Research Paper

Candidate genes involved in neural plasticity and the risk for attention-deficit hyperactivity disorder: a meta-analysis of 8 common variants

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Background: Attention-deficit hyperactivity disorder (ADHD) is an important psychiatric condition in terms of its prevalence and impact on quality of life. It has one of the highest heritabilities found in psychiatric disorders. A number of association studies exploring several candidate genes in different populations around the world have been carried out. The objective of the present study was to carry out a meta-analysis for 8 common variants located in 5 top candidate genes for ADHD (*BDNF*, *HTR1B*, *SLC6A2*, *SLC6A4* and *SNAP25*); these genes are known to be involved in synaptic transmission and plasticity. **Methods:** We performed a search for published genetic association studies that analyzed the candidate polymorphisms in different populations, and we applied state-of-the-art meta-analytical procedures to obtain pooled odds ratios (ORs) and to evaluate potential basis of heterogeneity. We included 75 genetic association studies in these meta-analyses. **Results:** A major part of the previously postulated associations were nonconsistent in the pooled odds ratios. We observed a weak significant association with a single nucleotide polymorphism (SNP) located in the 3′ UTR region of the *SNAP25* gene (rs3746544, T allele, OR 1.15, 95% confidence interval 1.01–1.31, $p = 0.028$, $I^2 = 0\%$). In addition to the low coverage of genetic variability given by these variants, phenotypic heterogeneity between samples (ADHD subtypes, comorbidities) and genetic background may explain these differences. **Limitations:** Limitations of our study include the retrospective nature of our meta-analysis with the incorporation of study-level data from published articles. **Conclusion:** To our knowledge, the present study is the largest meta-analysis carried out for ADHD genetics; previously proposed cumulative associations with common polymorphisms in *SLC6A4* and *HTR1B* genes were not supported. We identified a weak consistent association with a common SNP in the *SNAP25* gene, a molecule that is known to be central for synaptic transmission and plasticity mechanisms.

Introduction

Attention-deficit hyperactivity disorder (ADHD) has been identified as an important psychiatric condition in terms of its prevalence (around 5% worldwide) and its impact on quality of life for patients and their families.[1] It has one of the highest heritabilities found in psychiatric disorders (around 0.76), which has supported the development of many genetic association studies exploring a number of candidate genes in different populations around the world.[2] These studies have compared allele and genotype frequencies between patients and controls or their transmission within nuclear families.[3]

A large number of these genetic association studies have focused on the analysis of variations in dopaminergic and serotoninergic genes.[4] A recent meta-analysis of 3 dopaminergic genes found a significant association with polymorphisms in the *DRD4* and *DRD5* genes.[5] It has been postulated that a dysfunction of neuroplasticity mechanisms can be involved in the pathophysiology of ADHD and other common neuropsychiatric disorders.[6–8] In this respect, a recent general review about ADHD genetics suggested the possibility that variations in some candidate genes such as *SNAP25, SLC6A4* and *HTR1B* could be important risk factors for ADHD in different populations;[4] these genes are known to be involved in neurotransmission and neural plasticity. In addition, in recent years a number of publications have explored other polymorphisms

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in genes of relevance for synaptic function and plasticity such as *BDNF* and *SLC6A2*, as susceptibility factors for ADHD.[2] Recent genome-wide association studies of ADHD and related phenotypes show additional evidence supporting the role of neuroplasticity genes in the etiology of this disorder.[9,10]

To explore the possibility that some of these common variants may have a role as susceptibility factors for ADHD, we applied meta-analytic strategies to data from available association studies and considered possible factors that could account for heterogeneity between studies.

