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An international multicenter association study of the serotonin transporter gene in persistent ADHD

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Attention deficit hyperactivity disorder (ADHD) is a common behavioral disorder affecting children and adults. It has been suggested that gene variants related to serotonin neurotransmission are associated with ADHD. We tested the functional promoter polymorphism 5-HTTLPR and seven single nucleotide polymorphisms in *SLC6A4* for association with ADHD in 448 adult ADHD patients and 580 controls from Norway. Replication attempts were performed in a sample of 1454 Caucasian adult ADHD patients and 1302 controls from Germany, Spain, the Netherlands and USA, and a meta-analysis was performed also including a previously published adult ADHD study. We found an association between ADHD and rs140700 [odds ratio(OR) = 0.67; *P* = 0.01] and the short (S) allele of the 5-HTTLPR (OR = 1.19; *P* = 0.06) in the Norwegian sample. Analysis of a possible gender effect suggested that the association might be restricted to females (rs140700: OR = 0.45; *P* = 0.00084). However, the meta-analysis of 1894 cases and 1878 controls could not confirm the association for rs140700 [OR = 0.85, 95% confidence interval (CI) = 0.67–1.09; *P* = 0.20]. For 5-HTTLPR, five of six samples showed a slight overrepresentation of the S allele in patients, but meta-analysis refuted a strong effect (OR = 1.10, 95% CI = 1.00–1.21; *P* = 0.06). Neither marker showed any evidence of differential effects for ADHD subtype, gender or symptoms of depression/anxiety. In conclusion, our results do not support a major role for *SLC6A4* common variants in persistent ADHD, although a modest effect of the 5-HTTLPR and a role for rare variants cannot be excluded.

Keywords: Adult attention deficit hyperactivity disorder, comorbidity, depression, gender; *5-HTT*, 5-HTTLPR, serotonin, *SERT*, *SLC6A4*

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Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder. ADHD was initially considered a childhood condition, but recent studies have shown that symptoms often persist into adulthood (Faraone *et al*. 2006). Many genetic studies have focused on genes related to the dopaminergic system, principally because stimulant drugs, including methylphenidate and amphetamine, inhibit the dopamine (and norepinephrine) transporters. However, in mice lacking the dopamine transporter gene (*Dat1*) and exhibiting extreme hyperlocomotion (Giros *et al*. 1996), a calming effect of psychostimulants was still observed, which was not accompanied by any change in the dopamine level. It was therefore concluded that this effect was dependent on serotonergic neurotransmission (Gainetdinov *et al*. 1999), which was underscored by the calming effect of serotonin reuptake inhibitors in these animals. The serotonergic neurotransmission system is also considered a candidate for ADHD by its known influence on behavioral traits,

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such as aggression and impulsivity (Halperin *et al*. 1994; Lucki 1998), and by its role in brain development (Azmitia 2001).

The main regulator of synaptic serotonin concentration is the serotonin transporter, encoded by the *SLC6A4* gene (also known as *5-HTT* and *SERT*), mapped to human chromosome 17q11.1–q12 (Ramamoorthy *et al*. 1993). The most widely studied polymorphism in this gene is an insertion/deletion in the promoter region, the 5-HTTLPR. Functional studies on this polymorphism have demonstrated that the deletion [short (S)] variant reduces transcriptional efficiency of the gene (Lesch *et al*. 1996). *SLC6A4* has been implicated in a wide range of disorders with the shared feature of emotional dysregulation, such as depression and anxiety disorder (Murphy & Lesch 2008). It has been suggested that the long (L) allele is a risk variant for developing ADHD (Beitchman *et al*. 2003; Curran *et al*. 2005; Kent *et al*. 2002; Manor *et al*. 2001; Seeger *et al*. 2001; Zoroglu *et al*. 2002), although subsequent studies have been inconsistent (Brookes *et al*. 2006; Grevet *et al*. 2007; Heiser *et al*. 2006; Langley *et al*. 2003; Oades *et al*. 2008; Wigg *et al*. 2006; Xu *et al*. 2005), as shown in recent meta-analyses (Forero *et al*. 2009; Gizer *et al*. 2009).

The aim of this study was to examine the putative association between adult ADHD and variants in the *SLC6A4* gene region. Because it has been suggested that the 5-HTTLPR is associated with regulations of emotions, we also wanted to test if the S allele implicated in susceptibility to depression was differently associated in the group of ADHD patients who reported that they had experienced significant depression and anxiety. We first genotyped the 5-HTTLPR polymorphism and seven single nucleotide polymorphisms (SNPs) that tagged all common variants in the *SLC6A4* gene region in 448 clinically diagnosed adult Norwegian ADHD patients and 580 ethnically matched controls. We followed up the results by genotyping the two markers showing strongest association in an additional 1454 adult ADHD patients and 1302 controls from four populations from IMpACT, the International Multicentre persistent ADHD CollaboraTion. This co-operation was initiated in 2007 with the goal of promoting research on the genetics of adult ADHD and currently consists of research groups from Germany, Spain, the Netherlands, UK, USA and Norway. Additionally, we sequenced all coding exons in a subgroup of 93 Norwegian patients to search for possible coding variants with stronger effect.

