



Associations of Alzheimer’s Disease and Amyloid-related Polygenic Risk Scores with Dementia in Parkinson’s Disease

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Introduction

Parkinson’s disease (PD) is a common neurodegenerative disorder characterized by cardinal motor symptoms, including resting tremor, bradykinesia, rigidity, and postural instability. PD dementia (PDD) affects approximately 20-30% of PD patients, typically developing in the later stages of the disease. Understanding the risk factors that predispose PD patients to develop dementia is crucial for identifying at-risk individuals and developing targeted therapeutic strategies.

Emerging evidence suggests that (Alzheimer’s disease) AD genes may be linked to PD dementia, highlighting a potential overlap in the genetic basis of these two neurodegenerative disorders. Notably, the *APOE* gene, a major genetic risk factor for AD, has also been associated with an increased risk of dementia in PD patients. Up to 50% of patients with PD dementia have amyloid-β plaques and tau-containing neurofibrillary tangles, being the pathologic hallmark of AD.

A polygenic risk score (PRS) combines information from multiple genetic variants associated with a disease trait by summing up the weighted contributions of these genetic variants based on their effect sizes. It is useful for multifactorial disease such as PD and AD, in which multiple genetic variants were identified. PRS can identify individuals at a higher risk for disease and allows for proactive interventions and lifestyle modifications.

In this study, we aimed to identify SNVs that are associated with PDD by leveraging both genome-wide survival studies (GWSS) and PRS, assessing the predictive power of AD-PRS, amyloid β PRS and PD-PRS in a single ethnic PD patients.

Methods

Study Subjects

In this study, we aimed to identify SNVs that are associated with PDD by leveraging both genome-wide survival studies (GWSS) and PRS, assessing the predictive power of AD-PRS, amyloid β PRS and PD-PRS in a single ethnic PD patients.

Genetic tests

We performed genomic analysis using a Korean chip (K-CHIP). K-CHIP is a customized microarray chip containing single-nucleotide polymorphism (SNPs) designed by the Korean Biobank Array project to include genetic variants

related to chronic disease and the genetic characteristics of Koreans. Genomic coverage of K-CHIP is 95.38% for common variants (minor allele frequency ≥ 95%), and 73.65% for low-frequency variants (minor allele frequency < 5%).

Clinical data

Using electric medical records, we reviewed the year of PD symptom onset, the presence of dementia, the year of dementia diagnosis or the latest year of follow-up.

Polygenic risk scores

We used PRS constructed from previous studies for PD and AD in Asian and European populations, respectively. First, we searched previous polygenic risk score studies for PD and AD at PGS catalog, and we selected the studies using the most recent GWAS for Asian AD (PGS000779), Asian PD (PGS001353), European AD (PGS002280), and European PD (PGS000902). Additionally, we used PGS associated with amyloid positivity (optimized-PRS, PGS002731). PGS002280 and PGS002731 excluded *APOE*, which is the strongest genetic risk factor for AD to find *APOE*-independent genetic risk factors. Genetic risk scores were generated using pgs-calc v1.3.4 (<https://github.com/lukfor/pgs-calc>) based on summary statistics from above mentioned GWAS studies.

Results

Among 964 participants, 225 developed dementia during a median follow-up of 10 years. GWSS identified SNVs in *HS1BP3*, *PTPRM*, *APOE*, and *TOMM40* as being associated with PDD. Both the Asian AD-PRS (PGS000779; HR 1.31, 95% CI 1.19–1.45, $P < 0.001$) and the European AD-PRS (PGS0002280; HR 1.89, 95% CI 1.23–2.91, $P = 0.004$) were significantly associated with increased risk of PDD. In addition, the Aβ-PRS was associated with dementia in PD (HR 2.07, 95% CI 1.17–3.65, $P = 0.012$). In contrast, the PD-PRS was not significantly associated with PDD.

