Author's response to reviews

Title: An examination of the Apo-1/Fas promoter Mva I polymorphism in Japanese patients with multiple sclerosis

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PDF covering letter
Reviewer: Mr. Miguel Lucas

This is a well-done work that is based in the interest of apoptosis in MS and other autoimmune diseases. The apoptotic mechanism in the pathogenesis of MS is a sound hypothesis to select Fas as a candidate gene for susceptibility to MS. The lack of association of Fas to MS pointed in the paper of Niino et al. does not exclude the association to other genes of the apoptotic pathway and this should be stated in the text.

It is important to consider the results even in small groups like this for later meta analysis. The association studies can be impaired by population stratification but this problem can be overcome by transmission disequilibrium tests (TDT) in nuclear families. The analyses of TDT in trios of MS nuclear families should be done in future studies.

Discretionary revisions: A minor point is to include the degree of significance of the frequency of HLADRB1*1501 positive patients, in their MS population, somewhere in table 4 or in the text and to comment it in the discussion section.

Reply: I appreciate the Reviewer’s comments. I added the sentences regarding the degree of significance of the frequency of DRB1*1501 in table 4 and commented it in the discussion section.
The Authors examined the association between Mva I polymorphism of the Apo-1/Fas promoter gene in Japanese multiple sclerosis (MS) patients. Rational basis of the study was a positive LOD score near the chromosome 10q23/10q24, where the gene has been mapped, reported in UK and Canadian screens, a previous report of association of polymorphism with MS in another population and the role of candidate gene assigned to Apo-1/Fas. The study was performed on 114 MS patients, compared to 121 healthy population-matched controls. No evidence for a role of Mva I polymorphism in MS susceptibility was found. Moreover, no difference in the Mva I allele and genotype frequencies was found in DRB1*1501 (DR2) positive or negative patients. Stratification of patients according to age at onset showed a tendency to later onset in patients with A/A genotype. The main concern in this paper is the low number of subjects studied. Association studies in complex diseases may have a relatively high power if sample size is really consistent. Calculations as frequency of polymorphism in a determined population, number of alleles of polymorphism analyzed.. and others define the optimal size of sample. Considering that “western type” MS in Japanese is less common that in European countries and that comparison between ethnically different populations may be of aid in comprehension of MS pathogenesis, the study may be considered of interest despite the fact that sample size of patients is small. Nevertheless, number of controls must be consistently higher (almost twofold). This point is crucial. Moreover, data regarding “tendency” of A/A carriers to have a later onset cannot be stressed in absence of a statistical significance.

Reply: As the Reviewer commented, the number of MS patients in Japan is smaller than that in Western countries. So it is difficult to study with large population of MS in Japan. However, we think number of controls should be consistently higher, too. We deleted the data regarding “tendency” of A/A carriers to have a later onset.