Analysis of two language-related genes in autism: a case–control association study of *FOXP2* and *CNTNAP2*

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Impairment of language abilities is a common feature in autistic individuals. Heterozygous mutations in the Forkhead Box P2 (*FOXP2*) gene lead to a severe spoken language disorder. Recently, several studies have pinpointed the involvement of common variants of the Contactin-Associated Protein-Like 2 (*CNTNAP2*) gene, whose transcription is regulated by the product of *FOXP2*, in several disorders characterized by language impairments such as autism, specific language impairment (SLI), and selective mutism (SM). In the present study, common variants of the *FOXP2* and the *CNTNAP2* genes were analyzed through a case–control association study in 322 Spanish autistic patients and 524 controls. The results of this study suggest that common variants of *FOXP2* are unlikely to contribute to autism susceptibility, in agreement with previous findings. Furthermore, we failed to replicate in our sample a previous association finding of two single nucleotide polymorphisms (rs2710102 and rs7794745) in the *CNTNAP2* gene with autism. No evidence for the association of these genes with language traits was observed in our analysis. *Psychiatr Genet* 23:82–85 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Language impairments represent a frequent feature of the autism phenotype, and a considerable proportion of autistic individuals remain nonverbal throughout life (Rapin and Dunn, 2003). Several genes have been implicated in spoken language disorders, among others, Forkhead Box P2 (*FOXP2*) (7q31.1) and Contactin-Associated Protein-Like 2 (*CNTNAP2*) (7q35–7q36.1) (Newbury *et al.*, 2010). Interestingly, both genes map to chromosome 7q, where several linkage studies reported positive results in autism (Abrahams and Geschwind, 2008). Heterozygous mutations in *FOXP2* lead to a monogenic form of severe speech and language disorder (Lai *et al.*, 2001). This gene encodes a transcription factor involved in the regulation of numerous genes, including *CNTNAP2*, a member of the neurexin family (Vernes *et al.*, 2008). Recently, a homozygous mutation in *CNTNAP2* has been reported in Old Order Amish children from several families with seizures, language regression, and pervasive developmental disorder (Strauss *et al.*, 2006). Copy Number Variants (CNVs) or chromosome rearrangements in this gene have been reported recently in a wide spectrum of neuropsychiatric disorders such as autism, attention deficit hyperactivity disorder (ADHD), schizophrenia, epilepsy, Gilles de la Tourette, and mental retardation (Newbury *et al.*, 2010). Moreover, two association studies suggest that common variants of *CNTNAP2* may be involved in autism susceptibility: single nucleotide polymorphism (SNP) rs2710102 showed an association with the 'age at first word' trait in autistic patients (Alarcón *et al.*, 2008) and rs7794745 was associated with autism in an independent sample

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(Arking *et al.*, 2008). A recent study suggests that rs2710102 may influence early language acquisition in the general population (Whitehouse *et al.*, 2011). In addition, Tan *et al.* (2010) found a reduction in the cortex gray matter volume in males of the general population, homozygous for the minor allele of rs7794745. The results of these studies converge on *CNTNAP2*, suggesting that common variants in this gene may be involved in autism and influence language traits. The crucial role of *FOXP2* in human language development makes it an intriguing candidate gene for autism. For this reason, several mutation screening and association studies have been carried out (Newbury *et al.*, 2002; Wassink *et al.*, 2002; Gauthier *et al.*, 2003; Gong *et al.*, 2004; Li *et al.*, 2005; Marui *et al.*, 2005; Richler *et al.*, 2006), although only two studies in Chinese and Japanese autistic populations found a nominal association (Gong *et al.*, 2004; Li *et al.*, 2005). However, none of these studies achieved a comprehensive genetic coverage of *FOXP2*.

In the present work, we carried out a case–control association study between autism and 12 tagSNPs across the *FOXP2* gene and we also tested the markers rs7794745 and rs2710102 of *CNTNAP2* for replication purposes. Furthermore, we also analyzed the possible contribution of these genes to specific language traits in our autism sample.

