Exploring *DRD4* and Its Interaction With *SLC6A3* as Possible Risk Factors for Adult ADHD: A Meta-Analysis in Four European Populations

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Attention-deficit hyperactivity disorder (ADHD) is a common behavioral disorder affecting about 4–8% of children. ADHD persists into adulthood in around 65% of cases, either as the full condition or in partial remission with persistence of symptoms. Pharmacological, animal and molecular genetic studies support a role for genes of the dopaminergic system in ADHD due to its essential role in motor control, cognition, emotion, and reward. Based on these data, we analyzed two functional polymorphisms within the *DRD4* gene (120 bp duplication in the promoter and 48 bp VNTR in exon 3) in a clinical sample of 1,608 adult ADHD patients and 2,352 controls of Caucasian origin from four European countries that had been recruited in the context of the International Multicentre persistent ADHD CollaboraTion (IMpACT). Single-marker analysis of the two polymorphisms did not reveal association with ADHD. In contrast, multiple-marker meta-analysis showed a nominal association ($P = 0.02$) of the L-4R haplotype (dup120bp-48bpVNTR) with adulthood ADHD, especially with the combined clinical subtype. Since we previously described association between adulthood ADHD and the dopamine transporter *SLC6A3* 9R-6R haplotype (3'UTR VNTR-intron 8 VNTR) in the same dataset, we further tested for gene $\times$ gene interaction between *DRD4* and *SLC6A3*. However, we detected no epistatic effects but our results rather suggest additive effects of the *DRD4* risk haplotype and the *SLC6A3* gene. © 2011 Wiley-Liss, Inc.

Key words: attention-deficit hyperactivity disorder; case-control association study; neurotransmission; dopamine; psychiatric genetics

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a common behavioral disorder affecting 4–8% of children [Polanczyk et al., 2007] and is characterized by inappropriate and impairing levels of hyperactivity, impulsivity, and inattention. ADHD persists into adulthood in around 65% of cases either as the full condition or in partial remission with persistence of symptoms and with significant clinical impairment [Faraone et al., 2006; Lara et al., 2009]. A review of 20 twin studies in children estimated the heritability of ADHD to be around 76% [Faraone et al., 2005; Faraone and Mick, 2010].

Pharmacological studies, animal models, and molecular genetic studies support a role for genes of the dopamine, serotonin, and norepinephrine neurotransmitter systems in ADHD. Research, however, has mainly focused on the dopaminergic system due to

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its essential role in motor control, cognition, and reward. In this regard, magnetic resonance imaging suggests abnormalities in ADHD-affected children in neuro-anatomical areas rich in dopaminergic innervations [Ernst et al., 1999; Durston et al., 2005]. In addition, methylphenidate, amphetamine, and other psychostimulant drugs increase synaptic levels of dopamine and are effective in the control of ADHD symptoms through blockade of the dopamine transporter.

Among the different genes involved in dopaminergic neurotransmission, the dopamine receptor D4 (*DRD4*) has been widely considered in genetic studies of ADHD. The *DRD4* gene is located at chromosome 11p15.5, organized in 4 exons and encodes a G-protein-coupled receptor belonging to the dopamine D2-like receptor family. This family of receptors is expressed predominantly in the prefrontal cortex. *DRD4* contains a number of polymorphisms, one of which, a variable number of 48 bp tandem repeats (48bpVNTR), is located in the third exon of the gene. This exon encodes the putative third cytoplasmic loop of the receptor and modulates the receptor's signal transduction properties by altering intracellular cyclic AMP levels [Van Tol et al., 1992]. This polymorphism, with a unit that is repeated from 2 (2R) to 11 (11R) times, shows considerable inter-ethnic heterogeneity [Van Tol et al., 1992; Chang et al., 1996]. Although its effect on the *DRD4* function is still unknown, different pharmacological properties have been described for the distinct repeat lengths, with the 7R allele dampening the response of cells to dopamine [Asghari et al., 1995]. Other studies, however, showed no evidence of quantitative

differences in G-protein coupling among the *DRD4* 2R, 4R, and 7R alleles [Kazmi et al., 2000].

Since the publication of the initial study by LaHoste et al. [1996] showing association between the 7R allele of the 48bpVNTR and ADHD in children, many case-control and family-based association studies have been reported, although they show controversial results. After the first studies that identified the 7R as a risk allele for ADHD, most of the subsequent work solely tested this allele versus all the others [Castellanos et al., 1998; Comings et al., 1999; Muglia et al., 2000; Tahir et al., 2000; Curran et al., 2001; Mill et al., 2001; Langley et al., 2004; Gabriela et al., 2009]. Other studies differentiated between short (2R–5R) and long alleles (6R–11R) [Eisenberg et al., 2000; Hawi et al., 2000; Kotler et al., 2000; Manor et al., 2002]. However, only some of these studies focused on adult ADHD [Muglia et al., 2000; Smith et al., 2003; Johansson et al., 2008]. Johansson et al. [2008] found no association between the *DRD4* VNTR polymorphism and adulthood ADHD. On the other hand, Muglia et al. [2000] suggested a role of the 7R allele in adult ADHD and, finally, although performed in childhood ADHD samples, several meta-analyses have demonstrated a significant association between this *DRD4* allele and ADHD [Faraone et al., 2001; Faraone et al., 2005; Li et al., 2006; Gizer et al., 2009; Nikolaidis and Gray, 2010; Smith, 2010]. However, some of these meta-analyses detected significant heterogeneity in the effect size for *DRD4* in the different studies [Li et al., 2006; Gizer et al., 2009; Smith, 2010].