General information about the biological features of the 5 candidate genes analyzed herein is shown in Table 1. The *BDNF* gene encodes one of the main neurotrophic factors in the brain, *HTR1B* encodes one of the serotonin receptors, *SLC6A2* encodes the noradrenalin transporter, *SLC6A4* encodes the serotonin transporter and *SNAP25* encodes one of the main presynaptic proteins. All these genes are known to be involved in synaptic and neural plasticity, a central molecular mechanism responsible for many behavioural phenomena in normal and pathological conditions in humans and animals.[12]

Methods

We searched for genetic association studies analyzing polymorphisms in the *SLC6A4* (rs4795541 and intronic VNTR), *SNAP25* (rs3746544 and rs1051312), *BDNF* (rs6265 and rs56164415), *HTR1B* (rs6296) and *SLC6A2* (rs998424) genes in the PubMed database. We combined disease search terms "ADHD or attention-deficit hyperactivity disorder" with the respective search terms for the genes of interest: "BDNF or brain-derived neurotrophic factor," "HTR1B or serotonin receptor 1B," "SLC6A2 or norepinephrine transporter," "SLC6A4 or serotonin transporter" and "SNAP25 or synaptosomal-associated protein, 25kDa." In addition, we searched reference lists of relevant review and original papers and checked the supplementary files of high-throughput association studies of ADHD to identify additional papers not covered by the electronic search of abstracts.

We included articles published in English in peer-reviewed journals that described results from case–control or transmission disequilibrium test (TDT) studies analyzing the association of the selected candidate polymorphisms with ADHD in children or adults in different ethnic populations (the TDT was the main analytical approach used in the family-based studies). However, we did not include studies of quantitative measures of ADHD, response to medications or analyses of other markers (different from the selected candidate polymorphisms) in the candidate genes.

We extracted information about general features of the studies (e.g., sample sizes, phenotyping scales, genotyping methodologies, subtypes analyzed) from each article. In all cases of missing data, we contacted the respective authors to ask for allele frequencies that were not available in the main text of the papers or in their supplementary files.

For the meta-analysis procedures, we used the Catmap program (http://cran.r-project.org/web/packages/catmap/index.html); it is a freely available package specifically created for the meta-analysis of genetic association studies. It runs in the R statistical platform and allows for the joint analysis of case–control and family-based association studies and other advanced analysis approaches (e.g., implementation of fixed-effects or random-effects models, sensitivity analysis, cumulative meta-analysis).[13] We calculated the Q statistic for heterogeneity and, following recommendations in the area,[14] we used random-effects models for the calculations of the pooled odds ratios (ORs).

Table 1: General information about candidate genes for attention-deficit hyperactivity disorder

Gene	Symbol	Location	Size	Protein	Isoforms*	Exons	SNPs	nsSNPs	Blocks†	tSNPs	CNVs	Expression‡	No. studies§
Brain-derived neurotrophic factor	*BDNF*	11p13	66 857	247 aa	9/24	2	235	5	2	18	N	• cerebellum peduncles • hypothalamus • amygdala	189
5-HT receptor 1B	*HTR1B*	6q13	1260	390 aa	1/1	1	29	4	3	21	Y	• prefrontal cortex • hypothalamus • cerebellum peduncles	49
Solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2	*SLC6A2*	16q12.2	48 629	617 aa	5/7	14	447	17	9	47	Y	• subthalamic nucleus • prefrontal cortex • temporal lobe	39
Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	*SLC6A4*	17q11.1-q12	41 379	630 aa	1/4	15	424	14	2	16	N	• cerebellum • prefrontal cortex • caudate nucleus	589
Synaptosomal-associated protein, 25kDa	*SNAP25*	20p12-p11.2	88 589	206 aa	3/31	8	704	6	13	55	N	• cerebellum • cerebellum peduncles • occipital lobe	15

5-HT = serotonin; CNVs = copy number variants; nsSNPs = nonsynonymous single nucleotide polymorphisms; SNPs = single nucleotide polymorphisms; tSNPs = r^2-based tagging single nucleotide polymorphisms.
*Isoforms were identified in the UCSC genes track/AceView track.
†Haplotype blocks.
‡Expression information in brain tissues was retrieved from the SymAtlas database.[11]
§Number of published papers exploring variations in the respective genes.

