An association study of sequence variants in the forkhead box P2 (*FOXP2*) gene and adulthood attention-deficit/hyperactivity disorder in two European samples

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Objectives **Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder manifesting as symptoms of inattention, hyperactivity, and/or impulsivity. Learning disabilities co-occur with ADHD in 20–30% of cases and this high co-occurrence raises the possibility of a common etiological background. Forkhead box P2 (*FOXP2*) encodes a transcription factor involved in speech and language impairment and in the control of the corticobasal ganglia circuits known to be relevant in ADHD, suggesting a possible role of *FOXP2* in ADHD. Our aim was to carry out an association study between *FOXP2* and adulthood ADHD.**

Methods **We carried out a case–control association study in 643 adult ADHD patients and 619 controls from Germany and in 361 adult ADHD patients and 442 controls from Spain with 12 tagging single nucleotide polymorphisms covering the *FOXP2* gene.**

Results **The single-marker and multiple-marker analyses showed an association between *FOXP2* and combined ADHD in the German cohort [rs12533005: $P=0.0033$; odds ratio = 1.30 (1.09–1.56); rs12533005/rs1229761: $P=4.1e-04$; odds ratio = 1.38 (1.15–1.66)]. These positive results, however, were not confirmed in the Spanish sample.**

Conclusion **Although these preliminary findings provide a tentative evidence for the contribution of *FOXP2* to ADHD and suggest common genetic factors for this psychiatric disorder and learning disabilities, they should be interpreted with caution. Further studies in larger samples are needed to clarify the role of this transcription factor in ADHD. *Psychiatr Genet* 22:155–160 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder manifesting as symptoms of inattention, hyperactivity, and/or impulsivity that occurs in approximately 4–5% of children and adolescents and persists into adulthood in at least 30% of patients diagnosed during infancy (Biederman and Faraone, 2005; Kessler *et al.*, 2006; Fayyad *et al.*, 2007; Polanczyk *et al.*, 2007). Several follow-up studies have consistently demonstrated that children with ADHD show more academic and learning problems than controls and that this poor performance, which is strongly associated with academic failure, persists into adolescence (Biederman *et al.*, 1992).

Interestingly, learning disabilities co-occur with ADHD in 20–30% of cases and this high degree of comorbidity raises the possibility of a common etiological background (Pliszka, 1998; Kadesjo and Gillberg, 2001; Biederman, 2005; Bennett *et al.*, 2009). Among possible shared etiological factors, genes that contribute to the individual's ability to acquire reading and spelling skills, and thus playing relevant roles in speech and language, are strong candidates to predispose him/her to both ADHD and learning problems. In this sense, it is well known that genetic risk variants are involved in the predisposition to language impairment, abnormal reading development, and dyslexia (Fisher *et al.*, 2003; Taipale *et al.*, 2003;

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Bartlett *et al.*, 2004; SLI_Consortium, 2004; Cope *et al.*, 2005; Hannula-Jouppi *et al.*, 2005; MacDermot *et al.*, 2005; Meng *et al.*, 2005; Fisher and Francks, 2006; Schumacher *et al.*, 2006). The first direct evidence of a specific gene involved in the acquisition of speech and language emerged from rare mutations in the forkhead box P2 gene (*FOXP2*), which encodes a transcription factor, causing impairment in speech development, linguistic deficits, and learning difficulties (Gopnik and Crago, 1991; Fisher *et al.*, 1998; Vargha-Khadem *et al.*, 1998; Lai *et al.*, 2001; Marcus and Fisher, 2003). In addition, chromosomal alterations disrupting *FOXP2* are also associated with speech and language deficits (Sarda *et al.*, 1988; Lai *et al.*, 2000, 2001).

