The Effect of MAPT H1 and APOE ε4 on Transition from Mild Cognitive Impairment to Dementia

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SUPPLEMENTARY METHODS

Neuropsychological assessment

All individuals underwent a neuropsychological battery including Free and Cued Selective Reminding test (FCSRT) [1], the CERAD word list [2] and the logical memory subtest of the Wechsler Memory Scale (WMS) [3], Benton Visual Retention Test (BVRT) [4] and geometric Figure Recall (FRc), constructive praxis with Copy Figures (FC), Boston Naming test (BNT) [5], semantic and phonetic Verbal Fluency (VFs, VFp) [6], Raven Standard Progressive Matrices (RSPM) [7], and Trail Making Test (TMT) [8]. Geriatric Depression Scale (GDS) [9] was used to detect the presence of depressive symptoms. An Interview for Deterioration in Daily Activities in Dementia questionnaire (IDDD) [10] was used to measure the functional status in instrumental and basic daily activities. Global cognitive state was measured with the Mini-Mental State Examination (MMSE) [11] and the Information Memory Concentration Blessed test (IMCB) [12].
MAPT H1/H1 and APOE polymorphism genotyping

Five samples previously genotyped for APOE in our laboratory by restriction fragment length polymorphism analysis (HhaI restriction enzyme) were included in each TaqMan run as internal controls. Final-step analysis was performed in an ABI7300 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Allele calling was carried out using the allelic discrimination analysis module of the ABI Sequence Detection Software (Applied Biosystems, Foster City, CA, USA). rs45502095 is a 17q21 H1/H2 ins/del SNP; it was genotyped by PCR using a FAM-labeled reverse primer (forward primer: 5′-GGG CTG TTC TCT TCG AGA T AAG T-3′; reverse primer: 5′-FAM-ACC ACA AGA AGC CCT GTC AT -3′) followed by electrophoresis analysis on the ABI3100 Genetic Analyzer and the GeneMapper v.4.0 software (Applied Biosystems, Foster City, CA, USA).

Recruitment procedure

MCI subjects with other neurological diseases, as well as subjects with sensory impairment, stroke or systemic disease were excluded. In addition, subjects with illiteracy were excluded from the study since illiteracy could influence neuropsychological evaluation [13] and illiterate subjects seem to have an increased risk of MCI and dementia [14]. Subjects taking anticholinesterase inhibitors and antiglutamatergic drugs at initial evaluation were excluded as these drugs could potentially modify the disease course [15].

Among MCI subjects who progressed to dementia over time, diagnosis of AD (AD-p-MCI) was considered when they fulfilled NINCDS-ADRDA criteria [16] or non-AD dementia (non-AD-p-MCI) when NINDS-AIREN [17], McKeith [18] and Neary [19] criteria for AD, vascular dementia, Lewy body dementia and frontotemporal dementia (FTD) were fulfilled, respectively.

The first MCI sample included 266 MCI subjects who were prospectively followed during the period 2001–2008 at the Memory Disorders Unit at the Clínica Universidad de Navarra, Pamplona, Spain (Supplementary Figure 1, lower panel, sample 1). One hundred and fifty were excluded for loss of follow-up. All the MCI subjects included in the analysis were evaluated at the first visit using a complete neuropsychological battery (see Neuropsychological Assessment). Despite the fact that 211 individuals could not return to some of the follow-up visits, sixty-one of them underwent a Telephone Interview for cognitive status assessment (Supplementary Material, TiCog and Supplementary Figure 2) which included the Interview for Deterioration in Daily living activities in Dementia (IDDD) [20] and a short questionnaire to evaluate their cognitive status. This questionnaire is the result of the clinical experience of some of the co-authors who had worked in the assessment and diagnosis of dementia.

Sample 2 included 86 MCI subjects from the Geriatric and Neurology Department at the Hospital Clínico San Carlos, Madrid, Spain, recruited prospectively during the period 1999-2005 (Supplementary Figure 1). Demographic, clinical and neuropsychological data from sample 2 have been described previously [21,22].

An additional sample of 141 MCI subjects (sample 3) recruited prospectively from the Memory Disorders Unit at the Hospital Santa Creu i Sant Pau, Barcelona, Spain, during the period 2005-2009 was also analyzed. MCI subjects underwent the same assessment and neuropsychological battery as those of sample 1 (Supplementary Figure 1; Neuropsychological Assessment). Twenty-four subjects were excluded because there were no subsequent follow-up visits (Supplementary Figure 1).

Telephone Interview for Cognitive Status Assessment (TiCog)

Part A: Interview for Deterioration in Daily living Activities in Dementia (IDDD). Family relatives and MCI subjects were asked for the respective IDDD questionnaires [20].

