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# Polygenic effects on the risk of Alzheimer's disease in the Japanese population

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## Abstract

**Background** Polygenic effects have been proposed to account for some disease phenotypes; these effects are calculated as a polygenic risk score (PRS). This score is correlated with Alzheimer's disease (AD)-related phenotypes, such as biomarker abnormalities and brain atrophy, and is associated with conversion from mild cognitive impairment (MCI) to AD. However, the AD PRS has been examined mainly in Europeans, and owing to differences in genetic structure and lifestyle, it is unclear whether the same relationships between the PRS and AD-related phenotypes exist in non-European populations. In this study, we calculated and evaluated the AD PRS in Japanese individuals using genome-wide association study (GWAS) statistics from Europeans.

**Methods** In this study, we calculated the AD PRS in 504 Japanese participants (145 cognitively unimpaired (CU) participants, 220 participants with late mild cognitive impairment (MCI), and 139 patients with mild AD dementia) enrolled in the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) project. In order to evaluate the clinical value of this score, we (1) determined the polygenic effects on AD in the J-ADNI and validated it using two independent cohorts (a Japanese neuropathology (NP) cohort ( $n = 565$ ) and the North American ADNI (NA-ADNI) cohort ( $n = 617$ )), (2) examined the AD-related phenotypes associated with the PRS, and (3) tested whether the PRS helps predict the conversion of MCI to AD.

**Results** The PRS using 131 SNPs had an effect independent of *APOE*. The PRS differentiated between CU participants and AD patients with an area under the curve (AUC) of 0.755 when combined with the *APOE* variants. Similar AUC was obtained when PRS calculated by the NP and NA-ADNI cohorts was applied. In MCI patients, the PRS was associated with cerebrospinal fluid phosphorylated-tau levels ( $\beta$  estimate = 0.235,  $p$  value = 0.026). MCI with a high PRS showed a significantly increased conversion to AD in *APOE*  $\epsilon 4$  noncarriers with a hazard rate of 2.22. In addition, we also developed a PRS model adjusted for LD and observed similar results.

**Conclusions** We showed that the AD PRS is useful in the Japanese population, whose genetic structure is different from that of the European population. These findings suggest that the polygenicity of AD is partially common across ethnic differences.

**Keywords** Polygenic risk score, Alzheimer's disease, Mild cognitive impairment

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## Background

Alzheimer's disease (AD) is a neurodegenerative disease caused by environmental and genetic factors [1, 2]. Environmental factors, which are acquired and modifiable, associated with AD include smoking status, alcohol consumption, diet, and physical activity [3]. On the other hand, the heritability of AD is approximately 70%, and genetic factors are inborn and nonmodifiable [4, 5]. However, knowing one's genetic risk early in life can motivate one to improve modifiable factors. Indeed, sharing genetic test results with carriers of genetic risk for disease may promote behavioural changes rather than increase psychological distress [6, 7]. Thus, knowledge of the individual genetic risk of AD is expected to contribute to delaying the onset of AD and early therapeutic intervention.

The largest genetic risk factor for AD is the  $\epsilon 4$  allele of the apolipoprotein E (*APOE*) gene, but *APOE*  $\epsilon 4$  explains only approximately 10% of AD cases based on heritability [4, 5]. In addition, even when other AD-associated genetic variants found in previous genome-wide association studies (GWAS) are also considered, they do not explain all the genetic variance in AD patients [8], suggesting the existence of additional unknown AD-related genetic variants. To clarify this "missing heritability", polygenic effects that aggregate the small effects of many alleles have been proposed to underlie AD.

Polygenic risk score (PRS) is a measure to quantify the combined effect of genetic variants on an individual's risk for disease. The combination of the *APOE*  $\epsilon 4$  allele dose and PRS has been shown to improve disease prediction accuracy in the European population [9]. Moreover, the PRS is associated with AD-related phenotypes, such as brain volumes [10–12], brain amyloid-beta ( $A\beta$ ) burden [11, 12], and plasma phosphorylated tau [13], and has been reported to be useful in predicting conversion from mild cognitive impairment (MCI) to AD [14, 15].

However, the clinical application of the PRS must be approached with caution. One of several concerns is that the effects of the PRS are not consistent across different ancestries [16, 17]. This is because genetic structures, such as linkage disequilibrium (LD) blocks, are different across populations and because the GWAS summary statistics used as a weight for each single-nucleotide polymorphism (SNP) to calculate the PRS are based primarily on people of European ancestry. Taking a PRS calculation method based on GWAS summary statistics from European individuals and applying it to non-European individuals compromises prediction accuracy since the genetic risk of that population may not be reflected properly [18]. Therefore, for future clinical application of the AD PRS, it is necessary to evaluate the utility of this score in populations of different ancestry. In addition,

harmonization of protocols such as inclusion and exclusion criteria is critical for rigorous comparisons between different cohorts.

Therefore, in this study, we calculated the AD PRS in 504 Japanese participants (145 cognitively unimpaired participants, 220 participants with late MCI, and 139 patients with mild AD dementia) enrolled in the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) project and evaluated its effectiveness in the North American ADNI (NA-ADNI) cohort including North American 1070 participants. The J-ADNI study used a harmonized protocol to the NA-ADNI study. The previous comparative study of AD dementia between the US and Japan in the ADNI projects reported that MCI in the Japanese population shows similar progression profile as MCI in North America in terms of cognitive function [19]. We moreover validated the AD PRS using independent genomic data from 565 Japanese individuals with a neuropathological diagnosis by autopsy. Furthermore, we also examined the AD endophenotypes in association with PRS and tested whether the PRS is useful for predicting conversion from MCI to AD.

## Materials and methods

### Japanese participants from the J-ADNI cohort

Data used in the preparation of this article were obtained from the J-ADNI database deposited in the National Bioscience Database Center Human Database, Japan (Research ID: hum0043.v1, 2016) [19]. This database enrolled cognitively unimpaired (CU) participants, participants with late MCI, and patients with mild AD dementia (ADD) using criteria consistent with those of the North American ADNI (NA-ADNI) [20]. The J-ADNI was launched in 2007 as a public-private partnership led by Principal Investigator Takeshi Iwatsubo, MD. The J-ADNI was aimed to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of late MCI and mild ADD in the Japanese population. The J-ADNI did not recruit participants with early MCI. The ethics committees of the University of Tokyo, Osaka University and Niigata University approved the study.

A total of 715 volunteer participants between the ages of 60 and 84 years were diagnosed with late MCI or mild ADD or were CU and considered for inclusion in the J-ADNI. Of the 715 participants assessed for study eligibility, 537 met the criteria and were enrolled. Of these 537 participants, 508 (CU, 147; MCI, 221; ADD, 140) underwent genotyping analysis. Participants were evaluated every 6 or 12 months over a period of 36 months for CU and MCI participants and over a period of 24 months

for participants with ADD, as in the NA-ADNI. As detailed below, the J-ADNI collected various imaging, clinical and neuropsychological data from these participants in addition to the genomic data. These data were obtained from the database described above.

#### Japanese neuropathological cohort

An independent neuropathological (NP) cohort composed of 577 brain donors was used for PRS validation [21]. Of these donors, 365 control donors had little pathological findings associated with AD and 212 case donors had those consistent with AD. All ADD patients were neuropathologically diagnosed by senile plaque and neurofibrillary tangle. No neuropathological features of other neurodegenerative disorders such as dementia with Lewy body disease, frontotemporal lobar degeneration, and Parkinson's disease, were observed. Control individuals did not show the typical neuropathological hallmarks of AD. As no clinical diagnosis is provided in this cohort, the term case or control is used in this study. As shown below, 565 brain donors (358 controls and 207 cases) passed QC. The demographic data of all the participants from the NP cohort are shown in Table S1.

#### Genotyping, quality control, and imputation

Whole blood samples from 508 participants in the J-ADNI cohort and post-mortem frontal cortices from 577 donors in the NP cohort were genotyped using the Infinium Asian Screening Array (Illumina), containing 657,490 SNPs. *APOE* genotypes in each participant were determined by haplotypes derived from rs7412 and rs429358, which were genotyped using TaqMan Assays (Applied Biosystems). We excluded SNPs that (i) had duplicated genomic positions, (ii) had low call rates (<5%), (iii) deviated from Hardy–Weinberg equilibrium compared to controls ( $p < 1 \times 10^{-5}$ ), or (iv) had low minor allele frequency (<0.01). For QC purposes, we excluded participants who (i) had sex inconsistencies, (ii) had autosomal heterozygosity deviation ( $|F_{het}| \geq 0.2$ ), (iii) had <99% of their genotypes called, or (iv) were in the same family according to pi-hat (>0.2). Furthermore, we used principal component analysis to remove outliers based on the 1000 Genomes Project samples (Phase3 v5) [22]. Finally, 451,713 autosomal SNPs and the samples, including 504 participants from the J-ADNI cohort and 565 brain donors from the NP cohort passed the QC procedures.