Seaman et al. [1999] subsequently identified a second common genetic variant in *DRD4*, the 120 bp duplication (dup120bp) located 1.2 kb upstream of the *DRD4* translation initiation codon. The duplication contains consensus sequences for several transcription factors and modulates transcription of the *DRD4* gene. In this regard, the 240 bp allele (long or L allele) showed enhanced binding capacity for the Sp1 transcription factor in a mobility shift assay and exhibited lower transcriptional activity than the 120 bp allele (short or S allele) in transfected cell lines [D'Souza et al., 2004; Ronai et al., 2004; Kereszturi et al., 2007]. Several studies have tested association between the *DRD4* dup120bp polymorphism and ADHD but results are also controversial, showing no association [Barr et al., 2001; Todd et al., 2001; Brookes et al., 2005; Bhaduri et al., 2006; Gizer et al., 2009] or identifying either the L or S alleles as risk factors for ADHD [McCracken et al., 2000; Kustanovich et al., 2004; Kereszturi et al., 2007]. Accordingly, a recent meta-analysis performed by Gizer et al. [2009] found no association between childhood ADHD and either allele. So far, Arcos-Burgos et al. [2004] were the only researchers to study the role of a haplotype of both polymorphisms in ADHD and indeed found significant evidence for association with the S-7R *DRD4* haplotype.

Since both the 48bpVNTR and the dup120bp polymorphisms in *DRD4* may affect the receptor function through changes in amino acid sequence or promoter activity and to challenge the inconsistencies raised among previous case-control and family-based association studies, we aimed to investigate the possible involvement of these polymorphisms in ADHD in a large sample of adult patients and controls from Europe. We performed a meta-analysis of unpublished case-control data from four different countries (Germany, The Netherlands, Norway, and Spain) integrated in the International Multicentre persistent ADHD CollaboraTion (IMpACT) in a sample of 1,608 adult ADHD patients and 2,352

controls. Also, as several studies have shown epistatic [Roman et al., 2001; Gabriela et al., 2009] or additive effects [Carrasco et al., 2006] between *DRD4* and *SLC6A3* in ADHD or hyperactive-impulsive symptoms [Auerbach et al., 2010], we used previously published *SLC6A3* genotype data from IMpACT [Franke et al., 2010] to assess their potential combined contribution to adulthood ADHD.

MATERIALS AND METHODS

Patients and Controls

In total, 1,608 adult ADHD patients and 2,352 controls of Caucasian origin from four European countries (Spain, Germany, Norway, and The Netherlands) were recruited at four sites of IMpACT. Table I shows the clinical description of these patient cohorts. Diagnosis was blind to genotype. The study was approved by the ethics committee of each participating institution and informed consent was obtained from all subjects in accordance with the Helsinki Declaration.

Consensus eligibility criteria for the current study across all sites were a diagnosis of ADHD according to the diagnostic criteria of Diagnostic and Statistical Manual for Mental Disorders-IV (DSM-IV), onset before the age of 7 years via retrospective diagnosis (which was confirmed by a family member, wherever possible), lifelong persistence, and current diagnosis. Patients were extensively examined by psychiatrists experienced in adult ADHD and were evaluated for other psychiatric disorders with the Structured Clinical Interview of DSM-IV for axis-I (and axis-II) disorders (SCID-I, SCID-II) or semi-structured interviews. Most controls (except for the Norwegian samples and part of the German samples) were screened for the presence of ADHD and those scoring high on symptoms of the disorder were excluded (for a more detailed description of the different diagnostic instruments, see Sanchez-Mora et al., 2010).

DNA Isolation and Genotyping

Genomic DNA was isolated either from saliva using the Oragene DNA Self-Collection Kit (DNA Genotek Inc., Ottawa, Ontario, Canada) or from peripheral blood lymphocytes by the salting-out procedure [Miller et al., 1988].

Dup120bp *DRD4* polymorphism. Genotyping was carried out using standard PCR methods and amplification products were tested by electrophoresis on a 1.5% agarose gel and ethidium bromide staining (Germany, Spain, and The Netherlands) or visualized on an ABI 3100 sequencer and automatically called using the GeneMapper software (Applied Biosystems, Foster City, CA). Genomic DNA was amplified with primers 5'-GTTGTCTGTCTTTTCTCATTGTTTCCATTG-3' and 5'-GAAGGAGCAGG-CACCGTGAGC-3' for the Spanish, German, and Dutch samples and with a fluorescently labeled (FAM) reverse primer for the Norwegian samples. For the German, Spanish, and Norwegian samples, PCR reactions were carried out in a final volume of 10 μ l, containing 5 ng of genomic DNA, 0.5 pmol of each primer, 1 μ l PCRx Enhancer solution (10 $\times$; PCRx Enhancer System, Invitrogen, Breda, The Netherlands), 1 μ l PCRx Amplification Buffer (PCRx Enhancer System, Invitrogen), 0.2 μ M of each dNTP, 0.5 mM MgSO₄, and 1 U of Taq polymerase. Amplification conditions

TABLE I. Descriptive Characteristics of the IMPACT Samples From Four European Countries