On the basis of the comorbidity of learning disabilities with ADHD, we propose the *FOXP2* gene as a possible candidate involved in the genetic susceptibility to this psychiatric disorder. This hypothesis is also supported by additional data that include the control that *FOXP2* exerts on the activity of the corticobasal ganglia circuits known to contribute to ADHD (Bush *et al.*, 2005; Seidman *et al.*, 2005; Arnsten, 2006; Enard *et al.*, 2009; Lieberman, 2009), its association with other psychiatric disorders (Newbury *et al.*, 2002; Wassink *et al.*, 2002; Gauthier *et al.*, 2003; Gong *et al.*, 2004; Sanjuan *et al.*, 2005, 2006; Laroche *et al.*, 2008; Tolosa *et al.*, 2010), and the fact that mice carrying a human variant of *FOXP2* with two amino acid substitutions with a potential relevance in human evolution show altered exploratory behavior as well as dopamine levels, dendritic morphology, striatal gene expression patterns, and synaptic plasticity (Enard *et al.*, 2009; Lieberman, 2009). To test the involvement of *FOXP2* in ADHD, we carried out a case–control association study in 643 adult ADHD patients and 619 controls from Germany and 361 adult ADHD patients and 442 controls from Spain with 12 tagging single nucleotide polymorphisms (tagSNPs) covering the *FOXP2* gene in terms of linkage disequilibrium (LD).

Methods

In total, 1004 adult ADHD patients (68.6% combined, 25.3% inattentive, and 6.1% hyperactive–impulsive) and 1061 controls of Caucasian origin from Germany and Spain were recruited. Sixty-three percent of patients were men. The ADHD diagnosis was made on the basis of the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* (DSM-IV) Axis I and Axis II Disorders (SCID-I and SCID-II) and the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CADDID). The average age at assessment was 36.5 years (SD = 14.8) for patients and 29.5 years (SD = 12.0) for controls. The control sample matched for sex with the ADHD group, and in most of them DSM-IV ADHD symptomatology was excluded (except for 44% of the German sample). The clinical diagnosis of the patients was blind to genotype. The study was approved by the Ethics Committee of each institution, and informed consent was obtained from all participants. A more detailed description of ADHD patients and diagnostic instruments used has been published previously (Ribases *et al.*, 2009a; Sanchez-Mora *et al.*, 2010).

Genomic DNA was isolated either from peripheral blood lymphocytes by the salting-out procedure or using magnetic bead technology with the Chemagic Magnetic Separation Module I and the Chemagic DNA kit (Chemagen, Baesweiler, Germany) or from saliva using the Oragene DNA Self-Collection kit (DNA Genotek, Kanata, Ontario, Canada).

The LD pattern of the *FOXP2* gene plus 3 kb of flanking sequences was evaluated using the LD select software (University of Washington, Seattle, Washington, USA; Carlson *et al.*, 2004). tagSNPs were selected from the HapMap database (*http://www.hapmap.org*) at an r^2 threshold of 0.85 from all SNPs with a minor allele frequency (MAF) greater than 0.25. From the 13 selected SNPs assessed using an automated assay design pipeline (*http://ms.appliedbiosystems.com/snplex/snplexStart.jsp*), a proper design could not be achieved for one SNP (rs12670585; Table S1, Supplemental digital content 1, *http://links.lww.com/PG/A54*). All SNPs were genotyped using the SNPlex platform.

A detailed description of the statistical procedure has been published previously (Ribases *et al.*, 2008, 2009a, 2009b). The minimal statistical power was calculated as 58.2 and 47.9% for the German and Spanish samples, respectively, assuming an odds ratio (OR) of 1.3, a disease prevalence of 0.05, a significance level of 0.05, a MAF of 0.25, and a codominant model of inheritance.

The single-marker analysis was carried out considering the overall ADHD sample as well as the combined and inattentive clinical subgroups. The hyperactive–impulsive sample was not considered because of its limited sample size. The analysis of Hardy–Weinberg equilibrium ($P < 0.05$) and the comparison of genotype and allele frequencies under a log-additive model were carried out using the SNPassoc R package (Gonzalez *et al.*, 2007). As the Bonferroni correction is overconservative when background LD exists, correction for multiple testing was performed on the basis of the spectral decomposition of matrices of pairwise LD between SNPs using the SNPSpD software ($P < 0.0085$; Queensland Institute of Medical Research, Herston, Australia; *http://genepi.qimr.edu.au/general/daleN/SNPSpD/*; Nyholt, 2004). This correction takes into consideration the existing LD in the studied region and estimates the effective number of independent SNPs. In addition, the Bonferroni correction was considered when the combined and inattentive clinical subtypes were analyzed separately ($P < 0.0085/2 = 0.0042$).