Next, we performed phasing with Eagle v2.4.1 [23] and imputation with Minimac4 [24] using the whole-genome sequencing data of 3541 participants obtained from the BioBank Japan Project [25] and the 1000 Genomes Project [22] as reference genome data. After repeating the above QC procedure for the imputed SNP markers, we

excluded SNPs with poor imputation quality ( $r^2 \leq 0.3$ ). Finally, we obtained 7,633,670 SNPs and the samples, including the 504 participants from the J-ADNI (CU, 145; MCI, 220; and ADD, 139) and 565 brain donors from the NP cohort (control, 358; case, 207).

#### The NA-ADNI genetic data

The independent cohort data used in this study were obtained from the NA-ADNI [26]. The NA-ADNI was launched in 2003 as a public–private partnership led by Principal Investigator Michael W. Weiner, MD. The NA-ADNI was aimed to test whether serial MRI and PET data and the analysis of other biological markers and clinical and neuropsychological assessments can be combined to characterize the progression of MCI and early ADD.

SNP data from the NA-ADNI project were available for 1674 participants across ADNI 1 and ADNI GO/2. Genotyping was conducted using three different platforms: Human610-Quad, HumanOmniExpress and Omni 2.5 M (Illumina) [27]. The SNP data were imputed using the TOPMed imputation server after identical marker QC and sample QC as was used for the J-ADNI was performed. The SNP data analysed on each of the three platforms were imputed separately. After repeating the QC for the imputed SNP markers, we excluded SNPs with poor imputation quality ( $r^2 \leq 0.3$ ). If a participant was genotyped on more than one genotyping array, the dataset with the fewest missing values was selected.

According to the following procedures, we selected participants with predicted central European ancestry and self-reported white non-Hispanic ethnicity. For predicted ancestry, we used SNPweights software to infer genetic ancestry from genotyped SNPs [28]. The reference panel comprised European, West African, East Asian and Native American ancestral populations. Participants with predicted central European ancestry of 80% or more were retained. We obtained self-reported ethnicity information from the NA-ADNI database. The clinical diagnosis at the final visit was used to categorize the data. Furthermore, four participants who had significant memory concerns but no cognitive impairment were excluded. Finally, 1482 participants (CU, 377; MCI, 481; and ADD, 624) remained.

Of the 1482 participants, 412 participants were participants in the Alzheimer's Disease Genetics Consortium (ADGC) and were included in the meta-analysis of AD GWAS used as SNP weights in the PRS calculation described below. We analysed a set of 1070 participants (CU, 257; MCI, 453; and ADD, 360), excluding the 412 participants to avoid overfitting. The demographic data of all the participants from the NA-ADNI cohort are shown in Table S2.

### Calculation of the PRS and prediction accuracy

The PRS was calculated for each individual and is expressed as the following weighted sum:

$$PRS_i = \sum_{j=1}^M \beta_j x_{i,j} / M,$$

where  $PRS_i$  is the PRS for individual  $i$ ;  $M$  is the total number of SNPs used in the calculation;  $\beta_j$  is the weight of  $SNP_j$ , defined according to the effect size calculated by an independent GWAS; and  $x_{i,j}$  is the number of minor alleles of  $SNP_j$  that individual  $i$  has, thus has a value of 0, 1, or 2. In other words, the more minor alleles that are strongly associated with the disease, the higher the PRS.

SNPs included in the PRS were determined by the clumping and thresholding (C+T) method, the most common and supported method in AD studies [29, 30]. We used PRSice software implementing the C+T method to calculate the PRS [31]. The clumping method preferentially retains markers most strongly associated with disease from correlated markers in the same LD block. The thresholding method removes variants with GWAS  $p$  values greater than the selected  $p$  value threshold ( $p_T$ ) ( $p > p_T$ ). To determine the optimal  $p_T$ , we tested  $p_T$  values of  $5 \times 10^{-8}$ ,  $1 \times 10^{-6}$ ,  $1 \times 10^{-5}$ ,  $1 \times 10^{-4}$ ,  $1 \times 10^{-3}$ ,  $1 \times 10^{-2}$ , 0.05, 0.5, and 1.0. SNPs were weighted by their effect sizes (beta coefficient) from the AD GWAS in the European population [32].

The ability of the PRS to accurately classify CU participants and ADD patients was estimated in terms of (1) Nagelkerke's  $R^2$ , the proportion of the variance explained by the regression model and (2) the area under the receiver operator characteristic curve (AUC). To calculate Nagelkerke's  $R^2$ , we constructed a logistic regression model, including the PRS and the first two components from the multidimensional scaling (MDS) analysis (full model), and compared it to a model with only the first two MDS components (null model). We assessed the difference in Nagelkerke's  $R^2$  between the full and null models ( $R^2 = R^2_{Full} - R^2_{Null}$ ) and used the  $p_T$  corresponding to the highest value of Nagelkerke's  $R^2$ . The Nagelkerke's  $R^2$  was calculated by PRSice software using default parameters [31]. To avoid potential overfitting due to differences in LD between the European and Japanese populations, we used the LD score ( $R^2$ ) of the EUR population of 1000 Genomes in the LDpop Tool [33] to exclude SNPs suspected of LD using the criterion of  $R^2 > 0.5$ . In this analysis, when adjacent SNPs had  $R^2 > 0.5$ , one SNP with a lower GWAS  $p$ -value was selected to calculate PRS and the other was excluded. When more than one SNP was observed between two SNPs with  $R^2 > 0.5$ , all of them may be in the same LD block, and the SNP showing the lowest GWAS  $p$ -value was selected from this LD block.

The AUC was calculated based on the prediction results of the logistic regression model using the J-ADNI cohort as a test cohort. We also performed fivefold cross validation (CV) to evaluate a predictive performance in a test cohort. We estimated the 95% credible intervals by using the `ci.auc` function from the R package "pROC". DeLong's test was conducted to assess potential significant differences between curves using the `roc.test` function from the R package "pROC".

### CSF biomarkers

In the J-ADNI cohort, cerebrospinal fluid (CSF) samples were assayed for A $\beta$ (1–42), total tau (tTau), and phosphorylated tau (pTau) by using a multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with an Innogenetics (INNO-BIA AlzBio3; Ghent, Belgium) immunoassay kit-based reagent [34]. Of the 504 participants who underwent genotyping, 192 participants (CU, 52; MCI, 85; ADD, 55) also underwent CSF biomarker measurements at baseline.

### Structural MRI and PET imaging

All participants in the J-ADNI cohort underwent a structural MRI scan at a signal strength of 1.5 Tesla using a three-dimensional magnetization-prepared rapid-acquisition gradient-echo sequence according to a standardized protocol [35]. Cross-sectional and longitudinal processing streams in FreeSurfer, version 5.3, were used to estimate the atrophic changes in specific regions; we also evaluated the cortical thickness extracted in the longitudinal analysis. Of the 504 participants who underwent genotyping, the entorhinal cortex and hippocampus of 443 participants (CU, 133; MCI, 196; ADD, 114) was assessed by the FreeSurfer longitudinal stream. Each cortical thickness value was adjusted by the total intracranial volume.

Of the 504 participants, 315 and 162 individuals underwent a positron emission tomography (PET) scan using  $^{18}\text{F}$ -2-fluoro-2-deoxy-D-glucose (FDG) and  $^{11}\text{C}$ -Pittsburgh compound B (PiB), respectively. The PET scanning protocol was standardized to minimize the inter-site and inter-scanner variability [36]. All PET images went through the J-ADNI PET QC process [36]. The FDG PET images were classified into seven categories based on the criteria of Silverman et al. [37]. We analysed only PET images of 110 participants classified as having a normal pattern (N1 pattern) and 161 participants classified as having an AD pattern (P1 pattern). For PiB PET, the visual interpretation of four cortical areas on each side (frontal lobe, lateral temporal lobe, lateral parietal lobe, and precuneus/posterior cingulate gyrus) was evaluated by classifying PiB uptake in each cortical region as positive, equivocal, or negative. Cases with one or more



positive cortical areas were defined as amyloid scan positive, and those with negative results in all four cortical regions were defined as amyloid scan negative. Other cases were considered equivocal. We analysed 65 negative and 87 positive amyloid scans, excluding 10 participants who were judged to be equivocal.

