The Ubiquilin 1 Gene and Alzheimer’s Disease

TO THE EDITOR: Bertram et al. (March 3 issue)1 report that in two family-based cohorts, a genetic variant of the UBQ-8i single-nucleotide polymorphism on chromosome 9q22 putatively increased the risk of Alzheimer’s disease in an additive disease model. We attempted replication in a similarly ascertained but independent family-based data set based on 288 families in which linkage to microsatellites at 9q22.1 and 9q34.2 was demonstrated in a genome scan.2 In addition, we analyzed a previously described independent data set based on patients with Alzheimer’s disease and 1005 controls.3 We found no association between the risk of Alzheimer’s disease and UBQ-8i, or any of six additional single-nucleotide polymorphisms within the UBQLN1 gene, in either of the independent data sets. However, using age at onset as the trait of interest, we found a significant association between the putative UBQ-8i risk allele and an older age at onset in a recessive-disease model only in our case-control data set (Table 1). We found an additional, significant effect related to age at onset only in our family-based data set with a different single-nucleotide polymorphism in UBQLN1. Thus, although we found no evidence of risk with any single-nucleotide polymorphism in UBQLN1, our results suggest that age at onset may be germane and that additional, detailed examination of UBQLN1, including a search for the functional variant (or variants), is warranted.

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Table 1. UBQ-8i Allelic Associations.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Family-Based Data Set†</th>
<th>Patient–Control Data Set‡</th>
<th>P Value</th>
<th>Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk analysis</td>
<td>Family-Based Association Test</td>
<td>Logistic regression (additive model)</td>
<td>0.87</td>
<td>0.23</td>
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<tr>
<td>Analysis of age at onset</td>
<td>Pedigree Disequilibrium Test</td>
<td></td>
<td>0.96</td>
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<tr>
<td></td>
<td>Quantitative Transmission Disequilibrium Test</td>
<td>Linear regression (recessive model)</td>
<td>0.21</td>
<td>0.01</td>
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</tbody>
</table>

† All the patients with Alzheimer’s disease met the National Institute of Neurological Disorders and Stroke/Alzheimer’s Disease and Related Disorder Association case definition and were evaluated at Duke University Medical Center and Vanderbilt University Medical Center through the collaborative Alzheimer Project.
‡ In the patient–control data set, the mean (±SD) age at onset was 71.1±7.0 years (range, 50 to 59), and 63 percent of the subjects were women.
§ The Family-Based Association Test is described by Bertram et al., the Pedigree Disequilibrium Test by Martin et al., and the Quantitative Transmission Disequilibrium Test by Abecasis et al.


THE AUTHORS REPLY: We are pleased by Slifer and colleagues’ report of a significant genetic association between single-nucleotide polymorphisms in the UBQLN1 gene and the age at onset of Alzheimer’s disease in two separate and independent samples, providing further support for our original finding that UBQLN1 variants may influence the pathogenesis of Alzheimer’s disease. Given the significant age-at-onset effects in their samples, it is puzzling that they did not observe significant effects on the risk of disease, since these two traits are correlated. Possible explanations include allelic heterogeneity, lack of power in the risk analyses, and methodologic differences in sample ascertainment and statistical procedures.

It is also worth noting that the two original linkage signals (according to a binary phenotype definition) reported for the family-based sample analyzed by Slifer et al. were located more than 40 cm away (in either direction) from UBQLN1 and our linkage peak. Thus, their sample may not be optimal for detecting risk effects of the magnitude described in our initial report. Notwithstanding these differences, the fact that several UBQLN1 single-nucleotide polymorphisms now show an association with either the age at onset or the risk of Alzheimer’s disease in a number of independent samples suggests the possibility of linkage disequilibrium with one or more additional pathogenic variants.

Along these lines, since our original report, we have now found additional evidence of an association between the risk of Alzheimer’s disease and the T allele of a UBQLN1 promoter single-nucleotide polymorphism (rs12345514) in both the National Institutes of Mental Health family sample (P=0.02 by the Family-Based Association Test) and the Consortium on Alzheimer’s Genetics family sample (P=0.04). The combined data sets yielded the strongest evidence of an association (P=0.002), which is consistent with our previous findings. Collectively, these data suggest that the pathogenesis of Alzheimer’s disease may be influenced by changes not only in the splicing of UBQLN1, but also in its expression. Ultimately, meta-analysis of these and additional association studies should provide a more precise measure of the actual contribution of UBQLN1 variants to Alzheimer’s disease.

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