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The high producer variant of the Fc-receptor like-3 (*FCRL3*) gene is involved in protection against multiple sclerosis

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Abstract

Some polymorphisms in the *FCRL3* gene, a member of the Fc-receptor like family, have been associated with several autoimmune diseases and recently with multiple sclerosis (MS). We performed a case–control study of three SNPs in *FCRL3* gene in 645 MS patients and 786 controls, all Caucasians from the South of Spain. Genotype and allele frequencies of two SNPs (rs7528684/*FCRL3_3* and rs7522061/*N28D*), which were in high linkage disequilibrium (r^2=0.87), differed between MS cases and controls. The C allele of *FCRL3_3* was found to be protective for MS (per allele OR=0.81, 95% C.I.=0.70–0.94; *P*-value=0.007) as was the G variant of *N28D*, but no association was found for rs11264799/*FCRL3_4*. Haplotype analysis confirmed these associations with highly consistent effect sizes for haplotypes carrying the C allele of *FCRL3_3*.
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1. Introduction

Multiple sclerosis (MS) is a prototypic idiopathic neurodegenerative disease of the central nervous system (CNS) whose primary mechanism of injury is by inflammatory/autoimmune demyelination and, to variable degree, axonal damage. The clinical manifestations, prognosis and pathological features vary, both amongst entities within the broad spectrum of demyelinating disease and amongst subtypes of MS. There is strong evidence supporting that both genetic and epidemiological factors play important roles (Kantarci and Weinshenker, 2006; Dyment et al., 2004; Fedetz et al., 2006; Leyva et al., 2005; Matesanz et al., 2004). How these genetic and environmental factors exert their biological effects so as to account for the clinico-pathological heterogeneity in MS is not well defined (Kantarci and Weinshenker, 2006).

Recently, a functional variant, *FCRL3_3* (rs7528684), in the Fc-receptor like-3 (*FCRL3*) gene promoter, which alters the binding affinity of nuclear factor-kappaB and regulates *FCRL3* expression, has been reported to be associated with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), autoimmune thyroid disease (AITD) (Kochi et al., 2005) and multiple sclerosis, the latter finding from a Spanish case–control study (Martínez et al., 2007). The strongest association with RA has been observed for homozygous carriers of the C allele of the

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FCRL3_3 (rs7528684) polymorphism, located at −169 of the *FCRL3* promoter. This allele was found to produce higher promoter activity in a reporter gene assay and the binding affinity for the NF-kB transcription factor was altered (Kochi et al., 2005). The *FCRL3* gene is located at the 1q21 locus and the 1q21–23 region has been implicated in several autoimmune diseases such as psoriasis (Capon et al., 2001) and MS (Dai et al., 2001). Several *FCRL* and *FCG* receptor genes (*FCRL5, FCRL4, FCR, and FCRL2*) are located in this region.

FCRL3 encodes a glycoprotein that is a member of the immunoglobulin receptor superfamily, and although its precise function remains unknown, it contains immunoreceptor tyrosine-based activation and inhibition motifs in its cytoplasmic domain, suggesting that it plays a role in immune cell regulation (Ravetch and Bolland, 2001).

To determine whether *FCRL3* is associated with susceptibility to MS, we genotyped three SNPs, two in the promoter region and one in the 3rd exon producing an amino acid change, in 645 MS patients and 786 controls in a Caucasian population from the South of Spain and compared with the results of Martínez et al. (2007) recently obtained in a multiple sclerosis-association study with an independent Spanish cohort.

2. Methods

2.1. Study subjects

Both cases and controls were recruited in Granada, Málaga and Seville, all three cities within a 200 km radius in the South of Spain. Case samples comprised 645 patients with clinically defined MS according to Poser's criteria (Poser et al., 1983). They were obtained from three public hospitals: the Hospital Clínico in Granada ($n=130$), the Hospital Carlos Haya in Málaga ($n=357$) and the Hospital Virgen de la Macarena in Seville ($n=158$). The mean age at the sample collection of the cases was 36 years and mean age of controls at interview was 38 years. The percentage of females was 68% for cases and 52% for controls. All of these patients were classified as either RR or SP-MS cases. Controls were 786 blood donors with no history of inflammatory disease attending the blood banks of Granada ($n=411$), Sevilla ($n=186$) and Málaga ($n=189$). The study was approved by the Ethics Committees of each of the hospitals participating in the study and written informed consent was obtained from all participants.