### Neuropsychological tests

All participants in the J-ADNI cohort underwent the following neuropsychological tests: Mini-Mental State Examination (MMSE), Functional Assessment Questionnaire (FAQ), Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), and AD Assessment Scale-Cognitive Subscale (ADAS-Cog).

### Statistical analyses

Gene functional enrichment analysis of the closest genes around SNPs included in the PRS was performed using the Metascape database (<http://metascape.org/>) [38].

For the association analyses between the PRS and endophenotypes, we compared slopes with zero by linear regression model analyses. The covariates included age at baseline examination, sex, years of education, the first two principal components (PCs), and doses of *APOE*  $\epsilon 4$  and  $\epsilon 2$  alleles. *P* values were adjusted by false discovery rate (FDR) to avoid type I error.

Cox proportional hazards models using months of follow-up as a time scale were used to analyse the effects of PRSs on incident AD, presented as hazard ratios (HRs) and 95% confidence intervals (CIs) derived from a model with the following covariates: age at baseline examination, sex, years of education, the first two PCs, and dose of *APOE*  $\epsilon 4$  and  $\epsilon 2$  alleles. We analysed 208 MCI participants over a follow-up period of  $\geq 12$  months. Nonconverters were censored at the end of follow-up. Log-rank test was performed to examine the difference in conversion to AD between two PRS groups. This test was

performed using only the PRS without covariates because the covariates other than PRS could affect the differences between the groups. Cox proportional hazard model analyses and log-rank tests were performed using the *coxph* and *survdiff* functions from the R package “survival”, respectively.

## Results

### The PRS successfully distinguish ADD patients and CU individuals in the J-ADNI cohort

After quality control of the genotyping data, the J-ADNI cohort included the 504 participants. The group with ADD had a higher mean age (*p* value < 0.001), a lower mean length of education (*p* value < 0.001), and a higher frequency of *APOE*  $\epsilon 4$  carriers (*p* value < 0.001) than the CU group, whereas no differences were found in sex (*p* value = 0.429) or the frequency of *APOE*  $\epsilon 2$  carriers (*p* value = 0.292) (Table 1).

We investigated whether the PRSs that were calculated using the statistics from the AD GWAS in the European population [32] are useful for discriminating between patients with ADD and CU individuals in the Japanese population. We calculated PRSs for 145 CU participants and 139 patients with ADD from the J-ADNI cohort. Our model using 173 SNPs showed the highest predictive power at  $p_T < 1 \times 10^{-5}$  and had a Nagelkerke's  $R^2$  of 0.167 (left side of Table 2), indicating that it explained more than 15% of the variance between the CU and ADD groups.

Given the known predictive power of SNPs in the *APOE* region for AD, we next removed this region from our PRS calculation to evaluate the predictive power of other loci. To exclude the effect of *APOE*, we excluded  $\pm 500$  kb around *APOE* (Figure S1). This PRS, referred to as the PRS.noAPOE, was used in subsequent analyses. The predictive power of the PRS.noAPOE was the highest for  $p_T < 1 \times 10^{-5}$ , with a Nagelkerke's  $R^2$

**Table 1** Summary of the J-ADNI participants

	CU	MCI	ADD	<i>p</i> value
N	145	220	139	-
Age in years, mean $\pm$ SE	67.8 $\pm$ 0.472	72.8 $\pm$ 0.397	73.8 $\pm$ 0.563	< 2.00 $\times 10^{-16a}$
Sex (M:F)	72:73	106:114	59:80	0.429 <sup>b</sup>
Years of education, mean $\pm$ SE	13.8 $\pm$ 0.230	13.0 $\pm$ 0.189	12.5 $\pm$ 0.266	8.69 $\times 10^{-4a}$
<i>APOE</i> $\epsilon 4$ alleles (0:1:2)	109:34:2	106:97:17	55:62:22	2.31 $\times 10^{-10c}$
<i>APOE</i> $\epsilon 2$ alleles (0:1:2)	134:11:0	211:9:0	133:6:0	0.323 <sup>c</sup>

**Abbreviations:** CU Cognitively unimpaired, MCI Mild cognitive impairment, ADD Alzheimer's disease dementia, *APOE* Apolipoprotein E, SE Standard error, ANOVA analysis of variance

<sup>a</sup> One-way ANOVA

<sup>b</sup> Chi-squared test

<sup>c</sup> Fisher's exact test

**Table 2** Nagelkerke's R2 at different  $p$  value thresholds

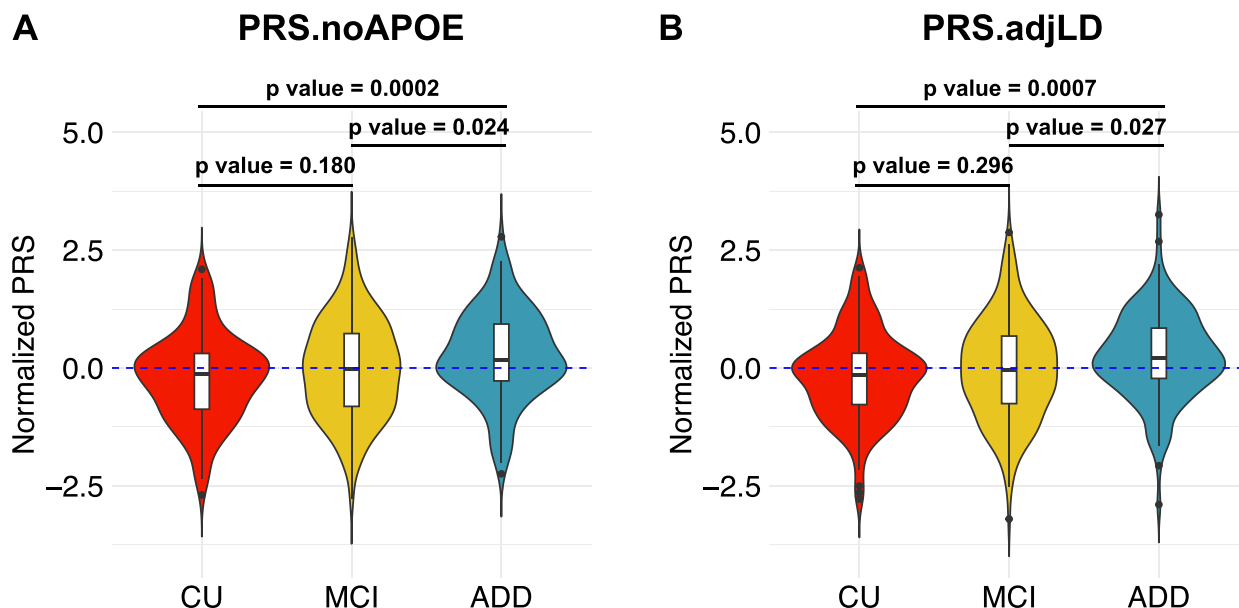
$p_T$	PRS (All SNPs)			PRS.noAPOE (except APOE region)		
	Nagelkerke's $R^2$	$p$ value	#SNPs	Nagelkerke's $R^2$	$p$ value	#SNPs
$p < 5 \times 10^{-8}$	0.148	$5.92 \times 10^{-8}$	81	0.081	$4.57 \times 10^{-5}$	44
$p < 1 \times 10^{-6}$	0.143	$9.91 \times 10^{-8}$	107	0.067	$2.07 \times 10^{-4}$	70
<b><math>p &lt; 1 \times 10^{-5}</math></b>	<b>0.167</b>	<b><math>1.40 \times 10^{-8}</math></b>	<b>173</b>	<b>0.085</b>	<b><math>3.18 \times 10^{-5}</math></b>	<b>131</b>
$p < 1 \times 10^{-4}$	0.091	$1.53 \times 10^{-5}$	410	0.029	0.013	364
$p < 1 \times 10^{-3}$	0.034	$6.85 \times 10^{-3}$	1,696	0.014	0.077	1,642
$p < 1 \times 10^{-2}$	0.004	0.324	10,101	0.007	0.213	10,041
$p < 0.05$	0.000	0.929	33,065	0.000	0.979	32,999
$p < 0.5$	0.005	0.288	121,721	0.004	0.332	121,647
$p < 1.0$	0.006	0.262	158,289	0.005	0.303	158,208

The highest accuracy was highlighted in bold

$P$  value was calculated by Wald test

of 0.085 (right side of Table 2). To remove the effect of APOE regions completely, we also validated PRS.nochr19 excluding SNPs located on chromosome 19. The predictive power of the PRS.nochr19 was the highest for  $p_T < 1 \times 10^{-5}$ , with a Nagelkerke's  $R^2$  of 0.082 (Table S3). To further avoid potential overfitting due to differences in LD between the European and Japanese populations, we excluded 18 SNPs with suspected LD in the European population from PRS.noAPOE (see "Methods").

