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Supplementary Data

# The Effect of *MAPT* H1 and *APOE* $\varepsilon$4 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].

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*MAPT H1/H1 and APOE polymorphism genotyping*

Five samples previously genotyped for *APOE* in our laboratory by restriction fragment length polymorphism analysis (*Hha*I 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 CTT TGC 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.

Supplementary Table 1
Demographics and *APOE* ε4 and *MAPT* H1/H1 frequencies of the longitudinal MCI series

| | Sample 1 | Sample 2 | Sample 3 |
|---|---|---|---|
| No. of subjects | 116 | 86 | 117 |
| Age at examination, y* | 73.3 (5.3) | 74.9 (7.3) | 73.4 (6.3) |
| Education, y* | 12.1 (4.4) | 7.9 (3.6) | 8.4 (4.2) |
| Male/Female | 69/47 | 30/56 | 62/55 |
| Follow-up, y* | 1.9 (1.1) | 2.4 (1.5) | 2.0 (1.1) |
| s-MCI/p-MCI | 77/39 | 27/59 | 68/49 |
| *APOEε* | | | |
| Allele ε4 frequency | 0.13/0.29 | 0.20/0.26 | 0.21/0.24 |
| ε4ε4 frequency | 0.01/0.13 | 0.07/0.03 | 0.03/0.04 |
| *MAPT* | | | |
| Allele H1 frequency | 0.72/0.73 | 0.67/0.76 | 0.68/0.73 |
| H1H1 frequency | 0.47/0.51 | 0.41/0.59 | 0.44/0.55 |

*Mean (SD). A slash separates data for s-MCI (mild cognitive impairment who remained cognitively stable) and p-MCI (mild cognitive impairment who developed dementia). *APOE*, apolipoprotein E gene. *MAPT*, microtubule-associated protein tau gene.

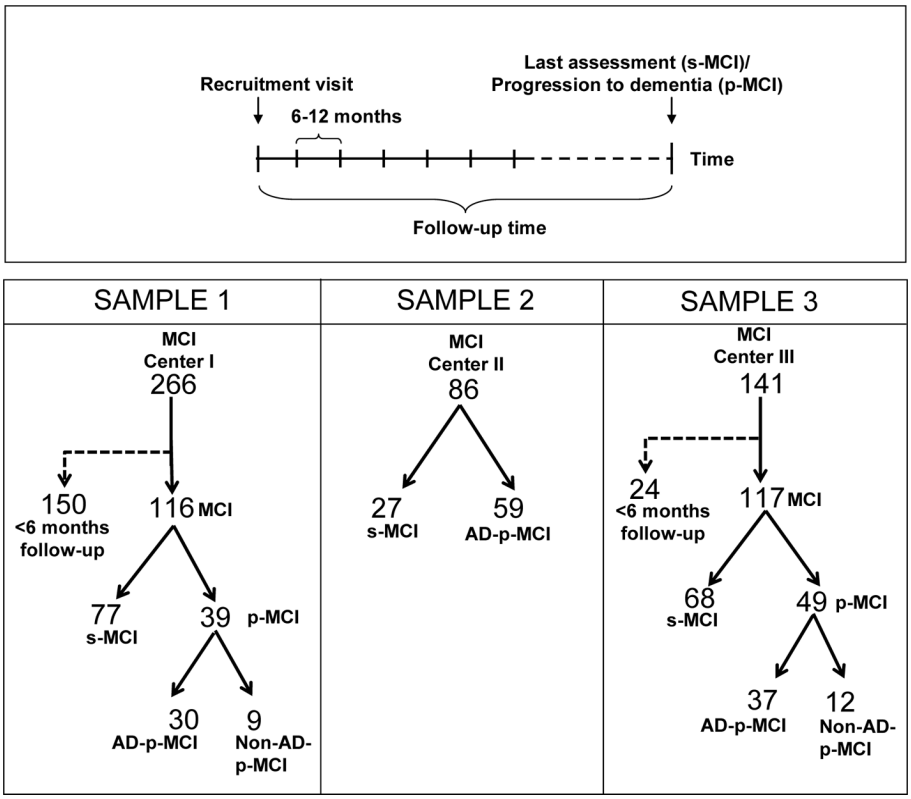
Sample 2 included 86 MCI subjects from the Geriatric and Neurology Department at the Hospital Clínico San Carlos, Madrid, Spain, recruited prospectively during the period 1999-2005 (Supplementary Figure 1). Demographic, clinical and neuropsychological data from sample 2 have been described previously [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 Figure 1.** Sample recruitment. *Upper panel*: Follow-up time variable used for the analyses. *Recruitment visit:* visit at which subjects were diagnosed with amnestic MCI. *Lower panel*: patient flow diagram showing the recruitment and follow-up procedure. MCI, mild cognitive impairment. s-MCI, mild cognitive impairment who remained cognitively stable. p-MCI, mild cognitive impairment who developed dementia. AD-p-MCI, mild cognitive impairment who progressed to AD. Non-AD-p-MCI, mild cognitive impairment who progressed to dementia other than AD.