Materials and methods

The autism cohort under study included 322 unrelated individuals (269 men, 53 women; average age: 17 years) fulfilling the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Ed. Text Revision (DSM-IV-TR) criteria for autism, Asperger disorder, or pervasive developmental disorder not otherwise specified on the basis of ADI-R (Autism Diagnostic Interview-Revised) and ADOS-G (Autism Diagnostic Observation Schedule-Generic) (Lord *et al.*, 1994; Lord *et al.*, 2000). Five hundred and twenty-four frequency sex-matched unrelated controls were recruited at the Blood and Tissues Bank of the Hospital Universitari Vall d'Hebron. Patients and controls were Spanish and Caucasian. Genomic DNA was extracted from peripheral blood lymphocytes using the salting-out method.

We selected SNPs covering all exons, introns, and 3–5 kb sequences upstream and downstream of the *FOXP2* gene. We minimized marker redundancy by evaluating linkage disequilibrium (LD) patterns and the distribution of haplotype blocks in the CEU population from the HapMap database project (release 20, *www.hapmap.org*). Twelve tagSNPs were selected with an r^2 value less than 0.85 from all SNPs with a minor allele frequency greater than 0.10. All markers in the *FOXP2* gene were genotyped using an SNPlex assay (Applied Biosystems, Carlsbad, California, USA) at the Barcelona node of the National Genotyping Center (CeGen, *www.cegen.org*).

Two markers in *CNTNAP2*, rs2710102 and rs7794745, were genotyped through PCR–RFLP analysis. Enzyme restriction was performed with *Ava*I (rs2710102) and *Tsp*509I (rs7794745). The details of primer sequences and protocols are available upon request. Analyses of Hardy–Weinberg equilibrium and the case–control association study were carried out using the SNPassoc R package (Gonzalez *et al.*, 2007). Haplotype-based case–control analysis in the *FOXP2* gene was carried out using Haploview 4.0 (Barrett *et al.*, 2005).

In addition, we assessed the possible genetic contribution of the studied markers to selected relevant variables of language traits in autism: 'age at first word' and 'age at first phrase'. These variables were checked for normality and homogeneity of variances using Kolmogorov–Smirnov and Levene tests, respectively. As 'age at first phrase' followed a normal distribution, the mean scores were compared among the different genotypes by one-way analysis of variance tests. For 'age at first word', in which normality was rejected, we used nonparametric tests (Kruskal–Wallis).

Results

We carried out a case–control association study of 14 SNPs in 322 patients and 524 controls to assess the genetic contribution of two language-related genes in autism. Twelve tagSNPs selected to capture the genetic variability of *FOXP2* and two markers of *CNTNAP2*, associated previously with autism, were tested in our cohort. All markers passed quality control thresholds: genotyping call rate >90%, $r^2 < 0.85$ from any other tagSNP (*FOXP2* gene), minor allele frequency >0.1, Hardy–Weinberg equilibrium ($P > 0.01$ in our control population). Genetic homogeneity in our sample was confirmed previously through the analysis of 46 unlinked genome-wide SNPs (Toma *et al.*, 2011).

The results of the case–control association study between single markers and autism are summarized in Table 1. No SNP reached a nominal association in *FOXP2* under the three genetic models considered in our analysis (additive, dominant, and recessive), with *P*-values ranging from 0.21 to 0.94. Also, no association was obtained for the two *CNTNAP2* markers (*P*-values from 0.12 to 0.88). Similar results were obtained when we excluded the Asperger individuals from the data set (*P*-values from 0.08 to 0.97, data not shown). Also, no evidence for an association was found when we considered men and women separately. LD patterns across the *FOXP2* gene are distributed in four LD blocks (block 1: rs12533005, rs10228350, rs10255943, rs10268637, rs10486026, and rs4727799; block 2: rs17137124 and rs1229761; block 3: rs7782412 and rs7799652; block 4: rs936146 and rs10953766). These blocks were assessed for association through haplotype analysis, but we failed to detect any association (all $P > 0.05$, data not shown).

