our recent article,[1] several other groups have reported evidence for MS susceptibility haplotypes tagged by HLA A*02 and HLA B*44 that are independent of the effect of HLA DRB1*1501. The analysis of extended haplotypes published by Chao and colleagues does not find the protective effect of HLA B*44, but its size is too modest to definitively reject the possibility that HLA B*44 (or HLA A*02) tagged haplotypes have a role in MS susceptibility. Thus, clearly, we agree that additional studies with many thousands of subjects with MS and high-resolution sequence data will be needed to definitively deconstruct the role of the MHC in MS susceptibility in terms of HLA A*02, HLA B*44, and the HLA DRB1 alleles that have not yet been consistently replicated across populations and studies.

Comparisons of our results with those of Chao and colleagues is also hampered by methodologic differences. Assessing MHC class I/HLA DRB1 haplotypes is a reasonable approach, but we felt that an assessment of single alleles was more appropriate. As noted in our article, HLA A*02 and HLA B*44 were the most associated alleles after HLA DRB1*1501; other DRB1 alleles had more modest evidence of association than these 2 class I alleles and may be secondary to class I associations. Thus, we did not feel it was appropriate to correct for other HLA DRB1 alleles. Cryptic population structure in our subjects self-reported to be of non-Hispanic European ancestry could affect the distribution of alleles, but even gross imbalance would not explain the full effect of our 2 MHC class I alleles. Uncorrected genome-wide association studies in North American populations of European ancestry can have genomic inflation factors of 1.2 or 1.3 prior to the removal of subjects who are population outliers, but even a very large genomic inflation factor of 2.0 would yield a significant corrected p value of 0.014 for HLA B*44 in our analysis. So, population stratification alone does not explain our result, although we cannot exclude the possibility that it may have contributed to our result since we do not have mathematical estimates of ancestry for our subjects. Family-based analyses such as the transmission disequilibrium test used by Chao and colleagues[4] have the advantage of obviating concerns about population stratification, but even the very large and useful family-based collection that they explored remains modest in size, limiting its statistical power when compared to existing case-control MS collections in the evaluation of common variants of modest effect.

Overall, we cannot say that HLA A*02 and HLA B*44 are causal alleles at this time; as noted in our article, they simply represent the best markers of 2 separate HLA DRB1*1501-independent effects within the MHC. We look forward to more studies from the MS genetics community to refine the exact variant or groups of variants that affect MS susceptibility outside of the association tagged by HLA DRB1*1501.

Philip L. De Jager, Boston, MA

Disclosure: See original article for full disclosure list.

1. Healy BC, Liguori M, Tran D, et al. HLA B*44: protective effects in MS susceptibility and MRI outcome measures. Neurology 2010;75:634–640.
2. Rioux JD, Goyette P, Vyse TJ, et al. Mapping of multiple susceptibility variants within the MHC region for 7 immune-mediated diseases. Proc Natl Acad Sci USA 2009; 106:18680–18685.
3. Lincoln MR, Montpetit A, Cader MZ, et al. A predominant role for the HLA class II region in the association of the MHC region with multiple sclerosis. Nat Genet 2005; 37:1108–1112.
4. Chao MJ, Barnardo MC, Lincoln MR, et al. HLA class I alleles tag HLA-DRB1*1501 haplotypes for differential risk in multiple sclerosis susceptibility. Proc Natl Acad Sci USA 2008;105:13069–13074.
5. Ramagopalan SV, Morris AP, Dyment DA, et al. The inheritance of resistance alleles in multiple sclerosis. PLoS Genet 2007;3:1607–1613.

CORRECTION

Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation

In the article "Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation" by V. Bril et al. (*Neurology*® 2011;76:1758–1765), there was an error in the article text regarding the dosage for the number needed to treat (NNT) and an error in the citation of references 7–9. "The NNT for a 50% reduction in pain was 4 at 600 g/day.[7–10]" should read "The NNT for a 50% reduction in pain was 4 at 600 mg/day.[10]" The authors regret the errors.

Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation

Neurology 2011;77;603
DOI 10.1212/WNL.0b013e31822b0fbc