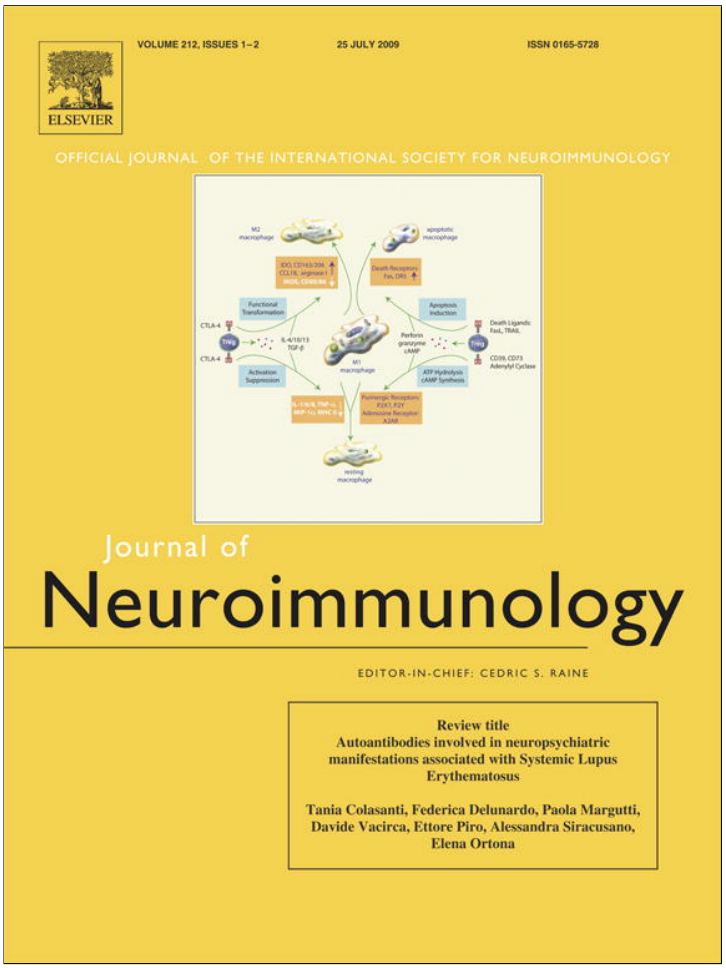

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Letter to the Editor

Comment to Tumour necrosis factor alpha gene –376 polymorphism in Hungarian patients with primary progressive multiple sclerosis

Marcelo Andrés Kauffman *, Andrés María Villa

Consultorio de Neurogenética, Consultorio de Neuroinmunología, Hospital JM Ramos Mejia, Buenos Aires, Argentina

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Dear Sirs,

We have read the article by Losonczi et al. (2009) and have found it very interesting. They concluded that TNF α –376G allele might be one of the factors responsible for progression in primary progressive multiple sclerosis (PPMS). We agree that TNF gene variants might be considered a candidate to be involved in the genetics of MS. However, as the authors partially mentioned, there have been different studies that have failed to find an association between these variants and MS susceptibility (Martinez et al., 2004). In fact, we have previously conducted a molecular epidemiological study in an Argentinean population with relapsing remitting MS and we did not find an association between TNF α –376 SNP and MS risk (Kauffman et al., 2007).

Replication failure frequently occurs in the field of complex genetics. This could be caused by several factors, which have been extensively discussed in previous studies (Colhoun et al., 2003). The aim of this letter is to point out some aspects of the work reported by Losonczi et al. that might influence the results obtained. They found an unusually high prevalence of the TNF α –376A allele in healthy controls. This prevalence is only comparable to what has been found in the genetically isolated population of Sardinia (Wirz et al., 2004). Particular HLA classes are over-represented in this Italian region (Sotgiu et al., 2002). Furthermore, an epistatic interaction between ApoE variants and HLA class II alleles was found to be associated with PPMS in the Sardinian population (Cocco et al., 2005). Thus, we consider that the results obtained by our colleagues might be reflecting an effect of untyped HLA alleles rather that a TNF one considering that TNF SNPs might be in linkage disequilibrium with HLA alleles. Therefore we think it would be valuable to investigate the HLA alleles of the subjects analyzed.

On the other hand, we think there is also a chance of false-positive results in the reported findings due to random variability. In order to control for this factor, some researchers have suggested that only highly conservative *p*-values should be accepted to reject the null hypothesis of no association (Colhoun et al., 2003) that can only be obtained in large samples of patients. In conclusion, we agree with Losonczi et al. that the association between the TNF α –376G allele and PPMS need to be further investigated in different and independent populations.

References

Cocco, E., Sotgiu, A., Costa, G., Murru, M., Mancosu, C., Murru, R., Lai, M., Contu, P., Marrosu, M., 2005. HLA-DR,DQ and APOE genotypes and gender influence in Sardinian primary progressive MS. Neurology 64, 564–566.

Colhoun, H.M., McKeigue, P.M., Davey Smith, G., 2003. Problems of reporting genetic associations with complex outcomes. Lancet 361, 865–872.

Kauffman, M.A., Moron, D.G., Sandoval, G., Sica, R.E., Garcea, O., Villa, A.M., 2007. Is tumor necrosis factor-376a promoter polymorphism associated with susceptibility to multiple sclerosis? Medicina-Buenos Aires 67, 436–438.

Losonczi, E., Bencsik, K., Nagy, Z.F., Honti, V., Szalczer, E., Rajda, C., Illes, Z., Matyas, K., Rozsa, C., Csepany, T., Fuvesi, J., Vecsei, L., 2009. Tumour necrosis factor alpha gene (TNF-alpha) –376 polymorphism in Hungarian patients with primary progressive multiple sclerosis. J. Neuroimmunol. 208, 115–118.

Martinez, A., Rubio, A., Urcelay, E., Fernandez-Arquero, M., De Las Heras, V., Arroyo, R., Villoslada, P., Montalban, X., De La Concha, E.G., 2004. TNF-376A marks susceptibility to MS in the Spanish population: a replication study. Neurology 62, 809–810.

Sotgiu, S., Pugliatti, M., Sanna, A., Sotgiu, A., Castiglia, P., Solinas, G., Dolei, A., Serra, C., Bonetti, B., Rosati, G., 2002. Multiple sclerosis complexity in selected populations: the challenge of Sardinia, insular Italy. Eur. J. Neurol. 9, 329–341.

Wirz, S., Morale, M., Marchetti, B., Barr, A., Sotgiu, S., Rosati, G., Pugliatti, M., Sanna, M., Giliberto, O., Bartfai, T., Conti, B., 2004. High frequency of TNF alleles –238A and –376A in individuals from northern Sardinia. Cytokine Growth Factor Rev. 26, 149–154.

* Corresponding author.
E-mail address: marcelokauffman@marcelokauffman.info (M.A. Kauffman).

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