel events (Li et al. 2003). A highly polymorphic dinucleotide repeat 18.5 kb 5′ of the gene has been described consisting of 12 alleles ranging from 134 to 156 bps in length with the 148-bp allele being the most common (Sherrington et al. 1993).

This dinucleotide repeat has been widely studied in relation to psychiatric disorders including ADHD (Hoenicka et al. 2007). The first study to test for an association with this polymorphism reported preferential transmission of the 148-bp allele to probands using HHRR and TDT analyses in a sample of 118 children diagnosed with ADHD (Daly et al. 1999). A subsequent meta-analysis that included this study as well as 3 subsequently published studies and 10 additional unpublished studies also reported a significant association between the 148-bp allele and ADHD with an odds ratio of 1.24 (Lowe et al. 2004a). This result was replicated in a more recent meta-analysis of published studies that reported a combined odds ratio of 1.34 (Li et al. 2006a). Notably, while the initial meta-analysis did not

detect significant heterogeneity among samples, the subsequent meta-analysis did report heterogeneity.

The present meta-analysis of association between childhood ADHD and the dinucleotide repeat flanking *DRD5* included all of the available data from six TDT (Barr et al. 2000a; Hawi et al. 2005; Kustanovich et al. 2004; Manor et al. 2004; Payton et al. 2001; Tahir et al. 2000b) and 3 Case-Control/HHRR (Bakker et al. 2005; Bobb et al. 2005; Mill et al. 2004a) studies, with the 148-bp allele considered the 'high-risk' allele. Results of this meta-analysis, shown in Fig. 6, indicated a significant, moderate association between ADHD and the 148-bp allele (fixed effects: OR = 1.22, 95% CI = 1.10–1.36, $\chi^2 = 13.91$, $P = 0.000095$; random effects: OR = 1.23, 95% CI = 1.06–1.43, $\chi^2 = 7.73$, $P = 0.0027$) with moderate and marginally significant heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 14.80$, $P = 0.063$; $I^2 = 46$). These results are consistent with those of the previous meta-analysis (Li et al. 2006a) in suggesting the presence of heterogeneity in effect sizes. Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study.

As noted, the studied dinucleotide repeat lies more than 18 kb upstream of the transcription start site for *DRD5*, and thus, it has been assumed that this repeat is unlikely to influence *DRD5* expression or function. Nonetheless, only a few studies have tested for associations between *DRD5* and ADHD beyond this repeat (Hawi et al. 2003; Lasky-Su et al. 2007b), perhaps due to the difficulty of genotyping polymorphisms that lie within the gene itself, rather than in adjoining pseudogenes (Housley et al. 2009). The results of

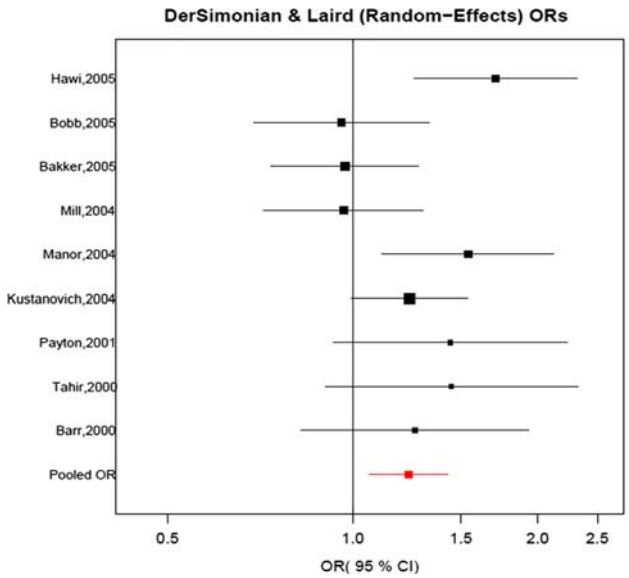

Fig. 6 Odds ratios (ORs) from random effects meta-analysis of ADHD and the microsatellite flanking *DRD5*

the present and previous meta-analyses strongly support association between *DRD5* and ADHD, thus additional studies are needed to further explore this relation and attempt to identify the functional polymorphism(s) within the gene that underlie this association. In addition, future studies of this microsatellite should be conducted to investigate the sources of the heterogeneity in effect sizes across studies.

Dopamine D3 receptor gene (DRD3)

The dopamine D3 receptor is a G protein-coupled receptor belonging to the D2 family of dopamine receptors, which act to inhibit adenylyl cyclase (Vallone et al. 2000). The dopamine D3 receptor gene (*DRD3*) has been mapped to chromosome 3q13.3 (Le Coniat et al. 1991). It is primarily expressed in the nucleus accumbens and substantia nigra, and has been shown to play an important role in incentive-based learning (Beninger and Banasikowski 2008). The initial study testing for association and linkage between *DRD3* and ADHD focused on a functional polymorphism in exon 1 that results in an amino acid change (Ser9Gly; rs6280) and a polymorphism in intron 5 (Barr et al. 2000b). The authors conducted a TDT analysis of 100 ADHD parent–child trios and reported no evidence of an association between ADHD and either *DRD3* polymorphism. Despite this initial negative result, a sufficient number of studies have since tested for association between the exon 1 SNP and ADHD to allow for meta-analysis.

The present meta-analysis of association between childhood ADHD and rs6280 of *DRD3* included data from four TDT (Barr et al. 2000b; Brookes et al. 2006a; Kirley et al. 2002; Payton et al. 2001) and two Case-Control/HHRR (Guan et al. 2008; Kopeckova et al. 2008) studies. Given that there are no reported significant associations between this polymorphism and ADHD in the literature, a 'risk' allele was not designated. Results of this meta-analysis, shown in Fig. 7, were non-significant (fixed effects: OR = 1.07, 95% CI = 0.95–1.21, $\chi^2 = 1.23$, two-tailed $P = 0.268$) with no evidence of heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 1.12$, $P = 0.952$; $I^2 = 0$). Due to the absence of heterogeneity, a random effects meta-analysis was not performed. Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study, as these remained very similar with the exclusion of each study in turn, including the first study and the studies with the highest and lowest odds ratios. In support of these negative findings, two studies that tested for association between ADHD and *DRD3* using additional SNPs spanning the length of the gene also failed to detect an ADHD–*DRD3* association (Brookes et al. 2006a; Guan et al. 2008). Thus, the present review does not support a relation between *DRD3* and ADHD.

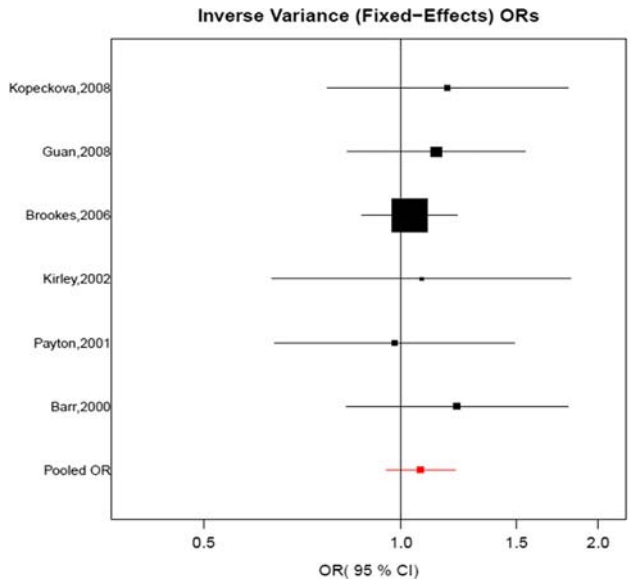

Fig. 7 Odds ratios (ORs) from meta-analysis of ADHD and the Ser9Gly (rs6280) *DRD3* SNP

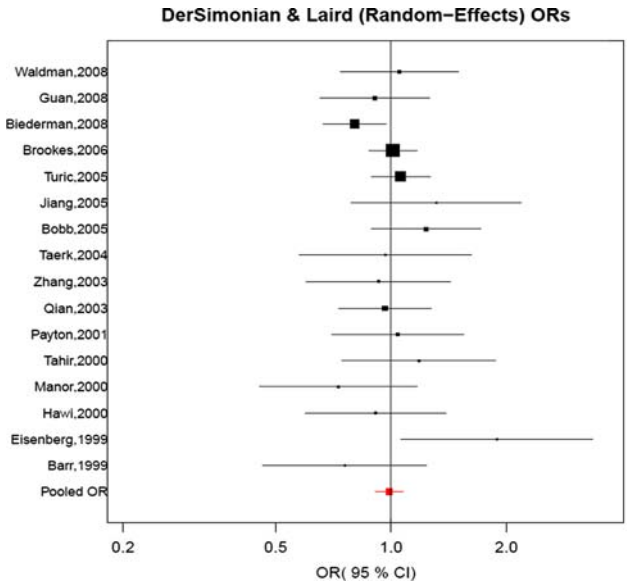

Fig. 8 Odds ratios (ORs) from fixed effects meta-analysis of ADHD and the *COMT val/met* SNP

Catechol-O-methyl-transferase (COMT)

Catechol-*O*-methyl-transferase (*COMT*) is an enzyme responsible for the degradation of the catecholamines dopamine and norepinephrine. It is highly expressed in frontal lobe regions where it plays an important role in regulating synaptic dopamine levels (Hong et al. 1998). *COMT* represents an interesting candidate gene for ADHD given that functional imaging (Pliszka et al. 1996; Schulz et al. 2004) and neuropsychological (Pennington and Ozonoff 1996; Willcutt et al. 2005) studies have suggested that frontal regions are implicated in ADHD. In addition, individuals diagnosed with velo-cardio-facial syndrome, which is caused by a hemizygous deletion of the chromosomal region in which *COMT* lies (22q11), exhibit ADHD-like symptoms, further suggesting a relation between this gene and ADHD (Driscoll et al. 1992).

Studies examining the association between *COMT* and ADHD have largely focused on a functional single nucleotide polymorphism (SNP) in exon 4 that leads to an amino acid substitution (valine → methionine). This polymorphism has been shown to substantially affect *COMT* enzyme activity, such that homozygosity for the valine allele shows 3–4 times greater activity than homozygosity for the methionine allele (Lotta et al. 1995; Scanlon et al. 1979; Weinshilboum and Dunnette 1981). Despite the potential relevance of this functional polymorphism to ADHD and an initial small study suggesting that the valine allele of this polymorphism was associated with increased risk for ADHD (Eisenberg et al. 1999), the majority of studies have reported negative results (Barr et al. 1999; Hawi et al. 2000b; Payton et al. 2001). Further, a previous meta-analysis failed to detect significant evidence for such an association (Cheuk and Wong 2006).

The present meta-analysis of the *val/met* exon 4 SNP (rs4680) included data from seven TDT studies (Barr et al. 1999; Biederman et al. 2008; Brookes et al. 2006a; Payton et al. 2001; Taerk et al. 2004; Turic et al. 2005; Waldman et al. unpublished data) and nine Case-Control/HHRR studies (Bobb et al. 2005; Eisenberg et al. 1999; Guan et al. 2008; Hawi et al. 2000b; Jiang et al. 2005; Manor et al. 2000; Qian et al. 2003; Tahir et al. 2000a; Zhang et al. 2003), with the valine allele designated as the 'high risk' allele. Results of this meta-analysis, shown in Fig. 8, indicated no association between ADHD and the *val/met* SNP (fixed effects: OR = 0.99, 95% CI = 0.92–1.06, $\chi^2 = 0.08$, $P = 0.615$; random effects: OR = 0.99, 95% CI = 0.91–1.08, $\chi^2 = 0.04$, $P = 0.575$) with non-significant and minimal heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 17.55$, $P = 0.287$; $I^2 = 15$). Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study, as these remained very similar with the exclusion of each study in turn, including the first study and the studies with the highest and lowest odds ratios.

In addition to studies examining the exon 4 *val/met* polymorphism rs4680, the present review also identified three studies that tested for association between *COMT* and ADHD using additional markers. The first study genotyped 2 additional markers in *COMT* (Turic et al. 2005), and 2 subsequent studies genotyped more than 20 markers across

the length of the gene (Brookes et al. 2006a; Guan et al. 2008). All three studies reported negative results, further suggesting the absence of an association between *COMT* and ADHD.

Despite these negative findings, however, two studies have suggested that gender may moderate an association between the *val/met COMT* polymorphism and ADHD. These studies presented evidence suggesting that the methionine allele conferred risk to ADHD in boys, whereas the valine allele conferred risk to ADHD in girls (Biederman et al. 2008; Qian et al. 2003). While a third study failed to detect such an effect (Turic et al. 2005), this sexually dimorphic result has some support in the literature with studies in both mice and humans suggesting that *COMT* is differentially expressed in males and females (Dempster et al. 2006; Gogos et al. 1998; Jiang et al. 2003). Nonetheless, these results should be interpreted with caution until further replicated. Thus, while the results of the present meta-analysis did not suggest an association between *COMT* and ADHD, future studies might consider testing gender as a moderator of this association.