We downloaded genotype data for the different candidate genes from the HapMap database (release23a; using additional 20 kb as both flanking 5′ and 3′ regions) for the Caucasian (CEU, from Northern Europe living in Utah, US), Asian (JPT+CHB, from Japanese living in Tokyo and Chinese living in Beijing) and African (YRI, Yoruba living in Nigeria) populations,[15] and we calculated the haplotype block and linkage disequilibrium structures with the Haploview and GOLD programs.[16,17] To enhance the visualization of haplotype block structure we modified the output from Haploview, incorporating physical distances into the linkage disequilibrium map. We retrieved physical positions of analyzed markers and their locations with respect to single nucleotide polymorphisms (SNPs) typed in the HapMap project from the UCSC genome browser[18] and retrieved information about candidate genes from the UCSC genome browser, the NCBI dbSNP database, GeneCards, SymAtlas and HuGE navigator.[11,18–21] In addition, we retrieved data about protein–protein interactions from the UniHI server.[22]

We assessed the evidence from the current meta-analysis by applying the Venice interim criteria,[23] as implemented by Allen and colleagues,[24] which are based on 3 main features: amount of evidence, consistency of replication and protection from bias (further details about the numerical analyses supporting these assessments are provided in Appendix 1, available at www.cma.ca/jpn).

Results

Information about the genetic markers included in this meta-analysis is shown in Table 2. We applied meta-analytical procedures to data from 75 studies that analyzed these 8 common variants in 5 candidate genes involved in neural transmission and plasticity. We included a number of meta-analyses examining 17 studies on rs4795541 (*SLC6A4*; $n = 16$), 10 studies on the VNTR in *SLC6A4* gene ($n = 9$), 14 studies on rs6265 (*BDNF*; $n = 12$), 3 studies on rs56164415 (*BDNF*; $n = 2$), 7 studies on rs3746544 (*SNAP25*; $n = 6$), 6 studies on rs1051312

Table 2: General information about candidate polymorphisms for attention-deficit hyperactivity disorder

Polymorphism	Alias	Gene	Position	Region	Alleles	MAF	Conservation*	Functional†	Coverage, %‡	Year§
rs6265	Val66Met	*BDNF*	chr11:27636492	Exon	A/G	0.18	Yes	Yes	84.71	2002
rs56164415	C270T	*BDNF*	chr11:27,678,311	Intron	C/T	0.06	Yes	No	84.71	2001
rs6296	G861C	*HTR1B*	chr6:78228979	Exon	C/G	0.34	Yes	No	36.76	1995
rs998424	MnlI	*SLC6A2*	chr16:54289447	Intron	C/T	0.33	No	No	0.00	1996
rs4795541	HTTLPR	*SLC6A4*	chr17:25588443–25588485	5′ region	s/l	0.4	No	Yes	0.00	1996
	HTT VNTR	*SLC6A4*	chr17:25,572,552–25,572,650	Intron	9/10/12	0.44	No	Yes	53.23	1996
rs3746544	MnlI	*SNAP25*	chr20:10235084	3′UTR	A/C	0.41	No	No	1.12	2000
rs1051312	DdeI	*SNAP25*	chr20:10235088	3′UTR	C/T	0.41	Yes	No	1.12	2000

MAF = minor allele frequency.
*Genomic position conserved in mouse.
†Evidence about allele-specific functional effects.
‡Fraction of haplotype block variation in the genomic region covered by polymorphism.
§Year in which the polymorphism was discovered.