We referred to this PRS adjusted for LD as the PRS.adjLD. A Nagelkerke's  $R^2$  of the PRS.adjLD was 0.075 ( $p$  value =  $9.31 \times 10^{-5}$ ). We analysed the PRS.noAPOE and PRS.adjLD in this study. The normalized values of the PRS.noAPOE and PRS.adjLD of the ADD patients were significantly higher than those of the CU and MCI participants ( $p$  value < 0.05, Tukey's honestly significant difference (HSD) test; Fig. 1), while there were no significant difference between the CU and MCI participants



**Fig. 1** The PRS.noAPOE in the ADD group was significantly higher than those in the CU and MCI groups. The PRS.noAPOEs (A) or PRS.adjLD (B) in each group were represented by violin plots (CU,  $n = 145$ ; MCI,  $n = 220$ ; ADD,  $n = 139$ ). Each violin plot includes the kernel probability density of the data at different values and the box plots with the median value and the interquartile range. Tukey's HSD test was used to perform multiple comparisons of PRSs among each group. We normalized the PRS distribution to have a mean of 0 and an SD of 1. CN = cognitively normal; MCI = mild cognitive impairment; ADD = Alzheimer's disease dementia

( $p$  value = 0.180 in PRS.noAPOE,  $p$  value = 0.296 in PRS.adjLD, Tukey's HSD test; Fig. 1). These results suggest that the PRS contribute to distinguish between ADD patients and CU individuals in J-ADNI cohort even when the *APOE* region is excluded.

### The PRS in combination with the *APOE* alleles improves predictive power

Next, we examined whether the PRSs and the characteristics of the participants independently influence the predictive power in J-ADNI cohort. The PRS.noAPOE and PRS.adjLD were not correlated with sex, years of education, age at baseline examination, or the dose of the *APOE*  $\epsilon 4$  or  $\epsilon 2$  allele, even when participants were stratified into CU, MCI, and ADD groups ( $p$  value > 0.05; Figures S2 and S3). These results suggest that these factors contribute independently to the discrimination of AD and that combinations of these factors improve discrimination accuracy. We constructed models including only the PRS.noAPOE or PRS.adjLD and doses of *APOE*  $\epsilon 4$  and  $\epsilon 2$  alleles. These models showed predictive performance of AUC = 0.755 in the model including PRS.noAPOE (95% CI = 0.695–0.807) and AUC = 0.748 in the model including PRS.adjLD (95% CI = 0.687–0.800) (Table 3). The predictive performance of a monogenic model of only *APOE* alleles without the PRS.noAPOE was AUC = 0.696 (95% CI = 0.640–0.751) (Table 3). The addition of polygenic effects significantly improved the predictive accuracy of the monogenic model using only *APOE* ( $p$  value =  $9.36 \times 10^{-4}$  in the PRS.noAPOE model,  $p$  value =  $2.59 \times 10^{-3}$  in the PRS.adjLD model,

DeLong test). Additionally, the PRS model incorporating *APOE* alleles independently (PRS.noAPOE + *APOE* doses) has higher accuracy than the PRS model that includes SNPs in the *APOE* region (PRS.incAPOE) (AUC = 0.706; 95% CI = 0.643–0.764;  $p$  value = 0.049, DeLong test). Therefore, we constructed a predictive model including the PRS.noAPOE, sex, years of education, age at baseline examination, and doses of *APOE*  $\epsilon 4$  and  $\epsilon 2$  alleles. This model showed discriminative performance of AUC = 0.855 in distinguishing between the ADD patients and CU individuals in the J-ADNI cohort (95% CI = 0.808–0.898) (Table 3). This tendency was conserved even when LD effects were adjusted (AUC = 0.853; 95% CI = 0.806–0.897). These predictive performances showed the similar tendencies when evaluated by fivefold CV (Table S4). Taken together, these results showed that the PRS based on European GWAS statistics was useful in discriminating between patients with ADD and CU participants in the Japanese population. Furthermore, the PRS had an effect independent of *APOE* alleles, and their combination improved predictive accuracy.

### The effect of our PRS model is replicated in the independent cohorts

To examine the predictive accuracy of PRS.noAPOE and PRS.adjLD in independent cohorts, we calculated the PRS values for 565 brain donors in the NP cohort (control, 358; case, 207) and 617 participants (CU, 257; ADD, 360) in the NA-ADNI using our PRS models. We note that the samples from the NP cohort received a definitive diagnosis based on

**Table 3** Predictive accuracy of each model

Model	Training cohort		Validation cohort			
	J-ADNI		NP		NA-ADNI	
	AUC	95% CI	AUC	95% CI	AUC	95% CI
PRS and <i>APOE</i> alleles						
<i>APOE</i> $\epsilon 4$	0.693	0.638–0.747	0.691	0.654–0.730	0.701	0.665–0.735
<i>APOE</i> $\epsilon 4 + \epsilon 2$	0.696	0.640–0.751	0.698	0.659–0.737	0.712	0.675–0.750
PRS.noAPOE	0.640	0.576–0.704	0.550	0.500–0.599	0.602	0.559–0.649
PRS.adjLD	0.639	0.574–0.704	0.541	0.493–0.589	0.594	0.552–0.640
PRS.incAPOE	0.706	0.643–0.764	0.628	0.590–0.625	0.679	0.639–0.720
PRS.noAPOE + <i>APOE</i> $\epsilon 4 + \epsilon 2$	0.755	0.695–0.807	0.731	0.686–0.773	0.730	0.692–0.767
PRS.adjLD + <i>APOE</i> $\epsilon 4 + \epsilon 2$	0.748	0.687–0.800	0.728	0.680–0.771	0.731	0.693–0.769
PRS and all covariates						
Age + Sex + (Education) + <i>APOE</i> $\epsilon 4$	0.837	0.788–0.883	0.725	0.681–0.770	0.710	0.670–0.750
Age + Sex + (Education) + <i>APOE</i> $\epsilon 4 + \epsilon 2$	0.838	0.789–0.883	0.723	0.679–0.768	0.706	0.665–0.746
Age + Sex + (Education) + <i>APOE</i> $\epsilon 4 + \epsilon 2$ + PRS.noAPOE	0.855	0.808–0.898	0.737	0.693–0.780	0.722	0.683–0.761
Age + Sex + (Education) + <i>APOE</i> $\epsilon 4 + \epsilon 2$ + PRS.adjLD	0.853	0.806–0.897	0.733	0.690–0.777	0.718	0.678–0.757

**Abbreviations:** Age, age at examination; Education, years of education. Years of education were not provided in the NP cohort

the typical neuropathological hallmarks of AD using autopsy brains. The logistic regression model constructed in the J-ADNI cohort was applied to each cohort to assess discrimination accuracy. The predictive performance of PRS.noAPOE for the NP cohort was lower than that for the J-ADNI cohort (AUC = 0.550 (95% CI = 0.500–0.599) in the PRS.noAPOE; AUC = 0.541 (95% CI = 0.493–0.589) in the PRS.adjLD), but when *APOE* alleles were added, the predictive performance was replicated (AUC = 0.731 (95% CI = 0.686–0.773) in the PRS.noAPOE model; AUC = 0.728 (95% CI = 0.680–0.771) in the PRS.adjLD model) (Table 3).

We also analysed the NA-ADNI cohort to verify the transferability of PRS.noAPOE in different ancestries. In the NA-ADNI cohort, the imputed genotyping data included 130 of the 131 SNPs used in the PRS.noAPOE. The PRS.adjLD model used all 113 SNPs. A similar analysis in the NA-ADNI cohort also showed that the predictive performance of PRS.noAPOE or PRS.adjLD in combination with *APOE* alleles were similar to that of the NP cohort (AUC = 0.730 (95% CI = 0.692–0.767) in the PRS.noAPOE model; AUC = 0.731 (95% CI = 0.693–0.769) in the PRS.adjLD model). These analyses showed the reproducibility of our PRS model in independent cohorts.

#### ADD in the J-ADNI shows the polygenicity related to immune pathway

In order to examine the polygenicity of our PRS, we compared a model including only the PRS.noAPOE with a single-variable model for each of the 131 SNPs comprising the PRS.noAPOE. The single models with individual SNPs showed AUCs of 0.499 to 0.605 (median AUC = 0.515), while the model including only the PRS.noAPOE showed an AUC of 0.640 (95% CI = 0.576–0.704) (Table 3 and S5), suggesting that the PRS.noAPOE reflects a polygenic effect. Here, SNPs with AUCs of less than 0.5 indicate protection rather than risk in our data.

