American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 144B:954–957 (2007)

Brief Research Communication

Family-Based Association Study of Neuregulin-1 Gene and Psychosis in a Spanish Sample

Araceli Rosa,[1]* M. Gardner,[1] M.J. Cuesta,[2] V. Peralta,[2] M. Fatjó-Vilas,[3] S. Miret,[4] M.E. Navarro,[5] D. Comas,[1] and L. Fañanás[3]

[1]*Unitat de Biologia Evolutiva, Facultat de Ciències de la Salut i de la Vida, Universitat Pompeu Fabra, Barcelona, Catalonia, Spain*
[2]*Psychiatric Unit, Virgen del Camino Hospital, Pamplona, Spain*
[3]*Unitat d'Antropologia, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain*
[4]*Mental Health Center of Psychiatry and Drug Addiction Service of the Hospital Santa Maria, Lleida, Barcelona, Spain*
[5]*Adolescents Area of Benito Menni Assistance Complex in Mental Health, Sant Boi de Llobregat, Barcelona, Spain*

Neuregulin 1 (NRG1) is one of the most exciting candidate genes for schizophrenia since its first association with the disorder in an Icelandic population. Since then, many studies have analyzed allele and haplotype frequencies in European and Asian populations in cases and controls yielding varying results. We investigated the association of NRG1 with psychosis in a total sample set of 575 individuals from 151 Spanish nuclear families. We tested eight SNPs across 1.2 Mb along NRG1 including regions previously associated to schizophrenia in association studies. After correction for multiple testing, the TDT analysis for each marker did not show a significant over-transmission of alleles from the parents to the affected offspring for any of the markers ($P > 0.05$). The haplotypic analysis with TRANSMIT and PDT did not show preferential transmission for any of the haplotypes analyzed in our sample. These results do not seem to suggest that the investigated NRG1 markers play a role in schizophrenia in the Spanish population, although the finding of a trend for association with one SNP in the 3′of the gene warrants further investigation.

KEY WORDS: neuregulin-1 gene; schizophrenia; family-based association study; Spanish population; haplotype

Please cite this article as follows: Rosa A, Gardner M, Cuesta MJ, Peralta V, Fatjó-Vilas M, Miret S, Navarro ME, Comas D, Fañanás L. 2007. Family-Based Association Study of Neuregulin-1 Gene and Psychosis in a Spanish Sample. Am J Med Genet Part B 144B:954–957.

INTRODUCTION

Chromosome 8p has been identified as a candidate locus for schizophrenia (SZ) by several genome-wide linkage scans. This was confirmed by two recent meta-analyses of published linkage data [Badner and Gershon, 2002; Lewis et al., 2003]. A positive finding of linkage in complex disorders may serve as a starting point for the identification of candidate genes. This was the case of the Neuregulin-1 gene (*NRG1*)(8p12) which was first identified after a genome-wide linkage scan of 33 extended Icelandic families involving 110 patients [Stefansson et al., 2002]. Markers in this gene were subsequently tested for association and a number of overlapping haplotypes were identified as being over-represented in schizophrenic patients compared to controls. The risk haplotypes shared a "common core haplotype" (Hap_{ICE}) consisting of five SNPs (SNP8NRG221132, SNP8NRG221533, SNP8NRG241930, SNP8NRG243177, SNP8NRG433E1006) and two microsatellites (478B14-848, 420M9-1395).

NRG1 is not however just a positional candidate gene, but also a pathophysiological candidate gene because of its involvement in processes hypothesized to be involved in schizophrenia such as neurodevelopment, regulation of glutamate, and other neurotransmitter receptors and synaptic plasticity [Harrison and Owen, 2003]. Furthermore, it affects the expression of GABA receptors in hippoccampus and neurite outgrowth, induces the expression of NMDA receptors, and plays a role in neuronal migration [Harrison and Law, 2006].

Since this first association with the disease, many other research groups have carried out association studies using other markers in addition to the SNPs and microsatellites reported by Stefansson and colleagues in different populations yielding varying results.