To minimize multiple testing and type I errors, we decided *a priori* to restrict the haplotype-based association study by considering only the clinical group that showed

positive signals in the single-marker analysis. Rather than simplifying the study to physically contiguous SNPs in the gene, the best two-marker haplotype from all possible combinations was identified, and afterwards additional markers (up to four) were added in a stepwise manner to the initial two-SNP haplotype. The multiple-marker analysis was carried out using the UNPHASED (MRC Biostatistics Unit, Institute for Public Health, Cambridge, UK) and PHASE (University of Chicago, Chicago, Illinois, USA) software as described previously (Ribases *et al.*, 2009a), and significance was estimated using 10 000 permutations.

Results

To assess whether common variants within the *FOXP2* gene are associated with ADHD, both single SNP and haplotype-based case–control association studies were carried out on 1004 adult patients (643 from Germany and 361 from Spain) and 1061 controls (619 from Germany and 442 from Spain). A total of 13 tagSNPs were initially selected for extensive coverage of the *FOXP2* genomic region. One of them, however, did not pass the SNPlex design pipeline and, thus, a total of 12 tagSNPs were finally included in the study (Table S1, *http://links.lww.com/PG/A54*).

All SNPs followed a distribution in Hardy–Weinberg equilibrium. The single-marker study under a log-additive model showed no evidence of an association between *FOXP2* and adulthood ADHD when the overall sample or the combined and inattentive types of ADHD from Spain were considered (data not shown). In contrast, a nominal association was found for rs10953766 and rs936146 in the German sample (Table 1). Patients from Germany were then subdivided according to the ADHD clinical subtype, and although no significant differences were found in the inattentive group, seven SNPs reached statistical significance in the German combined-type ADHD group: rs12533005, rs10255943, rs10268637, rs4727799, rs17137124, rs1229761, and rs936146 (Table 2). After correcting for multiple testing, rs12533005 [$P = 0.0033$; OR = 1.30 (1.09–1.56)] remained significantly associated with combined-type ADHD in the German dataset (Table 2).

To gain an insight into the *FOXP2* haplotype structure underlying these positive results, we assessed evidence for an association using a multiple-marker approach and identified a two-marker haplotype (rs12533005/rs1229761) associated with adulthood combined ADHD in the German cohort ($P = 0.0024$). Individual haplotypes showed three different combinations and revealed over-representation of the G–A allelic combination [$P = 4.1e-04$; OR = 1.38 (1.15–1.66)] and under-representation of the C–C haplotype [$P = 0.0057$; OR = 1.31 (1.08–1.58)] in this clinical sample (Table 3). We then considered the frequency of the G–A risk haplotype carriers (heterozygous and homozygous individuals) and confirmed the association between *FOXP2* and combined ADHD in the adult dataset from Germany [$P = 0.017$; OR = 1.46 (1.07–1.98)]. This allelic combination includes the *FOXP2* SNP rs12533005, which reached statistical significance in the single-marker analysis. In contrast, no significant differences were found when the rs12533005G/rs1229761A haplotype was evaluated in the Spanish sample.

Discussion

To our knowledge, this is the first study to investigate the involvement of the *FOXP2* gene in adulthood ADHD. Our results provide evidence for an association between the *FOXP2* locus and combined ADHD in at least one of the studied populations.

Converging evidences suggest that *FOXP2*, a gene reported to underlie learning disability, is a strong candidate involved in ADHD. First, there is a high co-occurrence

Table 1 Association study in 643 adult attention-deficit/hyperactivity disorder patients (431 combined, 164 inattentive, and 48 hyperactive–impulsive) and 619 unrelated controls from Germany

