RESEARCH LETTER

APOE ε2/ε4 Genotype a Risk Factor for Primary Progressive Aphasia in Women

Frontotemporal dementia (FTD) is a clinically and pathologically heterogeneous entity characterized by focal degeneration of the cerebral cortex, which may present with behavioral and cognitive symptoms, especially linguistic deficits. Genetic factors might play an important role in FTD, which is a relatively common cause of early-onset dementia. We reported that the frequency of the ε2/ε4 genotype of the apolipoprotein E (APOE; GenBank AF286472) gene is significantly increased in primary progressive aphasia (PPA), one of the syndromes associated with FTD. Primary progressive aphasia is characterized by progressive language impairment, while other cognitive functions remain relatively intact for at least the first 2 years of the course.

We examined 125 patients with a clinical diagnosis of probable FTD, including a subgroup of 39 patients with PPA and 343 age-matched controls (Table 1). Compared with controls, we observed a significant increase in ε2/ε4 genotype frequency in the overall FTD group and a highly significant increase in ε2/ε4 genotype frequency in the PPA subgroup. Compared with controls, a significant increase in ε4 allele frequency was detected in the FTD group, while a significant decrease in ε3 allele frequency was observed in the FTD group and in the PPA subgroup. The APOE ε2/ε4 genotype was detected in 5 patients affected by PPA (4 women and 1 man) and in 1 woman affected by FTD not belonging to the PPA subgroup. Therefore, APOE genotype and allele frequencies were further analyzed according to sex (Table 2).

In men, a significant decrease in ε3/ε3 genotype and ε3 allele frequencies and a significant increase in ε3/ε4 genotype and ε4 allele frequencies were observed in the overall group with FTD and in the PPA subgroup. Moreover, the ε4/ε4 genotype was detected only in men with FTD, with a significant increase in frequency in men with FTD.

In women, we observed a significant increase in ε2/ε4 genotype frequency in the FTD group and a highly significant increase in ε2/ε4 genotype frequency in the PPA subgroup.

Table 1. Apolipoprotein E Genotype and Allele Frequencies in Patients Affected by FTD and in the Subgroup With PPA Compared With Controls

<table>
<thead>
<tr>
<th>Genotype or Allele</th>
<th>FTD (n=127)</th>
<th>Controls (n=343)</th>
<th>P Valuec</th>
<th>OR (95% CI)c</th>
<th>PPA, No. (%)</th>
<th>OR (95% CI)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε2/ε2</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>ε2/ε3</td>
<td>13 (10.2)</td>
<td>33 (9.6)</td>
<td>&gt;.99</td>
<td>0.998 (0.498-1.999)</td>
<td>3 (7.7)</td>
<td>.70</td>
</tr>
<tr>
<td>ε2/ε4</td>
<td>6 (4.7)</td>
<td>4 (1.2)</td>
<td>.03</td>
<td>4.273 (1.185-15.404)</td>
<td>5 (12.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ε3/ε3</td>
<td>70 (55.1)</td>
<td>222 (64.7)</td>
<td>.09</td>
<td>0.694 (0.457-1.052)</td>
<td>20 (51.3)</td>
<td>.10</td>
</tr>
<tr>
<td>ε3/ε4</td>
<td>35 (27.6)</td>
<td>82 (23.9)</td>
<td>.47</td>
<td>1.189 (0.747-1.894)</td>
<td>11 (28.2)</td>
<td>.55</td>
</tr>
<tr>
<td>ε4/ε4</td>
<td>3 (2.4)</td>
<td>1 (0.3)</td>
<td>.07</td>
<td>8.410 (0.867-81.613)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>ε2</td>
<td>19 (15.2)</td>
<td>39 (11.4)</td>
<td>.31</td>
<td>1.341 (0.760-2.368)</td>
<td>8 (10.3)</td>
<td>.12</td>
</tr>
<tr>
<td>ε3</td>
<td>188 (74.0)</td>
<td>559 (81.5)</td>
<td>.01</td>
<td>0.647 (0.461-0.909)</td>
<td>54 (69.2)</td>
<td>.01</td>
</tr>
<tr>
<td>ε4</td>
<td>47 (18.5)</td>
<td>88 (12.8)</td>
<td>.03</td>
<td>1.543 (1.047-2.274)</td>
<td>16 (20.5)</td>
<td>.06</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FTD, frontotemporal dementia; NA, not applicable; OR, odds ratio; PPA, primary progressive aphasia.

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The results of the present study on a larger sample of patients with FTD and controls agree with our preliminary findings, suggesting that the ε2/ε4 genotype might represent a genetic risk factor for PPA, while the ε3 allele might have protective effects for PPA and FTD. Moreover, the present results suggest that the ε2/ε4 genotype might represent a genetic risk factor, particularly for women with PPA. In men with FTD, by contrast, the ε3 allele might represent a genetic risk factor, particularly for women with FTD. Women with the ε2 or ε4 allele frequency in men with FTD.4