	Germany	Netherlands	Norway	Spain	Pool	DRD4 Dup120bp	DRD4 48bpVNTR	DRD4 Dup120bp- 48bpVNTR
Controls								
Female	307 [53.6]	248 [50.7]	325 [55.6]	245 [34.8]	1,125 [47.8]	872 [42.3]	813 [44.2]	845 [46.0]
Male	266 [46.4]	241 [49.3]	260 [44.4]	460 [65.2]	1,227 [52.2]	1,190 [57.7]	1,027 [55.8]	990 [54.0]
Total	573 [24.36]	489 [20.79]	585 [24.87]	705 [29.97]	2,352	2,062	1,840	1,835
Age [mean and SD]	30.73 [9.8]	63.46 [18.07]	27.4 [7.16] ^a	45.26 [14.79]				
Cases								
Female	304 [48.8]	119 [50.0]	215 [47.4]	82 [28.0]	720 [44.8]	644 [44.5]	613 [43.6]	537 [43.2]
Male	319 [51.2]	119 [50.0]	239 [52.6]	211 [72.0]	888 [55.2]	803 [55.5]	794 [56.4]	709 [56.8]
Total	623 [38.7]	238 [14.8]	454 [28.2]	293 [18.22]	1,608	1,447	1,407	1,246
Age [mean and SD]	33.91 [10.12]	41.23 [11.35]	33.9 [11.6]	36.02 [16.83]				
ADHD subtype								
Combined type	422 [68.3]	202 [86.0]	327 [72.03]	194 [66.2]	1,145 [71.2]	1,037 [71.7]	991 [70.4]	883 [71.0]
Inattentive type	151 [24.4]	24 [10.2]	47 [10.35]	87 [29.7]	309 [19.2]	279 [19.3]	275 [19.5]	243 [19.5]
Hyperactive/impulsive type	45 [7.3]	9 [3.8]	15 [3.30]	12 [4.1]	81 [5.04]	67 [4.6]	72 [5.1]	58 [4.7]
Sub-threshold	—	—	45 [9.91]	—	45 [2.8]	44 [3.0]	45 [3.2]	44 [3.5]
Unknown	—	—	20 [4.41]	—	20 [1.2]	20 [1.38]	20 [1.42]	16 [1.04]

^aCalculated only for non-blood donors (n = 365).

consisted of an initial denaturation at 94°C for 1 min followed by 34 cycles of denaturation at 94°C for 1 min, annealing at 56.5°C for 1 min, and extension at 72°C for 1 min, with a final extension step at 72°C for 10 min. The amplification yielded distinct bands at 429 bp (short “S” allele) and 549 bp (long “L” allele). For Dutch samples, genotyping of the 120 bp tandem duplication polymorphism was carried out using a PCR-based method as described by Seaman et al. [1999]. PCR was performed on 62.5 ng genomic DNA using 0.4 μM of each of the primers described above, 0.25 mM dNTPs, 0.5 U Taq DNA polymerase (Invitrogen) in a PCR buffer containing 10 mM Tris-HCl pH 8.0, 50 mM KCl, 0.1% Triton X-100 (v/v), 0.015% gelatin (w/v), 5% DMSO (v/v), and 1.5 mM MgCl₂. The cycling conditions were 10 min 92°C followed by 35 cycles of 1 min 95°C, 1 min 58°C, 1 min 72°C. At the end of the protocol, 10 min at 72°C were added.

48 bp VNTR DRD4 polymorphism. Genotyping of the DRD4 48 bp VNTR polymorphism in exon 3 was performed according to the method used by Johansson et al. [2008] for samples from Norway and Spain. A protocol for PCR amplification and fragment analysis is available upon request. In short, DNA was amplified with the following primers: 5'-CGTACTGTGCGGCCTCAACGA-3' and FAM-5'-GACACAGCGCCTGCGTGATGT-3'. The reverse primer was fluorescently labeled and PCR products were visualized on an ABI 3100 sequencer and automatically called using the GeneMapper software (Applied Biosystems). All genotype calls were also manually inspected. Analysis of the results using GeneMapper showed fragment length at 598 bp (2 repeats), 646 bp (3 repeats), 694 bp (4 repeats), 742 bp (5 repeats), 790 bp (6 repeats), 836 bp (7 repeats), 884 bp (8 repeats), 930 bp (9 repeats), and 976 bp (10 repeats).

For the Dutch sample, the 48 bp repeat polymorphism was analyzed by simple sequence analysis on a genetic analyzer using

primers as described earlier [Lichter et al., 1993]. For the PCR amplification, 50 ng of genomic DNA, 1.25 μM fluorescent labeled forward primer (5'-Vic-GCGACTACGTGGTCTACTCG-3') and 1.25 μM reverse primer with PIG tail (5'-AGGACCCTCATGGCCTTG-3'), 0.4 mM dNTPs, 1× GCI Buffer TaKaRa (Lucron Bioproducts BV, Gennep, The Netherlands), 0.5 U TaKaRa LA Taq™ (Lucron Bioproducts BV), and 1 M betaine were used. The cycling conditions were 1 min 94°C followed by 35 cycles of 30 sec 94°C, 30 sec 58°C, 1 min 72°C, with a final 5 min step at 72°C. The PCR product was diluted 10 times and 1 μl of the diluted PCR product together with 9.7 μl formamide and 0.3 μl GeneScan-600 Liz Size Standard™ (Applied Biosystems, Nieuwerkerk aan de IJssel, The Netherlands) was analyzed on a 3730 Genetic Analyzer according to the protocol of the manufacturer. Analysis of the results using Genemapper showed fragment length at 378 bp (2 repeats), 426 bp (3 repeats), 474 bp (4 repeats), 522 bp (5 repeats), 570 bp (6 repeats), 618 bp (7 repeats), and 666 bp (8 repeats).