2.2. Genomic DNA isolation

High-molecular-weight DNA was isolated from whole blood using the Flexigene Kit (Qiagen, Hildren, Germany) according to the manufacturer's protocol.

2.3. SNP selection

All subjects were genotyped for 3 SNPs in the *FCRL3* gene, one C/T SNP (rs7528684) at the −169 position in the 5′ promoter region of the gene, another 5′ promoter G/A polymorphism (rs11264799) at position −110 of the gene, and a 3rd exonic polymorphism (rs7522061) at the 374G/A, which leads to the amino acid substitution, *N28D*. These three SNPs were designated as *FCRL3_3*, *FCRL3_4,* and *N28D* respectively consistent with previous studies (Kochi et al., 2005; Owen et al., 2007).

2.4. Genotyping

The three *FCRL3* polymorphisms were genotyped at the Madrid node (CNIO) of the Spanish National Genotyping Centre using Taqman. Assays on Demand C_1741825_10, C_17411826_10 and C_1741833_20 were supplied by Applied Biosystems. A total of 10 negative controls and 8 duplicates were included for each SNP as a quality control measure.

2.5. Statistical analysis

Hardy–Weinberg equilibrium was tested using χ^2 goodness-of-fit test. Differences in minor allele frequencies between cases and controls were tested for using Pearson's χ^2 test on 2×2 contingency tables. Odds ratios (ORs) and 95% Confidence Intervals (CIs) for comparisons between cases and controls were estimated by logistic regression using Stata SE v8. Haplotype frequencies were estimated and linkage disequilibrium (LD) measures (r^2) calculated using the Haploview software (Barrett et al., 2005) and compared between cases and controls using FamHap (v.12) software (Becker and Knapp, 2004). Assuming a minor allele frequency of 35% and a 0.05% prevalence of MS in the Spanish population (Fernández et al., 1994), we estimated that at the 5% significance level, this study had 99% power to detect genotypic odds ratios of the order reported in the first association study of RA in the Japanese population (OR=2.15, 95% C.I.=1.58–2.93). *P*-values reported are unadjusted for multiple testing unless stated otherwise. *P*-values were corrected for multiple testing by applying a permutation test based on 10,000 permutations, in each of which case–control status was randomly assigned conserving the observed proportions, χ^2 statistics calculated for each SNP tested and the maximum recorded for each permutation. The proportion of permutations for which the maximum χ^2 statistic was greater than that observed in the actual data for a given SNP was used as an estimate of the associated *P*-value, corrected for multiple testing.

3. Results

3.1. Polymorphisms and study groups

There was no evidence of departure from Hardy–Weinberg equilibrium among controls or cases for any of the three SNPs genotyped. We found that *FCRL3_3* and *N28D* were in high LD ($r^2=0.87$), with lower LD observed for each of these with *FCRL3_4* ($r^2=0.53$ and 0.49 respectively). The frequency of the C allele of *FCRL3_3* appeared to be higher in our control group (45.1%) than in the Japanese controls (37%) (Kochi et al., 2005), but similar to that among White North American controls (44.8%) (Hu et al., 2006) and to

Table 1
Genotype distributions for the three *FCRL3* SNPs in cases and controls

SNP/genotype	Cases *n* (%)	Controls *n* (%)	OR (95%CI)	*P*-value
N28D				
AA	209 (32.4)	211 (26.8)	1.00	
AG	315 (48.8)	406 (51.7)	0.78 (0.62–1.00)	0.047
GG	121 (18.8)	169 (21.5)	0.72 (0.53–0.98)	0.035
FCRL3_4				
GG	341 (53.1)	402 (52.2)	1.00	
AG	251 (39.1)	294 (38.2)	1.01 (0.81–1.26)	0.955
AA	50 (7.8)	74 (9.6)	0.80 (0.54–1.17)	0.249
FCRL3_3				
TT	227 (35.2)	226 (29.1)	1.00	
CT	318 (49.3)	400 (51.6)	0.79 (0.63–1.00)	0.052
CC	100 (15.5)	150 (19.3)	0.66 (0.49–0.91)	0.010

OR: odds ratio; CI: confidence interval.

that observed among controls in a recently published Spanish study of MS (44.9%) (Martínez et al., 2007). Genotype frequency distribution for the 3 SNPs between males and females in cases and controls were not different (data not shown).

