Progressive multiple sclerosis does not associate with rs996343 and rs2046748

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To the Editors

A genome-wide association study in a small case-control series of patients with progressive multiple sclerosis (PrMS; primary progressive (PPMS) and secondary progressive (SPMS)) identified an intergenic variant (rs996343) with a putative role in disease course.¹ Nominally significant associations were also identified in dipeptidyl-peptidase 6 (*DPP6*), which after further genetic characterization nominated rs2046748 as a determinant of MS course.² To further define the effect of rs996343 and rs2046748 on disease progression, we genotyped a series of MS patients and unrelated healthy controls from Canada.

Genetic analyses were performed in MS patients and unrelated healthy controls of European ancestry collected through the longitudinal Canadian Collaborative Project on the Genetic Susceptibility to Multiple Sclerosis (CCPGSMS).³ The ethical review boards at the University of British Columbia approved the study, and all participants provided informed consent. All patients were diagnosed with MS according to Poser or McDonald criteria.^{4, 5} A total of 1,984 MS patients and 843 controls were characterized in this study. Detailed clinical course was available for 1,634 patients (82.4%); the majority presented a clinical course consistent with relapsing remitting MS (RRMS) (n=891; 54.5%), and the remainder presented PPMS (n=408; 25.0%) or SPMS (n=335; 20.5%). Detailed demographics for each group are provided in Supplemental Table 1.

Genotyping of rs996343 and rs2046748 was performed using TaqMan probes as previously described.⁶ Allelic and genotypic associations were examined by the Chi-squared test. All SNPs were consistent with Hardy-Weinberg equilibrium.

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Conflict of Interest Statement

The authors declare that there is no conflict of interest.

Power analysis estimates for rs996343 assuming an additive model with a disease frequency of 0.001, a genotype relative risk of 0.7, and the minor allele frequency (MAF=0.41) observed in healthy controls indicates that our study has over 99% power to identify a positive association, at the significance level of 0.05, in the entire MS cohort or patients presenting RRMS, 99% for PrMS, 95% for PPMS and 92% for SPMS disease course. Applying the same model to rs2046748, assuming a MAF of 0.11 and a genotype relative risk of 1.82 we estimated over 99% power of detecting positive associations for the entire MS cohort, RRMS and PrMS patients, 98% for PPMS and 97% for SPMS.

Association analysis of rs996343 and rs2046748 in 1,984 MS patients and 843 controls from Canada did not identify a significant association between genotypic or allelic frequencies and susceptibility to MS for either variant. Similarly, significant associations for rs996343 or rs2046748 were not observed between healthy controls and RRMS, PPMS, SPMS or PrMS patients (Supplemental Table 1). Likewise, differences between RRMS and PrMS were not identified (data not shown).

Despite the large number of patients with MS and controls examined in this study, our data does not support a role for rs996343 and rs2046748 in the susceptibility to disease in the Canadian population. Moreover, the analysis of disease subtypes is also not supportive of the previously suggested effect on MS progression.^{1, 2} It should be noted that not all the replication groups from the original studies resulted in a significant association between the nominated variants and disease progression; these discrepancies were attributed to either a false positive signal in the discovery group or differences in population-specific allelic frequencies. The lack of support provided by our study indicates that the former hypothesis is more likely correct, suggesting that rs996343 and rs2046748 do not affect the development of PrMS. However, additional studies in Southern European populations are warranted.

Therapeutic strategies for MS are currently ineffective to treat the progressive phase of the disease. The reason for this failure can probably be attributed to targeting the immune system, which is likely to play a minor role in the accumulation of the neuronal and synaptic damage observed in the pathophysiology of PrMS.⁷ Comprehensive genetic studies in large cohorts of well-characterized patients with PrMS are necessary for the identification of variants, genes, and molecular pathways implicated in the onset of this progressive phase. Unraveling the etiology of PPMS and SPMS is paramount for the development of effective therapeutics to treat the underlying molecular causes of PrMS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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