For the German sample, PCR amplification was performed using Vent polymerase (New England Biolabs, Ipswich, MA) and a high denaturing temperature (98°C for 1 min) with a combined annealing and extension reaction for 5 min at 70°C. The primers were 5'-GCGACTACGTGGTCTACTCG-3' and 5'-AGGACCCTCATGGCCTTG-3'. Thirty PCR cycles were performed and subsequently, the reaction mixture was electrophoresed on a 2% Metaphor gel (FMC) with ethidium bromide. The lengths of the resulting PCR products are the same as describe above for the Dutch sample.

Statistical Analysis

Separate analysis of the four European samples. We first performed a single- and multiple-marker analysis on the samples

from the four IMPACT sites, separately, and then analyzed the pooled sample using a meta-analytical approach. Hardy–Weinberg equilibrium (HWE) in the control groups from each IMPACT node as well as in the whole control sample was assessed using a chi-squared test with the HWE software v.1.05 (www.linkage.rockefeller.edu/soft/linkutil). Genotype and allele frequencies of the dup120bp and 48bpVNTR polymorphisms were compared between cases and controls from each separate IMPACT site using a chi-squared test with the SNPassoc R package and the statistical package SPSS 15.0, respectively [Gonzalez et al., 2007]. Since the 48bpVNTR polymorphism is multiallelic (2R–11R alleles), rare [minor allele frequency (MAF) <5%] genotypes and alleles were grouped in a single class as “others.” Haplotype frequencies were estimated using the PHASE software [Stephens et al., 2001] and values below 5% were grouped as “others” in the association analysis.

Meta-analysis. To combine the individual results, we conducted a meta-analysis using the Meta R package (www.cran.r-project.org/web/packages/meta/index.html). The analysis of the minimal statistical power was performed post hoc using the Genetic Power Calculator software (www.pngu.mgh.harvard.edu/~purcell/gpc), assuming a dominant model, an odds ratio (OR) of 1.5, prevalence of 0.05, significance level of 0.05 and a MAF of 0.158 [Purcell et al., 2003]. We first tested heterogeneity among studies using the Q-statistic [Lau et al., 1997; Zintzaras and Hadjigeorgiou, 2004]. When no heterogeneity was present, the pooled OR was estimated using a fixed-effects model [Mantel and Haenszel, 1959]. A random-effect model was considered in those cases where heterogeneity was detected [Laird and Mosteller, 1990]. Meta-analysis was performed considering the whole ADHD sample, but also split by gender or ADHD clinical subtypes. The hyperactive-impulsive clinical sample could not be evaluated due to insufficient sample size.

For the dup120bp polymorphism, we determined the best genetic model to be used by estimating the three possible ORs and their 95% confidence intervals (CI) in the meta-analysis sample: OR1 (SS vs. LL), OR2 (SS vs. LS), and OR3 (LS vs. LL). If $OR1 = OR3 \neq 1$ and $OR2 = 1$, then a recessive model is suggested; $OR1 = OR2 \neq 1$ and $OR3 = 1$ indicates a dominant model and $OR1 > OR3 > 1$ (or $OR1 < OR2 < 1$ and $OR1 < OR3 < 1$) suggests a codominant model. When none of the OR values significantly deviated from 1, then meta-analyses were performed for the three different genetic models.

For the 48bpVNTR we minimized multiple-testing by restricting the meta-analysis to alleles or genotypes showing frequency differences >3% among cases and controls in at least one of the study populations. Thus, alleles 4R and 7R, and genotypes 4R4R, 4R7R, and 7R7R were considered for meta-analysis. For the analysis of the dup120bp/48bpVNTR haplotype we only considered the carriers of the three major allelic combinations, S-4R, L-4R, and L-7R. The EH software was used to test the presence of linkage disequilibrium between the two *DRD4* polymorphisms [Terwilliger and Ott, 1994].

***DRD4* × *SLC6A3* interaction analysis.** A logistic regression analysis was used to evaluate the independent and interactive effects of the *DRD4* and *SLC6A3* loci. For *DRD4* we considered the haplotype made up of the dup120bp L allele and the 4R allele of the 48bpVNTR polymorphism (L-4R), while for the *SLC6A3* gene

we considered the previously described risk haplotype comprising the 9R allele of the VNTR in the 3'UTR and the 6R allele of the VNTR in intron 8 (9R–6R), using pre-existing genotype data on our multicenter cohort of patients and controls [Franke et al., 2010]. A stepwise logistic regression procedure was implemented to compare two different regression models by a likelihood ratio test using the statistical package SPSS 15.0. In the first model, we considered the affection status as a dependent variable and the *DRD4* and *SLC6A3* haplotypes as predictive variables. In the second model, we included the interaction *DRD4* × *SLC6A3* as an independent variable.

RESULTS

A total of 1,608 adult ADHD patients and 2,352 controls from four IMPACT sites were genotyped for the *DRD4* dup120bp and/or the 48bpVNTR polymorphisms. The clinical description of the samples included in the study is shown in Table I.