Materials and methods

Subjects

The Norwegian sample consists of 448 Caucasians of Norwegian ancestry (237 males and 211 females) of more than 18 years of age, diagnosed with ADHD or hyperkinetic disorder using either the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) or International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) protocols. The majority was recruited by responding to invitation sent to their addresses, based on a Norwegian national registry of adult ADHD patients. The remaining patients were directly recruited from psychiatrists or outpatient clinics (Johansson *et al*. 2008). All patients provided written informed consent and filled in a questionnaire including the 18-item World Health Organization's Adult ADHD Self Report Scale (ASRS) (Kessler *et al*. 2005). ADHD combined, inattentive or impulsive/hyperactive subtypes were assessed using the ASRS with a cutoff of 17 or more on each subscale. Ten percent of the patients were defined as subthreshold and were excluded from subtype-specific analyses (Halleland *et al*. 2009). Depression and anxiety was extracted from self-reporting questionnaire data according to the following question: 'Have you experienced episodes of significant depression or anxiety?'. Patients with mental retardation were excluded from analyses.

The control group of 580 Norwegian adults (257 males and 323 females) consisted of 195 healthy blood donors (for whom only gender was known) and a random sample of 385 healthy volunteers (aged 18–40 years) recruited from all over Norway for the purpose of this study, described in more detail in Halmøy *et al*. (2010). No exclusion criteria were applied for the random controls.

Replication sample

The replication samples obtained through the IMpACT consortium included a total of 1454 cases and 1302 controls from Spain, Germany, the Netherlands and USA (Table 1). ADHD was diagnosed in accordance with the DSM-IV criteria; onset before the age of 7, lifelong persistence and current diagnosis. The depression and anxiety status was assessed by a psychiatrist (DSM-IV criteria) in the samples from the Netherlands and by the Structured Clinical Interview for DSM Disorders-1 in the German, Spanish and American samples. For more detailed description of the procedures and instruments used, please refer to the following references: Bekker *et al*. (2005), Franke *et al*. (2008), Jacob *et al*. (2007), Johansson *et al*. (2008), Kooij *et al*. (2005), Ramos-Quiroga *et al*. (2008) and Sanchez-Mora *et al*. (2009).

Genotyping

Norwegian sample

DNA was extracted from whole blood or saliva using the Oragene™ DNA Self-Collection Kit (DNA Genotek Inc., Ontario, Canada) and aliquoted into 96-well plates. Each plate contained DNA from both cases and controls and a minimum of two internal controls and two blank samples. The *SLC6A4* gene was tagged with seven SNPs based on HapMap build 35 (HAPLOVIEW software; Barrett *et al*. 2005), with minor allele frequency (MAF) threshold set to 5% and $r^2>0.8$ (pairwise tagging only). The SNPs were genotyped using the MassARRAY iPLEX System

Table 1: Characteristics of the samples studied

		Norway	Germany	The Netherlands	Spain	USA	Sum
Controls	Total (% males)	580 (44)	393 (50)	490 (49)	312 (65)	107 (43)	1882
Cases	Total (% males)	448 (53)	589 (53)	246 (49)	299 (72)	320 (41)	1902
Depression and/or anxiety	Total (% patients)	300 (67)	309 (79)*	164 (67)	150 (50)	168 (53)	1091
ADHD subtypes	Combined (%)	329 (73)	389 (66)	199 (81)	194 (65)	221 (69)	1332
	Inattentive (%)	46 (10)	146 (25)	22 (8.9)	88 (29)	89 (28)	391
	Hyperactive (%)	15 (3.3)	47 (8.0)	8 (3.3)	12 (4.0)	10 (3.1)	92

*Depression only, anxiety not specified.

(Sequenom, San Diego, CA, USA). The promoter insertion/deletion polymorphism, 5-HTTLPR, was amplified by the polymerase chain reaction (PCR) and genotyped by fragment analysis on the ABI3100 (Applied Biosystems, Foster City, CA, USA) using fluorescently labeled reverse primers (forward: 5′-GGCGTTGCCGCTCTGAATGC-3′; reverse: 5′-GAGGGACTGAGCTGGACAACCAC-3′) (Heils *et al*. 1996). The genotypes were automatically called using the GeneMapper software (Applied Biosystems), and they were subsequently manually inspected. Protocols for amplifications and fragment analysis are available upon request.