Adrenergic pathway

Dopamine beta hydroxylase (DβH)

The dopamine beta hydroxylase gene (*DβH*) has been mapped to chromosome 9q34 (Craig et al. 1988). Dopamine beta hydroxylase converts dopamine to norepinephrine, and thus represents an interesting candidate gene for ADHD given suggestions that the underlying pathophysiology of ADHD involves norepinephrine as well as dopamine dysregulation (Biederman and Faraone 2002; Pliszka et al. 1996). Further, *DβH* polymorphisms have been shown to strongly influence plasma levels of dopamine beta hydroxylase (Cubells et al. 2000; Zabetian et al. 2001, 2003), and low plasma levels of dopamine beta hydroxylase have been associated with conduct disorder (Bowden et al. 1988; Rogeness et al. 1989, 1982), which often co-occurs with ADHD (Hinshaw 1987).

The initial study to test for an association between ADHD and *DβH* was conducted by Daly et al. (1999) using a sample of 118 children diagnosed with ADHD. They reported a significant association with a SNP in intron 5 of *DβH* that results in a *Taq*I restriction site (rs2519152). Since this initial report, a sufficient number of studies have been published examining the relation between this *DβH* SNP and ADHD as well as two additional SNPs (rs1108580; rs1611115 [−1021C/T]) to allow for a meta-analysis of the association between ADHD and each SNP. Notably, the *DβH* SNPs rs1108580 and rs1611115 have shown evidence of an association with plasma levels of dopamine beta hydroxylase, whereas the *Taq*I polymorphism (rs2519152) has not (Cubells et al. 2000; Zabetian et al. 2001, 2003).

For the meta-analysis of the *Taq*I restriction polymorphism (rs2519152), data from one TDT study (Wigg et al. 2002) and five Case-Control/HHRR studies (Bhaduri and Mukhopadhyay 2006; Hawi et al. 2003; Kopeckova et al. 2008; Roman et al. 2002; Smith et al. 2003) were included, with the 'A2' allele considered the "high-risk" allele based on the initial study to test for an association between this SNP and ADHD (Daly et al. 1999). The results (Fig. 9a) were mixed with the fixed effects meta-analysis showing a trend towards an association between the A2 allele of the *Taq*I polymorphism and ADHD across studies (OR = 1.13, 95% CI = 0.96–1.35, $\chi^2 = 2.08$, $P = 0.074$), and the random effects meta-analysis failing to support such an association (OR = 1.12, 95% CI = 0.80–1.55, $\chi^2 = 0.43$, $P = 0.206$). Notably, significant and substantial evidence of heterogeneity in the study effect sizes was observed (Q-statistic $\chi^2 = 17.54$, $P = 0.004$; $I^2 = 71$). Sensitivity analyses suggested that the Smith et al. (2003) study provided the largest contribution to this heterogeneity, as removal of this study reduced the Q-statistic to a trend (Q-statistic $\chi^2 = 9.18$, $P = 0.057$; $I^2 = 56$) and led to a moderate increase in the evidence for an association (random effects: OR = 1.26, 95% CI = 0.94–1.68, $\chi^2 = 2.37$, $P = 0.062$). Nonetheless, a substantial level of heterogeneity remained even after removing this study.

As described, rs1108580 and rs1611115 have shown evidence of an association with plasma levels of dopamine beta hydroxylase (Cubells et al. 2000; Zabetian et al. 2001; Zabetian et al. 2003), which suggests they would be strong candidates for genetic association studies. One TDT study (Brookes et al. 2006a) and three Case-Control/HHRR (Bhaduri and Mukhopadhyay 2006; Guan et al. 2008; Kopeckova et al. 2008) studies were identified for the meta-analysis of rs1611115. This polymorphism has not shown significant evidence for association with ADHD in the extant literature, and as a result, a 'risk' allele was not designated. The meta-analysis of rs1611115 (see Fig. 9b for results) did not detect a significant association with childhood ADHD (fixed effects: OR = 0.98, 95% CI = 0.85–1.15, $\chi^2 = 0.03$, two-tailed $P = 0.855$; random effects: OR = 1.05, 95% CI = 0.83–1.33, $\chi^2 = 0.16$, two-tailed $P = 0.692$), and there was no significant evidence of heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 4.77$, $P = 0.189$; $I^2 = 37$). The meta-analysis of rs1108580 (Fig. 9c), which included data from one TDT study (Brookes et al. 2006a) and four Case-Control/HHRR (Bhaduri and Mukhopadhyay 2006; Guan et al. 2008; Hawi et al. 2003; Kopeckova et al. 2008) studies with the 'A' allele designated as the "high-risk" allele (Hawi et al. 2003), was similarly non-significant (fixed effects: OR = 1.08, 95% CI = 0.95–1.22, $\chi^2 = 1.37$, $P = 0.121$; random effects:

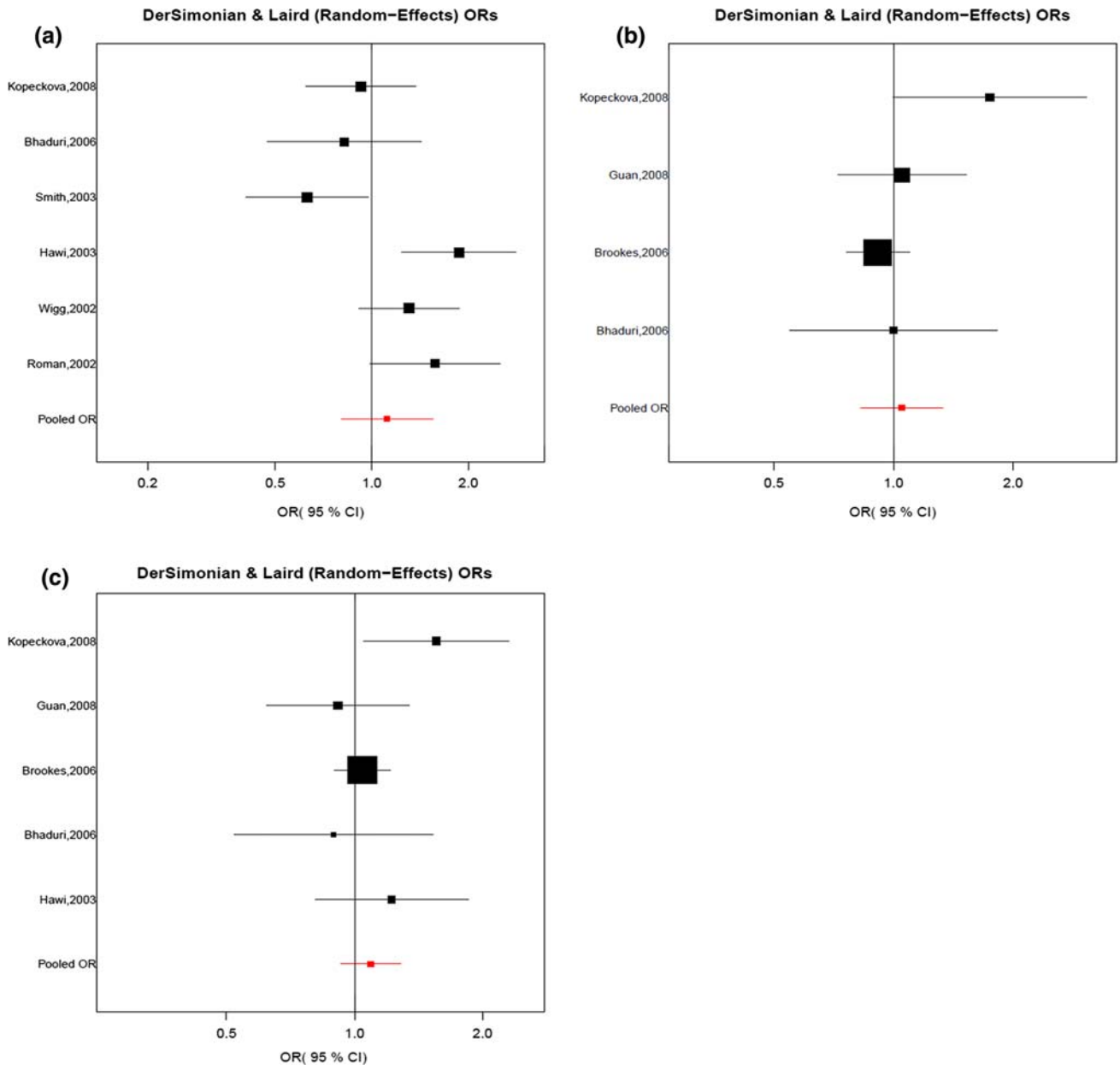

Fig. 9 Odds ratios (ORs) from random effects meta-analysis of ADHD and *DBH* SNPs. **a** The single study and pooled ORs for the association between ADHD and the *Taq*I (rs2519152) SNP. **b** The single study and pooled ORs for the association between ADHD and rs1611115. **c** The single study and pooled ORs for the association between ADHD and rs1108580

OR = 1.09, 95% CI = 0.93–1.28, $\chi^2 = 1.12$, $P = 0.145$) with no significant evidence of heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 5.04$, $P = 0.284$; $I^2 = 20$). Sensitivity analyses for both SNPs indicated that the pooled estimates of effect size and their significance did not depend on any particular study.

In summary, only the *Taq*I polymorphism showed a trend towards an association with childhood ADHD. As noted, significant heterogeneity was observed in the effect sizes for this relation across studies. Further, an inspection of the study-specific odds ratios (Fig. 9a) suggests that studies have reported significant evidence for association with both of the *Taq*I alleles. Thus, it is possible that the reported results are simply due to stochastic fluctuations in the data due to the use of small samples, or the *Taq*I polymorphism is in partial linkage disequilibrium with a true causal variant. As a result, further studies are needed to determine whether *DβH* is involved in the development of ADHD.

Norepinephrine transporter gene (SLC6A2)

The human norepinephrine transporter gene (*SLC6A2*), located on chromosome 16q12.2 (Gelernter et al. 1993),

codes for a protein responsible for the reuptake of norepinephrine from the synaptic cleft back into the presynaptic neuron (Pacholczyk et al. 1991). It is highly expressed in the frontal lobes and is actively involved in both noradrenergic and dopaminergic reuptake and regulation in this region (Stahl 2003). Thus, *SLC6A2* represents an interesting candidate gene for ADHD. Further interest has been generated from pharmacological studies suggesting reductions in ADHD symptoms through increases in dopamine and norepinephrine activity via both stimulant medications (Solanto 1998) and atomoxetine, a norepinephrine transporter antagonist (Michelson et al. 2002; Spencer et al. 2002).

Early candidate gene studies of *SLC6A2* selected 2–3 SNPs to test for association with ADHD, but failed to detect an association (Barr et al. 2002; McEvoy et al. 2002). More recent studies (Guan et al. 2008; Xu et al. 2005a) have selected SNPs spanning the length of *SLC6A2* to comprehensively test for association with ADHD. Conflicting results have been reported, with each study yielding evidence of an association, but differing in which specific SNPs are associated. The present review identified two SNPs that had been tested for association with ADHD in a sufficient number of studies to allow for a meta-analysis.

The first SNP (rs5569 or G1287A) is a synonymous SNP located in exon 9. Data were available for meta-analysis from three TDT (Barr et al. 2002; Brookes et al. 2006a; Kim et al. 2008) and two Case-Control/HHRR (Cho et al. 2008a; Guan et al. 2008) studies. Given that no previous studies had reported a significant association between this polymorphism and ADHD, no 'risk' allele was indicated. The results of the meta-analysis (shown in Fig. 10a) were nonsignificant (fixed effects: OR = 1.06, 95% CI = 0.95–1.18, $\chi^2 = 1.17$, two-tailed $P = 0.279$). No evidence of heterogeneity in effect sizes across studies was observed (Q-statistic $\chi^2 = 0.27$, $P = 0.992$; $I^2 = 0$), and as a result a random effects meta-analysis was not performed.

The second SNP (rs2242447) is a T → C transition located in intron 13. Data were available for meta-analysis from two TDT (Barr et al. 2002; Brookes et al. 2006a) and two Case-Control/HHRR (Guan et al. 2008; Xu et al. 2005a) studies. None of the individual studies had reported a significant association with this SNP, thus no 'risk' allele was indicated. As shown in Fig. 10b, no evidence for association was observed between childhood ADHD and rs2242447 (fixed effects: OR = 1.03, 95% CI = 0.91–1.16, $\chi^2 = 0.22$, two-tailed $P = 0.641$; random effects: OR = 1.04, 95% CI = 0.91–1.19, $\chi^2 = 0.29$, two-tailed $P = 0.589$), and there was no significant heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 3.51$, $P = 0.319$; $I^2 = 14$). Further, sensitivity analyses conducted for both *SLC6A2* SNPs indicated that the pooled estimates of effect size and their significance did not depend on any particular study, as these remained very similar with the exclusion of each study in turn, including the first study and the studies with the highest and lowest odds ratios.