Single-Marker Analysis

For the *DRD4* dup120bp polymorphism, genotypes from 1,447 patients (90%) and 2,062 controls (88%) were available for the single-marker analysis. No significant departure from HWE was observed, neither in the control group from each population nor in the pooled sample ($P > 0.05$). No significant association was detected when we compared genotype and allele frequencies between cases and controls from each separate site (Supplementary Table SI). Stratification of the ADHD samples according to gender or clinical subtype in the four separate populations resulted in a nominal association between the L allele of the dup120bp polymorphism and ADHD in males from Norway [$P = 0.009$, $OR = 1.69$ (1.14–2.56); Supplementary Table SII]. Nominal association was also observed in two samples when we considered the combined clinical subtype (Supplementary Table SIII): Norway [$P = 0.04$, $OR = 1.40$ (1.01–1.96)] and Spain [$P = 0.04$, $OR = 2.63$ (0.91–7.69)]. The evaluation of the best genetic model for the meta-analysis showed that none of the three ORs in the pooled sample significantly deviated from 1 [$OR1_{(SS \text{ vs. } LL)} = 1.23$ (95%CI: 0.82–1.84), $OR2_{(SS \text{ vs. } LS)} = 1.23$ (0.81–1.86), and $OR3_{(LS \text{ vs. } LL)} = 1.03$ (95% CI: 0.88–1.20)] and, thus, we performed meta-analysis considering the dominant, recessive, and codominant models. However, no significant association was found for dup120bp in the full ADHD sample (Table II), or when patients were subdivided by gender or clinical subtypes, in either of the three models (data not shown).

A total of 1,407 patients (87.5%) and 1,840 controls (78.2%) had genotypes available for the *DRD4* 48bpVNTR polymorphism. Genotype frequencies did not deviate significantly from HWE in any of the cohorts ($P > 0.05$). No significant association between the 48bpVNTR and ADHD was identified in any of the European samples, when studied separately (Supplementary Table SIV). As described above (Materials and Methods Section), only 4R/4R, 4R/7R, and 7R/7R genotypes were available for the meta-analysis. No association between the VNTR polymorphism and adult ADHD was seen in the full ADHD sample (Table III), even if gender or clinical subtypes were taken into account (data not shown).

TABLE II. Genetic Effect of the *DRD4* dup120bp Polymorphism on Adulthood ADHD**(a) Dominant model (LS + LL vs. SS)**

OR M-H, fixed, 95% CI	Study	Cases		Controls		Weight (%)	OR M-H, fixed, 95% CI	z	P-value
		SS	Total	SS	Total
1. Germany	22	515	18	483	32.82	1.15 [0.61–2.17]		
	2. Netherlands	6	189	13	485	13.03	1.19 [0.44–3.17]		
	3. Norway	6	448	11	464	19.68	0.55 [0.20–1.52]		
	4. Spain	7	295	30	630	34.48	0.48 [0.20–1.12]		
	Fixed-effects model	41	1,447	72	2,062	100	0.81 [0.54–1.21]	−1.02	0.30

Test of heterogeneity: $Q = 3.74$, $df = 3$, $P = 0.29$; $I^2 = 19.7\%$ [0–87.7%]**(b) Recessive model (LL vs. LS + SS)**

OR M-H, fixed, 95% CI	Study	Cases		Controls		Weight (%)	OR M-H, fixed, 95% CI	z	P-value
		LL	Total	LL	Total
1. Germany	356	515	338	483	32.69	0.96 [0.73–1.25]		
	2. Netherlands	139	189	351	485	15.81	1.06 [0.72–1.55]		
	3. Norway	344	448	355	464	23.19	1.27 [0.94–1.71]		
	4. Spain	190	295	411	630	28.32	0.96 [0.72–1.28]		
	Fixed-effects model	1,029	1,447	1,455	2,062	100	1.05 [0.90–1.22]	0.63	0.52

Test of heterogeneity: $Q = 2.36$, $df = 3$, $P = 0.50$; $I^2 = 0\%$ [0–80.5%]**(c) Overdominant model (LS vs. LL + SS)**

OR M-H, fixed, 95% CI	Study	Cases		Controls		Weight (%)	OR M-H, fixed, 95% CI	z	P-value
		LS	Total	LS	Total
1. Germany	137	515	127	483	30.13	1.01 [0.76–1.34]		
	2. Netherlands	44	189	121	485	16.30	0.91 [0.61–1.35]		
	3. Norway	98	448	118	464	28.36	0.82 [0.60–1.11]		
	4. Spain	98	295	189	630	25.21	1.16 [0.86–1.56]		
	Fixed-effects model	377	1,447	555	2,062	100	0.98 [0.83–1.14]	−0.24	0.80

Test of heterogeneity: $Q = 2.72$, $df = 3$, $P = 0.43$; $I^2 = 0\%$ [0–83.1%]S, short allele of the *DRD4* dup120bp polymorphism (120bp); L, long allele of the *DRD4* dup120 bp polymorphism (240 bp).**Multiple-Marker Analysis**

Linkage disequilibrium between the two studied polymorphisms in *DRD4* was assessed and shown to be negligible ($P = 0.99$). Genotypes from 1,246 patients (77%) and 1,835 controls (78%) were available for the two *DRD4* polymorphisms. Table IV summarizes

the estimated haplotype frequencies for the four populations considered in the study. The comparison of haplotype frequencies between cases and controls showed no association in any of the four separate cohorts. We subsequently performed a meta-analysis considering carriers of the three common *DRD4* haplotypes, S-4R, L-4R, and L-7R, and, after discarding the presence of