Replication samples from Spain, Germany, the Netherlands and USA

Genomic DNA was extracted from whole blood using the salting out method or from saliva using the Oragene™ DNA Self-Collection Kit (DNA Genotek Inc.). The 5-HTTLPR polymorphism was genotyped from each DNA sample using PCR. Amplification was performed with the primers according to the protocol described above and DNA products were resolved in 2% agarose gels. The SNP rs140700 was either genotyped in Norway (samples from Norway, Spain and the Netherlands) or in Germany (German samples) using the MassARRAY iPLEX System as described above. Genotyping for the replication samples from USA was conducted at the Psychiatric and Neurodevelopmental Genetics Unit of the Massachusetts General Hospital using a single base extension reaction with allele discrimination by MassARRAY mass spectrometry system (Sequenom, San Diego, CA, USA).

Statistical analyses

The statistical analyses of dichotomous traits were performed with the plink software (Purcell *et al*. 2007). All analyses were based on an additive allelic model. Stratification based on gender was achieved by subdividing the data in either male-only or female-only data files. Genotype distributions for all markers were consistent with Hardy–Weinberg Equilibrium, $P \geq 0.01$ for all countries. For the MassARRAY iPLEX analysis, 11 individuals were excluded because of low genotyping efficiency (missingness >0.3). Genotyping concordance was 100% ($n = 206$ comparisons) for this analysis, and the final genotyping call rate was >0.994. Analyses and visualization of linkage disequilibrium (LD) was performed with the haploview software (http://www.broadinstitute.org/haploview/haploview). The meta-analyses presented were performed with a random effects model (stata 8.2). Similar results were also obtained using the PLINK meta-analysis option (data not shown). For rs140700, the meta-analyses included Norwegian, German, Dutch, Spanish and American adult ADHD patients and controls from IMpACT. In the case of 5-HTTLPR, data from a published study on 312 Brazilian adult ADHD patients and 236 controls were also included (Grevet *et al*. 2007). Power calculations in the total sample were performed using the genetic power calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/cc2.html): Assuming an additive allelic model and using a significance level of 0.00625 (correction for eight markers tested), we had ~83% power to detect an effect at odds ratio(OR) = 0.75 for a disease allele frequency of 11% and 88% power to detect OR = 1.20 at a disease allele frequency of 40%.

All ORs estimated are presented for the minor allele. We termed $P < 0.05$ as nominally significant. All P values are presented without correction for multiple testing.

Sequencing

Ninety-three individuals from the Norwegian patient group were sequenced for the 13 protein-coding exons of *SLC6A4* (exon 3–15, NM_001045), including exon–intron boundaries, as well as the 3′UTR, all following a standard Sanger sequencing method. Primers were designed using Primer3 (http://frodo.wi.mit.edu/primer3), and the sequence analysis was performed on an ABI3730 DNA Analyzer (Applied Biosystems). All sequences were manually inspected using the SeqScape software (Applied Biosystems).

Results

Single-SNP analysis in the Norwegian sample

Table 1 shows the demographics for the 448 cases and 580 controls of the Norwegian sample, together with those of the replication samples from Germany, the Netherlands, Spain and USA.

Figure 1 shows the pairwise LD structure of the *SLC6A4* gene with the 5-HTTLPR and the seven tag SNPs in the Norwegian individuals. LD is low between the promoter region (rs16965628 and 5-HTTLPR) and SNPs in the core gene region. No SNP, or two-marker haplotype combination, could efficiently tag the 5-HTTLPR in the Norwegian data set.

The comparison of allele frequencies between Norwegian cases and controls showed an association between rs140700 and ADHD [OR = 0.67; 95% confidence interval (CI) = 0.50–0.91; $P = 0.01$] and a trend for overrepresentation of the 5-HTTLPR S allele in the ADHD patients (OR = 1.19; 95% CI = 0.99–1.42; $P = 0.06$) (Table 2). The stratification analysis by gender suggested that this association was mainly restricted to females (Table 3). Thus, four markers were associated with ADHD in females in the stratified analysis; rs4583306, rs140700, rs8076005 and 5-HTTLPR (strongest association for rs140700, $P = 0.00084$).

Replication attempts and meta-analyses

We next genotyped the 5-HTTLPR and rs140700 markers in four additional case–control samples of European descent from IMpACT. Random effect meta-analyses were performed as shown in Fig. 2. The analysis for the 5-HTTLPR also includes data from the only previously published study on this polymorphism in adult Brazilian ADHD patients (Grevet *et al*. 2007). There was a trend for an association between the 5-HTTLPR S allele and ADHD, which did not reach statistical significance: $P = 0.060$ and OR = 1.10 (95% CI = 1.00–1.21). All case samples (except for the German sample) had similar effect sizes and no heterogeneity was detected among them ($P = 0.79$). The meta-analysis of rs140700 did not support the results observed in the Norwegian sample (OR = 0.85; 95% CI = 0.67–1.09; $P = 0.20$). The results for the population-specific allelic association tests can be found in Tables S1 and S2. Allele frequencies were very similar in all populations apart from the slightly higher frequency of the 5-HTTLPR S allele found in the Spanish population. Stratification by gender or ADHD subtypes did not affect the results (Tables S3 and S4).