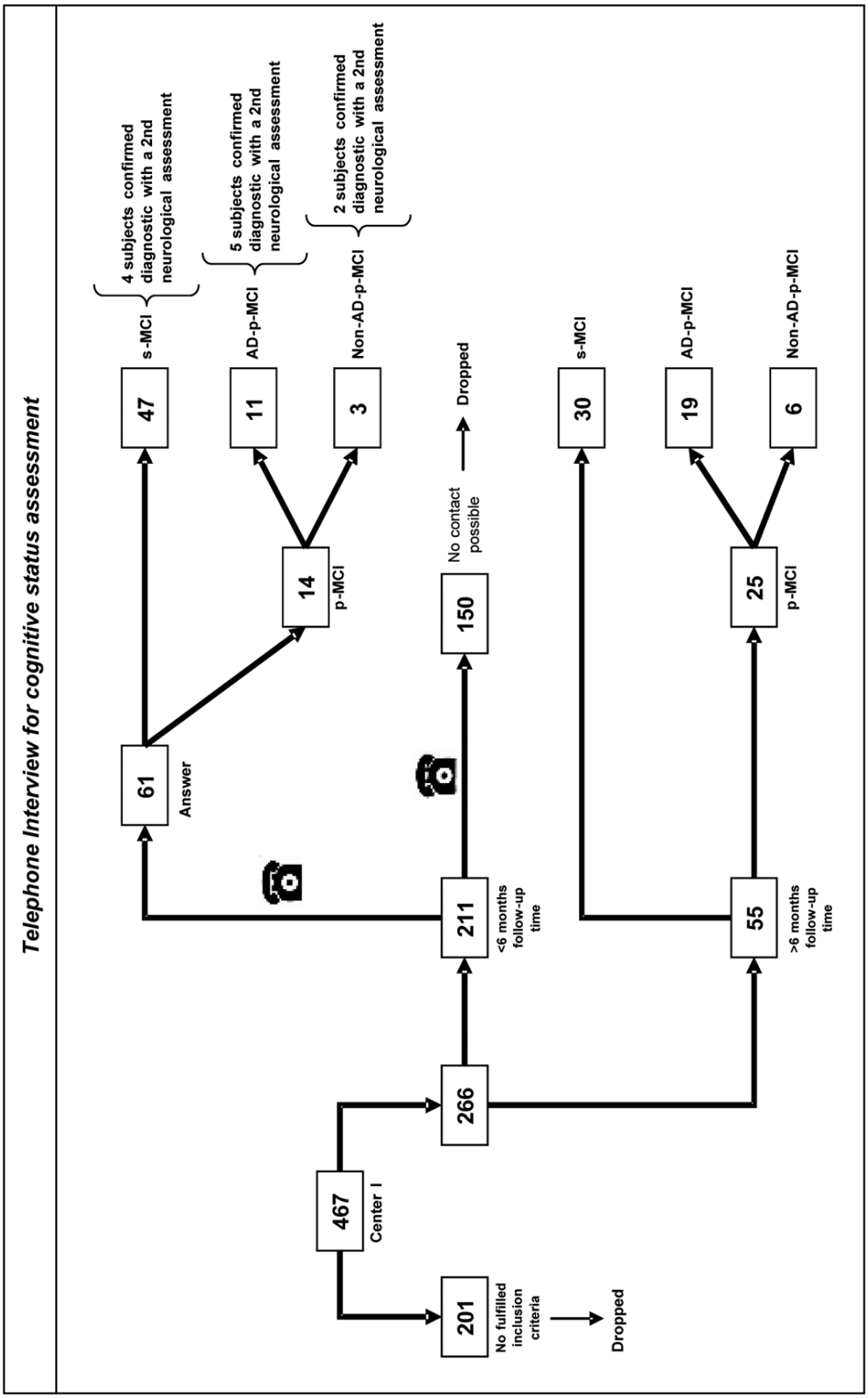
Disorders Unit? Question #2: Have you started taking any new medication since the last visit to the Memory Disorders Unit? Question #3: How would you assess the current state of your memory since the last visit to the Memory Disorders Unit? Has your memory improved? Or, on the contrary, has your memory worsened? Has your memory remained unchanged? Question #4: Are there things you have stopped doing because of your forgetfulness since your last visit to the Memory Disorders Unit? Question #5: Has any physician diagnosed you with dementia or Alzheimer's disease since your last visit to the Memory Disorders Unit?