3.2. Association of the FCRL3 variants with MS

Table 1 summarises the estimated genotype-associated odds ratios (ORs). There was no evidence that *FCRL3_4* was associated with MS (minor A allele frequencies of 27.2% and 28.1%, $P=0.6$). The variant alleles of both *N28D* and *FCRL3_3* were less common in cases than in controls (frequency=43.2% vs 47.3%, $P=0.027$ and frequency=40.2% vs 45.1%, $P=0.007$ respectively). After adjustment for multiple testing, association with *N28D* was only marginally significant (adjusted-$P=0.051$) and it was estimated that carriers of at least one G allele (dominant model) were at reduced risk of MS (OR=0.77, 95%CI=0.61–0.96). On the other hand, the association with *FCRL3_3* remained clearly statistically significant after correction for multiple testing (adjusted-$P=0.015$). Risk appeared to decrease with the number of C alleles carried in *FCRL3_3* and the estimated OR per C allele (codominant additive model) was 0.81 (95% CI=0.70–0.94, $P=0.007$).

3.3. FCRL3_3 haplotype association with MS

We examined whether haplotypes of *FCRL3* determined by the three SNPs genotyped were associated with the disease.

Table 2
Haplotype distribution between MS patients and healthy controls

Haplotype [a]		MS (n=642)	Controls (n=770)	OR (95% C.I.)	*P*-value
hap 1	AGT	0.564	0.525	1.445 (1.246–1.676)	0.037
hap 2	GAC	0.273	0.285	0.927 (0.786–1.094)	0.469
hap 3	GGC	0.127	0.159	0.771 (0.624–0.952)	0.016 [b]
hap 4	GGT	0.034	0.027	1.263 (0.817–1.953)	0.296

[a] Allele order: *N28D*/*FCRL3_4*/*FCRL3_3*.
[b] Bonferroni corrected *P*-value<0.05.

Table 3
Combined data analysis of the Martínez at al. data and this work respect to the *FCRL3_3* polymorphism association with multiple sclerosis

	T vs C	(TT+TC) vs CC (Risk allele T)	TT vs (CT+CC) (Risk allele C)
OR (T allele) [a], 95% CI	1.24 (1.10–1.4)	1.4 (1.12–1.74)	0.77 (0.65–0.91)
P-value	0.0003	0.0025	0.0031

[a] OR per C allele 0.80 (IC95%)=0.71–0.90), *P*-value=0.0003.

There was evidence of a difference in haplotype distribution between cases and controls (Global $\chi^2=10.36$, P-value=0.016, based on 3 degrees of freedom). Further haplotype analysis performed with the HaploView software (Barrett et al., 2005) is summarised in Table 2. We found that the GGC haplotype (hap 3 in Table 2) composed of the G allele at *N28D*, the G allele at *FCRL3_4* and the C allele at *FCRL3_3* was associated with protection from MS (OR=0.77, 95%CI=0.62–0.95, P-value=0.016). Hap1 (AGT) carrying the risk-associated allele T of *FCRL3_3*, was associated with increased risk (OR 1.45, 95%CI=1.25–1.68, $P=0.037$).

4. Discussion

This study investigates the association of three SNPs in the *FCRL3* gene with multiple sclerosis. Polymorphisms in this gene have been associated with different autoimmune disorders such as RA, Graves disease, Addison's disease and MS in Caucasian populations and with Hahimoto's thyroiditis in a Japanese cohort. The association of the *FCRL3_3* C allele with RA has been replicated in Japanese and Canadian populations, however with diminished effect sizes compared to the initial association studies (Ikari et al., 2006; Newman et al., 2006; Thabet et al., 2007). In contrast to these findings, well powered association studies of the *FCRL3_3* C allele in Caucasian cohorts from North America, UK and Spain have failed to replicate the association of *FCRL3_3* with RA and type 1 diabetes (T1D) (Martínez et al., 2006; Hu et al., 2006; Turunen et al., 2006; Smyth et al., 2006). However, this polymorphism has been associated with other autoimmune diseases such as Addison's disease and Graves' disease in Caucasian populations (Simmonds et al., 2006; Owen et al., 2007).