We examined the genes closest to 131 SNPs included in the PRS.noAPOE. We found the 96 closest genes located within  $\pm 100$  kb around the SNPs (Table S6). These genes were associated with leukocyte-mediated immunity (FDR =  $3.78 \times 10^{-5}$ ), haematopoietic cell lineage (FDR =  $4.45 \times 10^{-5}$ ), the amyloid precursor protein (APP) catabolic process (FDR =  $5.16 \times 10^{-5}$ ), regulation of transferase activity (FDR =  $3.57 \times 10^{-4}$ ), and glial cell proliferation (FDR =  $5.60 \times 10^{-3}$ ) (Table S7). The 89 closest genes in the PRS.adjLD also contained basically similar pathways (Tables S6 and S8). Overall, we found that the integrated scores of multiple SNPs around genes mainly

associated with immune pathways may explain the Japanese AD traits.

#### The PRS associates with AD-related phenotypes

To examine whether our PRS associates with clinical characteristics, we next investigated the correlation between the PRS.noAPOE or PRS.adjLD and AD-related phenotypes, namely CSF biomarker data and FDG and PiB PET brain imaging data. We performed linear regression model analyses based on three models controlling for seven covariates: age at baseline examination, sex, years of education, the first two PCs, and the doses of *APOE*  $\epsilon 4$  and  $\epsilon 2$  alleles. Model 1 controlled only age at baseline examination, sex, years of education, and the first two PCs. Models 2 and 3 took into the dose of *APOE*  $\epsilon 4$  allele in addition to Model 1. Model 3 also added the dose of *APOE*  $\epsilon 2$  allele as a full model.

The CSF tTau/A $\beta$ 42 and pTau/A $\beta$ 42 ratios were significantly associated with the PRS.noAPOE and PRS.adjLD values. These associations were basically maintained in all models (FDR < 0.05, Wald test; Table 4a and Fig. 2) and reflected the influences of tTau and pTau levels but not A $\beta$ 42 levels (Table S9).

To investigate the PRS effects to brain atrophy, we first tested the associations between the PRS and the volumes of the entorhinal cortex and hippocampus. Hippocampal volume showed a significant association with the PRSs in Model 1 that did not include *APOE* alleles, but this association did not remain significance after FDR correction ( $p$  value = 0.042 in the PRS.noAPOE,  $p$  value = 0.033 in the PRS.adjLD, Wald test; Table 4b). We investigated whether the PRSs contribute to the discrimination between the normal pattern (N1 pattern) and the AD pattern (P1 pattern) in FDG PET imaging and between negative and positive amyloid scans in PiB PET imaging. As a result, the PRSs were associated only with PiB PET imaging ( $p$  value = 0.024 in the PRS.noAPOE,  $p$  value = 0.030 in the PRS.adjLD, Wald test; Table 4c).

We also investigated the correlations between the PRSs and cognitive functions. The neuropsychological tests, including the ADAS-Cog, CDR-SB, FAQ, and MMSE, were significantly associated in all models (FDR < 0.01, Wald test; Table 4d).

We next stratified the participants into the CU, MCI and ADD groups and examined the association between the PRS.noAPOE or PRS.adjLD and each phenotype. Significant positive correlations between the PRSs and CSF tTau/A $\beta$  and between the PRSs and pTau/A $\beta$ 42 ratios were observed in only the MCI participants (FDR < 0.05, Wald test; Table 4a; Fig. 2). In contrast, these ratios remained stable or reached a plateau relative to the PRSs in the CU and ADD participants (Fig. 2), suggesting that the polygenic burden beyond *APOE* explains some of the



**Table 4** Associations between PRS and AD-related phenotypes

	Model 1 (Age, Sex, Education, PC1, PC2)		Model 2 (Age, Sex, Education, PC1, PC2, APOEε4)		Model 3 (Age, Sex, Education, PC1, PC2, APOEε4, APOEε2)	
	Beta (noAPOE, adjLD)	p value (noAPOE, adjLD)	Beta (noAPOE, adjLD)	p value (noAPOE, adjLD)	Beta (noAPOE, adjLD)	p value (noAPOE, adjLD)
4a CSF biomarker						
All subjects						
tTau/Aβ42	0.167, 0.159	<b>0.017<sup>a</sup>, 0.017<sup>a</sup></b>	0.149, 0.146	0.058, 0.053	0.163, 0.156	<b>0.040<sup>a</sup>, 0.039<sup>a</sup></b>
pTau/Aβ42	0.200, 0.168	<b>0.004<sup>b</sup>, 0.011<sup>b</sup></b>	0.188, 0.154	<b>0.013<sup>a</sup>, 0.033<sup>a</sup></b>	0.189, 0.155	<b>0.013<sup>a</sup>, 0.032<sup>a</sup></b>
CU subjects						
tTau/Aβ42	-0.082, 0.204	0.804, 0.522	-0.050, 0.265	0.888, 0.435	-0.131, 0.194	0.717, 0.579
pTau/Aβ42	-0.143, -0.010	0.488, 0.960	-0.134, 0.014	0.545, 0.948	-0.178, -0.029	0.430, 0.895
MCI subjects						
tTau/Aβ42	0.292, 0.277	<b>0.025<sup>a</sup>, 0.032<sup>a</sup></b>	0.294, 0.290	<b>0.043<sup>a</sup>, 0.043<sup>a</sup></b>	0.295, 0.292	<b>0.044<sup>a</sup>, 0.044<sup>a</sup></b>
pTau/Aβ42	0.363, 0.318	<b>0.004<sup>b</sup>, 0.011<sup>a</sup></b>	0.396, 0.355	<b>0.006<sup>a</sup>, 0.013<sup>a</sup></b>	0.396, 0.357	<b>0.007<sup>a</sup>, 0.014<sup>a</sup></b>
ADD patients						
tTau/Aβ42	-0.054, -0.042	0.665, 0.703	-0.053, -0.043	0.682, 0.703	0.026, 0.006	0.854, 0.959
pTau/Aβ42	0.066, 0.018	0.577, 0.866	0.070, 0.019	0.565, 0.862	0.084, 0.028	0.485, 0.796
4b Brain volume						
All subjects						
Entorhinal	-0.014, -0.024	0.776, 0.622	-0.008, -0.018	0.869, 0.714	-0.010, -0.019	0.836, 0.699
Hippocampus	-0.109, -0.115	<b>0.042, 0.033</b>	-0.101, -0.106	0.087, 0.073	-0.101, -0.106	0.088, 0.073
CU subjects						
Entorhinal	0.032, 0.024	0.512, 0.626	0.033, 0.024	0.509, 0.626	0.036, 0.033	0.495, 0.529
Hippocampus	0.041, -0.010	0.758, 0.943	0.041, -0.010	0.760, 0.942	0.043, -0.016	0.754, 0.908
MCI subjects						
Entorhinal	-0.355, -0.357	0.150, 0.156	-0.335, -0.344	0.180, 0.176	-0.332, -0.341	0.184, 0.180
Hippocampus	-0.064, -0.082	0.505, 0.407	-0.041, -0.071	0.694, 0.505	-0.043, -0.073	0.684, 0.497
ADD patients						
Entorhinal	0.108, -0.078	0.745, 0.811	0.084, -0.089	0.801, 0.788	0.112, -0.070	0.739, 0.832
Hippocampus	-0.043, -0.055	0.755, 0.688	-0.080, -0.072	0.574, 0.609	-0.069, -0.064	0.633, 0.652
4c PET imaging						
All subjects						
FDG (positive)	0.180, 0.193	0.189, 0.149	0.162, 0.174	0.260, 0.218	0.162, 0.172	0.262, 0.224
PiB (positive)	0.386, 0.359	<b>0.024<sup>a</sup>, 0.030</b>	0.446, 0.417	<b>0.025<sup>a</sup>, 0.030</b>	0.442, 0.412	<b>0.027, 0.033</b>
CU subjects						
FDG (positive)	-0.119, -0.070	0.729, 0.839	-0.109, -0.064	0.753, 0.852	-0.109, -0.061	0.755, 0.860
PiB (positive)	0.037, 0.068	0.923, 0.858	0.072, 0.221	0.874, 0.620	0.059, 0.194	0.899, 0.671
MCI subjects						
FDG (positive)	0.020, 0.053	0.942, 0.845	0.038, 0.077	0.892, 0.787	0.040, 0.076	0.888, 0.791
PiB (positive)	0.201, 0.175	0.489, 0.552	0.299, 0.320	0.432, 0.407	0.303, 0.327	0.433, 0.405
ADD patients						
FDG (positive)	-0.395, -0.232	0.357, 0.542	-0.390, -0.232	0.366, 0.545	-0.352, -0.195	0.417, 0.611
PiB (positive)	-0.716, -0.777	0.313, 0.196	-0.747, -0.935	0.314, 0.133	-0.716, -0.915	0.338, 0.146
4d Neuropsychological test						
All subjects						
ADAS	0.171, 0.127	<b>0.001<sup>b</sup>, 0.008<sup>b</sup></b>	0.163, 0.117	<b>0.002<sup>b</sup>, 0.019<sup>a</sup></b>	0.164, 0.116	<b>0.002<sup>b</sup>, 0.019<sup>a</sup></b>
CDRSB	0.188, 0.167	<b>6.29 × 10<sup>-5b</sup>, 0.001<sup>b</sup></b>	0.182, 0.160	<b>1.78 × 10<sup>-4b</sup>, 0.003<sup>b</sup></b>	0.182, 0.160	<b>1.84 × 10<sup>-4b</sup>, 0.003<sup>b</sup></b>
FAQ	0.166, 0.168	<b>3.93 × 10<sup>-4b</sup>, 3.58 × 10<sup>-4b</sup></b>	0.159, 0.161	<b>0.001<sup>b</sup>, 0.001<sup>b</sup></b>	0.159, 0.161	<b>0.001<sup>b</sup>, 0.001<sup>b</sup></b>