The Icelandic finding of association of Hap_{ICE} with schizophrenia was replicated first in a Scottish population [Stefansson et al., 2003] and later in a European sample (UK/Irish) [Williams et al., 2003]. Other Caucasian studies, however, have not replicated these findings or have found positive associations corresponding to markers or alleles other than those previously reported [Bakker et al., 2004; Corvin et al., 2004; Kampman et al., 2004; Thiselton et al., 2004; Duan et al., 2005; Ingason et al., 2006]. Associations between the Hap_{ICE} have also been reported in four Chinese samples [Yang et al., 2003; Li et al., 2004] two of which appear to identify the same haplotype in the same region [Tang et al., 2004; Zhao et al., 2004]. In Japanese samples, two studies have shown negative and positive associations respectively [Fukui et al., 2006; Iwata et al., 2004]. One possible source of between-study discrepancies is the difference between populations in allele and haplotype frequencies [Gardner et al., 2006].

Among the positive studies, the relative risk of Hap_{ICE} was between 1.25 and 2.2 suggesting that this locus confers a relatively minor risk for SZ. In addition, many different alleles and haplotypes have been associated with no variant uniformly implicated. Thus, until we can relate a specific sequence or functional variant to the risk, the evidence must be viewed as inconclusive and the likelihood of false positive and negative findings and publication bias should be considered.

*Correspondence to: Dr. Araceli Rosa, Unitat de Biologia Evolutiva, Departament de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra, Doctor Aiguader 88, 08003 Barcelona, Catalonia, Spain. E-mail: araceli.rosa@upf.edu

Received 28 August 2006; Accepted 18 January 2007

DOI 10.1002/ajmg.b.30511

In the present study, we investigated NRG1 for involvement with psychosis in a Spanish population using a family-based association study in a sample of parents–proband trios and parents–proband–healthy sib quadruplets. This represents the first study of this gene in a Spanish population. We tested NRG1 single-nucleotide polymorphisms (SNP) in the Hap_{ICE} region and at other points along the gene.

MATERIALS AND METHODS

The family-study sample consisted of 575 Spanish individuals from 151 nuclear families (29 triads-affected offspring with parents and 122 quadruplets-affected offspring with parents and healthy sib). Families were collected through 151 patients (113 male and 38 female with mean age = 24.4 years, SD = 6.5) affected by DSM-IV schizophrenia and schizophrenia spectrum disorders. Patients were recruited from consecutive admissions to the Psychiatric Unit of Virgen del Camino Hospital in Pamplona; the Mental Health Center of Psychiatry; and Drug Addiction Service of the Hospital Santa Maria in Lleida; and the Adolescents Area of Benito Menni Assistance Complex in Mental Health in Sant Boi de Llobregat. Symptom rating and diagnoses were established from information coming from interviews and direct observation of each patient during the index episode, information provided by close relatives, and also from a comprehensive review of medical records. Clinical symptoms and diagnoses were also assessed using the Comprehensive Assessment of Symptoms and History (CASH) [Andreasen et al., 1992]. The CASH was also used in siblings (53 male and 69 female with mean age = 27.3 years, SD = 6.62) and parents to confirm the lifetime absence of any psychotic disorder [further details, Rosa et al., 2004].

The study protocol was approved by the ethical committee of the three hospitals. Written informed consent was obtained from all the participants after the procedures were fully explained.

Genomic DNA was extracted from peripheral blood cells using standard methods. A total of eight SNPs were successfully genotyped using Applied Biosystems (AB) TaqMan Technology. The AB assay-on-demand service was used to order probes and primers for the SNPs rs763553*, rs385396, rs1462906, rs901561, rs10503929. The AB assay-by-design service was used to design the probes and primers for the SNPs SNP8NRG221132*#, SNP8NRG241930*#, SNP8NRGd131E1006*. Three of the SNPs were contained within the Hap_{ICE} region (*) and two of the SNPs (#) were those of Hap_{ICE}, the others were spaced along the gene (see Table I).

Hardy–Weinberg equilibrium was tested using the chi-square goodness-of-fit test.

To detect associations between any single marker and the disease, we used the Transmission Disequilibrium Test (TDT) [Spielman et al., 1993].

To test for association between haplotypes and disease, we used the TRANSMIT program which examines the transmission of multiple markers from parents to affected offspring [Clayton and Jones, 1999]. Additionally, we used the PDTPHASE program included in UNPHASED [Dudbridge, 2003] to conduct the Pedigree disequilibrium test (PDT) used for testing association in the presence of linkage in general pedigrees. PDT is a valid way to test families, as that included in the present study (e.g., quadruplets) that contribute with different amounts of information to the overall test.