## 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 *TIcog* 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 *TIcog* assessments underwent a subsequent neurological and neuropsychological as-




**Supplementary Figure 2.** Schematic representation of sample 1 and telephone interview for cognitive status assessment

Supplementary Table 2
Effect of *MAPT* and *APOE* polymorphisms on the time-to-progression to dementia in separate samples

| | Sample 1 | | | | Sample 2 | | | | Sample 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $\Delta^a$ | HR[b] | 95%CI[b] | p[b] | $\Delta^a$ | HR[b] | 95%CI[b] | p[b] | $\Delta^a$ | HR[b] | 95%CI[b] | p[b] |
| *APOE* $\varepsilon$4 (+) vs. $\varepsilon$4 (-) | 0.73 | 1.66 | 0.86–3.19 | 0.130 | 0.34 | 1.22 | 0.71–2.08 | 0.472 | 0.80 | 1.39 | 0.80–2.48 | 0.265 |
| *MAPT* H1/H1 vs. non-H1/H1 | 0.93 | 1.15 | 0.58–2.25 | 0.695 | 2.08 | 2.03 | 1.19–3.46 | **0.009** | 2.87 | 1.24 | 0.69–2.25 | 0.471 |
| *APOE* $\varepsilon$4 (+) H1/H1 vs. $\varepsilon$4 (-) non-H1H1 | n.a. | 2.03 | 0.73–5.64 | 0.172 | 2.21 | 2.31 | 1.13–4.75 | **0.023** | 2.87 | 2.03 | 0.83–4.93 | 0.119 |

[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

| Tasks | s-MCI ($n = 77$) | p-MCI ($n = 39$) | p |
|---|---|---|---|
| MMSE | 26.8 (2.2) | 25.7 (2.2) | **0.013** |
| GDS | 7.9 (5.4) | 7.2 (5.0) | n.s. |
| IDDD | 36.7 (5.4) | 35.9 (2.4) | n.s. |
| IMCB | 4.9 (2.9) | 5.2 (3.5) | n.s. |

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

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

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.

sessment in the Memory Disorders Unit which confirmed *TIcog* observations performed about one year before (mean follow-up: 1.3, SD = 1.0). No differences were found in demographics and global cognitive function variables at baseline among the MCI group who underwent *TIcog* assessments and the MCI subjects that continued with standard visits at the Memory Disorders Unit (Supplementary Table 7).

Cox regression analysis showed no statistically significant effect among MCI subjects of *MAPT* H1/H1 genotype or *APOE* $\varepsilon$4 allele on progression rate to dementia (Supplementary Table 2). Similarly, Kaplan-Meier analyses taking follow-up time as the dependent variable considering the presence of *APOE* $\varepsilon$4 allele or *MAPT* H1/H1 showed no significant differences ($p = 0.137$ and $p = 0.679$, respectively).

In order to investigate whether *APOE* and *MAPT* had an additive effect on the rate of progression to dementia, we categorized the sample according to the *MAPT* and *APOE* genotypes. Cox regression analysis suggested that MCI subjects carrying both *APOE* $\varepsilon$4 and *MAPT* H1/H1 progressed to dementia faster than MCI subjects having none of these variants. However, these results were not statistically significant (HR = 2.03, 95% CI = 0.73–5.64; $p = 0.172$). Kaplan-Meier analysis showed no statistically significant differences between *APOE* $\varepsilon$4 & *MAPT* H1/H1 MCI carriers and non-*APOE* $\varepsilon$4 & non-*MAPT* H1/H1 carriers. The difference between survival medians could not be calculated as less than 50% of non-*APOE* $\varepsilon$4 and non-*MAPT* H1/H1subjects 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

Supplementary Table 5
Baseline cognitive performance scores for sample 3 MCI groups

| Tasks | s-MCI | p-MCI | p |
|---|---|---|---|
| *Verbal memory* | | | |
| FCSRT | 38.9 (8.1) | 31.3 (12.3) | **0.003** |
| WMS | 7.2 (4.5) | 6.2 (4.6) | n.s. |
| CERAD | 1.6 (1.6) | 1.0 (1.3) | n.s. |
| *Visual memory* | | | |
| FRc | 9.5 (5.0) | 7.0 (3.5) | n.s. |
| FRcn | – | – | – |
| BVRT | 4.2 (7.9) | 6.2 (10.4) | n.s. |
| *Praxias and Naming* | | | |
| FC | 17.8 (1.9) | 18.5 (1.7) | n.s. |
| BNT | 45.1 (9.3) | 43.6 (6.4) | n.s. |
| *Executive function* | | | |
| VFp | 7.7 (3.0) | 8.5 (7.8) | n.s. |
| VFs | 13.9 (3.7) | 11.9 (4.1) | n.s. |
| RSPM | 24.0 (5.3) | 21.8 (7.0) | n.s. |
| TMTA | 96.9 (63.8) | 115.2 (60.7) | n.s. |
| TMTB | 253.9 (58.9) | 276.3 (53.9) | n.s. |