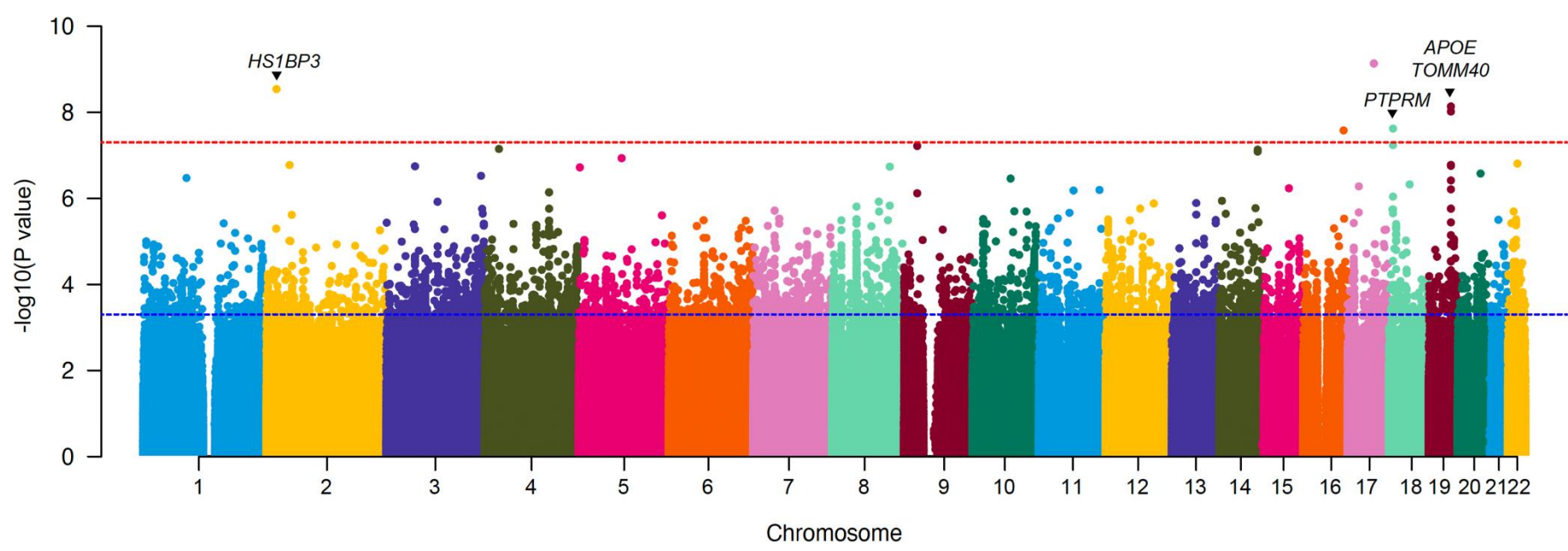


Figure 1. Manhattan plot of genome-wide survival study (GWSS). **Seven SNPs** were associated with dementia in PD ($P \leq 5 \times 10^{-8}$), including *APOE*, *TOMM40*, *HS1BP3*, *PTPRM*, and other 3 SNPs that were not found in dbSNP or ClinVar.

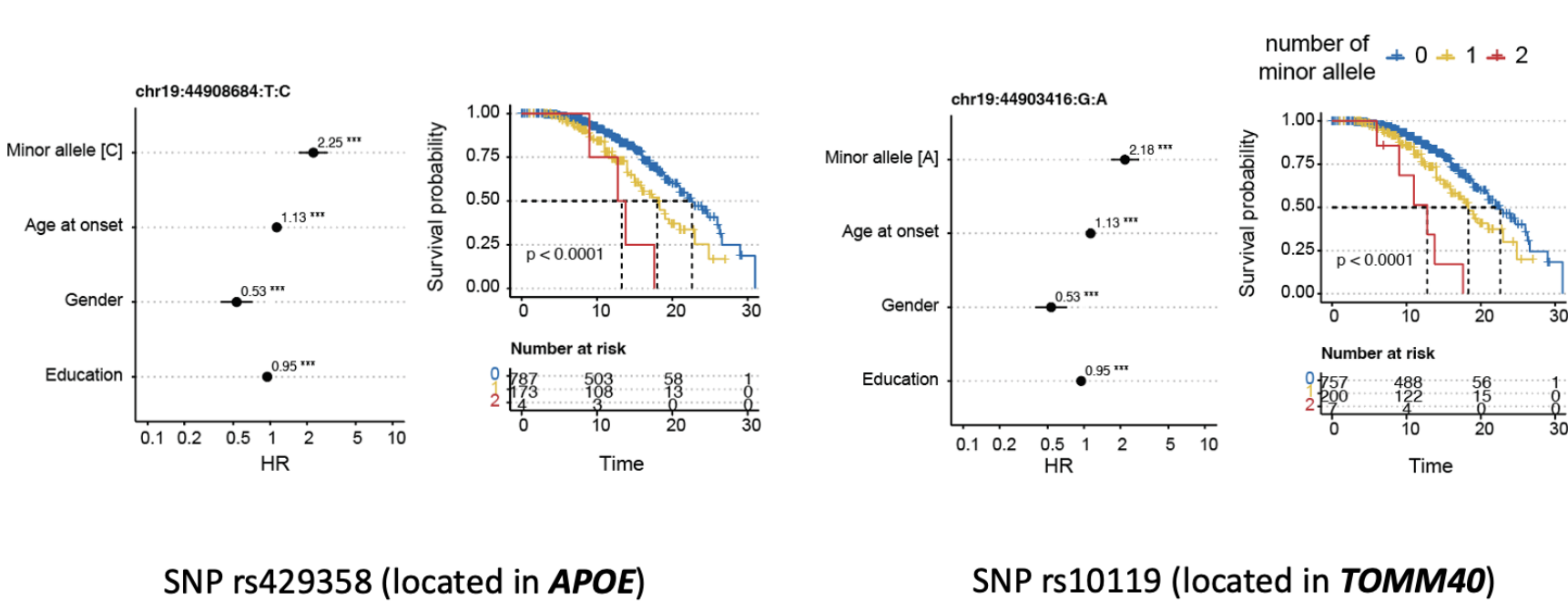


Figure 2. Dose effect of copy number of risk alleles for dementia in PD.