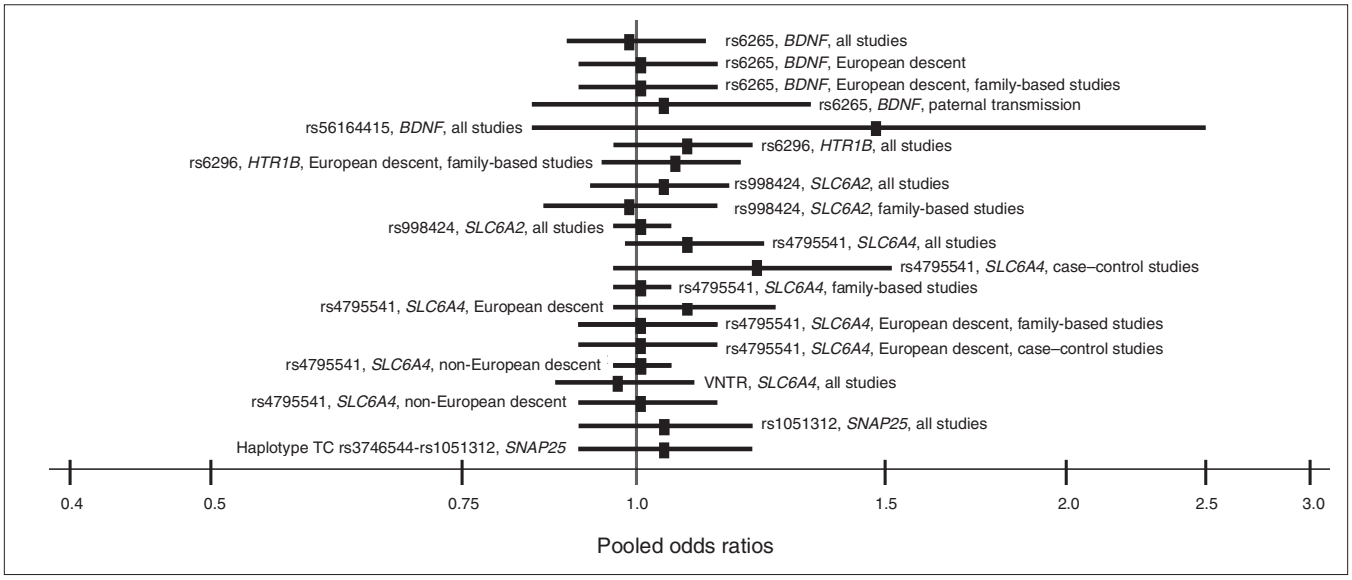

Fig. 1: Pooled odds ratios for different genotype/phenotype correlations that were nonsignificant in our meta-analysis.

(*SNAP25*; n = 5), 12 studies on rs6296 (*HTR1B*; n = 11) and 6 studies for the rs998424 polymorphism (*SLC6A2*; n = 6). Data about general features of the studies and the respective allele frequencies are provided in Appendix 2, available at www.cma.ca/jpn. Many of the studies used the TDT design, were mainly carried out in populations of European descent and were based on the DSM-IV diagnosis of ADHD. The composition of clinical samples was heterogeneous among studies, mainly in terms of ADHD subtypes and percents (e.g., the proportion of included patients with ADHD combined type varied between 29% and 100%) and types of comorbidities (e.g., the proportion of included patients with oppositional defiant disorder varied between 0% and 58%). Many of the studies reported a positive association in stratified analyses (e.g., in specific ADHD subtypes or parental transmissions) that were not evident in the total sample analyses (Fig. 1). Application of formal meta-analytical procedures using random-effects models showed that a major part of the pooled ORs were not significant for the total samples. In some cases, there was enough data (from 3 or more studies) to conduct a meta-analysis of stratified samples and the results were also mainly negative (Fig. 1). Respective pooled ORs for each association are presented in Appendix 3, available at www.cma.ca/jpn.

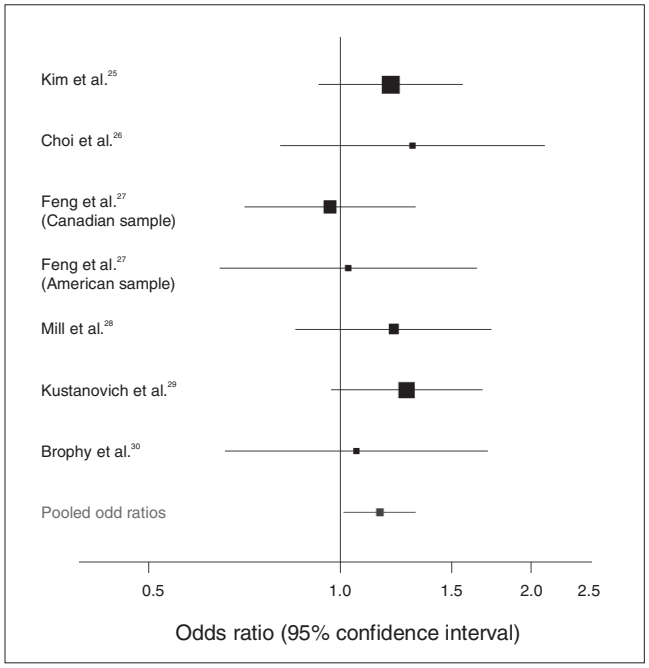

Fig. 2: Odds ratios for the A allele of the rs3746544 polymorphism in the *SNAP25* gene of individuals with attention-deficit hyperactivity disorder.