Table 1 Results of a case–control association study with single markers in the *FOXP2* and *CNTNAP2* genes in 322 autistic individuals and 524 controls from Spain

				P-value	
Gene	Marker	Number Ca;Co (MAF Ca;Co)	*P*-value (additive)	Genotype 11 vs. 12 + 22	Genotype 11 + 12 vs. 22
FOXP2	rs12533005	314;524 (0.46;0.45)	0.47	0.67	0.43
	rs10228350	320;522 (0.37;0.37)	0.94	0.43	0.21
	rs10255943	317;524 (0.3;0.28)	0.43	0.28	0.89
	rs10268637	320;521 (0.43;0.44)	0.70	0.78	0.71
	rs10486026	319;523 (0.21;0.21)	0.86	0.95	0.76
	rs4727799	317;523 (0.41;0.38)	0.23	0.31	0.35
	rs17137124	317;523 (0.48;0.50)	0.41	0.49	0.50
	rs1229761	319;524 (0.38;0.37)	0.63	0.91	0.44
	rs7782412	319;522 (0.45;0.46)	0.66	0.56	0.90
	rs7799652	303;513 (0.47;0.47)	0.90	0.51	0.36
	rs936146	319;524 (0.41;0.41)	0.90	0.87	0.67
	rs10953766	321;524 (0.49;0.47)	0.37	0.44	0.49
CNTNAP2	rs7794745	312;505 (0.39;0.39)	0.87	0.88	0.61
	rs2710102	309;490 (0.43;0.45)	0.46	0.12	0.60

P-values were obtained using the Cochran–Armitage trend test (additive model). *P*-values under the dominant (11 vs. 12 + 22) and recessive (11 + 12 vs. 22) models are also shown.
Ca, cases; Co, controls; MAF, minor allele frequency.

We also considered language endophenotypes in autistic individuals to gain more insight into the possible genetic influence of *FOXP2* and *CNTNAP2* on language impairments. The variable 'age at first word' did not show an association with any of the 14 markers considered ($P > 0.05$, data not shown), whereas two SNPs in *FOXP2* showed a nominal association with 'age at first phrase' (rs17137124, $P = 0.049$ and rs7782412, $P = 0.043$) (Table 2). However, these results were not significant after applying the Bonferroni correction for multiple testing.

Table 2 Two-way analysis of variance for 'age at first phrase' in autistic individuals: common variants in the *FOXP2* gene

Genotype	N[a]	X	SD	F	*P*-value
rs17137124 (*FOXP2*)					
22	21	42.7	16.8	–	–
24	51	41.4	16.5	3.11	0.049
44	26	32.8	13.3	–	–
rs7782412 (*FOXP2*)					
22	21	32.0	12.9	–	–
24	52	42.3	15.6	3.24	0.043
44	27	38.9	17.7	–	–

Fourteen SNPs in *FOXP2* and *CNTNAP2* were studied, but only SNPs showing a nominal association are shown here.
SNP, single nucleotide polymorphism; X, average number of months.
[a]Nonverbal individuals were excluded.

Discussion

During the last decade, the identification of mutations in *FOXP2* in a severe and rare form of speech impairment has prompted several studies aimed at assessing its possible role in language impairments frequently associated with autism. None of these mutational screenings or association studies clearly implicated this gene in autism, with the exception of two SNPs showing a weak association in Asian populations (Gong *et al.*, 2004; Li *et al.*, 2005). The case–control association study of 12 *FOXP2* tagSNPs carried out here did not show a significant association with autism or specific language traits. Taken together, these data suggest that it is unlikely that common variants in *FOXP2* may be at the genetic basis of autism. Despite this, recent findings highlight instead that low-frequency variants of *FOXP2* may be involved in a few cases of autism spectrum disorders (Schaaf *et al.*, 2011; Casey *et al.*, 2012).

