Correspondence

Research Letters

No Association Between Genetic Polymorphism at Codon 129 of the Prion Protein Gene and Primary Progressive Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disorder of the central nervous system. Approximately 10% to 20% of patients with MS are diagnosed with primary progressive MS (PPMS), defined as a disease course with gradual accumulation of disability without any clinical attacks or remission from onset.1 Primary progressive MS is considered by many to have more neurodegenerative characteristics than other MS phenotypes. In addition, and perhaps supportive of the notion that PPMS has a degenerative rather than an inflammatory pathogenesis, are that (1) immune therapies are ineffective, (2) the age at onset is typically around 40 years and thus significantly later than that of relapsing-remitting MS,2-5 and (3) that there appears to be no sex predilection.3

The endogenous cellular prion protein (PrPc) is an α-helical glycosphatidylinositol-anchored sialoglycoprotein. The PrPc protein is highly expressed in neurons, lymphoid cells, and myeloid cells. A single-nucleotide polymorphism (SNP) at codon 129 of the PrP gene (Prnp), which is located on chromosome 20p12, has been shown to have a significant effect on the clinical course of numerous nonprion neurodegenerative disorders of the central nervous system including Alzheimer disease, Down syndrome, and Wilson disease.6-10 In all of these disorders, methionine/valine heterozygosity is associated with less severe clinical disease. Finally, the Prnp129 SNP also appears to have a negative effect on long-term memory in adult and senescent healthy individuals.11-13 The mechanisms by which the Prnp SNP 129 alters central nervous system function remain to be elucidated.

Given that PPMS is considered a neurodegenerative disorder, we hypothesized in this study that Prnp SNP 129 has an effect on susceptibility to this distinct MS phenotype.

To determine whether the Prnp129 M/V SNP plays a role in PPMS susceptibility, we assessed the genotypes of 498 patients with PPMS and 600 healthy controls. Appropriate institutional review boards had approved all studies, and informed consent was obtained from all participants. Genotypes were generated by a TaqMan allelic discrimination assay on an ABI7900HT genotyping platform, using the Assay-by-Design service from Applied Biosystems (Foster City, California).

The female to male ratio among patients with PPMS was 1:1. No deviations from Hardy-Weinberg equilibrium were observed for genotypes in the patients (Table). There was no statistically significant difference in frequency of Prnp129 genotypes between patients with PPMS and controls (P = .14) (Table). There was also no difference in allelic frequency distributions between the 498 patients with PPMS and 979 patients with relapsing-remitting MS (P = .23) (Table). No difference in allelic transmission was observed in either subgroup.

While the results of this association analysis do not suggest the role of an SNP in Prnp129 in PPMS susceptibility, our study was almost certainly underpowered to conclusively eliminate this mutation as a susceptibility factor. Our negative results may also be consistent with recent pathological studies that suggested a strong association between inflammation and neurodegeneration in progressive MS.14 Therefore, in contrast to other typical neurodegenerative disorders, the pathology of progressive MS may be consistent with that of an inflammatory disease rather than degenerative disease in some patients.

We were unable to study the role of Prnp129 on the disease course of PPMS, as clinical and neuroimaging information was only available on a very small subset of patients. As larger patient databases are being developed, the role of Prnp129 on the disease course of PPMS could be examined.

<table>
<thead>
<tr>
<th>Disease Course</th>
<th>No.</th>
<th>Allele</th>
<th>Heterozygosity</th>
<th>P Value</th>
<th>Minor Allele</th>
<th>MAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPMS</td>
<td>498</td>
<td>A/G</td>
<td>0.49</td>
<td>0.239</td>
<td>G</td>
<td>0.36</td>
</tr>
<tr>
<td>RRMS</td>
<td>979</td>
<td>A/G</td>
<td>0.45</td>
<td>0.933</td>
<td>G</td>
<td>0.34</td>
</tr>
<tr>
<td>Control</td>
<td>600</td>
<td>A/G</td>
<td>0.42</td>
<td>0.304</td>
<td>G</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Abbreviations: MAF, minor allele frequency; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

aHardy-Weinberg equilibrium test.
oped, we will be able to study the effect of this SNP on clinical and paraclinical in patients with this disorder.

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Validation of Plasma Branched Chain Amino Acids as Biomarkers in Huntington Disease

While investigating body weight in a cohort of 32 patients at an early stage of Huntington disease (HD) and presymptomatic HD gene carriers, we found a significant decrease in the plasma branched-chain amino acids (BCAA) valine, leucine, and isoleucine in the HD group compared with 21 healthy controls. This systemic metabolic defect, which is indicative of hypercatabolism, was associated with early body weight loss in the HD group. We wanted to (1) try to replicate our initial findings in a larger HD cohort, and (2) assess the feasibility of using plasma BCAA as a biomarker in HD, ie, in a less controlled research environment than the initial study.1

Methods. After approval by the institutional ethics committees (Institut National de la Santé et de la Recherche Médicale, Recherche Biomédicale 03-48), we measured fasting levels of plasma BCAA as previously described1 in 16 presymptomatic HD gene carriers and 70 patients with HD at a mild, moderate, or severe stage of the disease who were seen consecutively at our outpatient clinic. Our control group consisted of 21 healthy individuals, previously described.1 To evaluate the multivariate associations, the LASSO (Least Absolute Shrinkage and Selection Operator) model selection technique was used with the adjusted $r^2$ statistic as the model selection criterion. The number of CAG codons was forced into these models with the Unified Huntington Disease Rating Scale (UHDRS), age, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), sex, and their 2-way interactions as possible covariates.

Results. Plasma valine, leucine, and isoleucine levels were significantly lower in the HD group compared with controls ($P = .02$, $<.001$, and .002, respectively). In addition, we found a significant decrease of valine, leucine, and isoleucine in moderately affected patients and patients at a severe stage of the disease (Figure). Leucine...


Error in Acknowledgments. In the Research Letter titled “No Association Between Genetic Polymorphism at Codon 129 of the Prion Protein Gene and Primary Progressive Multiple Sclerosis” by Stuve et al, published in the February issue of the Archives (2011;68[2]:264-265), an acknowledgment was left out of the Additional Contributions section. The authors would also like to thank the Accelerated Cure Project for Multiple Sclerosis for making available samples for the project. The article has been corrected online.