			Germany			
SNP	Position[a] (bp)	Minor allele	MAF cases	MAF controls	*P*-value[c]	OR (95% CI)
rs12533005	**113843291**	**C**	**0.451**	**0.493**	**0.034**	**1.19 (1.01–0.58)[b]**
rs10228350	113847899	T	0.371	0.341	0.116	–
rs10255943	113859679	A	0.293	0.317	0.199	–
rs10268637	113861493	T	0.436	0.405	0.114	–
rs10486026	113867671	G	0.218	0.197	0.211	–
rs4727799	113897804	C	0.369	0.398	0.141	–
rs17137124	113998050	T	0.456	0.494	0.056	–
rs1229761	114010959	C	0.355	0.388	0.100	–
rs7782412	114077651	C	0.437	0.457	0.327	–
rs7799652	114077719	G	0.484	0.459	0.232	–
rs936146	**114081641**	**C**	**0.475**	**0.430**	**0.025**	**1.20 (1.02–1.41)**
rs10953766	114100454	A	0.456	0.471	0.470	–

CI, confidence interval; *FOXP2*, forkhead box P2; LD, linkage disequilibrium; MAF, minor allele frequency; OR, odds ratio; SNP, single nucleotide polymorphism.
SNPs showing a nominal association with the disorder are given in bold.
[a]UCSC genome browser (*genome.ucsc.edu*), assembly NCBI36/hg18.
[b]When odds ratio<1, the inverted score is shown.
[c]Correction for multiple testing on the basis of the spectral decomposition (SpD) of matrices of pairwise LD between SNPs of the *FOXP2* gene ($P<0.0085$).

Table 2 Association study in 431 combined attention-deficit/hyperactivity disorder patients and 619 unrelated controls from Germany

			Germany			
SNP	Position (bp)[a]	Minor allele	MAF cases	MAF controls	*P*-value	OR (95% CI)
rs12533005	**113843291**	**C**	**0.428**	**0.493**	**0.0033[c]**	**1.30 (1.09–1.56)[b]**
rs10228350	113847899	T	0.379	0.341	0.066	–
rs10255943	**113859679**	**A**	**0.274**	**0.317**	**0.035**	**1.23 (1.01–1.51)[b]**
rs10268637	**113861493**	**T**	**0.449**	**0.405**	**0.046**	**1.20 (1.00–1.44)**
rs10486026	113867671	G	0.214	0.197	0.375	–
rs4727799	**113897804**	**C**	**0.344**	**0.398**	**0.015**	**1.26 (1.04–1.51)[b]**
rs17137124	**113998050**	**T**	**0.442**	**0.494**	**0.020**	**1.23 (1.03–1.47)[b]**
rs1229761	**114010959**	**C**	**0.328**	**0.388**	**0.0065**	**1.28 (1.07–1.54)[b]**
rs7782412	114077651	C	0.433	0.457	0.272	–
rs7799652	114077719	G	0.489	0.459	0.197	–
rs936146	**114081641**	**C**	**0.481**	**0.430**	**0.020**	**1.23 (1.03–1.47)**
rs10953766	114100454	A	0.440	0.471	0.160	–

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; *FOXP2*, forkhead box P2; LD, linkage disequilibrium; MAF, minor allele frequency; OR, odds ratio; SNP, single nucleotide polymorphism.
SNPs showing an association with the disorder are given in bold.
[a]UCSC genome browser (*genome.ucsc.edu*), assembly NCBI36/hg18.
[b]When odds ratio <1, the inverted score is shown.
[c]Correction for multiple testing on the basis of the spectral decomposition (SpD) of matrices of pairwise LD between SNPs of the *FOXP2* gene, and Bonferroni's correction considering the two clinical subtypes of combined and inattentive ADHD ($P<0.0042$).

Table 3 Haplotype analysis of 12 *FOXP2* single nucleotide polymorphisms in a clinical sample of 431 adult combined attention-deficit/hyperactivity disorder patients and 619 controls using the UNPHASED software

Marker haplotype[a]	Global *P*-value	Best haplotype-specific *P*-value (adjusted *P*-value)	Haplotype-specific OR (95%CI)
1 8	**0.0022**	**4.1e – 04 (0.0014)**	**1.38 (1.15–1.66)**
1 8 11	0.0017	0.017 (0.028)	1.23 (1.01–1.50)
1 5 8 11	0.0047	0.025 (0.024)	1.28 (1.00–1.63)
	Cases *n* (%)	Controls *n* (%)	Haplotype-specific *P*-value; OR (95%CI)
1 8			
C A	94 (11.6)	155 (13.6)	0.19
C C	253 (31.3)	425 (37.4)	0.0059; 1.31 (1.08–1.58)[b]
G A	461 (57.1)	558 (49.0)	4.1e – 04; 1.38 (1.15–1.66)