TABLE III. Genetic Effect of the *DRD4* 48bpVNTR Polymorphism on Adulthood ADHD

(a) Comparison of the 4R4R genotype versus others

OR M-H, fixed, 95% CI	Study	Cases		Controls		Weight (%)	OR M-H, random, 95% CI	z	P-value
		4R4R	Total	4R4R	Total
1. Germany	200	436	63	156	20.98	1.25 [0.86–1.81]		
	2. Netherlands	102	236	193	476	24.39	1.11 [0.81–1.53]		
	3. Norway	179	449	190	488	28.12	1.03 [0.79–1.35]		
	4. Spain	109	289	290	631	26.51	0.71 [0.53–0.94]		
	Fixed-effects model	590	1,410	736	1,751	100	0.97 [0.84–1.13]	−0.27	0.78

Test of heterogeneity: $Q = 7.34$, $df = 3$, $P = 0.06$; $I^2 = 59.1\%$ [0–86.4%]

(b) Comparison of 7R7R genotypes versus others

OR M-H, fixed, 95% CI	Study	Cases		Controls		Weight (%)	OR M-H, fixed, 95% CI	z	P-value
		7R7R	Total	7R7R	Total
1. Germany	29	436	7	156	16.90	1.41 [0.60–3.30]		
	2. Netherlands	8	236	24	476	26.53	0.66 [0.29–1.19]		
	3. Norway	20	449	26	488	41.20	0.82 [0.45–1.49]		
	4. Spain	16	289	15	631	15.37	2.40 [1.17–4.93]		
	Fixed-effects model	73	1,410	72	1,751	100	1.12 [0.78–1.59]	0.63	0.52

Test of heterogeneity: $Q = 7.29$, $df = 3$, $P = 0.06$; $I^2 = 58.9\%$ [0–86.3%]

(c) Comparison of the 4R7R genotypes versus others

OR M-H, random, 95% CI	Study	Cases		Controls		Weight (%)	OR M-H, random, 95% CI	z	P-value
		4R7R	Total	4R7R	Total
1. Germany	89	436	37	146	23.0	0.75 [0.48–1.17]		
	2. Netherlands	50	236	121	335	24.34	0.47 [0.32–0.69]		
	3. Norway	124	429	136	488	21.64	1.19 [0.90–1.58]		
	4. Spain	85	289	157	631	24.72	1.25 [0.92–1.71]		
	Fixed-effects model	348	1,390	451	1,600	100	0.87 [0.56–1.35]	−0.61	0.53

Test of heterogeneity: $Q = 19.3$, $df = 3$, $P = 0.0002$; $I^2 = 84.5\%$ [61.1–93.8%]4R: 4 repeats of the *DRD4* 48bpVNTR polymorphism; 7R: 7 repeats of the *DRD4* 48bpVNTR polymorphism.

heterogeneity between the four samples using the Q-statistic, we observed an under-representation of the S-4R allelic combination in the ADHD sample [$P = 0.01$; OR = 0.78 (0.65–0.95); Table IV]. We also performed multiple comparisons stratifying by gender and by clinical subtype and confirmed these differences in females

[$P = 0.04$, OR = 0.73 (0.54–0.99); Supplementary Table SV]. Interestingly, when we considered patients with the ADHD combined subtype only, we observed an increased frequency of carriers of the L-4R risk haplotype [$P = 0.02$; OR = 1.29 (1.04–1.61)] in addition to an under-representation of the S-4R

TABLE IV. Pooled Analysis Considering S-4R Carriers of the *DRD4* dup120bp-48bp VNTR Haplotype in 1,246 Adulthood ADHD Patients and 1,835 Controls

OR M-H, fixed, 95% CI	Study	Cases		Controls		Weight (%)	OR M-H, fixed, 95% CI	z	P-value
		S-4R	Total	S-4R	Total				
Germany	1. Germany	60	327	33	120	16.69	0.59 [0.65–0.96]		
Netherlands	2. Netherlands	32	187	99	478	19.53	0.79 [0.50–1.22]		
Norway	3. Norway	67	443	91	544	29.34	0.88 [0.62–1.25]		
Spain	4. Spain	62	289	176	693	34.44	0.80 [0.57–1.11]		
Fixed effect model	Fixed-effects model	221	1,246	399	1,835	100	0.78 [0.65–0.95]	–2.39	0.01
Test of heterogeneity: $Q = 1.78$, $df = 3$, $P = 0.62$; $I^2 = 0\%$ [0–74.1%]									

S, short allele of the dup120bp polymorphism [120 bp]; 4R, 4 repeats of the 48bpVNTR polymorphism.

allelic combination [$P = 0.01$ OR = 0.75 (0.60–0.94)] in this clinical dataset (Table V).