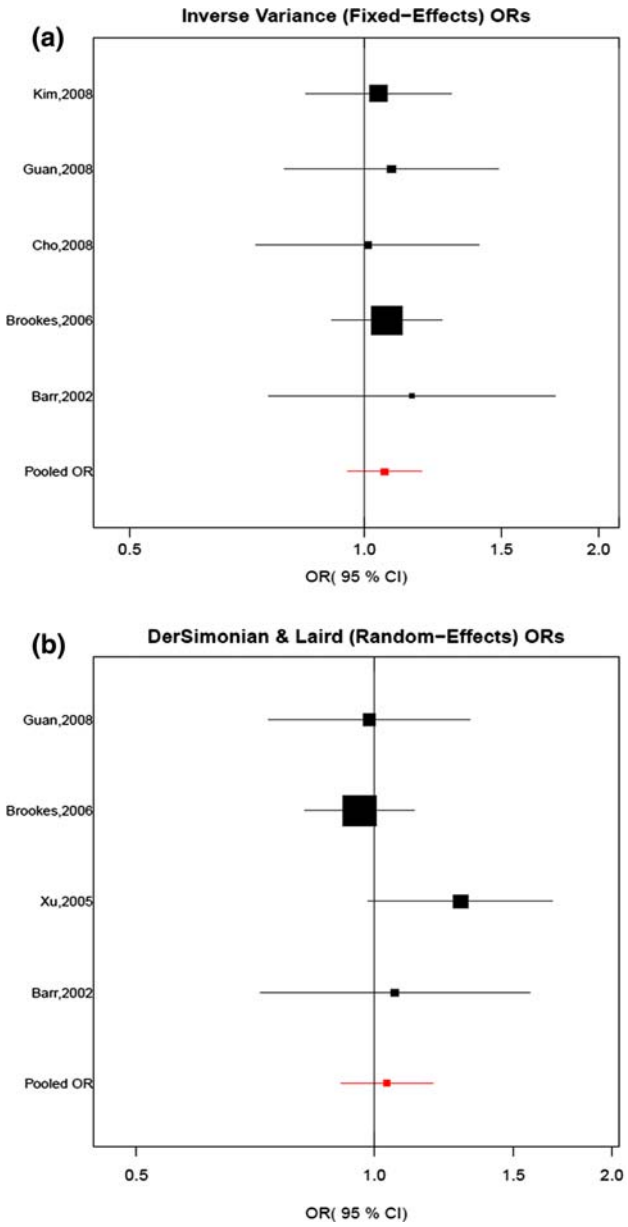

Fig. 10 Odds ratios (ORs) from meta-analysis of ADHD and *SLC6A2* SNPs. **a** The single study and pooled ORs for the fixed effects meta-analysis of the association between ADHD and rs5569. **b** The single study and pooled ORs for the random effects meta-analysis of the association between ADHD and rs2242447

Despite these negative results, compelling reasons remain for future studies to investigate the relation between ADHD and the norepinephrine transporter gene. First, significant ADHD–*SLC6A2* associations have been reported, though due to a lack of consistency in the *SLC6A2* SNPs genotyped across studies, these associations could not be evaluated via meta-analysis. Nonetheless, the results of these studies suggest that a true susceptibility locus that has

yet to be examined or widely studied may reside within *SLC6A2*. In support of this hypothesis, a common, functional A/T SNP (rs28386840) at position −3081 upstream of the transcription initiation site has been identified and associated with ADHD (Kim et al. 2006a). This SNP is positioned within a sequence critical for cell type-specific promoter function of the *SLC6A2* gene, and the T-allele of this polymorphism significantly reduced promoter function relative to the A-allele (Kim et al. 2006a). Based on such evidence, future studies investigating the relations between ADHD and *SLC6A2* are warranted despite the negative evidence for association with the two SNPs reported in the present review.

Alpha 2A adrenergic receptor (ADRA2A)

The alpha-2A-adrenergic receptor gene (*ADRA2A*) has been mapped to chromosome 10q23-q25 (Yang-Feng et al. 1987). Adrenergic neurotransmitter systems are hypothesized to influence attentional processes and certain aspects of executive control (Arnsten 2006), and thus, *ADRA2A* represents an interesting candidate gene for ADHD. Specific evidence supporting *ADRA2A* involvement in the etiology of ADHD comes from studies suggesting that alpha 2a-adrenoreceptors in the prefrontal cortex influence executive functions such as attention, inhibitory control, and working memory (Arnsten and Li 2005; Waldman et al. 2006), which are impaired in children with ADHD (Pennington and Ozonoff 1996; Willcutt et al. 2005). Further, methylphenidate, which is commonly prescribed to treat ADHD symptoms, has been shown to increase catecholaminergic activity through increased stimulation of alpha-2A-adrenergic receptors (Andrews and Lavin 2006).

The first study to test for association and linkage between *ADRA2A* and ADHD genotyped 94 families for a SNP in the promoter region that creates a MspI restriction site (rs1800544), but a TDT failed to yield evidence for association (Xu et al. 2001). Since this initial study, nine independent studies have been published examining the association of ADHD with this SNP and additional polymorphisms within *ADRA2A* (Bobb et al. 2005; Brookes et al. 2006a; Cho et al. 2008b; Deupree et al. 2006; Guan et al. 2008; Park et al. 2005; Roman et al. 2003; Schmitz et al. 2006; Stevenson et al. 2005). In the present review, we conducted a meta-analysis of studies testing for association between ADHD and 3 *ADRA2A* polymorphisms (rs1800544, rs1800545, and rs553668).

For the meta-analysis of association between childhood ADHD and the *ADRA2A* MspI restriction polymorphism (rs1800544), data from five TDT (Brookes et al. 2006a; Deupree et al. 2006; Park et al. 2005; Wang et al. 2006; Xu et al. 2001) and six Case-Control/HHRR (Bobb et al. 2005; Cho et al. 2008b; Guan et al. 2008; Roman et al. 2003; Schmitz et al. 2006; Stevenson et al. 2005) studies were included, with the G allele considered the "high-risk" allele based on previous research (Park et al. 2005). Results of this meta-analysis, shown in Fig. 11a, were non-significant (fixed effects: OR = 1.00, 95% CI = 0.90–1.10, $\chi^2 = 0.00$, $P = 0.473$; random effects: OR = 0.99, 95% CI = 0.89–1.11, $\chi^2 = 0.01$, $P = 0.542$) with no significant evidence of heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 12.20$, $P = 0.272$; $I^2 = 18$). Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study.

In addition to the MspI polymorphism, *ADRA2A* HhaI (rs1800545) and DraI (rs553668) restriction fragment length polymorphisms have been studied in relation to ADHD. Three TDT studies (Brookes et al. 2006a; Deupree et al. 2006; Park et al. 2005) and one Case-Control/HHRR study (Guan et al. 2008) were identified for the meta-analysis of the HhaI polymorphism (rs1800545). Given that no previous studies have reported a significant association between this polymorphism and ADHD, a 'risk' allele was not designated. Results of this meta-analysis, shown in Fig. 11b, were nonsignificant (fixed effects: OR = 0.99, 95% CI = 0.81–1.21, $\chi^2 = 0.01$, two-tailed $P = 0.914$) with no significant evidence of heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 1.55$, $P = 0.670$; $I^2 = 0$). Due to the absence of heterogeneity, a random effects meta-analysis was not performed. Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study.

For the meta-analysis of the DraI restriction polymorphism (rs553668), data from three TDT (Deupree et al. 2006; Park et al. 2005; Wang et al. 2006) studies and one Case-Control/HHRR study (Cho et al. 2008b) were included, with the 'T' allele considered the "high-risk" allele based on the initial study to test for an association between this SNP and ADHD (Park et al. 2005). The results (Fig. 11c) did not show evidence of a significant association between the DraI polymorphism and ADHD across studies (fixed effects: OR = 0.92, 95% CI = 0.78–1.09, $\chi^2 = 0.87$, $P = 0.825$; random effects: OR = 0.94, 95% CI = 0.66–1.34, $\chi^2 = 0.12$, $P = 0.638$) but significant and substantial evidence of heterogeneity in the study effect sizes was observed (Q-statistic $\chi^2 = 8.09$, $P = 0.044$; $I^2 = 63$). Further sensitivity analyses suggested that the Park et al. (2005) study provided the largest contribution to this association and heterogeneity, as removal of this study reduced the Q-statistic to non-significance (Q-statistic $\chi^2 = 2.58$, $P = 0.275$; $I^2 = 22$), and altered the effect size estimates of association across studies (random effects: OR = 0.86, 95% CI = 0.70–1.08, $\chi^2 = 1.64$, $P = 0.900$).

Overall, the present review provides little evidence to support the involvement of *ADRA2A* in the etiology of ADHD. Nonetheless, the heterogeneity in effect sizes

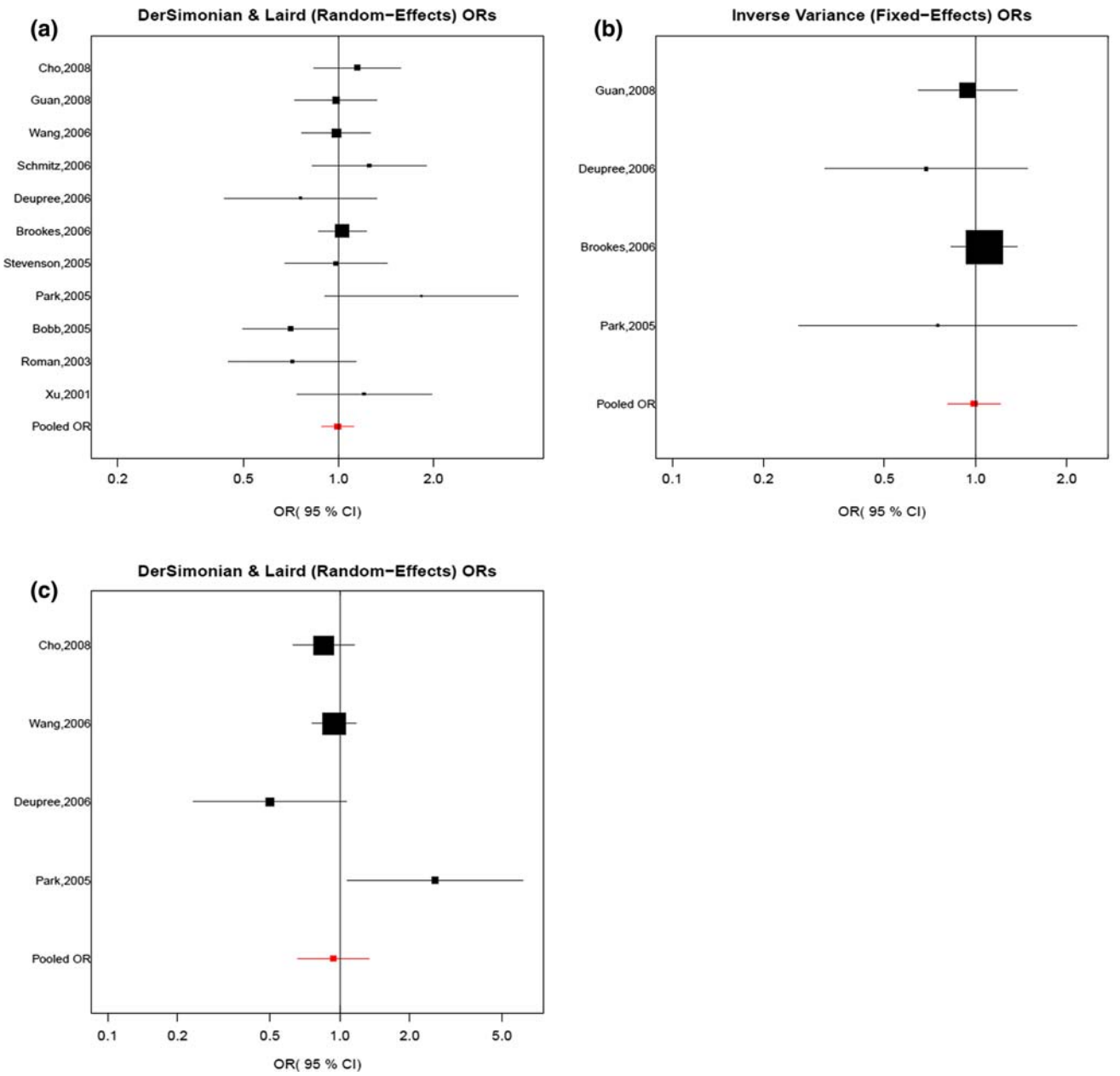

Fig. 11 Odds ratios (ORs) from meta-analysis of ADHD and *ADRA2A* SNPs. **a** The single study and pooled ORs for the random effects meta-analysis of the association between ADHD and the MspI (rs1800544) SNP. **b** The single study and pooled ORs for the fixed effects meta-analysis of the association between ADHD and the HhaI (rs1800545) SNP. **c** The single study and pooled ORs for the random effects meta-analysis of the association between ADHD and the DraI (rs553668) SNP

observed among studies testing for an association between ADHD and the DraI polymorphism suggest that some future research exploring this heterogeneity may be warranted. For example, two studies have reported that there may be an association between ADHD and *ADRA2A* that is specific to inattentive ADHD symptoms (Roman et al. 2003; Schmitz et al. 2006). This would not explain the heterogeneity observed in the present meta-analysis, however, given that Park et al. (2005) observed significant associations between both symptom dimensions and *ADRA2A* polymorphisms. Thus, additional sources of heterogeneity would need to be explored to explain the present result.