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; *FOXP2*, forkhead box P2; OR, odds ratio.
The best haplotype combination is given in bold.
[a]1, rs12533005; 5, rs10486026; 8, rs1229761; 11, rs936146.
[b]Downrepresented in ADHD patients in comparison with the controls.

between ADHD and learning disabilities (Pliszka, 1998; Vargha-Khadem *et al.*, 1998; Kadesjo and Gillberg, 2001; Lai *et al.*, 2001; Biederman, 2005; MacDermot *et al.*, 2005; Bennett *et al.*, 2009). Second, Stevenson *et al.* reported that approximately 75% of the factors contributing to the association between ADHD and spelling disabilities were due to shared genetic factors, and different genes have been associated with both ADHD and reading disabilities, such as the ones encoding the dopamine receptor D4, Neurensin 1, and the doublecortin domain-containing protein 2 (*DRD4*, *NRSN1*, and *DCDC2*) (Gillis *et al.*, 1992; Stevenson *et al.*, 1993; Levy *et al.*, 1996; Willcutt *et al.*, 2001, 2010; Hsiung *et al.*, 2004; Couto *et al.*, 2009). Third, *FOXP2* controls the activity of the corticobasal ganglia circuits known to be relevant in ADHD (Bush *et al.*, 2005; Seidman *et al.*, 2005; Arnsten, 2006; Enard *et al.*, 2009). Fourth, after the introduction of two amino acid substitutions with a potential relevance in human evolution into the endogenous *FOXP2* gene, mice carrying this human variant of *FOXP2* showed altered exploratory behavior as well as dopamine levels, dendritic morphology, striatal gene expression patterns, and synaptic plasticity (Enard *et al.*, 2009; Lieberman, 2009). Finally, although controversial, association studies and mutation screening analyses support the involvement of *FOXP2* in other psychiatric disorders such as schizophrenia and autism (Newbury *et al.*, 2002; Wassink *et al.*, 2002; Gauthier *et al.*, 2003; Gong *et al.*, 2004; Sanjuan *et al.*, 2005, 2006; Laroche *et al.*, 2008; Tolosa *et al.*, 2010). Thus, we suggest that sequence variants in *FOXP2* could be predisposing factors to deficits in different executive functions found in ADHD patients, including working memory and verbal fluency deficits (Schweitzer *et al.*, 2000, 2006; Gallagher and Blader, 2001; Hervey *et al.*, 2004; Arnsten and Li, 2005).

An association between ADHD and *FOXP2* was identified in only one of the two studied cohorts. The smaller sample size of the Spanish combined ADHD dataset (230 vs. 431 German patients) or differential LD distribution

across populations could explain the failure to replicate the association between *FOXP2* and combined ADHD. Clinical heterogeneity and differences in the frequency of comorbid disorders co-occurring with ADHD may have also contributed to these divergent results. In addition, the present association study raises another methodological consideration. Although adequate SNP coverage was achieved ($r^2 > 0.85$), MAF was set at greater than 0.25 and, thus, we cannot rule out less common sequence variants within *FOXP2* contributing to the overall inherited susceptibility to ADHD. Further studies in other cohorts and deep-sequencing of this genomic region are required to establish replication in other populations and to identify the sequence variants directly involved in the genetic background of this psychiatric disorder.

Although we hypothesize that *FOXP2* may contribute to the basis of a common genetic background for ADHD and learning disabilities, it remains unknown whether patients with ADHD plus learning disabilities represent a distinct group, as we have no information on comorbid learning disabilities in our ADHD cohorts. Therefore, it would be interesting to explore different aspects of language and learning impairments as well as other comorbid conditions in future studies.

Conclusion

This preliminary study suggests the participation of *FOXP2* in the ADHD combined subtype. These results, however, should be interpreted with caution and further studies in larger datasets need to be performed to shed light on the role of the *FOXP2* gene in ADHD.

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Conflicts of interest

There are no conflicts of interest.

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