FOXP2 regulates the transcription of *CNTNAP2*, a language-related gene that belongs to the neurexin family. Recently, *de novo* chromosomal rearrangements including *CNTNAP2*, but also other genes, have been described in autistic individuals with speech delay (Bakkaloglu *et al.*, 2008; Rossi *et al.*, 2008; Poot *et al.*, 2009). Moreover, deletions encompassing *CNTNAP2* and several adjacent genes have been described in cases of schizophrenia and epilepsy associated with mental retardation and speech delay (Friedman *et al.*, 2008). These genetic rearrangements include several genes in addition to *CNTNAP2*, so it is likely that additional genes may contribute toward the cognitive impairments described in these patients. Interestingly, CNVs encompassing only the *CNTNAP2* gene region have been found in patients with schizophrenia, epilepsy, or attention deficit hyperactivity disorder, in whom no language impairments were described (Friedman *et al.*, 2008; Elia *et al.*, 2010; Mefford *et al.*, 2010). Also, common and rare variants in *CNTNAP2* have been implicated in autism: rare missense changes were identified in a few individuals (Bakkaloglu *et al.*, 2008) and common variants were found to be associated with the disease: rs7794745 (Arking *et al.*, 2008) and rs2710102 (Alarcón *et al.*, 2008). However, in our cohort of 322 autistic patients and 524 healthy individuals, these two SNPs were not found to be associated with autism or language traits. Insufficient genetic power because of limited sample size, heterogeneity among samples, or differences in the LD patterns among populations may explain the lack of replication.

In conclusion, we corroborate previous findings confirming that common variants of *FOXP2* are not involved in

susceptibility to autism. Moreover, we failed to replicate positive results of two common variants of the *CNTNAP2* gene (rs2710102 and rs7794745) associated previously with autism and language traits, suggesting that further research is required to elucidate the role of this gene in autism.

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Conflicts of interest

There are no conflicts of interest.

References

Abrahams BS, Geschwind DH (2008). Advances in autism genetics: on the threshold of a new neurobiology. *Nat Rev Genet* **9**:341–355.

Alarcón M, Abrahams BS, Stone JL, Duvall JA, Perederiy JV, Bomar JM, *et al.* (2008). Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. *Am J Hum Genet* **82**: 150–159.

Arking DE, Cutler DJ, Brune CW, Teslovich TM, West K, Ikeda M, *et al.* (2008). A common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism. *Am J Hum Genet* **82**:160–164.

Bakkaloglu B, O'Roak BJ, Louvi A, Gupta AR, Abelson JF, Morgan TM, *et al.* (2008). Molecular cytogenetic analysis and resequencing of contactin associated protein-like 2 in autism spectrum disorders. *Am J Hum Genet* **82**:165–173.

Barrett JC, Fry B, Maller J, Daly MJ (2005). HaploView: analysis and visualization of LD and haplotype maps. *Bioinformatics* **21**:263–265.

Casey JP, Magalhaes T, Conroy JM, Regan R, Shah N, Anney R, *et al.* (2012). A novel approach of homozygous haplotype sharing identifies candidate genes in autism spectrum disorder. *Hum Genet* **131**:565–579, *doi:10.1007/s00439-011-1094-6*.

Elia J, Gai X, Xie HM, Perin JC, Geiger E, Glessner JT, *et al.* (2010). Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. *Mol Psychiatry* **15**:637–646.

Friedman JI, Vrijenhoek T, Markx S, Janssen IM, van der Vliet WA, Faas BH, *et al.* (2008). CNTNAP2 gene dosage variation is associated with schizophrenia and epilepsy. *Mol Psychiatry* **13**:261–266.

Gauthier J, Joober R, Mottron L, Laurent S, Fuchs M, De Kimpe V, *et al.* (2003). Mutation screening of FOXP2 in individuals diagnosed with autistic disorder. *Am J Med Genet A* **118A**:172–175.

Gong X, Jia M, Ruan Y, Shuang M, Liu J, Wu S, *et al.* (2004). Association between the FOXP2 gene and autistic disorder in Chinese population. *Am J Med Genet B Neuropsychiatr Genet* **127B**:113–116.

Gonzalez JR, Armengol L, Sole X, Guino E, Mercader JM, Estivill X, *et al.* (2007). SNPassoc: an R package to perform whole genome association studies. *Bioinformatics* **23**:644–645.