Serotonergic pathway

Serotonin transporter gene (SLC6A4; 5HTT)

The serotonin transporter gene (*SLC6A4*; *5HTT*) is located on the long arm of chromosome 17 (Gelernter et al. 1995). It codes for a solute carrier protein responsible for the

reuptake of serotonin from the synaptic cleft back into the presynaptic neuron (Heils et al. 1996; Lesch et al. 1996), and thus represents a primary mechanism for the regulation of serotonergic activity in the brain. *5HTT* is expressed in brain regions implicated in attention, memory, and motor activities such as the amygdala, hippocampus, thalamus, putamen, and anterior cingulate cortex (Frankle et al. 2004; Oquendo et al. 2007). Based on such evidence, *5HTT* represents a strong functional candidate for ADHD, which is further strengthened by studies suggesting its involvement in the etiology of impulsivity (Halperin et al. 1997; Spivak et al. 1999; Stein et al. 1993) and in modulating stimulant response in alleviating hyperactivity (Gainetdinov et al. 1999). *5HTT* represents a strong positional candidate as well given that multiple genome scans have found linkage or association of ADHD to the 17q11.1-q12 region in which *5HTT* is located (Arcos-Burgos et al. 2004b; Ogdie et al. 2003).

A functional polymorphism in the promoter region of the gene (the *5HTTLPR*) is one of the most frequently studied genetic markers in psychiatric genetic research and has been extensively tested for association with depressive and anxiety disorders and related traits (Lotrich and Pollock 2004; Munafo et al. 2005; Schinka et al. 2004; Sen et al. 2004). The *5HTTLPR* is a 44-bp insertion/deletion yielding long and short alleles. The long variant is associated with more rapid serotonin reuptake resulting in lower levels of active serotonin, whereas the short variant appears to be associated with reduced serotonin reuptake resulting in higher levels of active serotonin (Lesch et al. 1996). Twenty case-control or within-family studies have been conducted testing for association between ADHD and the *5HTTLPR*. The first study was conducted in a sample of 98 Israeli parent–proband trios, and reported an over-representation of the long allele of the *5HTTLPR* only among children diagnosed with the ADHD Combined subtype (Manor et al. 2001). Similar to the results for other psychiatric disorders and genetic markers, this ADHD-*5HTTLPR* association replicated in some subsequent studies but not in others.

Ten TDT (Banerjee et al. 2006; Heiser et al. 2007; Kent et al. 2002; Kim et al. 2005a; Li et al. 2007; Waldman et al. unpublished data; Wigg et al. 2006; Xu et al. 2008, 2005b) and nine Case-Control/HHRR (Beitchman et al. 2003; Curran et al. 2005; Guimares et al. 2007; Kopeckova et al. 2008; Langley et al. 2003; Manor et al. 2001; Seeger et al. 2001; Zhao et al. 2005; Zoroglu et al. 2002) studies were identified for the present meta-analysis of the association between childhood ADHD and the *5HTTLPR* with the long variant designated as the "risk" allele. Results of this meta-analysis, shown in Fig. 12, indicated a significant but modest association between ADHD and the *5HTTLPR* "long" allele (fixed effects: OR = 1.10, 95% CI = 1.02–1.17, $\chi^2 = 7.13$, $P = 0.004$; random effects: OR = 1.17, 95% CI = 1.02–1.33, $\chi^2 = 5.40$, $P = 0.010$) with substantial heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 52.80$, $P = 0.00003$; $I^2 = 66$). Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study, as these remained very similar with the exclusion of each study in turn, including the first study and the studies with the highest and lowest odds ratios.

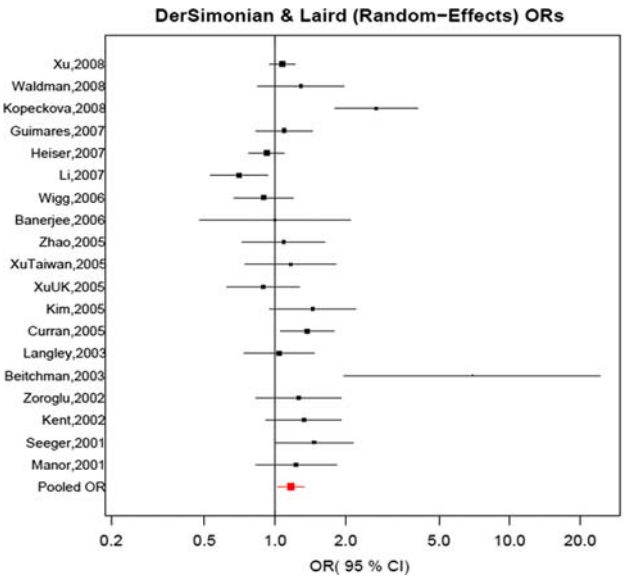

Fig. 12 Odds ratios (ORs) from random effects meta-analysis of ADHD and the *5HTTLPR*

Given that significant heterogeneity in effect sizes across studies investigating the association between the *5HTTLPR* and ADHD was observed, a clear priority for future research is investigating the sources of this heterogeneity. Two early studies suggested that the *5HTTLPR*-ADHD association might be specific to the combined ADHD subtype (Manor et al. 2001; Seeger et al. 2001), which could indicate that differences in the proportion of ADHD subtype diagnoses across study samples might contribute to the observed heterogeneity. Nonetheless, a more recent study utilizing the IMAGE sample failed to observe such an association among children diagnosed with the combined ADHD subtype (Xu et al. 2008). This would suggest that additional variables need to be identified that can explain the heterogeneity in effect sizes for the *5HTTLPR*-ADHD association.

In addition to the *5HTTLPR*, a 17-bp repeat in intron 2 (STin2) and a SNP in the 3′ UTR (rs3813034) of *5HTT* have been repeatedly studied in relation to childhood ADHD. The STin2 has been shown to act as a transcription regulator with the 12-repeat allele demonstrating enhanced transcription relative to the 10-repeat allele (Fiskerstrand et al. 1999; MacKenzie and Quinn 1999). The function of

the 3′UTR SNP is not known, though it lies within a putative polyadenylation site, and thus could influence mRNA stability (Battersby et al. 1999).

For the meta-analysis of association between childhood ADHD and the *5HTT* STin2 polymorphism, two TDT (Li et al. 2007; Xu et al. 2008) and seven Case-Control/HHRR (Banerjee et al. 2006; Heiser et al. 2007; Kim et al. 2005a; Langley et al. 2003; Xu et al. 2005b; Zoroglu et al. 2002) studies were identified. Based on an initial study reporting reduced prevalence of the 12-repeat allele among children diagnosed with ADHD (Zoroglu et al. 2002), the 10-repeat allele of the STin2 polymorphism was designated as the "risk" allele. The results of the fixed-effects meta-analysis, shown in Fig. 13a, indicated no association between ADHD and the *5HTT* STin2 polymorphism (fixed effects: OR = 1.01, 95% CI = 0.92–1.10, $\chi^2 = 0.03$, $P = 0.428$) with no heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 4.08$, $P = 0.850$; $I^2 = 0$). Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study. A random-effect meta-analysis was not performed given the absence of heterogeneity in effect sizes across studies.

Two TDT (Kent et al. 2002; Wigg et al. 2006) and three Case-Control/HHRR (Heiser et al. 2007; Xu et al. 2005b) studies were identified for the meta-analysis of the association between childhood ADHD and the *5HTT* rs3813034 3′UTR SNP. The initial study testing this association reported preferential transmission of the "T" allele to ADHD probands in a sample of 113 children (Kent et al. 2002), and thus, the "T" allele was designated as the "risk" allele in the present meta-analysis. The results, shown in Fig. 13b, indicated a non-significant and weak association between ADHD and the *5HTT* rs3813034 SNP (fixed effects: OR = 1.04, 95% CI = 0.89–1.20, $\chi^2 = 0.23$, $P = 0.317$; random effects: OR = 1.05, 95% CI = 0.87–1.26, $\chi^2 = 0.26$, $P = 0.304$) with non-significant heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 5.71$, $P = 0.222$; $I^2 = 30$). Sensitivity analyses indicated that these results did not depend on any particular study. In summary, the present review provides significant evidence of an association between ADHD and the *5HTTLPR*, but failed to detect an association with the STin2 and rs3813034 polymorphisms.

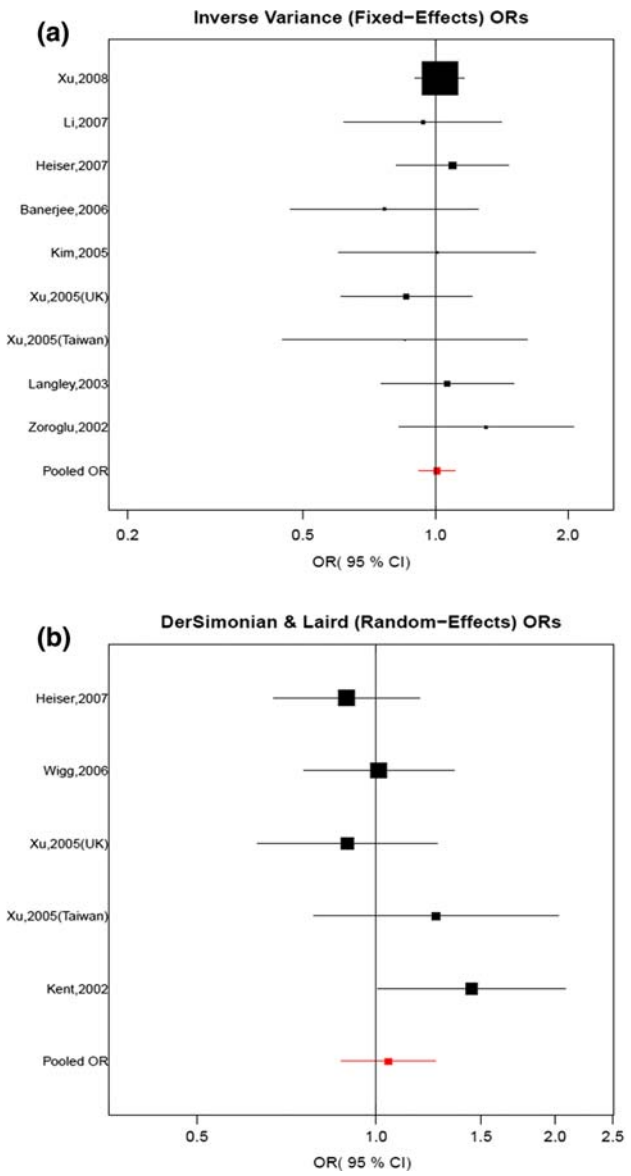

Fig. 13 Odds ratios (ORs) from meta-analysis of ADHD and *5HTT* SNPs. **a** The single study and pooled ORs for the fixed effects meta-analysis of the association between ADHD and the STin2 VNTR. **b** The single study and pooled ORs for the random effects meta-analysis of the association between ADHD and the rs3813034 3′UTR SNP

Serotonin 1B receptor (HTR1B; 5HT1B)

Serotonin dysregulation has been related to impulsive and aggressive behavior in children (Halperin et al. 1997; Spivak et al. 1999), and thus has been hypothesized to play a causal role in ADHD. In addition to the serotonin transporter, a number of researchers have investigated associations between ADHD and genes that code for receptors in the serotonin system (Heiser et al. 2007; Ribases et al. 2009). The most widely studied serotonin receptor gene in relation to ADHD is the serotonin 1b receptor (*HTR1B*; *5-HT1B*). It has been mapped to chromosome 6q13 (Jin et al. 1992) and consists of a single exon (Demchyshyn et al. 1992). *HTR1B* is a G protein-coupled receptor that inhibits cyclic AMP formation (Murphy et al. 1998). It is highly expressed in the dorsal raphe nucleus, which is involved in the sleep/wake cycle, and to lesser degrees in the striatum and frontal regions such as the dorsolateral prefrontal cortex (Ichikawa et al. 2005). *HTR1B* "knockout" mice show increased aggression and impulsive behavior (Brunner and Hen 1997; Saudou et al. 1994), fail to show

the normal hyperlocomotion associated with amphetamine administration (Saudou et al. 1994), and display an increased response to novel stimuli (Malleret et al. 1999).

Given such evidence, several studies have tested for association between polymorphisms in *HTR1B* and ADHD. The first such study used the HHRR to test for association between a G → C transition at nucleotide position 861 (G861C; rs6296) and ADHD in a sample of 273 nuclear families, and reported significant preferential transmission of the 'G' allele to ADHD probands (Hawi et al. 2002). Including this study, ten independent studies were identified that tested for an association between *HTR1B* and ADHD, and two polymorphisms, rs6296 (G861C) and rs6298, were genotyped in a sufficient number of studies to conduct a meta-analysis. Only the results for the meta-analysis of rs6296 are presented, however, as these two polymorphisms have been shown to be in perfect LD (International HapMap Consortium 2003), a greater number of studies have tested for an association with rs6296, and those studies that genotyped rs6298 also genotyped rs6296.

For the meta-analysis of rs6296, data were available from four TDT (Brookes et al. 2006a; Ickowicz et al. 2007; Li et al. 2005; Smoller et al. 2006) and five Case-Control/HHRR (Bobb et al. 2005; Guan et al. 2008; Hawi et al. 2002; Heiser et al. 2007; Ribases et al. 2009) studies. Based on the initial study (Hawi et al. 2002), the 'G' allele was designated as the 'risk' allele. Results of this meta-analysis, shown in Fig. 14, indicated a modest but significant association between ADHD and the *HTR1B* rs6296 "G" allele (fixed effects: OR = 1.11, 95% CI = 1.02–1.20, $\chi^2 = 5.45$, $P = 0.010$) with no heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 7.92$, $P = 0.441$; $I^2 = 0$). A random effects meta-analysis was not conducted given the absence of heterogeneity across studies. Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study, as these remained very similar with the exclusion of each study in turn, including the first study and the studies with the highest and the lowest odds ratios. Thus, the present review provides significant evidence suggesting an association between childhood ADHD and *HTR1B*.