Coexisting symptoms of depression/anxiety

As shown in Table 1, 67% of the Norwegian patients reported having experienced 'significant depression and/or anxiety'. In the other populations, the fractions of patients who had suffered from one or both of these conditions varied between 50 and 79%. Because the 5-HTTLPR S allele has been implicated in susceptibility to these psychiatric disorders, we next restricted the analysis to the group of ADHD patients with symptoms of depression/anxiety. However, the strength of association did not increase for any of the eight markers tested in the Norwegian sample (data not shown),

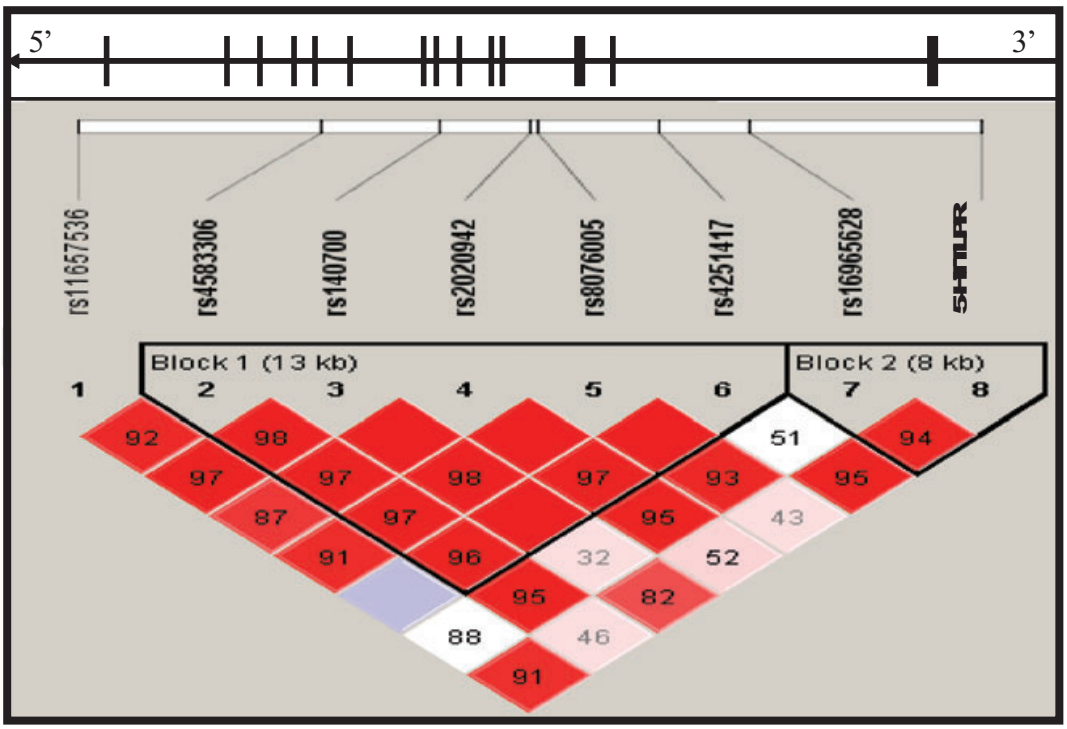

Figure 1: Upper part: SLC6A4, running 3′ to 5′, with exons (black boxes) and introns. Lower part: markers tested and pairwise LD (D′) between them. Haplotype blocks as defined by the method of Gabriel *et al*. (2002) are indicated.

Table 2: Individual markers, minor allele frequencies, *P* values and ORs for the comparison of allele frequencies between Norwegian ADHD cases and controls

Marker	Minor/major allele	MAF cases	MAF controls	*P*	OR (95% CI)
rs11657536	A/G	0.02	0.03	0.30	0.74 (0.42–1.31)
rs4583306	G/A	0.45	0.42	0.12	1.15 (0.97–1.37)
rs140700	A/G	0.08	0.11	0.011	0.67 (0.50–0.91)
rs2020942	A/G	0.37	0.38	0.43	0.93 (0.78–1.11)
rs8076005	G/A	0.18	0.20	0.27	0.88 (0.70–1.10)
rs4251417	A/G	0.10	0.11	0.30	0.86 (0.65–1.14)
rs16965628	G/C	0.08	0.08	0.86	0.97 (0.70–1.35)
5-HTTLPR	S/L	0.44	0.40	0.061	1.19 (0.99–1.42)