Lai CS, Fisher SE, Hurst JA, Vargha-Khadem F, Monaco AP (2001). A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature* **413**:519–523.

Li H, Yamagata T, Mori M, Momoi MY (2005). Absence of causative mutations and presence of autism-related allele in FOXP2 in Japanese autistic patients. *Brain Dev* **27**:207–210.

Lord C, Rutter M, Le Couteur A (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* **24**:659–685.

Lord C, Risi S, Lambrecht L (2000). The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* **30**:205–223.

Marui T, Koishi S, Funatogawa I, Yamamoto K, Matsumoto H, Hashimoto O, *et al.* (2005). No association of FOXP2 and PTPRZ1 on 7q31 with autism from the Japanese population. *Neurosci Res* **53**:91–94.

Mefford HC, Muhle H, Ostertag P, von Spiczak S, Buysse K, Baker C, *et al.* (2010). Genome-wide copy number variation in epilepsy: novel susceptibility loci in idiopathic generalized and focal epilepsies. *PLoS Genet* **6**:e1000962.

Newbury DF, Bonora E, Lamb JA, Fisher SE, Lai CS, Baird G, *et al.* (2002). FOXP2 is not a major susceptibility gene for autism or specific language impairment. *Am J Hum Genet* **70**:1318–1327.

Newbury DF, Fisher SE, Monaco AP (2010). Recent advances in the genetics of language impairment. *Genome Med* **2**:6.

Poot M, Beyer V, Schwaab I, Damatova N, Van't Slot R, Prothero J, *et al.* (2009). Disruption of CNTNAP2 and additional structural genome changes in a boy with speech delay and autism spectrum disorder. *Neurogenetics* **11**: 81–89.

Rapin I, Dunn M (2003). Update on the language disorders of individuals on the autistic spectrum. *Brain Dev* **25**:166–172.

Richler E, Reichert JG, Buxbaum JD, McInnes LA (2006). Autism and ultraconserved non-coding sequence on chromosome 7q. *Psychiatr Genet* **16**:19–23.

Rossi E, Verri AP, Patricelli MG, Destefani V, Ricca I, Vetro A, *et al.* (2008). A 12 Mb deletion at 7q33-q35 associated with autism spectrum disorders and primary amenorrhea. *Eur J Med Genet* **51**:631–638.

Schaaf CP, Sabo A, Sakai Y, Crosby J, Muzny D, Hawes A, *et al.* (2011). Oligogenic heterozygosity in individuals with high-functioning autism spectrum disorders. *Hum Mol Genet* **20**:3366–3375.

Strauss KA, Puffenberger EG, Huentelman MJ, Gottlieb S, Dobrin SE, Parod JM, *et al.* (2006). Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. *N Engl J Med* **354**:1370–1377.

Tan GC, Doke TF, Ashburner J, Wood NW, Frackowiak RS (2010). Normal variation in fronto-occipital circuitry and cerebellar structure with an autism-associated polymorphism of CNTNAP2. *Neuroimage* **53**:1030–1042.

Toma C, Hervás A, Balmaña N, Salgado M, Maristany M, Vilella E, *et al.* (2011). Neurotransmitter systems and neurotrophic factors in autism: association study of 37 genes suggests involvement of *DDC*. *World J Biol Psychiatry doi: 10.3109/15622975.2011.602719*.

Vernes SC, Newbury DF, Abrahams BS, Winchester L, Nicod J, Groszer M, *et al.* (2008). A functional genetic link between distinct developmental language disorders. *N Engl J Med* **359**:2337–2345.

Wassink TH, Piven J, Vieland VJ, Pietila J, Goedken RJ, Folstein SE, *et al.* (2002). Evaluation of FOXP2 as an autism susceptibility gene. *Am J Med Genet* **114**:566–569.

Whitehouse AJ, Bishop DV, Ang QW, Pennell CE, Fisher SE (2011). CNTNAP2 variants affect early language development in the general population. *Genes Brain Behav* **10**:451–456, *doi: 10.1111/j.1601-183X.2011.00684.x*.