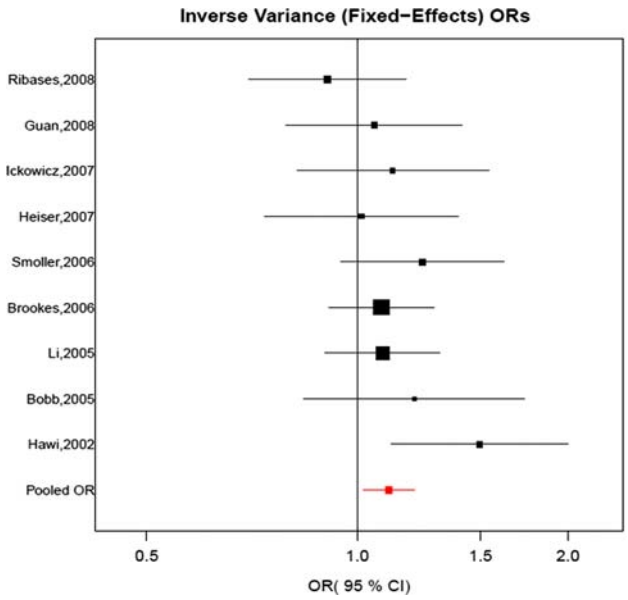

Fig. 14 Odds ratios (ORs) from the fixed effects meta-analysis of ADHD and the rs6296 *HTR1B* SNP

Serotonin 2A receptor (HTR2A; 5HT2A)

In addition to *HTR1B*, the serotonin 2A receptor (*HTR2A*; *5-HT2A*) has received significant attention as a candidate gene for ADHD. *HTR2A* has been mapped to chromosome 13q15-q21 (Sparkes et al. 1991) and consists of three exons (Chen et al. 1992). It codes for a G-coupled protein that serves to stimulate phospholipase C activity, which leads to increased protein kinase C activity (Lesch 2001). *HTR2A* is highly expressed throughout the cortex as well as in regions such as the hippocampus, amygdala, and nucleus accumbens (Dwivedi and Pandey 1998). Evidence suggesting the involvement of *HTR2A* in ADHD comes from studies demonstrating that the inhibition of serotonin 2A receptors attenuates the increases in dopamine activity and hyperlocomotion caused by amphetamine administration (O'Neill et al. 1999) and anti-psychotic medications such as clozapine (Martin et al. 1998).

Three polymorphisms in *HTR2A* have been studied in relation to a number of psychiatric conditions (see Norton and Owen 2005 for a review). These include a nonsynonymous C → T transition at nucleotide 1,354 in exon 3 that leads to a histidine to tyrosine change (rs6314 or His452Tyr) (Erdmann et al. 1996; Ozaki et al. 1996), a silent T → C polymorphism at nucleotide position +102 (rs6313) (Warren et al. 1992), and an A → G polymorphism that is 1,438 nucleotides upstream of the transcription start site (rs6311). The first study to test for association between ADHD and *HTR2A* genotyped rs6313 and rs6314 in a sample of 143 parent–child trios selected for ADHD (Quist et al. 2000). The authors reported preferential transmission of the 'T' allele of rs6314 to ADHD probands using the TDT, but detected no evidence of association to rs6313. Since this initial report, nine additional studies were identified that tested for an association between *HTR2A* and ADHD using one or more of the polymorphisms described. Thus, sufficient data were provided to conduct meta-analyses of all three SNPs.

For the meta-analysis of the association between ADHD and rs6314 (His452Tyr), two TDT (Brookes et al. 2006a; Quist et al. 2000) and four Case-Control/HHRR (Bobb et al. 2005; Guimares et al. 2007; Hawi et al. 2002; Heiser

et al. 2007) studies were identified. Based on the initial report (Quist et al. 2000), the 'T' allele was designated as the 'risk' allele. The results for this meta-analysis (Fig. 15a) were non-significant (fixed effects: OR = 1.02, 95% CI = 0.86–1.21, $\chi^2 = 0.07$, $P = 0.392$; random effects: OR = 1.05, 95% CI = 0.82–1.34, $\chi^2 = 0.16$, $P = 0.343$) with moderate but nonsignificant evidence of heterogeneity (Q-statistic $\chi^2 = 8.71$, $P = 0.121$; $I^2 = 42$). Sensitivity analyses for this polymorphism, as well as similar analyses conducted for each of the polymorphisms described below, indicated that the pooled estimates of effect size and their significance did not depend on any particular study, as these remained very similar with the exclusion of each study in turn, including the first study and the studies with the highest and lowest odds ratios.

Population genetic data have suggested that rs6313 and rs6311 are in near perfect linkage disequilibrium (International HapMap Consortium 2003), which would indicate that these markers would provide redundant information in tests of association. Nonetheless, there was imperfect

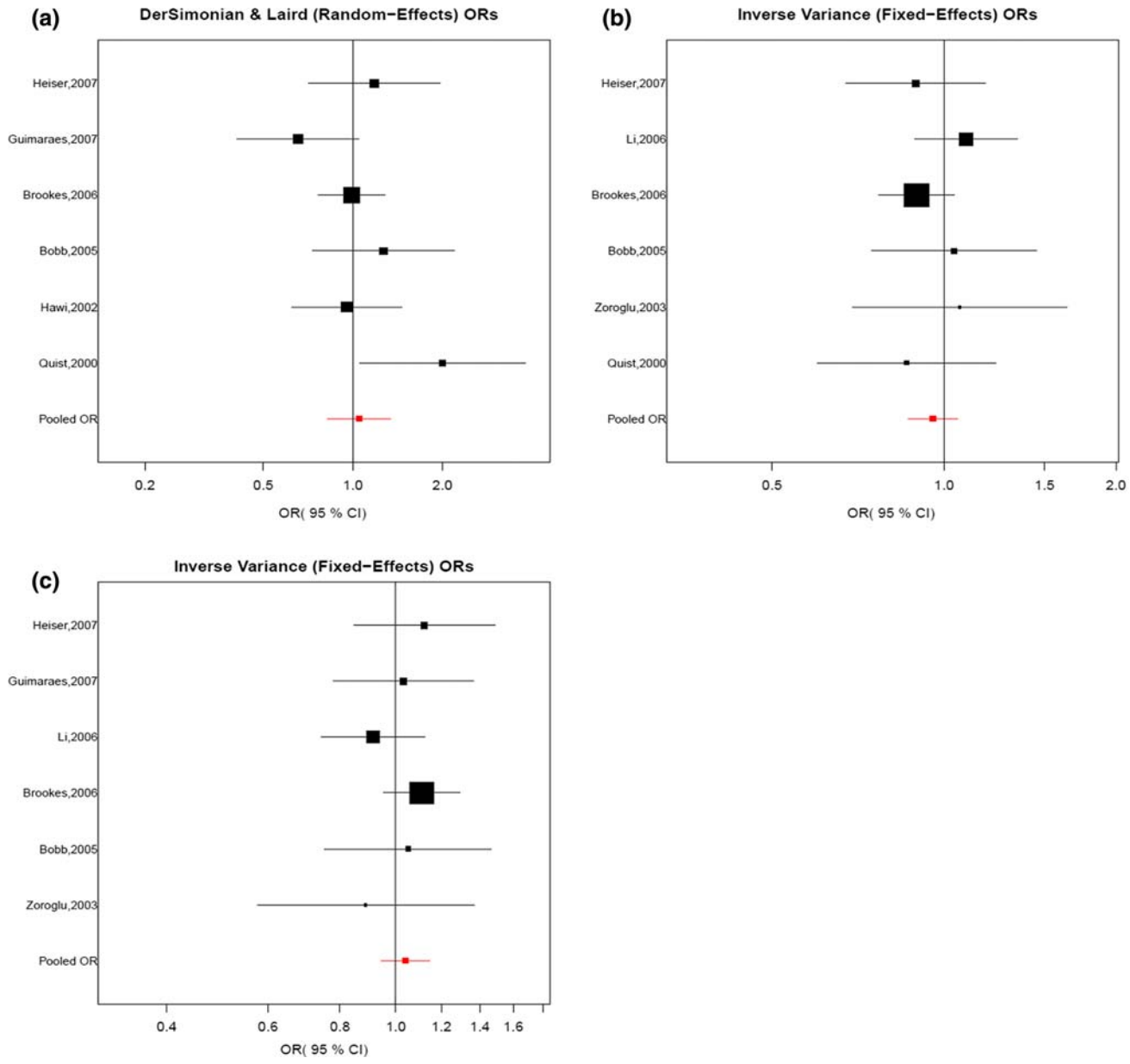

Fig. 15 Odds ratios (ORs) from meta-analysis of ADHD and *HTR2A* SNPs. **a** The single study and pooled ORs for the random effects meta-analysis of the association between ADHD and rs6314. **b** The single study and pooled ORs for the fixed effects meta-analysis of the association between ADHD and rs6313. **c** The single study and pooled ORs for the fixed effects meta-analysis of the association between ADHD and rs6311

overlap in ADHD association studies that genotyped these two polymorphisms, and thus meta-analyses were conducted for the association of ADHD with each marker. For rs6313, three TDT (Brookes et al. 2006a; Li et al. 2006b; Quist et al. 2000) and three Case-Control/HHRR (Bobb et al. 2005; Heiser et al. 2007; Zoroglu et al. 2003) studies were identified. Given that no previous studies had reported a significant association between this polymorphism and ADHD, no 'risk' allele was indicated. The results of the meta-analysis (shown in Fig. 15b) were nonsignificant (fixed effects: OR = 0.96, 95% CI = 0.86–1.06, $\chi^2 = 0.77$, two-tailed $P = 0.379$). No evidence of heterogeneity in effect sizes across studies was observed (Q-statistic $\chi^2 = 3.36$, $P = 0.644$; $I^2 = 0$), and as a result a random effects meta-analysis was not performed. For rs6311, two TDT (Brookes et al. 2006a; Li et al. 2006b) and four Case-Control/HHRR (Bobb et al. 2005; Guimares et al. 2007; Heiser et al. 2007; Zoroglu et al. 2003) studies were identified with no 'risk' allele indicated, given the lack of previous evidence suggesting an association between this polymorphism and ADHD. Similar to the results for rs6313, the results of this meta-analysis (Fig. 15c) were non-significant (fixed effects: OR = 1.04, 95% CI = 0.94–1.14, $\chi^2 = 0.57$, two-tailed $P = 0.449$) with no evidence for heterogeneity (Q-statistic $\chi^2 = 2.97$, $P = 0.705$; $I^2 = 0$). Thus, the present meta-analytic results do not suggest an association between childhood ADHD and *HTR2A*.

Tryptophan hydroxylase genes (TPH1 and TPH2)

Tryptophan hydroxylase catalyzes tryptophan to 5-hydroxytryptophan (5HT), which is subsequently decarboxylated to form the neurotransmitter serotonin. Thus, tryptophan hydroxylase is the rate-limiting enzyme in the production of serotonin. Two isoforms of tryptophan hydroxylase have been identified. The first is coded by the gene *TPH1*, which has been mapped to chromosome 11p15.3-p14 (Craig et al. 1991). This gene was originally believed to be totally responsible for tryptophan hydroxylase expression in the brain, thus was studied as a candidate gene for mood disorders (see Oswald et al. 2004 for a review) as well as impulsivity and aggressiveness (Roy and Linnoila 1988) and ADHD (Brookes et al. 2006a; Tang et al. 2001). More recent data suggest a second isoform coded by the gene *TPH2*, located on chromosome 12q21.1, is responsible for tryptophan hydroxylase expression in the brain (Walther et al. 2003). Thus, recent association studies of ADHD have focused on *TPH2* rather than *TPH1*.

Several studies tested for an association between *TPH1* and ADHD before it was discovered that this gene is not responsible for tryptophan hydroxylase expression in the brain. These studies largely focused on a silent A → C transition in intron 7 of the gene (rs1800532). Two TDT (Brookes et al. 2006a; Li et al. 2006c) and two Case-Control/HHRR (Ribases et al. 2009; Tang et al. 2001) studies were identified that tested for an association between this SNP and childhood ADHD and were appropriate for meta-analysis. Because the initial studies investigating this association reported negative results, a 'risk' allele was not indicated. The results of this meta-analysis (shown in Fig. 16) did not support an association between rs1800532 and ADHD (fixed effects: OR = 0.99, 95% CI = 0.89–1.10, $\chi^2 = 0.06$, two-tailed $P = 0.813$; random effects: OR = 0.97, 95% CI = 0.83–1.12, $\chi^2 = 0.19$, two-tailed $P = 0.662$), though there was moderate but non-significant evidence of heterogeneity (Q-statistic $\chi^2 = 5.10$, $P = 0.164$; $I^2 = 41$). Thus, the present meta-analysis is not suggestive of an association between ADHD and *TPH1*.