Part B: Short cognitive interview. Question #1: Have you had any disease since your last visit to the Memory...
SUPPLEMENTARY RESULTS

Sample 1

Among the 116 subjects with MCI eligible for statistical analyses in sample 1, seventy-seven (66.4%) remained cognitively stable at the time of their last assessment (mean follow-up time: 2.0 years; SD = 1.1), whereas 39 subjects (33.6%) had progressed to dementia (mean follow-up time: 1.9; SD = 1.0; Supplementary Table 1). p-MCI subjects had at baseline lower scores in MMSE, verbal and visual memory tests than cognitively s-MCI (Supplementary Tables 3 and 4). Among the MCI subjects who developed dementia, most of them showed AD-type dementia (76.9%), whereas nine subjects developed other types of dementia (one developed FTD, four AD plus vascular dementia type and four developed vascular dementia; Supplementary Figure 1).

Among the MCI subjects who underwent the Ttcog assessment (n = 61; Supplementary Figure 2), eleven subjects progressed to AD, three subjects to non-AD dementia and 47 remained at the non-demented MCI stage. Five subjects who progressed to AD-type dementia and two subjects who converted to non-AD-type dementia according to Ttcog assessments underwent a subsequent neurological and neuropsychological as-
Supplementary Figure 2. Schematic representation of sample 1 and telephone interview for cognitive status assessment.
we categorized the sample according to the additive effect on the rate of progression to dementia, 0.137 and \( p = 0.679 \), respectively). Kaplan-Meier analysis showed no statistically significant differences between \( APOE \) 4 allele & \( MAPT \) H1/H1 MCI carriers and non-\( APOE \) 4 carriers.

**Supplementary Table 2**

Effect of \( MAPT \) and \( APOE \) polymorphisms on the time-to-progression to dementia in separate samples

<table>
<thead>
<tr>
<th></th>
<th>Sample 1</th>
<th></th>
<th></th>
<th></th>
<th>Sample 2</th>
<th></th>
<th></th>
<th></th>
<th>Sample 3</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \Delta^a )</td>
<td>HR(^b)</td>
<td>95% CI(^b)</td>
<td>( p^b)</td>
<td>( \Delta^a )</td>
<td>HR(^b)</td>
<td>95% CI(^b)</td>
<td>( p^b)</td>
<td>( \Delta^a )</td>
<td>HR(^b)</td>
<td>95% CI(^b)</td>
<td>( p^b)</td>
</tr>
<tr>
<td>( APOE ) 4 (+) vs. 4 (-)</td>
<td>0.73</td>
<td>1.66</td>
<td>0.86–3.19</td>
<td>0.130</td>
<td>0.34</td>
<td>1.22</td>
<td>0.71–2.08</td>
<td>0.472</td>
<td>0.80</td>
<td>1.39</td>
<td>0.80–2.48</td>
<td>0.265</td>
</tr>
<tr>
<td>( MAPT ) H1/H1 vs. non-H1/H1</td>
<td>0.93</td>
<td>1.15</td>
<td>0.58–2.25</td>
<td>0.695</td>
<td>2.08</td>
<td>2.03</td>
<td>1.19–3.46</td>
<td><strong>0.009</strong></td>
<td>2.87</td>
<td>1.24</td>
<td>0.69–2.25</td>
<td>0.471</td>
</tr>
<tr>
<td>( APOE ) 4 (+) H1/H1 vs. 4 (-) non-H1/H1</td>
<td>n.a.</td>
<td>2.03</td>
<td>0.73–5.64</td>
<td>0.172</td>
<td>2.21</td>
<td>2.31</td>
<td>1.13–4.75</td>
<td><strong>0.023</strong></td>
<td>2.87</td>
<td>2.03</td>
<td>0.83–4.93</td>
<td>0.119</td>
</tr>
</tbody>
</table>

\(^a\) Difference between medians expressed in years from Kaplan-Meier analysis. \(^b\) Results from Cox regression analysis. CI, coefficient interval. (+), carriers. (-), non-carriers. HR, Hazard Ratio. \( APOE \), Apolipoprotein E gene. \( MAPT \), microtubule-associated protein tau gene. n.a., non-available. \( p \) values lower than 0.05 are highlighted in bold.