Table 3: Individual markers, minor allele frequencies, *P* values and ORs in females and males of the Norwegian sample

		Females				Males			
		MAF				MAF			
Marker	Minor/major allele	Cases	Controls	*P*	OR (95% CI)	Cases	Controls	P	OR (95% CI)
rs11657536	A/G	0.02	0.03	0.085	0.48 (0.20–1.13)	0.03	0.02	0.67	1.20 (0.52–2.74)
rs4583306	G/A	0.46	0.40	0.047	1.29 (1.00–1.65)	0.45	0.44	0.90	1.02 (0.79–1.31)
rs140700	A/G	0.05	0.11	0.00084	0.45 (0.27–0.72)	0.10	0.11	0.68	0.92 (0.60–1.39)
rs2020942	A/G	0.38	0.39	0.61	0.94 (0.73–1.21)	0.36	0.37	0.63	0.94 (0.72–1.22)
rs8076005	G/A	0.15	0.21	0.029	0.69 (0.50–0.96)	0.20	0.19	0.59	1.09 (0.80–1.50)
rs4251417	A/G	0.10	0.12	0.55	0.89 (0.60–1.31)	0.10	0.11	0.42	0.85 (0.56–1.27)
rs16965628	G/C	0.07	0.08	0.45	0.83 (0.52–1.34)	0.09	0.08	0.68	1.10 (0.70–1.74)
5-HTTLPR	S/L	0.44	0.37	0.016	1.36 (1.06–1.75)	0.44	0.44	0.98	1.00 (0.78–1.29)