The ε2 allele might play a pathogenic role in other neurodegenerative conditions, as it might increase the risk of Parkinson disease. Patients with FTD carrying the ε4 allele show β-amyloid protein deposits more frequently than ε4 noncarriers, although β-amyloid deposition in FTD could be unrelated to primary pathological processes.5 Even if we cannot exclude the possibility that the association between ε2/ε4 genotype and PPA may be due to the insufficient size of our samples, such an association may be explained by molecular positive heterosis. When a certain chromosomal locus has 2 different alleles (for example, alleles A and B), heterozygosity occurs when a subject has both of the 2 alleles, A and B, and can be therefore defined as an AB heterozygote, while subjects having only the A or B allele can be defined as AA homozygotes and BB homozygotes, respectively. Usually, in a 2-allele polymorphism (where a single chromosomal locus has the 2 alleles, A and B), if the allele A is strongly associated with a certain phenotypic effect, subjects carrying the AA genotype (AA homozygotes) should show the greatest phenotypic effect, subjects carrying the BB genotype (BB homozygotes) should show the least phenotypic effect, and AB heterozygotes should show an intermediate phenotypic effect. Molecular positive heterosis is a counter-intuitive phenomenon that occurs when subjects heterozygous for a specific genetic polymorphism (for example, AB heterozygotes) show a significantly greater phenotypic effect (positive heterosis) for a quantitative or dichotomous trait than homozygotes for either allele (AA homozygotes and BB homozygotes).6 Although the possible mechanisms involved in molecular positive heterosis are only partially known, this is a relatively common phenomenon that has been shown in several disorders and may be sex-specific, namely, it may be observed only in either men or women.6 Thus, in our series, women with the APOE ε2/ε4 genotype showed an increased risk for PPA compared with women with either ε2/ε2 or ε4/ε4 homozygosity. Further studies are needed to confirm the role of ε2/ε4 genotype as a risk factor in women with PPA and to clarify the possible pathogenic mechanisms related to APOE in this syndrome.

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COMMENTS AND OPINIONS

Mediterranean Dietary Pattern, Mild Cognitive Impairment, and Progression to Dementia

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carmeas et al1 reported the results of a very interesting community-based study, the Washington Heights–Inwood Columbia Aging Project involving 2364 nondemented individuals in New York, New York, in which adherence to a traditional Mediterranean diet (MeDi) was associated with a borderline reduction in the risk of developing mild cognitive impairment (MCI) and a reduction in the risk of progression from MCI to Alzheimer disease (AD). In this sample, these associations did not attenuate even when simultaneously adjusting for many commonly considered potential confounders (age, sex, ethnicity, education, apolipoprotein E [APOE] genotype, caloric intake, and body mass index). Scarmeas and colleagues also found that an association between higher adherence to the MeDi and lower risk of conversion to AD was much more prominent for subjects who had MCI without memory impairment.

We greatly appreciated these and previous findings from the Washington Heights–Inwood Columbia Aging Project, in which higher adherence to the MeDi was associated with a significant reduction in risk of incident AD2 (without vascular mediation)3 and with decreased AD mortality.4 In fact, the MeDi could be an interesting model to further study the association between dietary patterns and predementia syndromes given the suggested role of many components of this diet in contrasting cognitive impairment.5 Findings from the Italian Longitudinal Study on Aging6 demonstrated that in an 8.5-year follow-up, high levels of monounsaturated fatty acids, polyunsaturated fatty acids, and total energy intake were significantly associated with decreased age-related cognitive decline. Furthermore, in the same sample,7 high levels of polyunsaturated fatty acids intake appeared to have a borderline nonsignificant trend for a protective effect against the development of MCI. Finally, alcohol consumption was associated with a decrease in the rate of progression of MCI to dementia.8 9 The wide diffusion of the whole-diet approach used by Scarmeas and colleagues has undeniable advantages, but some concerns exist.10 In particular, as underlined for previous studies on the same sample,11 12 using such a score in an American population might not adequately represent conformity with the traditional MeDi. Another recent study on diet and mortality in the United States considered alternate cut points because of concern that the median intake of some dietary components might be lower in the US population than in a Mediterranean population.13 Furthermore, these authors correctly defined the diet of their US sample only as a Mediterranean dietary pattern and not as a properly defined MeDi. Using this approach in a sensitivity analysis, the authors assigned points to only the highest intakes, and the diets consumed were in this manner more compatible with the traditional MeDi.

Moreover, in the Washington Heights–Inwood Columbia Aging Project, the general MCI prevalence (23.9%) and amnestic MCI prevalence (7.4%) appeared to be abnormally larger with respect to most other population-based studies.14 In fact, population-based studies estimate the prevalence of MCI to be more than double that of dementia. However, the diagnostic criteria and referral patterns used vary between studies, causing discrepant prevalence estimates.15 In the Italian Longitudinal Study of Aging, we used a more general concept of MCI, selecting these patients with MCI on the basis of the memory loss.16 Prevalence estimates of general MCI in other worldwide population-based studies are consistent with those reported in the Italian Longitudinal Study of Aging (3.2%):17 3% in France, 3.1% in Germany, 3.02% in Canada, and 3.2% in the United States (Monongahela Valley Independent Elders Survey study), with 1 notable exception.18 The Cardiovascular Health Study Cognition Study16 found an amnestic MCI prevalence of 6% among 599 participants, whereas the overall prevalence of MCI, including the MCI subtype of multiple cognitive domains slightly impaired, was 19% among 2470 participants. Other population-based studies reported higher prevalence rates (6.1%-15%) but with MCI constructs different from the amnestic variants.19 Therefore, it is possible that in the Washington Heights–Inwood Columbia Aging Project, a percentage of cognitively unimpaired subjects were diagnosed as having MCI. The 1.5-SD cutoff score used by Scarmeas and colleagues to define cognitive impairment is very conservative with respect to the criteria proposed by most other studies (<10% instead of about 15%). Also, unadjusted punctual estimates for test for trend (hazard ratio, 0.85 for the risk of incident MCI for subjects who were cognitively normal at the first evaluation vs 0.82 for the risk of incident Alzheimer disease for subjects with MCI at the first evaluation) were very similar but with an interesting different influence of negative confounding in the 2 adjusted models.11 There was no difference in the percentage of APOE ε4 allele carriers between subjects who were cognitively unimpaired and those with MCI. Other stud-