**Table 4** (continued)

	Model 1 (Age, Sex, Education, PC1, PC2)		Model 2 (Age, Sex, Education, PC1, PC2, APOEε4)		Model 3 (Age, Sex, Education, PC1, PC2, APOEε4, APOEε2)	
	Beta (noAPOE, adjLD)	p value (noAPOE, adjLD)	Beta (noAPOE, adjLD)	p value (noAPOE, adjLD)	Beta (noAPOE, adjLD)	p value (noAPOE, adjLD)
MMSE	-0.160, -0.149	<b>0.001<sup>b</sup>, 0.002<sup>b</sup></b>	-0.152, -0.141	<b>0.002<sup>b</sup>, 0.005<sup>b</sup></b>	-0.152, -0.141	<b>0.002<sup>b</sup>, 0.005<sup>b</sup></b>
CU subjects						
ADAS	-0.118, 0.045	0.592, 0.837	-0.119, 0.045	0.591, 0.837	-0.111, 0.057	0.617, 0.795
CDRSB	-1.178, -0.835	0.152, 0.305	-1.208, -0.883	0.152, 0.290	-1.217, -0.896	0.150, 0.284
FAQ	0.291, 0.359	0.473, 0.368	0.294, 0.359	0.470, 0.369	0.287, 0.349	0.483, 0.385
MMSE	-0.153, -0.228	0.454, 0.258	-0.153, -0.229	0.459, 0.258	-0.140, -0.212	0.503, 0.303
MCI subjects						
ADAS	0.194, 0.193	0.098, 0.107	0.176, 0.185	0.147, 0.136	0.182, 0.192	0.133, 0.123
CDRSB	0.146, 0.162	0.289, 0.251	0.144, 0.160	0.297, 0.256	0.149, 0.166	0.280, 0.241
FAQ	0.119, 0.145	0.239, 0.161	0.121, 0.146	0.233, 0.159	0.118, 0.143	0.246, 0.168
MMSE	-0.065, -0.062	0.604, 0.626	-0.055, -0.056	0.661, 0.664	-0.045, -0.046	0.720, 0.722
ADD patients						
ADAS	-0.048, -0.026	0.719, 0.844	-0.057, -0.029	0.671, 0.824	-0.057, -0.029	0.672, 0.826
CDRSB	0.102, 0.063	0.290, 0.501	0.109, 0.066	0.260, 0.485	0.097, 0.060	0.318, 0.528
FAQ	0.078, 0.056	0.327, 0.472	0.093, 0.062	0.248, 0.430	0.088, 0.060	0.275, 0.450
MMSE	0.036, 0.045	0.794, 0.734	0.031, 0.044	0.823, 0.746	0.033, 0.045	0.810, 0.740

β estimates and p value were calculated by a linear regression model. P value was corrected in each subject group. Statistically significance was highlighted in bold

<sup>a</sup> FDR < 0.05

<sup>b</sup> FDR < 0.01

heterogeneity in MCI, especially in terms of tau-related biomarker.

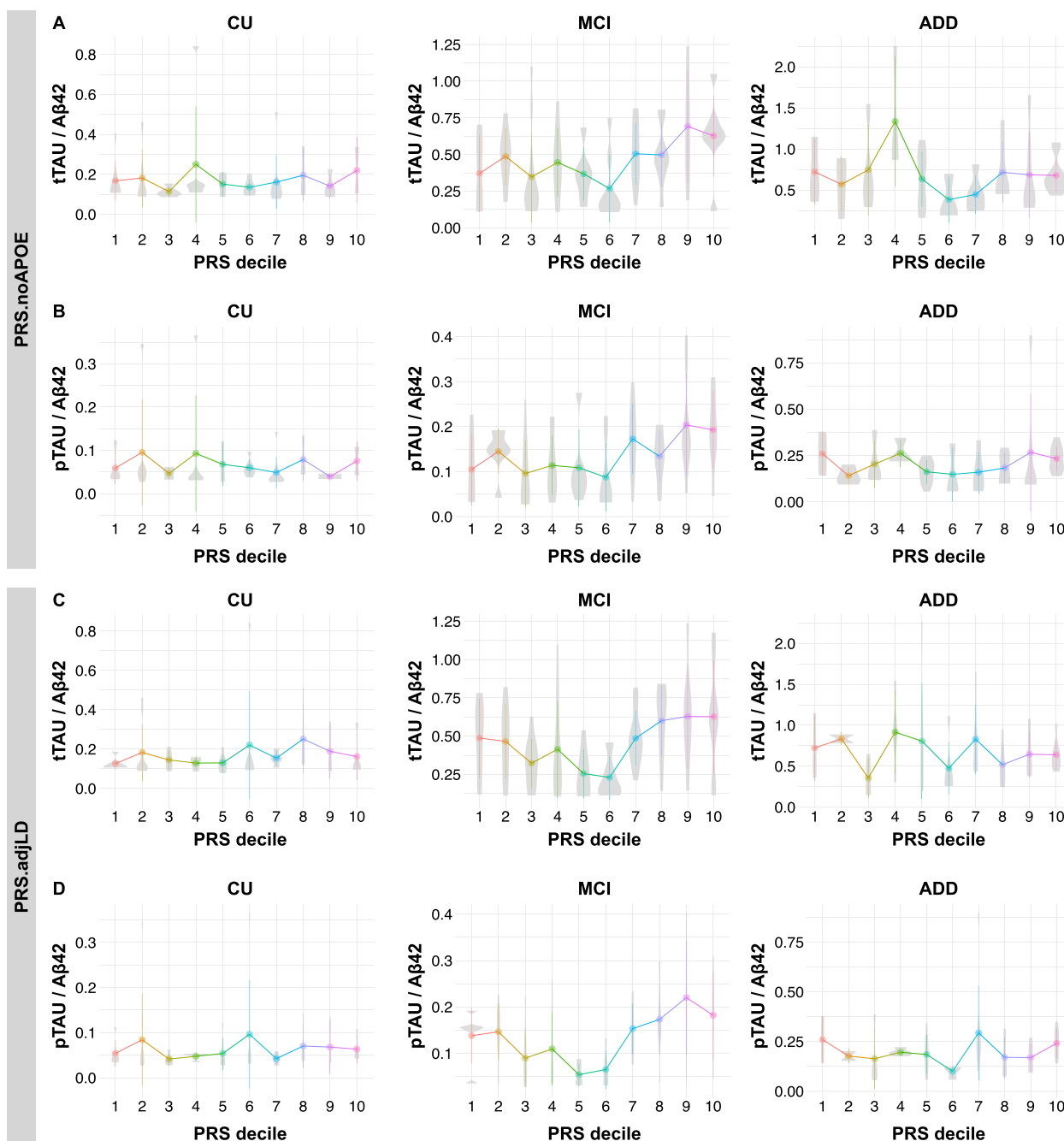
#### APOE ε4 non-carriers with high PRS are at high risk of AD conversion

Finally, we examined difference in conversion to AD in the participants with MCI stratified by PRS. We divided MCI participants into three groups based on the PRS.noAPOE or PRS.adjLD distribution of all participants. We compared the conversion to AD of MCI participants in the 1st tertile, referred to as the low-PRS group, and of MCI participants in the 3rd tertile, noted as the high-PRS group. We performed Cox proportional hazard model analysis controlling seven covariates: age at baseline examination, sex, years of education, the first two PCs, and the doses of APOE ε4 and ε2 alleles. We did not find significantly different conversion patterns between the high- and low-PRS groups ( $p$  value = 0.202 in the PRS.noAPOE,  $p$  value = 0.236 in the PRS.adjLD, log-rank test; Table 5a and Fig. 3).