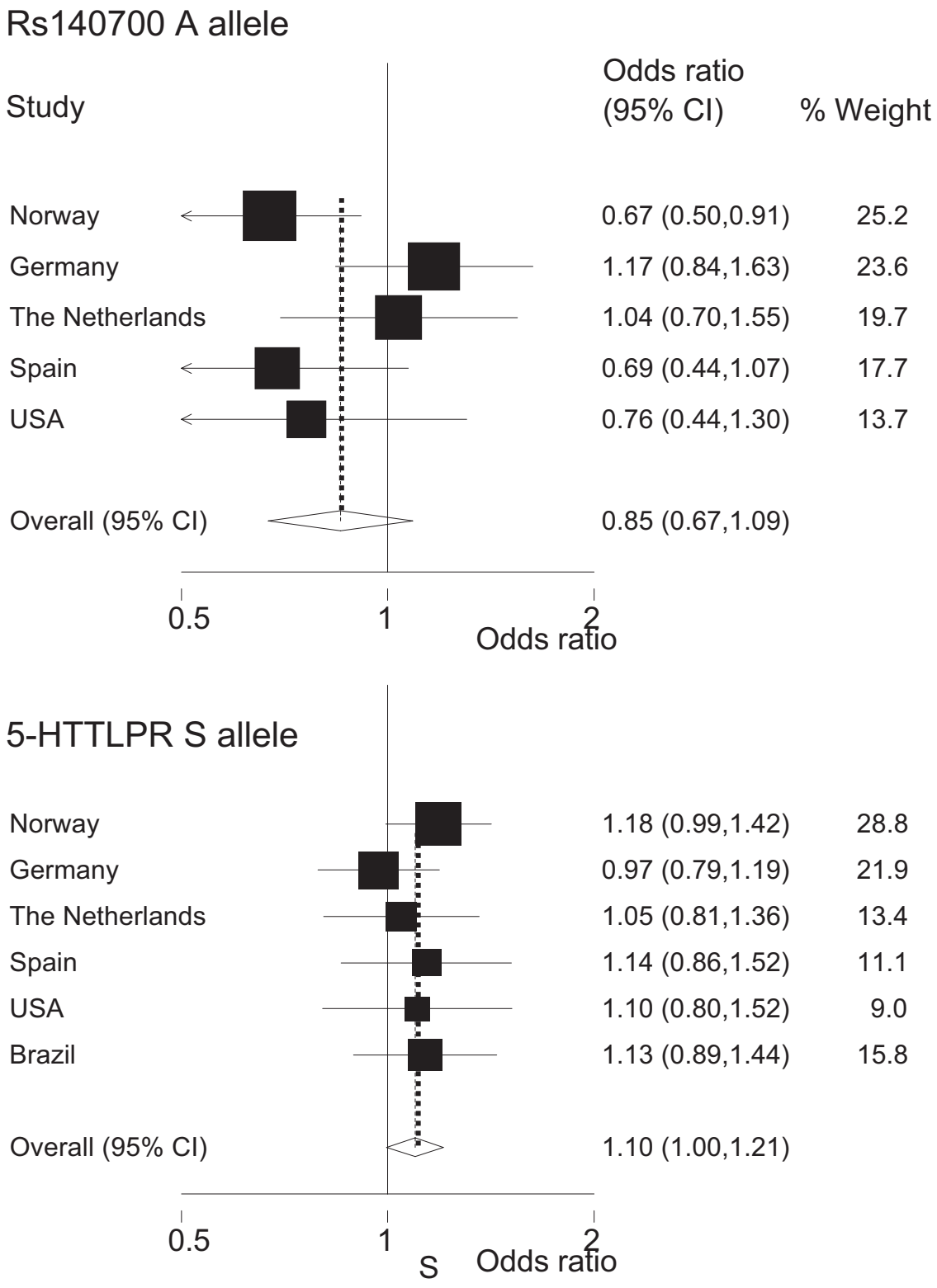

Figure 2: Meta-analysis of rs140700 in 1894 adult ADHD patients and 1878 controls (upper panel) and 5-HTTLPR in 1977 adult ADHD patients and 1650 controls (lower panel).

neither when all patients from the five IMpACT nodes were analyzed together (rs140700: $P = 0.08$; 5-HTTLPR: $P = 0.10$) (Fig. 3) nor after gender stratification (data not shown).

SLC6A4 sequencing for rare variants

Sequencing of all coding exons in 93 Norwegian patient samples revealed one silent mutation (c.924T>C) not previously described and two rare but already identified nonsynonymous variants (rs6352: p.Gly56Ala and rs6355: p.Lys605Asn), all present in the heterozygous state. Additionally, the common SNP rs1042173, located in the 3′UTR, was detected at a MAF of 48% in the sequenced samples (Table S5).

Discussion

The principal aim of this study was to investigate the possible association between adult ADHD and *SLC6A4* using a Norwegian sample for an exploratory analysis and replication in four other populations. We first genotyped seven tag SNPs and the promoter insertion/deletion 5-HTTLPR polymorphism in the Norwegian sample and found that the rare allele of rs140700 was associated with lower risk of ADHD (OR = 0.67; 95% CI = 0.50–0.91; $P = 0.01$). However, we were not able to replicate this finding in the other cohorts. We also found a trend toward an overrepresentation of the 5-HTTLPR S allele among the Norwegian cases (OR = 1.19; 95% CI = 0.99–1.42; $P = 0.06$). Replication attempts showed that the frequency of the S allele was slightly increased in cases as compared with controls in five of six populations (1977 patients and 1650 controls), including the previously reported Brazilian sample. Although results from the pooled analysis were not statistically significant (OR = 1.10; 95% CI = 1.00–1.21; $P = 0.06$), it is not possible to refute an association between the 5-HTTLPR S allele and persistent ADHD at the current time.

Contrary to our results, most of the initial studies on children with ADHD suggested that the long allele of 5-HTTLPR was associated with ADHD risk (Beitchman *et al*. 2003; Curran *et al*. 2005; Kent *et al*. 2002; Manor *et al*. 2001; Seeger *et al*. 2001; Zoroglu *et al*. 2002). These earliest studies looked at relatively small groups of patients (number of cases varied between 41 and 240). However, Faraone *et al*. (2005) used a meta-analysis approach to merge the results and found a pooled OR of 1.31 (95% CI = 1.09–1.59) for the L allele in childhood ADHD. More recently although, several studies have failed to find significant associations between ADHD and *SLC6A4*. Notably, the IMAGE multicenter study showed only a small and nonsignificant overtransmission of the L allele in 1020 families with 1166 ADHD cases (mainly combined subtype) (Xu *et al*. 2008). Furthermore, two very recent meta-analyses combining nearly fully overlapping sets of studies (Forero *et al*. 2009; Gizer *et al*. 2009) reached slightly different conclusions; only Gizer *et al*. were able to find a nominally significant effect ($P = 0.01$) for the L allele. Hence, considering the lack of consistent findings in childhood ADHD and taking into account the results from the present study of adult ADHD, it seems likely that the *SLC6A4* region does not harbor common susceptibility variants with a major effect on ADHD across the life span. However, we cannot rule out that the 5-HTTLPR or another variant in LD with this marker might be associated with ADHD, but with an effect size considerably lower than previously estimated. Based on our results, it can be estimated that a sample of more than 5600 cases and 5600 controls would be needed to achieve a power of 80% to detect an OR of 1.1 at the $P = 0.006$ level (study-wide significance after Bonferroni correction for eight tested markers).