Interaction Between *DRD4* and *SLC6A3*

Since we previously described an association of adulthood ADHD with the *SLC6A3* 9R-6R haplotype (3'UTR VNTR-intron 8 VNTR) in the same dataset [Franke et al., 2010], we further tested for gene $\times$ gene interactions between the ADHD-associated haplotypes of *DRD4* and *SLC6A3*. Genotypes from 1,208 patients (75%) and 1,290 controls (55%) were available for the four polymorphisms in the two genes. Although no evidence for epistatic effects was detected, the simultaneous presence of the two risk haplotypes, *DRD4* L-4R and *SLC6A3* 9R-6R, increased the risk for ADHD in both the ADHD sample as a whole [$P = 3.04 \times 10^{-5}$; OR 1.66 (1.31–2.11)] and in the combined clinical subtype [$P = 2.66 \times 10^{-5}$; OR = 1.74 (1.35–2.26)]. Thus, the OR for ADHD subjects carrying the *DRD4* L-4R haplotype rose from 1.09 (0.90–1.32) to 1.66 (1.31–2.11) in those patients also carrying the *SLC6A3* 9R-6R allelic combination. Similar results were obtained in the combined type ADHD clinical subtype (Fig. 1) and indicate additive effects between risk haplotypes at these two loci.

DISCUSSION

In the present study we performed a meta-analysis in a large sample of 1,608 adulthood ADHD patients and 2,352 unrelated controls from four European countries to evaluate the role of the *DRD4* dup120bp and 48bpVNTR polymorphisms in the persistent form of the disorder. Although nominal association with dup120bp was observed in some of the populations considered in this study, no evidence for a role of either polymorphism in ADHD was detected when they were considered separately in the entire sample. The multiple-marker analysis, however, supports a contribution of the L-4R (dup120bp-48bpVNTR) haplotype to adulthood ADHD, mainly to the combined clinical subtype, although these findings

should be viewed with caution given the many (albeit highly correlated) statistical tests performed. These results support a connection between *DRD4* and the persistence of the ADHD symptoms across the life span, in line with previous follow-up studies [Biederman et al., 2009].

Many association studies between *DRD4* and ADHD have been performed, although results are often controversial. In this regard, although our data in the single-marker analysis are in agreement with previous reports showing no association between ADHD and the 48bpVNTR polymorphism [Roman et al., 2001; Todd et al., 2001; Bakker et al., 2005; Brookes et al., 2005; Carrasco et al., 2006; Johansson et al., 2008; Sonuga-Barke et al., 2008], they are contrary to others having reported on association between the 7R allele and the disorder [Rowe et al., 1998; Faraone et al., 2001; Maher et al., 2002; Wohl et al., 2005; Brookes et al., 2006; Li et al., 2006; Gizer et al., 2008, 2009; Biederman et al., 2009; Langley et al., 2009; Nikolaidis and Gray, 2010]. Likewise, our results for the *DRD4* dup120bp polymorphism are in line with most of the literature, including a recent meta-analysis [Barr et al., 2001; Todd et al., 2001; Mill et al., 2003; Kirley et al., 2004; Brookes et al., 2005; Bhaduri et al., 2006; Gizer et al., 2009], but not with findings from the first two association analyses of this variation [McCracken et al., 2000].

Due to the heterogeneity of populations, methodologies and statistical tests used, it is difficult to establish direct comparisons between all these reports. In the case of the 48bpVNTR, allele frequencies of this multiallelic polymorphism vary considerably across ethnic groups. The 4R allele is the most prevalent one and appears in all populations. However, 7R is frequent among Americans but rare among Asians and 2R is frequent in Asia but uncommon among Americans [Van Tol et al., 1992; Chang et al., 1996; Ding et al., 2000; Wang et al., 2004]. In addition, some studies collapse different alleles into long and short categories (6R–8R vs. 2R–5R) [Eisenberg et al., 2000; Manor et al., 2002] and others only consider the most frequent alleles among Caucasians (4R and 7R) [Roman et al., 2001; Bellgrove et al., 2005]. Because grouping several frequent alleles in a single category or considering only

TABLE V. Pooled Analysis Considering the (a) S-4R and (b) L-4R Carriers of the *DRD4* dup120bp-48bpVNTR Haplotype in 788 Combined ADHD Patients and 1,835 Controls

(a) S-4R

	Study	Cases		Controls		Weight (%)	OR M-H, fixed, 95% CI	z	P-value
		S-4R	Total	S-4R	Total
1. Germany	41	204	33	120	18.12	0.66 [0.39–1.12]		
	2. Netherlands	30	168	99	478	23.08	0.83 [0.52–1.30]		
	3. Norway	34	231	91	544	25.25	0.85 [0.56–1.31]		
	4. Spain	36	190	176	693	33.54	0.68 [0.45–1.02]		
	Fixed-effects model	140	788	399	1,835	100	0.75 [0.60–0.94]	–2.42	0.01

Test of heterogeneity: $Q = 0.98$, $df = 3$, $P = 0.80$; $I^2 = 0\%$ [0–53.2%]

(b) L-4R

	Study	Cases		Controls		Weight (%)	OR M-H, fixed, 95% CI	z	P-value
		L-4R	Total	L-4R	Total
1. Germany	153	204	93	120	20.27	0.87 [0.51–1.48]		
	2. Netherlands	130	168	366	478	29.82	1.04 [0.68–1.59]		
	3. Norway	196	226	422	544	22.77	1.88 [1.22–2.91]		
	4. Spain	158	190	540	693	27.13	1.38 [0.91–2.11]		
	Fixed-effects model	637	788	1,421	1,835	100	1.29 [1.04–1.61]	2.31	0.02

Test of heterogeneity: $Q = 6.14$, $df = 3$, $P = 0.10$; $I^2 = 51.1\%$ [0–83.8%]

S, short allele of the dup120bp polymorphism [120 bp]; L, Long allele of the dup120bp polymorphism [240 bp]; 4R, 4 repeats of the 48bpVNTR polymorphism.

variants described in previous analyses may result in loss of crucial genetic information, we included all frequent alleles separately and grouped the less frequent variants (<5%) into a single group.