In order to correct for multiple testing and to assess a correct *P* value, we used the Single Nucleotide Polymorphism Spectral Decomposition method (SNPSpD) [Nyholt, 2004].

RESULTS

We genotyped a total of eight markers along the neuregulin-1 gene; genotype frequencies of all SNPs in the group of patients, unaffected siblings and parents were in Hardy–Weinberg equilibrium ($P > 0.05$ for all the comparisons).

The independent statistical analysis of each NRG1 marker did not show a trend for preferential transmission of any allele from heterozygous parents to the affected offspring for markers from 1 to 7 (chi-squared for allele wise TDT, $P > 0.05$) (Table I).

Only marker 8 (rs10503929) revealed a statistically significant *P*-value for the transmission disequilibrium test (chi-squared for allele wise TDT: 3.83; $P > 0.03$), which was lost when corrected for multiple testing using the SNPSpD. This trend was not observed in the group of healthy sibs where the transmission of the alleles was not different from that predicted by random assortment. The healthy siblings constituted a control for the affected offspring to eliminate false positive results due to generalized segregation distortion at the locus.

The TDT power calculator [Ferreira et al., 2007] was used to estimate power for the TDT analyses. Based on the number of families in our sample, under a relative risk of 2 for NRG1 and assuming the disease allele having frequency of 10%, we had 95% power to detect a significant association at 0.05 significance level. Keeping all parameters unchanged except for the marker minor allele frequency, we had respectively, 90.5%, 88.1%, and 85% power to detect a significant association if the markers had a minor allele frequency of 0.2, 0.3, and 0.5.

As haplotype analysis has more accuracy and statistical power than the analysis of individual SNPs in linkage disequilibrium, we estimated haplotype frequencies using

TABLE I. SNPs Analyzed Along the NRG Gene (Identifiers, Polymorphic Site, and Distances) and Transmission Disequilibrium Test Results for Each Marker

Marker	SNP identifiers[a]	Alleles[b]	Distance to marker 1 (base pairs)	Transmission of alleles[c]		*P*-value
				Observed	Expected	
1	rs763553	C/T	0	116/130	121.3/124.7	0.33
2	SNP8NRG221132	G/A	28 258	260/32	259.4/32.6	0.88
3	SNP8NRG241930	G/T	48 841	148/70	145.4/72.6	0.57
4	SNP8NRGd131E1006	G/A	52 873	124/32	123.8/32.2	0.95
5	rs385396	A/C	362 643	249/27	254.3/21.7	0.09
6	rs1462906	T/C	451 141	279/7	280.2/5.8	0.53
7	rs901561	A/G	698 011	194/100	192.3/101.7	0.75
8	rs10503929	T/C	1 168 516	263/25	255.3/32.7	0.03

[a]SNP identifiers given according to NCBI or DeCode SNP numbers.
[b]Second allele is the rare allele.
[c]The transmission data are given for the common variant and rare variant.

TABLE II. Results of 2-Marker and 3-Marker Haplotype in Parent–Proband Transmissions for TRANSMIT

Haplotypes	Estimated frequencies	Transmissions		χ^2-test	*P*-value
		Observed	Expected		
Marker 2-3:					
GT	0.23	63.1	65.1	0.28	0.59
AT	0.11	29.6	30.6	0.08	0.78
GG	0.65	192.9	190.2	0.31	0.57
AG	0.01	2.4	1.9	0.23	0.65
Marker 2-3-4:					
GTG	0.21	52.6	56.5	1.17	0.28
ATG	0.11	28.6	29.6	0.08	0.78
GGG	0.47	138.6	134.5	0.86	0.34
AGG	0.01	2.4	2.0	0.19	0.67
GGA	0.03	9.2	8.1	0.69	0.32
GTA	0.17	48.6	49.3	0.05	0.80

the two analyzed markers in the HAP_{ICE} (SNP8NRG221132, SNP8NRG241930) and also adding SNP8NRGd131E1006 within the HAP_{ICE} The global chi-square result from TRANSMIT program did not reveal patterns of preferential transmission from parents to affected offspring for the three marker haplotype (global chi-square test = 2.84, $P = 0.7$). Neither were statistically significant results obtained when markers 2 and 3 (markers included in the HAP_{ICE}) were considered (global chi-square test = 0.6, $P = 0.9$) (Table II).