Despite stronger evidence supporting a role for *TPH2* involvement in the etiology of ADHD, evidence for its association with ADHD has been relatively mixed. Two initial studies supported a relation between ADHD and *TPH2*, with one study reporting an association with two SNPs located in the promoter region (Walitza et al. 2005), and a second study reporting an association with SNPs in introns 5 and 8 (Sheehan et al. 2005). Sufficient data were available to conduct meta-analyses of the association between ADHD and two SNPs in intron 5 (rs1843809 and rs1386493).

For rs1843809, data were available from four TDT studies (Brookes et al. 2006a; Mick et al. unpublished data; Sheehan et al. 2005, 2007). Based on the initial report, the T allele was designated as the 'risk' allele (Sheehan et al.

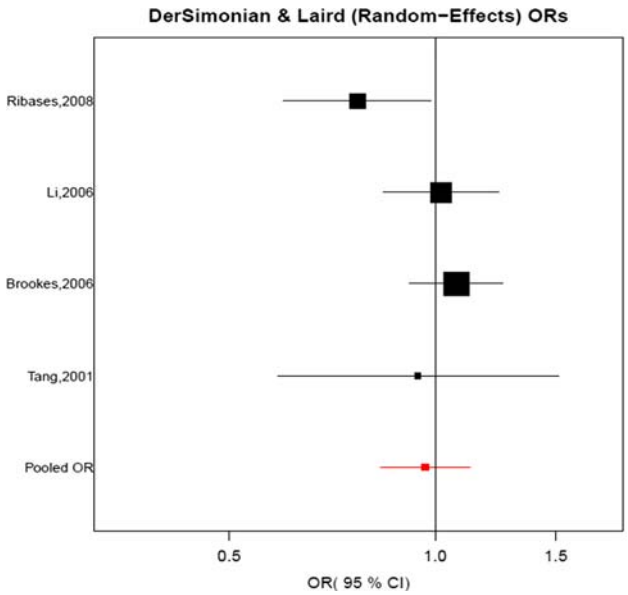

Fig. 16 Odds ratios (ORs) from the Random effects meta-analysis of ADHD and the rs1800532 *TPH1* SNP

2005). Results of the meta-analysis (Fig. 17a) were nonsignificant (fixed effects: OR = 0.96, 95% CI = 0.82–1.12, $\chi^2 = 0.26$, $P = 0.696$; random effects: OR = 1.15, 95% CI = 0.73–1.82, $\chi^2 = 0.35$, $P = 0.276$) though significant and substantial heterogeneity in effect sizes was observed across studies (Q-statistic $\chi^2 = 19.46$, $P = 0.0002$; $I^2 = 84$). A review of the forest plot depicting these effect sizes (Fig. 17a) suggested that this heterogeneity was largely due to the significant associations of Sheehan et al. (2005) and Brookes et al. (2006a) that were reported for opposing alleles. Sensitivity analyses suggested that the Sheehan et al. (2005) study provided the largest contribution to the observed heterogeneity as removing this study from the analysis reduced the Q-statistic to nonsignificance (Q-statistic $\chi^2 = 5.46$, $P = 0.065$; $I^2 = 63$) though removing the Brookes et al. (2006a) study also led to a substantial reduction in heterogeneity (Q-statistic $\chi^2 = 7.35$, $P = 0.025$; $I^2 = 73$). Further, removing the Sheehan et al. (2005) study yielded little change in the evidence for association (random effects: OR = 0.91, 95% CI = 0.66–1.25, $\chi^2 = 0.34$, $P = 0.720$), whereas removing the Brookes et al. (2006a) study yielded evidence for association that approached a statistical trend (random effects: OR = 1.38, 95% CI = 0.84–2.29, $\chi^2 = 1.61$, $P = 0.102$). Nonetheless, these findings should be interpreted with caution given that they are based on just three studies.

Similar results were obtained for the meta-analysis of the association between ADHD and rs1386493. The 'T' allele was designated as the high-risk allele based on the single study that reported a significant association between this SNP and ADHD (Brookes et al. 2006a). The same four TDT studies included in the meta-analysis for rs1843809 also provided appropriate data for this meta-analysis (Brookes et al. 2006a; Mick et al. unpublished data; Sheehan et al. 2005, 2007). The results, shown in Fig. 17b, were again nonsignificant (fixed effects: OR = 1.12, 95% CI = 0.96–1.30, $\chi^2 = 2.20$, $P = 0.069$; random effects: OR = 1.04, 95% CI = 0.77–1.40, $\chi^2 = 0.06$, $P = 0.400$) though there was a trend towards an association for the fixed effects analysis. Notably, however, substantial evidence of heterogeneity in effect sizes was again observed across studies (Q-statistic $\chi^2 = 9.76$, $P = 0.021$; $I^2 = 69$) that was largely due to the significant associations of Sheehan et al. (2005) and Brookes et al. (2006a) that were reported for opposing alleles (Fig. 17b). Sensitivity analyses suggested that the Brookes et al. (2006a) and Sheehan et al. (2005) studies both provided substantial contributions to the observed heterogeneity as removing either study from the analysis reduced the Q-statistic to non-significance (Brookes et al. (2006a) removed: Q-statistic $\chi^2 = 2.58$, $P = 0.274$; $I^2 = 22$; Sheehan et al. (2005) removed: Q-statistic $\chi^2 = 3.49$, $P = 0.174$; $I^2 = 43$). Further, removing the Sheehan et al. (2005) study resulted in a trend for association (random effects: OR = 1.18, 95% CI = 0.93–1.49, $\chi^2 = 1.92$, $P = 0.083$), whereas removing the Brookes et al. (2006a) study yielded little change in the evidence for association (random effects: OR = 0.91, 95% CI = 0.71–1.17, $\chi^2 = 0.54$, $P = 0.769$). These results should be interpreted cautiously, however, given that like those described for rs1843809, they are based on three studies.

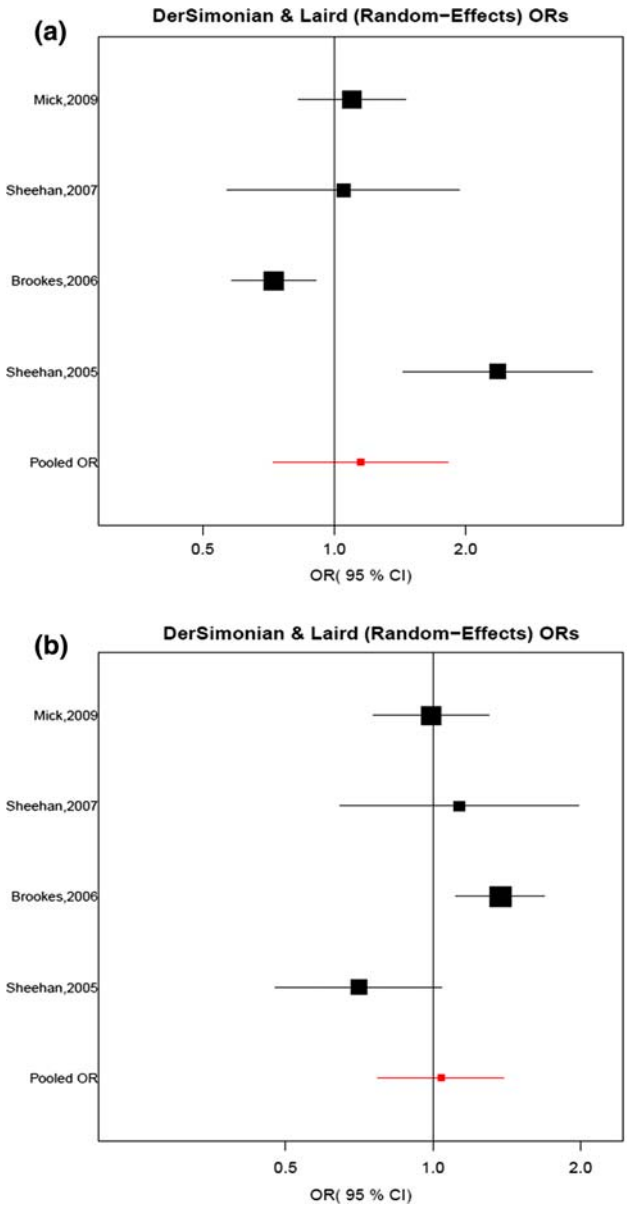

Fig. 17 Odds ratios (ORs) from the random effects meta-analysis of ADHD and *TPH2* SNPs. **a** The single study and pooled ORs for the association between ADHD and rs1843809. **b** The single study and pooled ORs for the association between ADHD and rs1386493

The observed heterogeneity in effect sizes across studies for the two meta-analyzed *TPH2* SNPs makes it difficult to draw definitive conclusions regarding the relation between ADHD and *TPH2*. Given that studies have reported significant

evidence for association with specific SNPs but with opposing alleles, it is possible that a susceptibility locus for ADHD lies within or near *TPH2* that is in partial linkage disequilibrium with the meta-analyzed SNPs. Thus, further research is necessary to explore a potential ADHD-*TPH2* association.

Monoamine oxidase A (MAOA)

The monoamine oxidase genes are contiguous to one another on chromosome Xp11.23 (Lan et al. 1989) and encode enzymes involved in the metabolism of dopamine, serotonin, and norepinephrine. Given that each of these neurotransmitters is thought to play a role in ADHD, the two monoamine oxidase genes, *MAOA* and *MAOB*, are interesting candidates for association with ADHD. Further, treatment studies have suggested that monoamine oxidase inhibitors can reduce ADHD symptom levels (Zametkin et al. 1985). More specific support for *MAOA* as a candidate gene for ADHD comes from a linkage study conducted in a large Dutch family demonstrating a relation between *MAOA* and impulsive, aggressive behavior (Brunner et al. 1993). In addition, an *MAOA* knockout mouse has been shown to display increased levels of aggressive behavior associated with increased levels of monoaminergic neurotransmitter levels (Cases et al. 1998). Given such evidence, *MAOA* has received more attention as a candidate gene for ADHD then *MAOB*.

Initial association studies of ADHD and *MAOA* focused on a dinculeotide repeat near *MAOA*, and while both studies reported significant evidence of an association, a different allele was associated with ADHD in each study (Jiang et al. 2001; Payton et al. 2001). Recent studies have focused largely on a functional 30-bp VNTR 1.2 kb upstream of the gene that has been previously associated with impulsivity and aggression (Caspi et al. 2002; Manuck et al. 2000). This polymorphism consists of alleles of 2, 3, 3.5, 4, and 5 copies with evidence suggesting the 2 and 3 repeat alleles are less efficiently transcribed than the longer alleles (Deckert et al. 1999), though there is some evidence to suggest that the 5 allele also results in less efficient transcription (Meyer-Lindenberg et al. 2006; Sabol et al. 1998). Nonetheless, the majority of studies testing for association between this polymorphism and ADHD have relied on the classification system described by Deckert et al. (1999) in which the 2- and 3-repeat alleles are considered 'low-activity' alleles and the 3.5-, 4-, and 5-repeat alleles are considered 'high-activity' alleles.

Three TDT (Domschke et al. 2005; Manor et al. 2002b; Xu et al. 2007a) and three Case-Control/HHRR (Das et al. 2006; Lawson et al. 2003; Lung et al. 2006) studies were identified for meta-analysis that had tested for an association between this *MAOA* VNTR and ADHD. Based on the initial study of this association (Manor et al. 2002b), the 3.5-, 4-, and 5- repeat alleles were designated as the 'risk' alleles and contrasted against the 2- and 3-repeat alleles. Results, shown in Fig. 18, indicated a non-significant and weak association between ADHD and the high activity alleles (fixed effects: OR = 1.02, 95% CI = 0.84–1.24, $\chi^2 = 0.04$, $P = 0.424$; random effects: OR = 1.02, 95% CI = 0.72–1.43, $\chi^2 = 0.01$, $P = 0.464$) with substantial heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 15.28$, $P = 0.009$; $I^2 = 67$). Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study, as these remained very similar with the exclusion of each study in turn, including the first study and the studies with the highest and lowest odds ratios.

Based on these results, a priority for future research is investigating sources of the heterogeneity in effect sizes across studies. Notably, a potential gene × environment interaction has been reported regarding the association between aggression and the *MAOA* VNTR. These studies suggested that the relation between experiencing maltreatment as a child and subsequently engaging in antisocial behavior in adolescence and adulthood was moderated by *MAOA* genotype at this locus (Caspi et al. 2002; Manuck et al. 2000). Specifically, individuals with the 'low-activity' alleles (i.e., 2- and 3-repeats) showed a stronger relation between childhood maltreatment and subsequent antisocial behavior than individuals with the 'high-activity' alleles (i.e., 3.5-, 4-, and 5-repeats). These studies suggest that environmental variables could moderate the association between ADHD and *MAOA*, thus explaining some of the

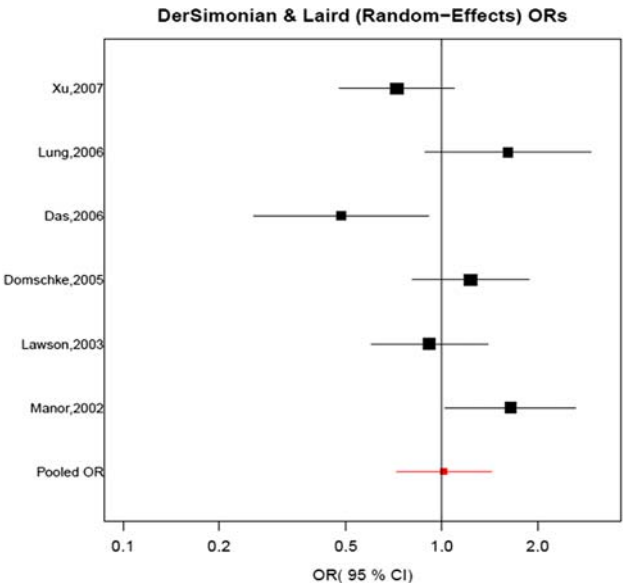

Fig. 18 Odds ratios (ORs) from the random effects meta-analysis of ADHD and the *MAOA* promoter VNTR

heterogeneity in effect sizes observed in the present meta-analysis.