Furthermore, it is also possible that *SLC6A4* polymorphisms might be important in subgroups of ADHD patients and/or influence other psychiatric symptoms among some ADHD patients. The 5-HTTLPR variant has been implicated in a wide range of psychiatric disorders, such as depression, anxiety, autism, bipolar disorder and obsessive compulsive disorder (OCD). Many of these diagnoses are overrepresented among adult ADHD patients (Caspi *et al*. 2003; Hariri *et al*. 2002; Sen *et al*. 2004). For example, as many as 67% of the Norwegian patients reported that they had experienced episodes of significant depression and/or anxiety. Similar numbers were also found using structured interviews in the other populations included in this study (range: 50–79%). We therefore tested the hypothesis that this subgroup of patients would be more likely to show an association with the 5-HTTLPR S allele than the patients who had not experienced such symptoms. However, restricting the analyses exclusively to the patients who reported depression/anxiety did not change the results (Fig. 3), neither did we find any difference when comparing patients with and without these symptoms. Still, if the 5-HTTLPR S allele is in fact related to these symptoms which are very frequent among adults with ADHD in particular, it could be part of the explanation of the somewhat different findings in adult and childhood samples.

It has been proposed that there are gender-specific variations in different aspects of serotonergic neurotransmission, such as the rates of central nervous system (CNS) serotonin synthesis (Nishizawa *et al*. 1997) and the density of certain serotonin receptors in the CNS (Biver *et al*. 1996; Costes *et al*. 2005). Likewise, other reports have suggested that the effects of tryptophan depletion and serotonin reuptake inhibitors, as well as the association between 5-hydroxyindoleacetic acid levels in cerebrospinal fluid and 5-HTTLPR genotypes, are different between females and males (Kornstein *et al*. 2000; Williams *et al*. 2003). Voyiaziakis *et al*. (2009) recently reported an association between a *SLC6A4* polymorphism and OCD in females, and for ADHD it has been suggested that variants in *SLC6A4* and several other ADHD candidate genes show dimorphic patterns of association between genders (Biederman *et al*. 2008). However, males have been highly overrepresented in most genetic studies performed on childhood ADHD, prohibiting investigation of gender effects. The IMAGE study consisted of almost 90% boys (Xu *et al*. 2008), which is very different from the almost 1:1 ratio found in the clinical adult samples included in this current study. It was therefore interesting to note that the Norwegian data suggested a