Our data are in accordance with the results recently obtained in a MS association study by Martínez et al. (2007), based on a Spanish series of 400 cases and 508 controls. In both studies, genotype frequencies at the SNP *FCRL3_3* differed similarly and significantly between MS patients and controls, and differential distribution between cases and controls at the *FCRL3_4* was not significant for both studies. A combined analysis of both cohorts (Table 3) increased the significance of association and revealed that the C allele of *FCRL3_3* is protective for MS (OR=0.80, $P=0.0003$). Similar results have been reported for Addison's disease in Caucasian patients for which the *FCRL3_3* C allele appears to be protective (Owen et al., 2007).

The C allele of *FCRL3_3* has been shown to alter the binding affinity of NF-kB, which correlates with higher levels of

FCRL3 expression in B cells both in vivo and in vitro (Kochi et al., 2005), suggesting that the association with different autoimmune pathologies is due to a "higher producer phenotype" (Vandenbroeck and Goris, 2003). This "higher producer phenotype" may be a genetic determinant implicated in conferring protection against MS and Addison's disease. Therefore, the same *FCRL3* allele seems to be associated with opposing effects for two inflammatory diseases, MS and RA, suggesting different pathogenic mechanisms. The experimental treatment of a MS group with a TNF alpha blocker, Lenercept, was found to produce an exacerbation rather than a decrease of inflammation process (Kantarci and Weinshenker, 2006). The similar products, Etanercept and Infliximab, have been tried in RA and Crohn's disease and some patients receiving these treatments experienced inflammatory-demyelination in the CNS (Kantarci and Weinshenker, 2006). It is also possible that this allele plays a role in susceptibility only in the presence of certain triggers or in interaction with other genetic variants specific to each disease or unevenly distributed among populations. Indeed, an epistatic interaction between the *FCRL3* and NFkappaB1 genes for RA susceptibility has been described in a Spanish study. Furthermore, a restriction of the association of *FCRL3_3* with RA to *PTPN22* 1858T-homozygous individuals has been reported in a Canadian population (Martínez et al., 2006; Newman et al., 2006).

The apparently moderate association of the *FCRL3_3* and *N28D* polymorphisms with protection against MS might be explained by disease complexity that makes the potential set of genes involved in the pathology in each patient heterogeneous and by the complex inheritance response and disease heterogeneity (Dyment et al., 2004; Comi et al., 2000; Steinman et al., 2002; Lucchinetti et al., 2004; Pittock et al., 2007). On the other hand, we cannot rule out that the association observed between the *FCRL3_3* polymorphism and MS may be due to a causal SNP located elsewhere within the block of linkage disequilibrium (LD) that contains the 5′ region of the *FCRL3* gene, or with other causal variants at the near chromosomal region, such as the *FCRL2* gene which could have more relevance in the MS pathology. Although the SNPs analyzed in this work were chosen on the basis of maximal association and LD in the FCRL gene cluster (*FCRL5, FCRL4, FCRL3, FCRL2, FCRL1* and *CD5L*) in different populations and autoimmune diseases in previous works (Kochi et al., 2005; Owen et al., 2007).

Given the heterogeneity in associations of *FCRL3* with different pathologies in different populations, future large-scale association studies of the extended haplotype block containing both *FCRL3* and *FCRL2* across different ethnic groups will be useful to illustrate the mechanisms by which different genetic and environmental factors contribute to complex diseases in subjects with distinct ethnic backgrounds. In summary, all these data suggest that this locus may affect susceptibility to different autoimmune diseases across different populations. The fact the initial association (Martínez et al., 2007) of *FCRL3_3* with MS has been replicated and extended in this work in an independent case–control study with almost double the sample size, indicates that the evidence for the involvement of *FCRL3* in multiple sclerosis susceptibility is solid.

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