Several other explanations could also account for the inconsistent findings observed among previously reported *DRD4* studies. Differences in sample size, comorbidities, and proportions of clinical subtypes or genders may result in discordant results. Limited sample sizes may provide imprecise or incorrect estimates of the magnitude of the observed effects. The present meta-analysis provides an adequate statistical power (>99%) to detect an association of small effect. Additionally, in the case of gender-specific associations, differences in the male:female proportion among studies may also contribute to variability. In this regard, although nominal and site-specific, we found male-specific association signals in the Norwegian sample when samples were stratified according to gender. Whether the different ADHD clinical subtypes share genetic risk factors has been still poorly explored. The association between ADHD and the *DRD4* risk haplotype detected in the present study was observed in the combined but not in the inattentive clinical subtype. Our results are in agreement with previous studies supporting the validity of the different DSM-IV

subtypes, mainly the combined subtype, and suggesting the participation of differential genetic factors in distinct ADHD clinical groups [Rasmussen et al., 2004; Larsson et al., 2006; Sobanski et al., 2008; Ribasés et al., 2009]. Interestingly, Smith [2010] performed a meta-analysis of 28 association studies between ADHD and the 48bpVNTR in *DRD4* and observed that increases in the proportion of combined ADHD patients within an ADHD sample were associated with an increase in the magnitude of the effect. These results are consistent with the hypothesis that *DRD4* is more strongly associated with combined ADHD than with inattentive ADHD and are in line with the hypothesis that hypofunctioning in mesocortical and mesolimbic dopaminergic pathways better characterize the etiology of combined ADHD than inattentive ADHD [Sagvolden et al., 2005; Smith, 2010]. This view is supported by the fact that variation in *DAT1*, another dopaminergic gene, is also more strongly associated with combined ADHD than with inattentive ADHD (e.g., Waldman et al., 1998). Moreover, it is possible that consideration of neuropsychological traits, comorbidities or personality data, not included in the present study, may help in the future to obtain better association signals with *DRD4* than the analysis of the sole ADHD condition. Finally, since most of

FIG. 1. Graphical representation showing the analysis of gene $\times$ gene interactions between the *DRD4* and *SLC6A3* genes. The simultaneous presence of the two risk haplotypes, *DRD4* L-4R and *SLC6A3* 9R-6R, increased the risk for ADHD in both the pooled ADHD sample (A) and the combined clinical subtype sample (B). These results suggest additive effects of the risk haplotypes at these two loci on ADHD.

previous research on the *DRD4* gene has focused on childhood patients (only four studies having considered the 48bpVNTR polymorphism in adulthood ADHD [Muglia et al., 2000; Smith et al., 2003; Boonstra et al., 2008; Johansson et al., 2008], differential proportion of remitting and persisting ADHD within the children samples may also explain discordant results among studies [Brookes et al., 2006; Gornick et al., 2007; Langley et al., 2009]. In this regard, Shaw et al. [2007] showed in a longitudinal study that the 7R allele was associated with a better clinical outcome and with differences in cortical thickness in regions that are important in attention control. These neuroanatomical changes were most apparent early in development and resolved by late adolescence. In addition, Johansson et al. [2008] showed a trend towards protective effects of the 7R allele in adults with ADHD, results that suggest a different effect of the 7R allele in child and adulthood ADHD and could explain previous controversial results. However, another recent study by Biederman et al. [2009] showed increased risk of ADHD persistence due to the 7R allele.

The identification of different alleles at the same markers as susceptibility factors for ADHD in several studies and the failure to consistently replicate positive associations suggest that the dup120bp and the 48bpVNTR polymorphisms may not be themselves the causative variants that increase disease risk but are in linkage disequilibrium with a true causative variant within the same gene. Further deep-sequencing of this genomic region may allow identification of the functional *DRD4* variants directly involved in the genetic background of ADHD. In that regard, it is interesting to note that an increased burden of rare variants has been observed in the 7R allele of *DRD4* in children with ADHD [Grady et al., 2003].

In addition, we detected preliminary evidence of additive, but not epistatic, effects for *DRD4* and *SLC6A3* in ADHD. Since

SLC6A3 is expressed in subcortical regions whereas *DRD4* is expressed in frontal cortex, the two genes may indeed be expected to increase ADHD risk by acting in independent pathways [Durstun et al., 2005]. However, it is difficult to draw a final conclusion about the combined participation of these two genes in ADHD symptomatology as several studies have described discordant results [Roman et al., 2001; Kim et al., 2005; Carrasco et al., 2006; Qian et al., 2007; Gabriela et al., 2009].

In summary, the results of the present study showed nominal association between the L-4R haplotype (dup120bp-48bpVNTR) and adulthood combined ADHD through a meta-analysis of four European populations. Our results also suggest an additive effect between this *DRD4* risk haplotype and *SLC6A3*. Replication in other datasets is warranted to confirm these results and to better understand the involvement of the *DRD4* and *SLC6A3* genes in the predisposition to the persistent form of ADHD.

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