LETTER

Reply to Brynedal et al.: Accumulating genetic and functional evidence for a role of *CD58* in multiple sclerosis

I am pleased that our recent article (1) has led to further exploration of the role of the *CD58* locus in multiple sclerosis (MS) by Brynedal et al. (2).

Brynedal et al. (2) report strong evidence of replication for the presence of the MS susceptibility allele that we reported within the *CD58* locus. The minor allele of their best markers tags the protective *CD58* haplotype. These data from Swedish subjects, in addition to more modest evidence of replication from an Australian cohort (3) and consistent data from a recent genome scan in MS subjects of European ancestry (4), validate the role of *CD58* in MS susceptibility. Our large fine-mapping study suggests that rs2300747, which is in strong linkage disequilibrium with the Swedish SNPs, is the marker most strongly correlated with MS susceptibility. While the causal *CD58* variant remains elusive today, we nonetheless clearly have multiple robust markers for its effect with which to inform functional analyses of this molecule in MS.

The letter from Brynedal et al. is particularly informative in this regard because the authors report decreased RNA expression of *CD58* in cerebrospinal fluid samples from subjects with MS relative to healthy subjects. Thus, diminished *CD58* expression in MS is occurring in the central nervous system and not just in peripheral blood (5). This information will help to guide future investigations into the functional consequences of variation in *CD58* expression and perhaps into the utility of testing existing drugs that target this pathway in MS. The efficacy of one such drug, alefacept (an IgG1:CD58 fusion protein), in psoriasis (6) suggests that the *CD58* locus may also emerge as a more general autoimmunity susceptibility locus once it is powerfully explored in other human inflammatory diseases.

Philip L. De Jager[1]

Center for Neurologic Diseases, Department of Neurology, Brigham & Women's Hospital and Harvard Medical School, Boston, MA 02115; Partners Center for Personalized Genetic Medicine, Boston, MA, 02115; and Program in Medical & Population Genetics, Broad Institute of Harvard University and Massachusetts Institute of Technology, Cambridge, MA 02142

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Author contributions: P.L.D.J. wrote the paper.

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[1]E-mail: pdejager@rics.bwh.harvard.edu.

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