When we examined the contribution of each variable, we found that the dose of the APOE ε4 allele significantly affected the conversion to AD (HR = 1.604, 95% CI = 1.153–2.230, and  $p$  value = 0.005 in the PRS.noAPOE; HR = 1.560, 95% CI = 1.102–2.209, and  $p$  value = 0.012 in the PRS.adjLD, Wald test; Table 5a),

suggesting that this difference in conversion between the two PRS groups was influenced by the APOE ε4 allele dose. Therefore, we stratified MCI participants into those with and without APOE ε4. In that analysis, we found that in the PRS.noAPOE, among MCI participants without APOE ε4, the high-PRS group showed a significantly higher conversion to AD than the low-PRS group ( $p$  value = 0.031, log-rank test; Table 5a and Fig. 3A). Moreover, the PRS.noAPOE significantly contributed to the difference in AD conversion between the two groups (HR = 2.216; 95% CI = 1.058–4.643;  $p$  value = 0.035, Wald test; Table 5a). We also found no difference in AD conversion among MCI participants with APOE ε4 ( $p$  value = 0.292, log-rank test; Table 5a and Fig. 3A). In the PRS.adjLD, no significance was observed (Table 5b and Fig. 3B). These results suggested that polygenic effects increase the risk of AD conversion, particularly in MCI subjects without APOE ε4.

On the other hand, in APOE ε4 carriers, a single factor, namely, APOE ε4, may explain much of the AD conversion risk. As expected, there was no significant difference between the APOE ε4 noncarrier group with high-PRS and the APOE ε4 carrier group ( $p$  value = 0.595 in the PRS.noAPOE,  $p$  value = 0.345 in the PRS.adjLD, log-rank test; Figure S4). Although age differences between the groups compared in the above analysis could have



**Fig. 2** The PRS.noAPOE and PRS.adjLD correlated with CSF Tau/Aβ42 ratios in the MCI. CSF tTau/Aβ42 (A, C) and pTau/Aβ42 (B, D) ratios by decile of PRS are shown in each diagnostic group. The participants were divided into ten groups based on the PRS.noAPOE, ranging from the lowest group (1st decile) to the highest group (10th decile). CN = cognitively normal; MCI = mild cognitive impairment; ADD = Alzheimer's disease dementia

affected the results, there were no differences in age at baseline examination between the low- and high-PRS groups or between the converted and nonconverted participants ( $p$  value > 0.05, Wilcoxon rank-sum test; Figure S5). These results suggest that the PRS contributes to the conversion to AD in participants without APOE ε4.

### Discussion

In this study, we evaluated the utility of the PRS for AD in a Japanese cohort. The results showed that the PRS had an effect independent of APOE and showed relatively high predictive accuracy when combined with APOE ε4. In addition, this effect was replicated in the

**Table 5** Polygenic risk of conversion of MCI to AD

5a PRS.noAPOE									
	All MCI subjects			MCI subjects without <i>APOE</i> ε4			MCI subjects with <i>APOE</i> ε4		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
PRS (High group)	1.301	0.847–1.998	0.230	2.216	1.058–4.643	<b>0.035</b>	0.985	0.770–1.259	0.902
Age	1.070	0.846–1.353	0.574	1.069	0.725–1.578	0.736	0.961	0.687–1.344	0.816
Sex (Male)	0.858	0.532–1.383	0.529	0.589	0.257–1.353	0.212	0.983	0.539–1.793	0.956
Education year	0.791	0.605–1.035	0.087	0.745	0.452–1.229	0.249	0.856	0.610–1.202	0.37
PC1	0.939	0.769–1.146	0.534	0.769	0.541–1.093	0.143	1.034	0.795–1.343	0.806
PC2	0.954	0.753–1.209	0.697	1.028	0.713–1.481	0.884	0.900	0.647–1.251	0.529
<i>APOE</i> ε4 alleles	1.604	1.153–2.230	<b>0.005</b>	NA	NA	NA	1.108	0.516–2.382	0.793
<i>APOE</i> ε2 alleles	1.447	0.440–4.755	0.543	1.665	0.492–5.635	0.412	NA	NA	NA
Log-rank test (high vs low PRS)			0.202			<b>0.031</b>			0.292
5b PRS.adjLD									
	All MCI subjects			MCI subjects without <i>APOE</i> ε4			MCI subjects with <i>APOE</i> ε4		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
PRS (High group)	1.161	0.752–1.792	0.500	1.547	0.727–3.296	0.258	1.030	0.812–1.305	0.809
Age	1.137	0.902–1.433	0.278	1.251	0.819–1.912	0.301	1.011	0.742–1.379	0.943
Sex (Male)	0.736	0.445–1.219	0.234	0.571	0.234–1.394	0.219	0.808	0.425–1.538	0.516
Education year	0.927	0.714–1.205	0.573	0.873	0.531–1.435	0.592	0.962	0.689–1.344	0.821
PC1	0.909	0.738–1.119	0.368	0.682	0.460–1.011	0.057	1.042	0.801–1.355	0.758
PC2	0.927	0.733–1.173	0.529	1.006	0.697–1.452	0.975	0.910	0.663–1.249	0.558
<i>APOE</i> ε4 alleles	1.560	1.102–2.209	<b>0.012</b>	NA	NA	NA	1.201	0.543–2.658	0.651
<i>APOE</i> ε2 alleles	0.708	0.169–2.965	0.636	0.709	0.163–3.085	0.647	NA	NA	NA
Log-rank test (high vs low PRS)			0.236			0.174			0.650

**Abbreviations:** HR Hazard ratio, 95% CI 95% confidence interval, *APOE* apolipoprotein E

Cox proportional hazard model: Conversion/follow-up = PRS (Low = 0, High = 1) + Age + Sex (Female = 0, Male = 1) + Education year + PC1 + PC2 + *APOE* ε4 alleles + *APOE* ε2 alleles

HR, 95% CI, and *p*-value were calculated by a Cox proportional hazard model controlling age at examination, sex, education years, the first two PCs, and the doses of *APOE* ε4 and ε2 alleles. Statistically significant was highlighted in bold

cohort with a neuropathological diagnosis and the protocol-harmonized independent NA-ADNI cohort. The PRS was significantly associated with CSF tau levels in MCI participants, and MCI with a high PRS was associated with an elevated risk of AD conversion in *APOE* ε4 noncarriers.