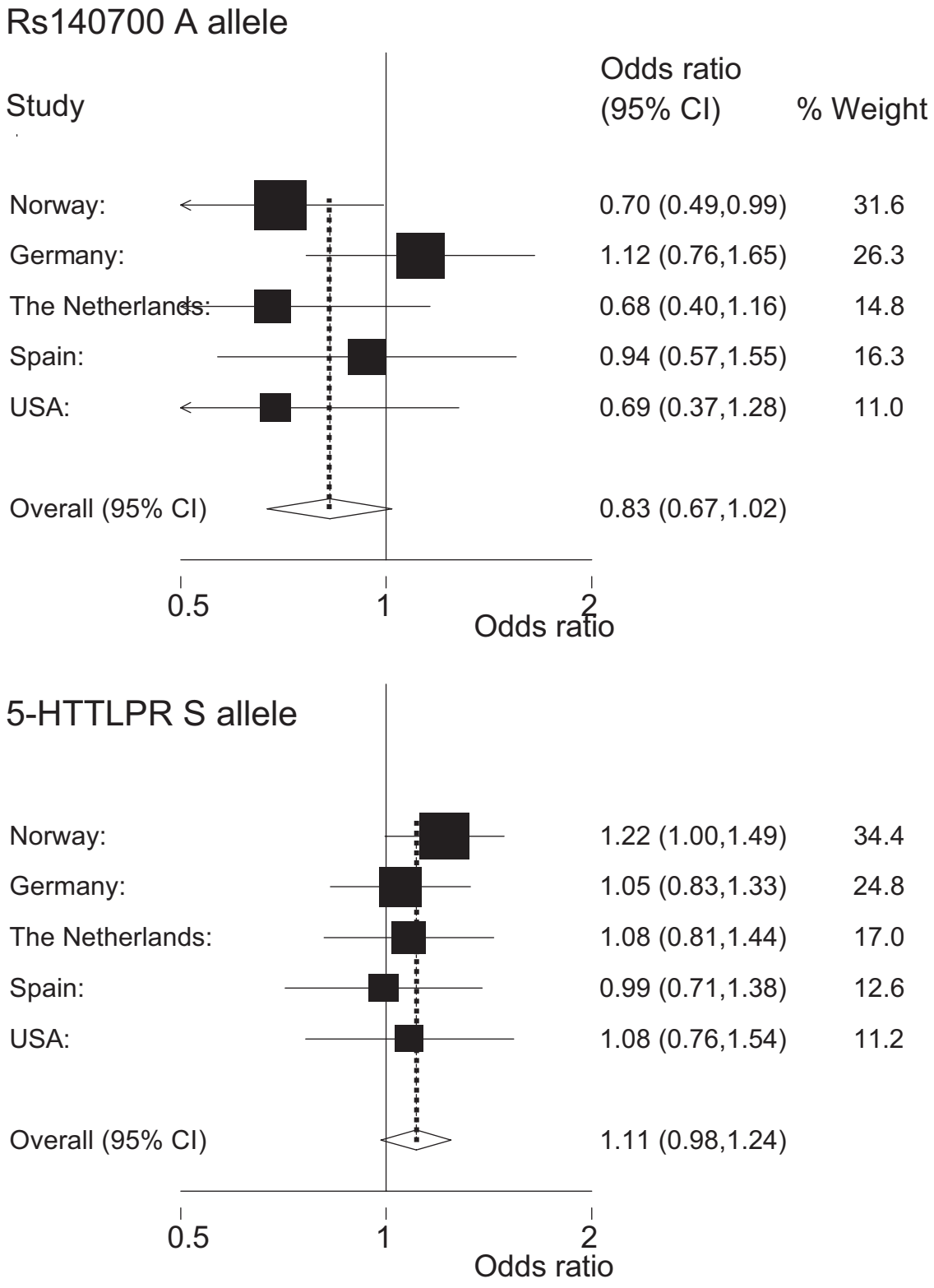

Figure 3: Meta-analysis of rs140700 and 5-HTTLPR restricted to ADHD patients with symptoms of depression/anxiety and controls.

serotonergic effect only in the women. This result was, however, not supported by the replication attempts. So while this illustrates that great care should be taken when analyzing multiple phenotypes, including possible gender effects (Ioannidis *et al*. 2009), it also emphasizes the importance of a more balanced gender recruitment into future studies of ADHD.

We cannot exclude that other factors, such as different recruitment strategies (childhood vs. adult samples), varying diagnostic traditions between countries or other sources of heterogeneity, might conceal a potential underlying genetic risk variant in the region and explain some of the inconsistent findings in the literature. However, the similar ADHD subtype distribution and occurrence of other psychiatric symptoms across IMpACT populations suggest that the total IMpACT sample used in the current study is rather homogeneous. Another limitation is that we have not excluded controls with ADHD symptoms in the Norwegian sample. However, the loss of power is relatively low if we assume that the prevalence of ADHD is no higher among our controls than the prevalence estimated in the general population.

The potential of gene–environment interactions has been much debated for the 5-HTTLPR. It has been suggested that carriers of the S allele exposed to traumatic life events exhibit more depressive symptoms (Caspi *et al*. 2003) and more commonly develop posttraumatic stress disorder (Xie *et al*. 2009) than individuals homozygous for the L allele. Considering ADHD, studies have found that the L allele has a protective effect on severity of the disorder for ADHD patients exposed to many adverse life events (Muller *et al*. 2008) and that the L allele reduce the patients' sensitivity to family environment (Sonuga-Barke *et al*. 2009). We can therefore not exclude the possibility of gene–environment interactions contributing to the etiology of ADHD in our populations. However, a very recent meta-analysis by Risch *et al*. (2009) pointed to the challenges associated with gene–interaction studies, and they were not able to detect any evidence of interaction between 5-HTTLPR genotype and stressful life events on depressive symptoms.

It has also been suggested that rare variants might contribute to common psychiatric traits (Dong *et al*. 2009; Elia *et al*. 2009; Walsh *et al*. 2008). We found nonsynonymous *SLC6A4* variants in 4 of 93 fully sequenced ADHD patients (4.3% carrier rate). These changes, although rare, have been previously described also in other populations and are probably unlikely to have strong impact on ADHD, and very large samples will be needed to test if any of these rare variants are involved in psychiatric disorders. Hence, until large-scale resequencing efforts have been performed (Manolio *et al*. 2009), it is not possible to exclude that rare *SLC6A4* coding variants might impact vulnerability toward psychiatric conditions, including ADHD.

In conclusion, our data show that there are no common variants within the *SLC6A4* gene region with a strong effect on adult ADHD across Caucasian populations. However, we cannot reject the possibility of the *SLC6A4* gene contributing to the disorder, for instance through a low effect size, through other psychiatric symptoms commonly associated with ADHD or by other rare variants.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: The allelic distribution of 5-HTTLPR with *P* values and ORs in six adult ADHD populations.

Table S2: The allelic distribution of rs140700 with *P* values and ORs in five adult ADHD populations.

Table S3: 5-HTTLPR and rs140700 in all populations with gender stratification.

Table S4: 5-HTTLPR and rs140700 in cases with the respective subtypes vs. controls in four populations.

Table S5: SNPs found when sequencing the exons of SLC6A4 in DNA from 93 ADHD patients.

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