

IL7RA Polymorphisms and Susceptibility to Multiple Sclerosis

TO THE EDITOR: Two independent, well-powered studies have recently identified the interleukin-7 receptor α (*IL7RA*) gene as a susceptibility gene for multiple sclerosis,^{1,2} thus extending and confirming earlier observations.^{3,4} A functional, nonsynonymous single-nucleotide polymorphism (SNP), rs6897932, located in the alternatively spliced sixth

exon of the gene, was highlighted as the susceptibility-modifying polymorphism, with the C allele increasing the risk of disease (odds ratio, approximately 1.2).^{1,2}

We genotyped nine haplotype-tagging SNPs in *IL7RA* in two independent case-control collections from Olmsted County, Minnesota, and Belfast,

Table 1. Allele Count and Frequency of *IL7RA* SNPs in Patients with Multiple Sclerosis and Controls.*

SNP and Allele	Olmsted County			Belfast		
	Allele Count and Frequency		P Value	Allele Count and Frequency		P Value
	Cases	Controls		Cases	Controls	
	no. (%)			no. (%)		
rs7711202						
A	103 (24.8)	233 (28.2)	0.334	311 (33.7)	319 (30.1)	0.083
G	313 (75.2)	593 (71.8)		611 (66.3)	741 (69.9)	
rs11567751						
C	296 (71.2)	606 (73.4)	0.409	686 (74.1)	785 (73.9)	0.933
T	120 (28.8)	220 (26.6)		240 (25.9)	277 (26.1)	
rs11567762						
A	55 (13.2)	116 (14.0)	0.691	143 (15.4)	145 (13.6)	0.251
G	361 (86.8)	710 (86.0)		783 (84.6)	919 (86.4)	
rs6897932						
C	320 (77.3)	576 (69.7)	0.005	690 (74.5)	780 (73.6)	0.638
T	94 (22.7)	250 (30.3)		236 (25.5)	280 (26.4)	
rs3822733						
G	121 (29.2)	222 (26.9)	0.397	240 (25.9)	280 (26.3)	0.840
A	293 (70.8)	602 (73.1)		686 (74.1)	784 (73.7)	
rs987107						
T	117 (28.3)	218 (26.4)	0.485	240 (26.0)	272 (25.8)	0.932
C	297 (71.7)	608 (73.6)		684 (74.0)	782 (74.2)	
rs11567777						
A	413 (99.3)	823 (99.6)	0.391	923 (99.7)	1054 (99.2)	0.198
T	3 (0.7)	3 (0.4)		3 (0.3)	8 (0.8)	
rs3194051						
A	295 (70.9)	603 (73.0)	0.438	686 (74.1)	784 (73.8)	0.896
G	121 (29.1)	223 (27.0)		240 (25.9)	278 (26.2)	
rs10491434						
T	297 (71.4)	605 (73.2)	0.490	685 (74.1)	787 (74.0)	0.932
C	119 (28.6)	221 (26.8)		239 (25.9)	277 (26.0)	

* Data are for 463 patients with multiple sclerosis and 532 healthy controls from Belfast and for 208 patients with multiple sclerosis and 413 controls from Olmsted County. All single-nucleotide polymorphisms (SNPs) were successfully genotyped, with a minimum genotyping success rate of 99.5%, and only one deviation from Hardy-Weinberg equilibrium was detected ($P=0.002$ for rs7711202 in cases of multiple sclerosis in Olmsted County). All genotyping was performed at the same site (Belfast) with the use of Sequenom technology. *IL7RA* denotes the interleukin-7 receptor α gene.

Northern Ireland, neither of which, to our knowledge, has previously been tested for *IL7RA* (Table 1). Clinical and demographic data for both collections have been described elsewhere.⁵ Analysis of the Olmsted County genotype data revealed an association between multiple sclerosis and the rs6897932*C allele ($P=0.00504$; 10,000-permutation-corrected $P=0.035$; odds ratio, 1.5; 95% confidence interval [CI], 1.1 to 2.0). However, this association was not found in the Belfast collection. CC genotype counts (vs. T carriage) were increased in patients with multiple sclerosis, as compared with controls, in Olmsted County ($P=0.0049$; odds ratio, 1.6; 95% CI, 1.1 to 2.3).

Haplotype analysis showed that in the Olmsted County patients with multiple sclerosis, the frequency of the GCGTACAAT haplotype was decreased (22%, vs. 30% in controls; uncorrected $P=0.0023$; 10,000-permutation-corrected $P=0.02$) and that of the GCGCACAAT haplotype was increased (21%, vs. 13% in controls; uncorrected $P=0.0003$; 10,000-permutation-corrected $P=0.0035$). In contrast, no such differences were observed in the Belfast collection.

The association between rs6897932 and multiple sclerosis in the Olmsted County collection appeared to be much stronger than anticipated on the basis of the recent studies^{1,2} and was therefore detectable in a collection that in principle was underpowered. The absence of an association in

the Belfast collection may reflect heterogeneity of the population or lack of statistical power.

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