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. 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, Figure Copy. BNT, Boston Naming test. VFp, Verbal Fluency-phonetic. VFs, Verbal Fluency-semantic. RSPM, Raven Standard Progressive Matrices. TMTA, Train Making Test-part A. TMTB, Trail Making Test-part B. (–): data not available. n.s, not statistically significant.

Supplementary Table 6
Baseline cognitive performance scores for the combined sample according to *APOE* $\varepsilon$ and *MAPT* status

| | *APOE* $\varepsilon$4 (+) | *APOE* $\varepsilon$4 (-) | P |
|---|---|---|---|
| MMSE | 25.39 | 26.03 | 0.052 |
| FCRST | 37.74 | 38.99 | 0.329 |
| FRc | 6.34 | 7.09 | 0.364 |
| | *MAPT* H1/H1 | *MAPT* non-H1/H1 | p |
| MMSE | 25.74 | 25.83 | 0.780 |
| FCRST | 38.69 | 38.41 | 0.824 |
| FRc | 7.50 | 6.16 | 0.067 |

*APOE*, Apolipoprotein E gene. *MAPT*, microtubule-associated protein tau gene.

of *APOE* $\varepsilon$4 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* $\varepsilon$4 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* $\varepsilon$4 and *MAPT* H1/H1 progressed earlier to dementia than non-carriers (median difference: 2.21 years; Supplementary Table 2).

Supplementary Table 7
Demographic data and global cognitive status data in *TIcog* subjects (sample 1). ANOVA analysis between subjects who only underwent standard visits; subjects with telephonic interview assessment (*TIcog*); and subjects with telephonic interview assessment plus a standard visits (*TIcog* + standard visit)

| | Standard visits only | TI*cog* | p | TIcog + standard visits | p |
|---|---|---|---|---|---|
| Age at examination, y* | 73.4 (5.3) | 73.2 (5.5) | n.s. | 73.3 (5.3) | n.s. |
| Education, y* | 12.2 (4.5) | 11.6 (3.9) | n.s. | 14.2 (5.6) | n.s. |
| Male/Female | 31/24 | 27/23 | n.s. | 11/0 | **0.004** |
| MMSE | 26.6 (2.2) | 26.2 (2.3) | n.s. | 26.5 (2.6) | n.s. |
| GDS | 7.8 (5.3) | 8.5 (5.3) | n.s. | 3.3 (2.7) | **0.011** |
| IDDD | 36.3 (3.5) | 36.7 (5.5) | n.s. | 35.7 (5.1) | n.s. |
| IMCB | 5.1 (3.3) | 5.0 (3.0) | n.s. | 4.0 (2.6) | n.s. |

*Mean (SD); *p values* lower than 0.05 are highlighted in bold. 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 8
Global cognitive function scores for sample 3 MCI groups

| Tasks | s-MCI | p-MCI | p |
|---|---|---|---|
| MMSE | 27.0 (2.4) | 26.5 (2.8) | n.s. |
| GDS | 10.7 (7.0) | 10.9 (4.7) | n.s. |
| IDDD | 38.0 (5.5) | 42.0 (9.2) | **0.041** |
| IMCB | – | – | – |

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. (–): data not available. n.s, not statistically significant.

### *Sample 3*

We increased the number of subjects studied to further investigate the results obtained in samples 1 and 2 by analyzing another independent MCI longitudinal sample (sample 3) of 117 non-demented MCI subjects. Sixty-eight subjects with amnestic MCI remained cognitively stable (58.1%; mean follow-up: 2.2 years; SD = 1.1) whereas 49 subjects progressed to dementia (41.9%; mean follow-up: 1.7 years; SD = 1.1; see Supplementary Figure 2). Among the MCI subjects who progressed to dementia, thirty-seven MCI subjects developed AD (75.5%) and 12 developed other non-AD-type dementias over time (five subjects progressed to FTD, five to AD plus vascular dementia type and two developed vascular dementia). Scores of neuropsychological tests are summarized in Supplementary Tables 5 and 8. Cox regression analysis showed no statistically significant results in sample 3, although the hazard ratios obtained in most of the analyses were similar

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* $\varepsilon$4 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* $\varepsilon$4 and *MAPT* H1/H1 variants progressed earlier to dementia than non-carriers (median difference: 2.87 years; Supplementary Table 2).

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