Predictability of polygenic risk score for progression to dementia and its interaction with APOE ε4 in mild cognitive impairment

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Abstract

Background: The combinatorial effect of multiple genetic factors calculated as a polygenic risk score (PRS) has been studied to predict Alzheimer’s disease (AD) risk and evidence suggests that the predictability of PRS can be affected by the presence of APOE ε4 allele substantially. Therefore, we aimed to evaluate the predictability of PRS on disease progression to AD depending on APOE ε4 carrier status and its interaction with APOE ε4 in mild cognitive impairment (MCI).

Method: We analyzed 732 MCI patients from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort with those who progressed to AD within 5 years post-baseline (n=270) and remained stable as MCI (n=462). The predictability of PRSs including and excluding the APOE region (PRS+APOE and PRS-APOE) on the conversion to AD and its interaction with APOE ε4 carrier status were assessed using Cox regression analyses. Gene set enrichment analysis of single nucleotide polymorphisms (SNPs) selected for PRS calculation was performed.

Result: PRS+APOE (hazard ratio (HR) 1.468, 95% CI 1.335–1.615) and PRS-APOE (HR 1.293, 95% CI 1.157–1.445) both were associated with a significantly increased risk of progression to dementia in MCI (Table 1). The interaction between PRS+APOE and APOE ε4 carrier status was significant with a p-value of 3.78×10^-2 (Table 2). The association of PRSs with progression risk was stronger in APOE ε4 non-carriers (PRS+APOE: HR 1.710, 95% CI 1.244–2.351, PRS-APOE: HR 1.429, 95% CI 1.182–1.728) than APOE ε4 carriers in MCI (PRS+APOE: HR 1.167, 95% CI 1.005–1.355, PRS-APOE: HR 1.172, 95% CI 1.020–1.346) (Table 1 and Figure 1). Gene set enrichment analysis identified 27 significant pathways including those linked to amyloid, lipid, and protein metabolisms (Figure 2).

Conclusion: The results demonstrated that PRSs showed a significant interaction with APOE ε4 carrier status and PRSs including and excluding APOE regions could predict conversion of MCI to dementia with a stronger association in APOE ε4 non-carriers than APOE ε4 carriers. This indicates PRS as a potential genetic predictor particularly for progression of MCI patients with no APOE ε4 alleles.
Figure 1. Hazards ratios of PRS in MCI with and without APOE ε4 using a restricted cubic spline curve

A. MCI with APOE ε4

B. MCI without APOE ε4

Abbreviation: MCI = mild cognitive impairment; PRS = polygenic risk score

FIGURE 1

Figure 2. Gene ontology biological pathways and cellular component pathways

A. Gene ontology biological pathways

B. Gene ontology cellular component pathways

FIGURE 2
## Table 1

Table 1. Association of PRS and *APOE* e4 status with disease progression to dementia according to z-scores in all MCI, MCI *APOE* e4 carriers, and MCI *APOE* e4 non-carriers

|                          | All MCI (N = 732) | MCI with *APOE* e4 (N = 378) | MCI without *APOE* e4 (N = 353) |
|--------------------------|-------------------|-------------------------------|---------------------------------|
| **PRS**−*APOE**          | 1.468 (1.335−1.615) | 1.167 (1.005−1.355) | 1.710 (1.244−2.351) |
| (2.30×10⁻¹⁵)             | 4.16×10⁻²         | 9.30×10⁻⁴                  |
| **PRS**−*APOE**          | 1.293 (1.157−1.445) | 1.172 (1.020−1.346) | 1.429 (1.182−1.728) |
| (5.19×10⁻⁶)              | 2.47×10⁻²         | 2.19×10⁻⁴                  |
| **APOE** e4 carrier status | 2.678 (2.066−3.470) | NA                           | NA                              |
| (9.70×10⁻¹⁴⁺)            |                  | NA                           | NA                              |

PRS−*APOE* was calculated PRS after including SNPs within ±1Mb-regions surrounding the *APOE* gene, whereas PRS−*APOE* was calculated PRS after excluding SNPs within ±1Mb-regions surrounding the *APOE* gene.

Abbreviation: HR = hazard ratio; NA = not analyzed; PRS = polygenic risk score; SNP = single nucleotide polymorphism

Data for * 3 subjects, † 1 subject, †† 2 subjects, ‡ 343 subjects, ‡‡ 191 subjects, and ‡§ 152 subjects were not available.

## Table 2

Table 2. Cox regression analysis with an interaction term between PRS and *APOE* e4 carrier status

|                          | Coefficient | Standard error | p-value  |
|--------------------------|-------------|----------------|----------|
| **Age**                  | 0.034       | 0.009          | 1.94×10⁻⁴ |
| **Female**               | 0.116       | 0.127          | 3.57×10⁻¹ |
| **PRS**−*APOE**          | 0.531       | 0.162          | 1.10×10⁻³ |
| **APOE** e4 carrier status | 0.681     | 0.176          | 1.14×10⁻⁴ |
| **PRS**−*APOE* **APOE** e4 carrier status | -0.372 | 0.179          | 3.78×10⁻² |

PRS−*APOE* was calculated PRS with SNPs within the 1Mb-region surrounding the *APOE* gene.

Abbreviation: PRS = polygenic risk score; SNP = single nucleotide polymorphism