**Supplementary Table 3**

Global cognitive function scores for sample 1 MCI groups

<table>
<thead>
<tr>
<th></th>
<th>s-MCI (n = 77)</th>
<th>p-MCI (n = 39)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>26.8 (2.2)</td>
<td>25.7 (2.2)</td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td>GDS</td>
<td>7.9 (5.4)</td>
<td>7.2 (5.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>IDDD</td>
<td>36.7 (5.4)</td>
<td>35.9 (2.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>IMCB</td>
<td>4.9 (2.9)</td>
<td>5.2 (3.5)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Values are means (SD); \( p \) values lower than 0.05 are highlighted in bold. s-MCI, mild cognitive impairment who remained cognitively stable. p-MCI, mild cognitive impairment who developed dementia. MMSE, Mini-Mental State Examination. GDS, Geriatric Depression Scale. IDDD, Interview for Daily activities Deterioration in Dementia. IMCB, Information-Memory-Concentration Blessed Test. n.s., not statistically significant.

**Supplementary Table 4**

Baseline cognitive performance scores for sample 1 MCI groups

<table>
<thead>
<tr>
<th></th>
<th>s-MCI</th>
<th>p-MCI</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCSRT</td>
<td>41.1 (6.7)</td>
<td>35.7 (10.5)</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>WMS</td>
<td>5.8 (3.7)</td>
<td>5.3 (4.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>CERAD</td>
<td>1.7 (1.5)</td>
<td>1.0 (1.2)</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>Visual memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRc</td>
<td>7.3 (5.4)</td>
<td>4.5 (4.7)</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>FRcn</td>
<td>1.9 (0.4)</td>
<td>1.8 (0.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>BVRT</td>
<td>3.2 (1.3)</td>
<td>3.6 (1.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Praxias and Naming</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FC</td>
<td>18.7 (3.3)</td>
<td>18.8 (4.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>BNT</td>
<td>43.4 (9.4)</td>
<td>44.0 (7.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VfP</td>
<td>10.9 (4.2)</td>
<td>11.7 (4.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>VfS</td>
<td>13.2 (4.4)</td>
<td>12.5 (3.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>RSPM</td>
<td>23.1 (5.4)</td>
<td>23.1 (5.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>TMTA</td>
<td>71.2 (29.0)</td>
<td>64.8 (34.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>TMTB</td>
<td>196.0 (81.0)</td>
<td>197.2 (86.0)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Values are means (SD); \( p \) values lower than 0.05 are highlighted in bold. s-MCI, mild cognitive impairment who remained cognitively stable. p-MCI, mild cognitive impairment who developed to dementia. FCSRT, Free and Cued Selective Reminding test. WMS, logical memory test from the Wechsler Memory Scale. CERAD, word list learning. FRc, Figures Recall. FRcn, Figures Recognition. BVRT, Benton Visual Retention test. FC, Figures Copy. BNT, Boston Naming test. VfP, Verbal Fluency-phonetic. VfS, Verbal Fluency-semantic. RSPM, Raven Standard Progressive Matrices. TMTA, Trail Making Test-part A. TMTB, Trail Making Test-part B. n.s., not statistically significant.

& non-\( MAPT \) H1/H1 carriers. The difference between survival medians could not be calculated as less than 50% of non-\( APOE \) 4 and non-\( MAPT \) H1/H1 subjects progressed to dementia.

**Sample 2**

Among the 86 MCI subjects recruited in sample 2, twenty-seven remained cognitively stable (31.4%; mean follow-up: 3.8 years; SD = 1.0), whereas 59 progressed to dementia of AD type (68.6%; mean follow-up: 1.8 years; SD = 1.2). Cox regression analysis showed no statistically significant differences in progression rate to dementia depending on the presence...
of APOE ε4 allele (Supplementary Table 2). Among MAPT H1/H1 MCI carriers there was an increased progression rate (HR = 2.03, 95% CI = 1.19–3.46; p = 0.009). Cox regression analysis showed that MCI subjects carrying both APOE ε4 and MAPT H1/H1 progressed to dementia faster than MCI subjects having none of these variants (HR = 2.31, 95% CI = 1.13–4.75; p = 0.023). MCI carriers of both APOE ε4 and MAPT H1/H1 progressed earlier to dementia than non-carriers (median difference: 2.21 years; Supplementary Table 2).
to those of samples 1 and 2, suggesting that one of the reasons for the lack of significance for some tests could be owed to the small sample size (Supplementary Table 2). Though not statistically significant, Cox regression suggested that APOE ε4 and MAPT H1/H1 genotypes had an additive effect in progression to AD (HR=2.03, 95% IC=0.83-4.93, p = 0.119), which was greater than each variant separately (Supplementary Table 2). Kaplan-Meier analysis suggested that MCI carriers of both APOE ε4 and MAPT H1/H1 variants progressed earlier to dementia than non-carriers (median difference: 2.87 years; Supplementary Table 2).

References


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