Cholinergic pathway

Nicotinic acetylcholine receptor 4 (CHRNA4)

Several lines of evidence have suggested a relation between the nicotinic neurotransmitter system and ADHD symptoms. For example, nicotine administration has been shown to improve attention and working memory deficits in adults diagnosed with ADHD (Levin 2002) and nicotine agonists have been shown to reduce ADHD symptom severity (Wilens et al. 2006). In addition, nicotine administration has been shown to significantly alter dopamine activity and produce increased locomotor activity in genetically intact mice (Fung and Lau 1988; Grady et al. 1992) and *DAT1* knockout-mice (Weiss et al. 2007a; Weiss et al. 2007b). Given such evidence, researchers have begun to examine different aspects of the nicotinergic system and nicotine receptors specifically, with the nicotinic acetylcholine receptor α4 subunit gene (*CHRNA4*) receiving the most attention thus far.

CHRNA4 has been mapped to chromosome 20q13.2, and is highly expressed in the frontal lobes (Steinlein et al. 1995). Kent et al. (2001) conducted the first study to test for linkage and association between *CHRNA4* and ADHD. Using a TDT, they reported negative evidence of association between ADHD and a single polymorphism in exon 5 of the gene in a sample of 70 children diagnosed with ADHD. More recent studies have focused on two SNPs in exon 5 of the gene (rs2273506 and rs6090384) (Bobb et al. 2005; Todd et al. 2003), though additional studies have conducted more thorough screens of *CHRNA4* using SNPs spanning the length of the gene (Brookes et al. 2006a; Guan et al. 2008; Lee et al. 2008).

Three TDT (Brookes et al. 2006a; Lee et al. 2008; Todd et al. 2003) and two Case-Control/HHRR (Bobb et al. 2005; Guan et al. 2008) studies were identified for the present meta-analysis of association between childhood ADHD and *CHRNA4*. These five studies included tests of association with one or more of the exon 5 SNPs in *CHRNA4* described above (rs2273506 and rs6090304). For the meta-analysis of rs2273506, the 'T' allele was designated as the risk allele based on the initial report (Todd et al. 2003). The results (Fig. 19a) suggested a trend towards an association with ADHD (fixed effects: OR = 1.19, 95% CI = 0.92–1.54, $\chi^2 = 1.82$, $P = 0.089$). There was no significant evidence of heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 2.34$, $P = 0.504$; $I^2 = 0$), thus a random effects meta-analysis was not conducted. A sensitivity analysis indicated that the trend for an association between ADHD and rs2273506 was largely driven by a single study (Todd et al. 2003), as removal of this study reduced the trend towards association to nonsignificance (fixed effects: OR = 1.09, 95% CI = 0.83–1.45, $\chi^2 = 0.44$, $P = 0.258$).

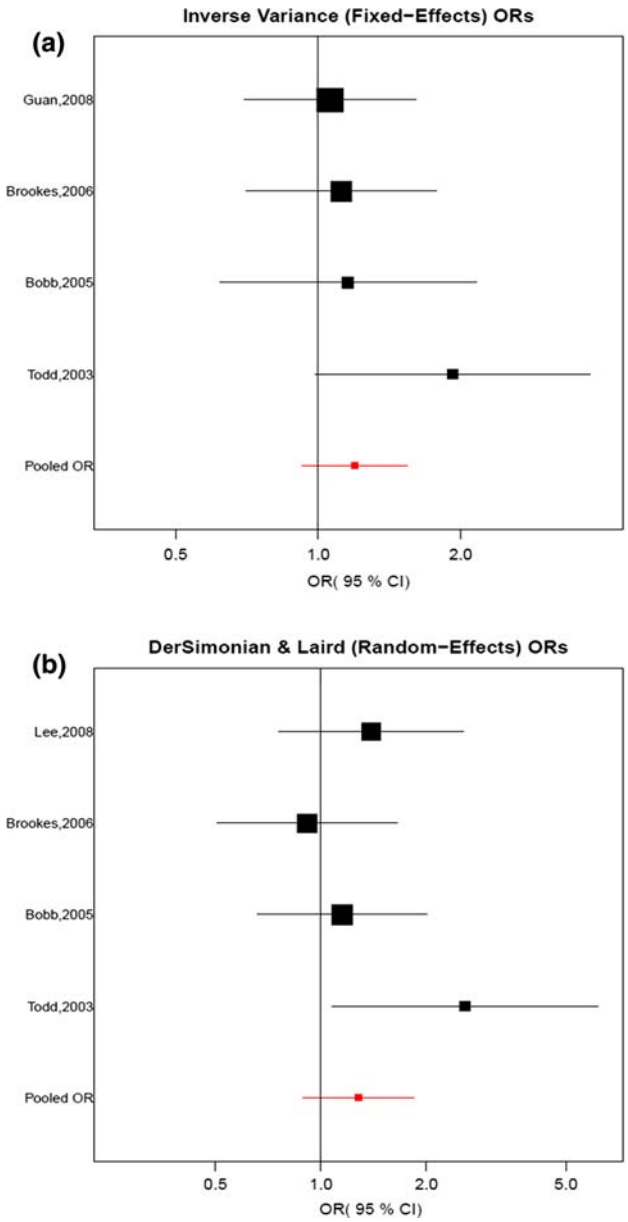

Fig. 19 Odds ratios (ORs) from the meta-analysis of ADHD and *CHRNA4* SNPs. **a** The single study and pooled ORs for the fixed effects meta-analysis of the association between ADHD and rs2273506. **b** The single study and pooled ORs for the meta-analysis of the association between ADHD and rs6090384

For the meta-analysis of rs6090384 (Fig. 19b), the 'T' allele was designated as the 'risk' allele again based on the initial report (Todd et al. 2003). The results of this meta-analysis also suggested a trend towards association with childhood ADHD (fixed effects: OR = 1.25, 95% CI = 0.92–1.72, $\chi^2 = 2.04$, $P = 0.076$; random effects: OR = 1.28, 95% CI = 0.89–1.84, $\chi^2 = 1.76$, $P = 0.093$) with

no significant evidence of heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 3.91$, $P = 0.271$; $I^2 = 23$). Sensitivity analyses indicated this association reached significance after removing the Brookes et al. (2006a) study (random effects: OR = 1.44, 95% CI = 0.96–2.17, $\chi^2 = 3.15$, $P = 0.038$), though removing any of the other studies reduced the trend to non-significance (data not shown). It is likely that the fluctuations in the significance of this association observed in the sensitivity analyses were influenced by the small number of studies included in the meta-analysis.

In summary, the present review suggests a possible association between childhood ADHD and *CHRNA4*. These results should be interpreted with caution, however, given that only four studies were included in the meta-analyses of both *CHRNA4* SNPs. Nonetheless, *CHRNA4* continues to represent an interesting candidate gene for ADHD given the suggested associations between the nicotinergic neurotransmitter system and ADHD.

Nervous system development pathways

Synaptosomal-associated protein 25 gene (SNAP-25)

Recent studies testing for genetic influences that underlie ADHD have begun to consider candidate genes outside of the major neurotransmitter systems. Like the candidate genes discussed thus far, these genes are typically selected based on their function and the plausibility of their putative etiological role for ADHD. *SNAP-25,* which has been mapped to chromosome 20p11.2 (Maglott et al. 1996), is an example of such a gene that has received considerable attention in relation to ADHD. It codes for a protein involved in axonal growth and synaptic plasticity, as well as in the docking and fusion of synaptic vesicles in presynaptic neurons necessary for the regulation of neurotransmitter release (Sollner et al. 1993). The coloboma mouse strain, which has been bred lacking one copy of the SNAP-25 gene following a radiation-induced deletion, displays hyperactive behavior and provides a potential animal model of ADHD (Hess et al. 1992).

Several studies have tested for linkage and association between *SNAP-25* and ADHD, and these studies have consistently genotyped multiple SNPs within the gene rather than focusing on any single polymorphism. As a result, seven polymorphisms within or near *SNAP-25* were included in four studies as required for meta-analysis in the present review. To aid in the presentation of the data, only the meta-analytic results for four SNPs that were genotyped in five or more studies were included in the present review of the association between childhood ADHD and *SNAP-25*. These include rs362987 located in intron 4, rs363006 located in intron 6, rs3746544 in the 3′UTR, and rs1051312 also in the 3′UTR. The three SNPs not included are rs1889189 located in the 5′ flanking region, rs6039806 located in intron 2, and rs8636 located in the 3′UTR, all of which yielded nonsignificant results, though significant heterogeneity was observed in the effect sizes across studies for rs6039806 (data not shown).

For the meta-analysis of the association between ADHD and rs362987, four TDT studies (Brookes et al. 2006a; Feng et al. 2005a; Kim et al. 2007) and one Case-Control/HHRR study (Guan et al. 2008) were identified. Given the significant association reported in the initial study examining this relation (Feng et al. 2005a), the ‘A’ allele was designated as the risk allele. The results of the meta-analysis (Fig. 20a) were nonsignificant (fixed effects: OR = 1.00, 95% CI = 0.90–1.12, $\chi^2 = 0.01$, $P = 0.461$; random effects: OR = 1.00, 95% CI = 0.84–1.18, $\chi^2 = 0.00$, $P = 0.488$), though there was suggestive evidence of heterogeneity in the effect sizes observed across studies (Q-statistic $\chi^2 = 7.80$, $P = 0.099$; $I^2 = 49$). The meta-analysis for rs363006 (Fig. 20b) included five TDT (Brookes et al. 2006a; Feng et al. 2005a; Kim et al. 2007; Renner et al. 2008) and two Case-Control/HHRR studies (Guan et al. 2008; Mill et al. 2004b), and also yielded nonsignificant results (‘G’ allele—fixed effects: OR = 0.98 95% CI = 0.86–1.11, $\chi^2 = 0.10$, $P = 0.626$; random effects: OR = 0.99, 95% CI = 0.86–1.15, $\chi^2 = 0.01$, $P = 0.547$). No significant heterogeneity in effect sizes across studies was observed for the meta-analysis of rs363006 (Q-statistic $\chi^2 = 6.94$, $P = 0.326$; $I^2 = 14$). Sensitivity analyses for these polymorphisms indicated that the pooled estimates of effect size and their significance did not depend on any particular study.

In contrast to these negative results, the analysis of rs3746544, which lies in the 3′UTR, provided significant evidence supporting an association between ADHD and *SNAP-25*. Four TDT studies (Feng et al. 2005a; Kim et al. 2007; Kustanovich et al. 2003) and three Case-Control/HHRR studies (Brophy et al. 2002; Choi et al. 2007; Mill et al. 2004b) were identified for this meta-analysis. Given that previous studies had not reported a significant association between this polymorphism and ADHD, a ‘risk’ allele was not designated. Nonetheless, the results of the meta-analysis, shown in Fig. 20c, provided evidence of a significant association between ADHD and the ‘T’ allele of rs3746544 (fixed effects: OR = 1.15, 95% CI = 1.01–1.31, $\chi^2 = 4.71$, two-tailed $P = 0.030$) with no evidence of heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 2.69$, $P = 0.847$; $I^2 = 0$). Due to this lack of heterogeneity a random effects meta-analysis was not conducted for this association. Sensitivity analyses for rs3746544 indicated that the significance of this result did not depend on any particular study.