Table 1. Asian AD-PRS (PGS000779) and increased risk of dementia in PD.

Asian AD-PRS (PGS000779, number of SNPs = 7)			
Parameter	Hazard ratio	95% CI	P value
Asian AD-PRS (PGS000779)			
Age	1.13	1.11–1.15	<0.001
Female	0.55	0.41–0.74	<0.001
Education	0.95	0.92–0.98	<0.001
Asian AD-PRS	1.31	1.19–1.45	<0.001

HR = 1.31 (95% CI: 1.19–1.45, $P < 0.001$)

Table 2. European AD-PRS was associated with increased risk of dementia in PD.

European AD-PRS (PGS002280, number of SNPs = 62)			
Parameter	Hazard ratio	95% CI	P value
European AD-PRS (PGS002280)			
Age	1.13	1.11–1.15	<0.001
Sex	0.53	0.39–0.71	<0.001
Education	0.95	0.92–0.97	<0.001
European AD-PRS	1.89	1.23–2.91	0.004

Table 3. Amyloid positivity PRS was associated with increased risk of dementia in PD.

Amyloid Positivity PRS (PGS002731, number of SNPs = 12)			
Parameter	Hazard ratio	95% CI	P value
amyloid-PRS (PGS002731)			
Age	1.13	1.11–1.15	<0.001
Sex	0.54	0.40–0.72	<0.001
Education	0.95	0.92–0.98	<0.001
amyloid-PRS	2.07	1.17–3.65	0.012

Table 4. PRS analyses for dementia in PD.

Asian PD-PRS (PGS001353, number of SNPs = 6)			
Parameter	Hazard ratio	95% CI	P value
Age	1.13	1.11–1.15	<0.001
Female	0.52	0.39–0.70	<0.001
Education	0.94	0.92–0.97	<0.001
Asian PD-PRS	1.15	0.81–1.62	0.442
European PD-PRS (PGS000902, number of SNPs = 74)			
Parameter	Hazard ratio	95% CI	P value
Age	1.13	1.11–1.15	<0.001
Female	0.52	0.39–0.71	<0.001
Education	0.95	0.92–0.97	<0.001
European PD-PRS	0.96	0.74–1.24	0.749

Table 5. Univariate Cox Regression analysis for each variant of AD-PRS.

RSID	Locus	chr	Effect allele	Hazard ratio	P-value
Asian AD-PRS (PGS000779)					
rs429358	<i>APOE</i>	19	C	2.25 (1.71–2.97)	7.68x10 ⁻⁹
rs11556505	<i>TOMM40</i>	19	T	1.73 (1.34–2.24)	3.02x10 ⁻⁵
rs519113	<i>NECTIN2</i>	19	G	1.50 (1.18–1.92)	9.27x10 ⁻⁴
rs7412	<i>APOE</i>	19	T	0.51 (0.31–0.85)	0.009
European AD-PRS (PGS002280)					
rs5848	<i>GRN</i> , <i>FAM171A2</i>	17	T	1.37 (1.10–1.69)	<0.001
rs7068231		10	G	1.28 (1.05–1.57)	0.02
rs12592898	<i>CTSH</i>	15	G	1.82 (1.11–2.99)	0.02
rs13237518	<i>TMEM106B</i>	7	C	1.26 (1.03–1.54)	0.02
rs785129	<i>HS3ST5</i> , <i>HDAC2-AS2</i>	6	T	0.78 (0.64–0.97)	0.02
rs679515	<i>CRI</i>	1	T	1.61 (1.05–2.49)	0.03
rs12590654	<i>SLC24A4</i>	14	G	1.23 (1.01–1.50)	0.04
Amyloid beta-PRS (PGS002731)					
rs138190086	<i>ACE</i>	17	A	2.21 (1.12–4.33)	0.02
rs4844610	<i>CRI</i>	1	A	1.51 (0.98–2.33)	0.06

Discussion

In this study, we analyzed genetic factors associated with the development of dementia in PD patients, specifically through the use of genome-wide survival study and polygenic risk scores. Among 964 Korean patients with PD, 22.2% of the patients developed dementia during median 10 years of follow-up. In GWSS, we found SNPs in *APOE*, *TOMM40*, *HS1BP3*, and *PTPRM* genes were associated with PD dementia. Next, PRS for AD, but not PRS for PD was associated with increased risk of PD dementia. Especially, amyloid positivity PRS, which is closed associated with AD was also significantly associated with PD dementia, even after excluding *APOE* gene.

Our study has limitations. First, the study population was relatively small. Instead, we tried to increase the quality of data using long-term clinical data, and we tried to overcome this by using previous PGS. Second, we included only 5,535,200 SNPs. Further studies using whole-genome sequencing in large number of populations could validate our findings.

Nevertheless, our findings offer important insights into the genetic underpinnings of PD dementia and highlight potential biomarkers for identifying at-risk individuals.