There was a significant pooled OR for the T allele of the rs3746544 SNP in the *SNAP25* gene after including all available studies: OR 1.15, 95% confidence interval (CI) 1.01–1.31, p = 0.028 (460 transmissions v. 402 nontransmissions in 6 TDT studies; $\tau^2 \leq 0$, Q statistic p = 0.86, I^2 = 0%; Fig. 2).[25–30] In addition, tau2 (an estimate of the between-study variance used for the calculation of random-effects models) was equal to or less than 0 for this pooled OR; in these cases, the fixed-effects and random-effects models are mathematically equivalent. In terms of the Venice interim criteria,[23] the evidence for this association with a marker in *SNAP25* can be defined as weak (AAC grades; Appendix 1).

We did not find evidence for the paternal overtransmission of the G allele of the rs6296 SNP in the *HTR1B* gene (OR 1.37, 95% CI 0.99–1.90, p = 0.06, Q statistic p = 0.045, I^2 = 62.6%, Appendix 4, available at www.cma.ca/jpn [Fig. S9]), which contrasts with a positive pooled OR that was previously reported for a smaller set of studies.[31]

Analysis of HapMap data for these candidate genes showed that several of the analyzed markers cover a minor fraction of the genetic variability in those genomic regions. Data about haplotype block structures and linkage disequilibrium patterns in different populations for the candidate genes are presented in Figure 3 and Appendix 4, available at www.cma.ca/jpn (Fig. S3–S8).

Discussion

An examination of publication trends in PubMed and HuGE navigator (Appendix 4, Fig. S1) showed that there were 198 publications about 61 candidate genes for ADHD. The first was published in 1995. These publications mainly involved populations of European descent; there is a clear need for the analysis of ADHD candidate genes in other regions, including Asia, Latin America and Africa. In addition to these 198 publications, there were 4 published meta-analyses for 4 of the genes: *DAT1*, *DRD4*, *DRD5* and *COMT*[5,32–34] (see Appendix 1 for a comparison between genetic association studies of ADHD and schizophrenia).

It has been postulated that a dysfunction of neuroplasticity mechanisms can be involved in the pathophysiology of ADHD and other common neuropsychiatric disorders.[6–8] We have applied meta-analytical procedures[14] to available data examining 8 common polymorphisms in 5 candidate genes for ADHD. The functional interactions for these genes involved in neural plasticity are shown in Appendix 4,

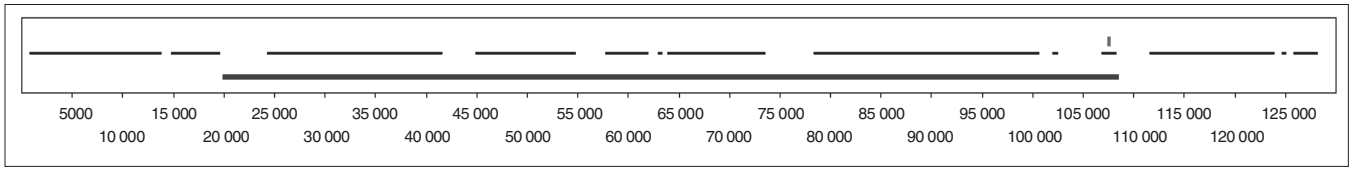

Fig. 3: Haplotype block structure of the *SNAP25* gene region (around 130 kb) in the Caucasian population (Northern European descent, living in Utah) from HapMap release 23a. The solid line indicates the position of the *SNAP25* gene, the vertical line shows the position of the 2 studied single nucleotide polymorphisms in the 3′ UTR region and the broken line indicates the location of haplotype blocks.