It is interesting to note that a nearby SNP also in the 3′UTR of *SNAP-25* failed to support an association with

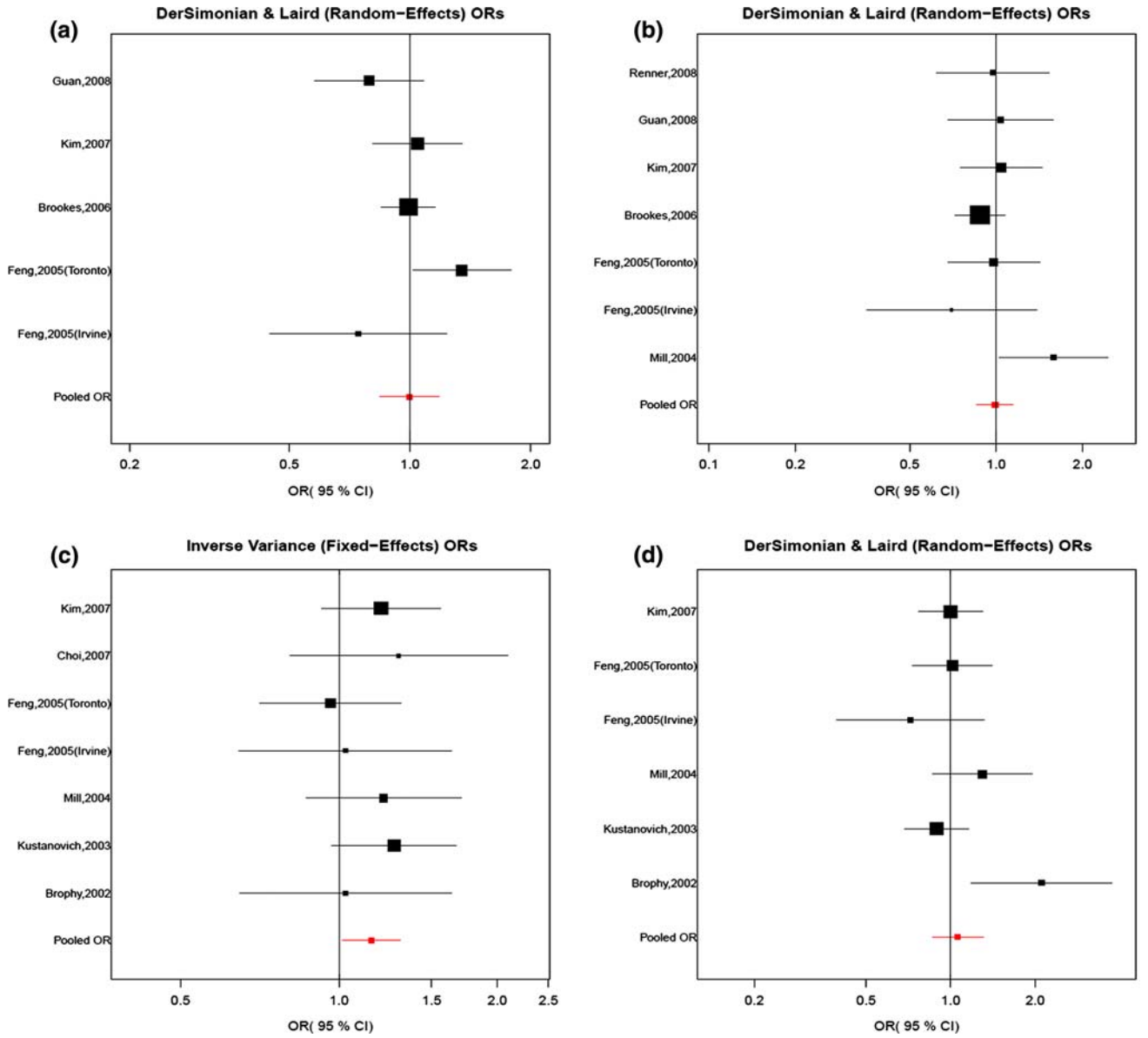

Fig. 20 Odds ratios (ORs) from meta-analysis of ADHD and *SNAP-25* SNPs. **a** The single study and pooled ORs for the random effects meta-analysis of the association between ADHD and rs362987. **b** The single study and pooled ORs for the random effects meta-analysis of the association between ADHD and rs363006. **c** The single study and pooled ORs for the fixed effects meta-analysis of the association between ADHD and rs3746544. **d** The single study and pooled ORs for the random effects meta-analysis of the association between ADHD and rs1051312

ADHD. Four TDT (Feng et al. 2005a; Kim et al. 2007; Kustanovich et al. 2003) and two Case-Control/HHRR (Brophy et al. 2002; Mill et al. 2004b) studies were identified that examined the association between ADHD and rs1051312. Based on the original report (Brophy et al. 2002), the 'T' allele was designated as the 'risk' allele. Results of the meta-analysis (Fig. 20d) were nonsignificant (fixed effects: OR = 1.03, 95% CI = 0.89–1.18, $\chi^2 = 0.14$, $P = 0.356$; random effects: OR = 1.06, 95% CI = 0.86–1.31, $\chi^2 = 0.30$, $P = 0.298$). Nonetheless, moderate evidence of heterogeneity in effect sizes across studies that approached significance was observed (Q-statistic $\chi^2 = 9.70$, $P = 0.084$; $I^2 = 48$). Sensitivity analyses suggested that the largest contribution to the observed heterogeneity came from the Brophy et al. (2002) study given that removal of this study substantially reduced the significance of the Q-statistic ($\chi^2 = 3.38$, $P = 0.497$; $I^2 = 0$), as well as reducing the evidence for association between this polymorphism and ADHD (random effects: OR = 0.98, 95% CI = 0.85–1.14, $\chi^2 = 0.07$, $P = 0.602$).

In summary, several studies have comprehensively tested for association between *SNAP-25* and ADHD with

multiple polymorphisms spanning the length of the gene. Among these polymorphisms, the 3′UTR SNP rs3746544 yielded evidence of a modest but significant association between childhood ADHD and *SNAP-25*. Thus, further studies are needed to determine whether rs3746544 represents the functional variant underlying this association or whether another polymorphism in strong linkage disequilibrium with rs3746544 is responsible for the reported association.

Brain derived neurotrophic factor gene (BDNF)

The brain-derived neurotrophic factor gene (*BDNF*) has been mapped to chromosome 11p13 (Maisonpierre et al. 1991). Brain-derived neurotrophic factor belongs to a family of proteins, known as neurotrophins, involved in promoting neurogenesis, neuronal survival, and synaptic plasticity (Mattson 2008). *BDNF* has been shown to influence the mesolimbic and corticolimbic reward pathways in the brain by modulating their response to dopamine (Guillin et al. 2001). In addition, *BDNF* has been shown to enhance the effects of stimulants on these dopaminergic pathways (Hall et al. 2003; Horger et al. 1999) making it an interesting candidate gene for ADHD (Tsai 2003).

A common polymorphism resulting in a valine to methionine amino acid substitution at codon 66 (Val66Met; rs6265) has been identified in *BDNF* that has been shown to influence the intracellular trafficking and activity-dependent secretion of BDNF in brain (Chen et al. 2004; Egan et al. 2003). Four TDT (Brookes et al. 2006a; Kent et al. 2005; Lee et al. 2007; Schimmelmann et al. 2007) and four Case-Control/HHRR (Friedel et al. 2005; Guan et al. 2008; Xu et al. 2007b) studies were identified for meta-analysis that tested for association between this Val66Met polymorphism and ADHD. Based on previous research (Egan et al. 2003; Kent et al. 2005), the 'G' or Valine allele was designated as the 'risk' allele. Results of this meta-analysis, shown in Figure 21, were nonsignificant (fixed effects: OR = 1.01, 95% CI = 0.91–1.12, $\chi^2 = 0.02$, $P = 0.406$). There was no evidence of heterogeneity in effect sizes across studies (Q-statistic $\chi^2 = 6.31$, $P = 0.504$; $I^2 = 0$), thus a random effects meta-analysis was not conducted. Sensitivity analyses indicated that the pooled estimates of effect size and their significance did not depend on any particular study. Thus, the present meta-analysis does not support an association between ADHD and the Val66Met polymorphism in *BDNF*. It should also be noted that despite an initial report suggesting that the Val66Met polymorphism was associated with ADHD only through paternal inheritance (Kent et al. 2005), subsequent studies failed to replicate this result (Lee et al. 2007; Schimmelmann et al. 2007). Thus, there is currently little evidence to suggest a relation between ADHD and *BDNF*.

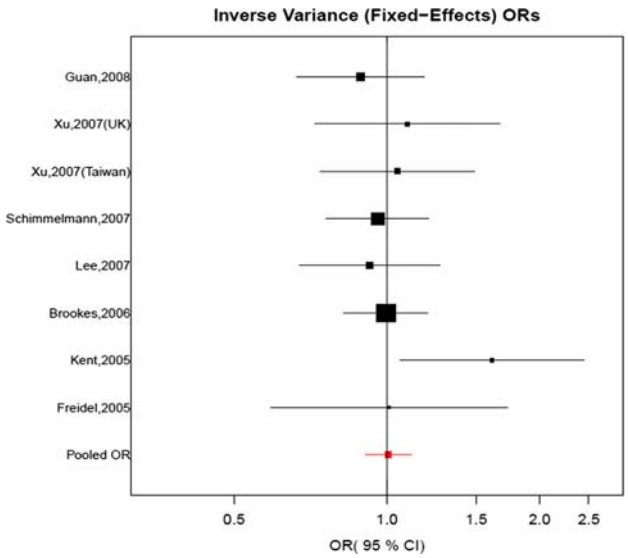

Fig. 21 Odds ratios (ORs) from the fixed effects meta-analysis of ADHD and the Val66Met (rs6265) *BDNF* SNP

Discussion

Several polymorphisms in candidate genes were associated with childhood ADHD, including several markers in the dopaminergic and serotonergic systems, and suggested associations in *CHRNA4* and *SNAP25*. The associated markers included SNPs as well as VNTRs some of which lay within coding regions and others within regulatory regions, though further research is needed to determine if these markers represent true causal variants as their function generally remains unknown. Heterogeneity in effect sizes across studies characterized several of the reviewed markers, including some that showed significant evidence for association and others that did not. This highlights the need for future studies that examine differences in sample and methodological characteristics that can explain such heterogeneity and point to ways of maximizing associations.

Significant associations with candidate gene polymorphisms in this review were modest in magnitude, with Odds ratios ranging from 1.12 to 1.33. There are several possible reasons why the effect sizes for associations between childhood ADHD and candidate gene polymorphisms are so modest. First, related to the point above, heterogeneity both within and across studies in sample characteristics or important methodological features may result in a dilution of the true effect size by mixing together samples in which the association is strong with those in which it is weak or non-existent. Studies may differ considerably in methodological rigor and quality in ways that could have a significant impact on their likelihood of detecting a significant

association and the estimation of its magnitude. Along these lines, very few studies reported any quality control analyses other than tests of Hardy–Weinberg equilibrium, and many studies omitted such tests or reported their results in a cursory fashion (e.g., whether or not they were significant). Researchers should endeavor to provide additional psychometric data on their assessment procedures (e.g., reliability and validity) and analyses of the quality of the genotyping conducted. The latter might include call rates, similarity of obtained allele frequencies to those in public databases (e.g., the International HapMap Consortium 2003), and repeated genotyping consistency.

Second, all of the associations we meta-analyzed and reviewed herein were for single polymorphisms in genes. It is conceivable that while any single genetic marker confers only a small risk for disorder, considering multiple markers in a gene in tandem may result in larger effects. Although researchers have begun genotyping multiple markers in candidate genes, analyses of association are typically conducted on each marker singly (and occasionally in haplotypes). Use of recently developed multilocus tests of association between a disorder or trait and multiple markers across a gene may yield more substantial effect sizes and stronger evidence for association (Xu et al. 2006).

Third, it is possible that our best guesses regarding candidate genes for ADHD based on their function and perceived etiological relevance are just not good enough. Many psychiatric and medical genetics researchers have become profoundly skeptical of the candidate gene approach given the plethora of associations that have failed to replicate despite highly plausible etiological relevance and the enthusiasm over positive results from an initial study. This has led many to invest more strongly in genome wide association scans (GWAS), of which the first few for ADHD are beginning to appear (see review by Franke et al. 2009, this issue). It is possible that associations with the positional candidates that emerge from such exploratory searches will be more replicable and show stronger effects than the functional candidate genes that have been studied to date. Consistent with this, replicable associations were found for three of the functional candidate genes (*5HTT*, *DAT1*, and *SLC6A2*) that have also emerged as positional candidates from extant genome scans of ADHD. Promising positional candidates (e.g., *DOCK3*) and positional/functional hybrid candidates (e.g., *SLC9A9*, *CDH13*) are beginning to be investigated in association studies of ADHD. Nonetheless, it also is quite possible that any genes that we find to be associated with ADHD will have similarly small effect sizes, in keeping with the multifactorial polygenic etiology that is thought to characterize ADHD and other psychiatric disorders. This possibility only highlights the need for much larger sample sizes than those that currently characterize association studies of ADHD. Such samples, both from single sites and from multi-site studies that are becoming the norm in psychiatric and medical genetics, will greatly facilitate the detection of replicable associations and more accurate estimation of the magnitude of risk conferred, as well as allow us to leave behind genes that while plausible candidates are not borne out by the empirical evidence.

The present study attempted to provide a quantitative review of frequently studied candidate gene polymorphisms for ADHD. Though meta-analysis provides a rigorous method for integrating findings for commonly studied candidate genes, this approach cannot be applied to genes that have only recently been suggested as candidates or have been under-studied to this point. Thus, several genes that have shown promising evidence for association with childhood ADHD could not be included in the present review. For example, dopa decarboxylase (*DDC*), which is involved in dopamine and serotonin synthesis, has been associated with childhood ADHD in several studies (Brookes et al. 2006a; Guan et al. 2008; Hawi et al. 2001; Ribases et al. 2009), but these studies have used largely non-overlapping SNP sets to test for association. Similarly, genes such as the dopamine D1 receptor gene (*DRD1*; Misener et al., 2004; Bobb et al., 2005), the dopamine D1 receptor interacting protein gene (*DRD1IP; CALCYON*—Laurin et al., 2005), and the serotonin 1D receptor gene (*HTR1D*—Li et al. 2006d; Ribases et al. 2009) are promising candidates given significant evidence of association with ADHD in preliminary reports. While we have tried to quantitatively summarize the current findings from candidate gene studies of ADHD, future meta-analytic reviews will be necessary as investigations of the genes that underlie ADHD continue to progress.

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