Results obtained using PDTPHASE did not show overtransmission for any of the analyzed haplotypes either (global test for two-marker haplotype: $P = 0.9$ and for three-marker haplotype: $P = 0.8$).

DISCUSSION

Taken as a whole, the published studies suggest that the core Icelandic at-risk haplotype, $Hap_{ICE,}$ of the NRG1 gene might play a role in schizophrenia in European populations [Tosato et al., 2005; Li et al., 2006; Munafo et al., 2006]. However, because of the mixed results in different populations and the failure to pinpoint the individual functional or causative genetic variant associated, further association studies in new samples with different geographical origin are essential. This idea is highlighted by a recent study, which pointed the marked population differences in NRG1 allele and haplotype frequencies worldwide and how these could have played a role in the variability of results in the genetic association studies to date [Gardner et al., 2006]. A major consequence is that a finding of association in one population may not be applicable to other populations with a different population history and could explain why some replications have been found in populations historically connected such as Icelandic, Scottish, and Irish populations [Helgason et al., 2000].

In the present family-based association study using 151 Spanish families, we examined whether a given allele or haplotype of the neuregulin-1 gene was associated with schizophrenia and schizophrenia spectrum disorders. In the single marker analysis, from all the SNPs analysed, only marker 8 (rs10503929), a missense mutation that causes amino acid change (Thr/Met) situated in exon 11 of the 3′ region of the gene, revealed statistically significant association in the single marker analysis that disappeared after correction for multiple testing.

Despite the fact that the only association found in our study is not statistically significant after correction for multiple testing using the method based on spectral decomposition (SNPSpD), our observation of association with this marker in the 3′ end of the gene can not be dismissed entirely given that this finding is consistent with those of some other groups [Li et al., 2004; Petryshen et al., 2005; Lachman et al., 2006; Schwab et al., 2006; Walss-Bass et al., 2006]. From all these studies, two were conducted in European samples [Petryshen et al., 2005; Schwab et al., 2006]. Petryshen and colleagues were unable to detect association between previously reported NRG1 European risk haplotypes and schizophrenia in a Portuguese sample although they detected association with other haplotypes including two haplotypes in the uninvestigated 3′ end of the gene. In the same way, Schwab and colleagues have shown association between the same marker as the present study (rs10503939) in a sample of 125 families from Germany. The pathophysiological significance of these preliminary data with NRG1 SNPs that are known to cause a change in amino acid sequence, remains unknown but the increasing frequency of findings with markers (or haplotypes) at the 3′ end of NRG1 being reported recently warrants further investigations. Exon 11 of the NRG1 gene codes for a C-Terminal transmembrane domain, NRG1 isoforms that contain this region remain attached to the membrane playing a role in proteolytic cleavage and release of the bioactive fragment of the protein [Liu et al., 1998]

In summary, our results show that the marker described to be associated to schizophrenia in the Icelandic, Scottish, and British population are not associated in a Spanish population. However, for many reasons, NRG1 gene is still a good candidate gene for schizophrenia and schizophrenia spectrum disorders: first because of the prior evidence for linkage to 8p; second by the relevance of the known functions of neuregulin-1 to the disease process, and lastly the schizophrenia-like phenotype seen in NRG1 mutant mice [Falls, 2003]. The finding that specific markers in the 3′ of the gene could play a role in the pathogenesis of psychosis support the interest in exploring markers in this region in future association studies of neuregulin-1 in order to reach consensus.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contribution of all patients and their family members; without their cooperation, this work would have not been possible. We also thank to Fermín Serrano, Alfredo Martínez-Larrea (Virgen del Camino Hospital), Sílvia Campanera (Hospital Sta Maria in Lleida), and the research team of Benito Menni Assitance Complex for their participation in the recruitment and assessment of the families; R. Anglada, S. Plaza, Servei de Genòmica (UPF) and M. Vallés for their generous technical assistance and Dr. Jo Knight for her comments on the manuscript. This work was supported by grants from the Fundació La Marató de TV3

(014430/31), Spanish Ministry of Health, Instituto de Salud Carlos III, RETIC RD06/0011/0007 REM-TAP Network and Dirección General de Investigación, Ministerio de Educación y Ciencia (BFU2004-04208/BMC and BFU2006-01235/BMC) and Direcció General de Recerca, Generalitat de Catalunya (2005SGR/00608).

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