Figure S2 (*SNAP25* is part of the SNARE complex and appears as central in terms of interactions with other neural proteins). Several of the papers reported associations only in the stratified analysis and not in the total samples of ADHD, which makes comparisons among the studies difficult. It has been shown that analysis of several subtypes may be an important contributing factor to false-negatives arising from multiple testing.[35] We found a significant cumulative association with the T allele of the rs3746544 SNP in the *SNAP25* gene (population attributable risk 6%). In terms of the Venice interim criteria, the cumulative evidence for this association can be considered as being weak. This marker is not known to have allele-dependent functional effects; it is possible that it is in linkage disequilibrium with genetic variations of functional relevance (located in protein-coding or regulatory regions).

Faraone and colleagues[4] in their general review about ADHD genetics stated that they found significant ORs of 1.19 (1.03–1.38) for rs3746544 (*SNAP25*) in family-based studies, 1.31 (1.09–1.59) for *HTTLPR* in case–control studies and 1.44 (1.14–1.83) for rs6296 (*HTR1B*) in family-based studies; however, there were no data or details about the specific studies included or the meta-analytic procedures that were used.

Phenotypic heterogeneity is an evident issue in the analyzed studies. There were important differences in terms of clinical features such as the relative compositions of included subtypes and comorbidities.[2] A major part of the genetic markers analyzed in the present study were identified in the pre-HapMap era (and in some cases before the completion of the Human Genome Project)[36] and do not capture the complete variability in those genomic regions; however, some of them are genetic variations with described allele-specific functional effects.[2] In terms of implications for ongoing genome-wide association studies for ADHD,[9,10] it is important to highlight that some candidate genes such as *HTR1B* are underrepresented in commonly used genotyping chips (0 and 1 SNPs present in the Illumina 650K and the Affymetrix 6.0 genotyping platforms, respectively, compared with 21 tagging SNPs in that genomic region).[15,18]

Sample sizes of many of the studies included in our meta-analysis are in the low range compared with genetic studies in other psychiatric diseases (meta-analyses for schizophrenia are based on an average size of more than 3500 participants). This can be explained in part by the use of family-based approaches (e.g., the TDT), which have the inherent disadvantage of the effective samples being substantially smaller than the initial samples.[3]

To our knowledge, the present study is the largest meta-analysis of ADHD genetics. A recent meta-analysis of 3 dopaminergic genes found a significant association with common polymorphisms in the *DRD4* (OR 1.34, 95% CI 1.23–1.45, $p < 0.001$ for the 7-repeat, 33 studies, population attributable risk 5%) and *DRD5* genes (OR 1.34, 95% CI 1.21–1.49, $p < 0.001$ for the 148 bp allele, 9 studies, population attributable risk 12%).[5] Our current results suggest that a common variation in *SNAP25*, in addition to polymorphisms in the *DRD4* and *DRD5* genes, may be significantly associated with ADHD (out of 9 genes formally tested in meta-analyses).[5,32–34]

Limitations

Our study has 3 main limitations, which are also inherent in many meta-analyses[14] of association studies in psychiatric genetics. The first was the retrospective nature of our meta-analysis, incorporating data from published studies. The second was the inclusion of study-level data. The third was the study of polymorphisms with limited coverage of the respective candidate genes. The development of prospective meta-analyses will facilitate the control of possible publication biases and the inclusion of individual-level data.[14] Ongoing studies using information of genome-wide linkage disequilibrium patterns from HapMap data[15] will lead to studies of multiple polymorphisms with a better coverage of the candidate genes.

It is expected that future systematic analysis of animal models of ADHD will identify additional variations in genes involved in synaptic plasticity (synaptogenomics)[7,37] as important genetic risk factors for ADHD (see Appendix 1 for an overview of recent results from genome-wide association studies of ADHD related to neural plasticity). In this context, HapMap-based analysis of common variants, including further genome-wide association studies, to complement the exploration of rare variants in different populations around the world will be fundamental.[36]

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