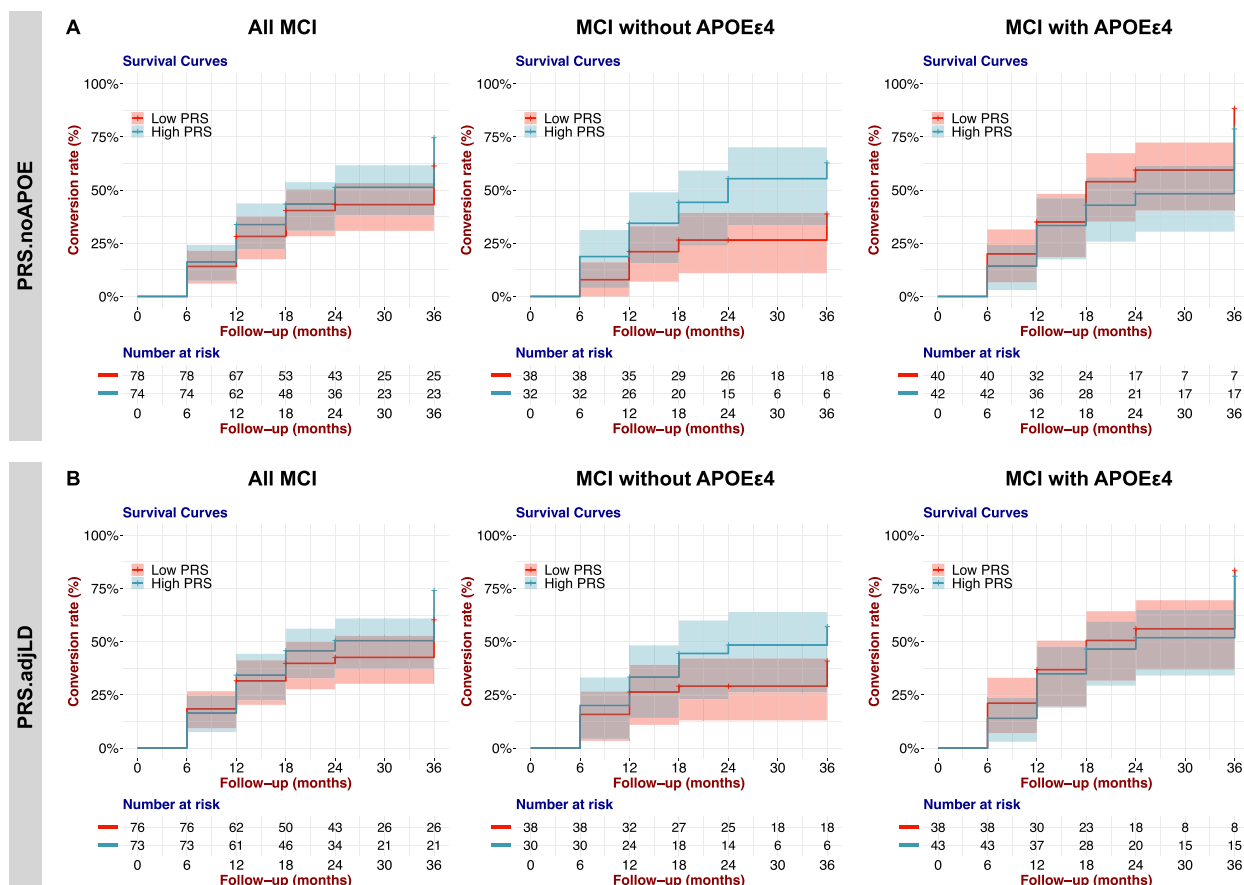
Despite the difference in genetic structure between the European and Japanese populations [39], the PRS developed in this study, PRS.noAPOE, showed meaningful predictive accuracy. We also developed PRS.adjLD, which avoids overfitting due to differences between European and Japanese LD blocks, and showed that PRS.adjLD had similar accuracy. Such predictive accuracy may be achieved because all participants were diagnosed according to unified inclusion and exclusion criteria and harmonized standardized diagnostic criteria using the same neuropsychological tests (MMSE, CDR-SB, and Wechsler Memory Scale Logical Memory II). The optimal *p* value threshold for the PRS excluding the *APOE* region was also similar to that reported in previous studies,  $p_T < 1 \times 10^{-5}$  [5, 10, 40]. Moreover, while dozens of

SNPs were incorporated into these previous PRSs, 131 or 113 SNPs were included to calculate the PRS in our study. This difference in the number of SNPs is likely due to differences in genetic structure such as LD blocks. Hence, even if there are ancestral differences, adding a few dozen SNPs may preserve accuracy.

We also examined potential overfitting due to differences in LD between European and Japanese populations, which may cause a small reduction in predictive accuracy. On the other hand, it is possible that SNPs in the same LD in Japanese are independent (i.e. linkage equilibrium) in European population. In this case, underfitting may occur and the actual predictive accuracy may be underestimated. To solve this issue, a larger AD GWAS data derived from Japanese population will be needed, and this warrants further investigation.

There is no consensus on the number of SNPs that should be included in the AD PRS. According to a systematic review of PRS studies in AD, PRSs of AD can be organized into two groups: PRSs containing relatively large numbers of SNPs, ranging from 4431 to 359,500,





**Fig. 3** The high-PRS group was more likely to convert to AD than the low-PRS group in the APOE ε4 non-carrier individuals with MCI. Kaplan–Meier survival curves for conversion rates of MCI to AD in the low-PRS group (1st tertile) and the high-PRS group (3rd tertile). The shaded area represents the 95% confidence interval

and PRSs containing relatively small numbers, ranging from 5 to 31 [41]. The latter group is referred to as the oligogenic effect, in contrast to the polygenic effect [42]. From this perspective, our PRS apparently represents an oligogenic effect. Notably, a relatively small number of SNPs has the advantage of providing an inexpensive gene panel. In addition, a PRS composed of many SNPs may be sensitive to geographic differences in genetic structure, whereas a PRS composed of a few dozen SNPs is robust to population bias [43, 44]. However, we should note that our PRS may reflect ancestral differences due to the use of European GWAS statistics. In the future, more robust polygenic effects could be verified by using GWAS statistics for large groups of East Asians, including Japanese individuals.

In our study, the genes contributing to the PRS.noAPOE or PRS.adjLD were associated with APP degradation, immunity, and glial cell proliferation. Genetic variants found in a recent AD GWAS were associated with the APP catabolic process and tau protein binding

[45]. In addition, many of the genes affected by their genetic variants are expressed in microglia [45]. An analysis of cognitively healthy centenarians in addition to ADD patients and healthy controls revealed that the PRS associated with the immune system was lower in the centenarian group independent of APOE ε4, indicating that immune system function is involved in AD resistance [46]. Therefore, our results suggest that common factors related to AD may be shared in the vulnerability of clearance mechanisms and neuroimmune surveillance in the brain among different population.

In our study, the PRS.noAPOE and PRS.adjLD showed significant correlations with CSF tTau/Aβ42 and pTau/Aβ42 ratios only in individuals with MCI. Tau but not Aβ42 strongly influenced this result even controlling APOE effect. CU and AD are relatively homogeneous in terms of AD-related biomarker changes. However, MCI is a heterogeneous condition, in which CSF biomarkers are highly variable with dynamic changes. Because of this variation in CSF biomarkers, significant correlations

with PRS were observed in MCI group. Interestingly, NA-ADNI studies have shown that the PRS is associated beyond *APOE* with CSF tau but not CSF A $\beta$ 42 [44, 47]. From the above, independent studies in different ancestry groups have confirmed that polygenic effects are associated with tau-related biomarkers, especially in individuals with MCI.

Although our results are noteworthy, we must approach the clinical application of our PRS with caution at this stage because the predictive accuracy of our PRS alone is not very high. Similar to currently available PRSs, few biomarkers can perfectly distinguish disease or not; most markers bear some uncertainty. AD and MCI are explained not only by genetic aspects such as PRS, but also by anatomic aspects such as MRI and PET imaging and biological aspects such as CSF biomarkers [48], suggesting that combining multiple biomarkers could compensate for each other's weaknesses in predictive performance. PRS will allow individuals' disease risk to be assessed at a relatively early stage, leading to future lifestyle modification and disease prevention.

There were several limitations to this study. First, the CU participants included in the J-ADNI were relatively young. We acknowledge that these CU participants include potential patients who will develop AD in the future. Considering the average age of onset of AD and the allele frequency of *APOE*  $\epsilon$ 4 in the Japanese population, future work should ideally include CU participants that are over 70 years old [49]. Second, because the number of participants available for the study was small, there was limited power to identify relationships between the PRS and some phenotypes. Larger studies are needed to validate the results of this study. Therefore, combining samples from multiple East Asian cohorts, including cohorts from Japan, is necessary for analysis.

## Conclusion

This study demonstrated that the AD PRS showed a relatively high performance in the Japanese population, despite differences in genetic structure from the European population. Furthermore, this PRS was replicated in the independent Japanese and European cohorts. The AD PRS correlated with phenotypes such as CSF tau levels in MCI. The AD PRS predicted the development of AD in MCI participants without *APOE*  $\epsilon$ 4. The application of the PRS will allow us to know an individuals' disease risk at a relatively early life stage, which may lead to future lifestyle modification and disease prevention.

## Abbreviations

PRS	Polygenic risk score
AD	Alzheimer's disease
J-ADNI	Japanese Alzheimer's Disease Neuroimaging Initiative

<i>APOE</i>	Apolipoprotein E
A $\beta$	Amyloid-beta
MCI	Mild cognitive impairment
GWAS	Genome-wide association study
MRI	Magnetic resonance imaging
CU	Cognitively unimpaired
ADD	Alzheimer's disease dementia
NA-ADNI	North American Alzheimer's Disease Neuroimaging Initiative
C + T	Clumping and thresholding
AUC	Area under the receiver operator characteristic curve
MDS	Multidimensional scaling
CSF	Cerebrospinal fluid
tTau	Total tau
pTau	Phosphorylated tau
PET	Positron emission tomography
FDG	<sup>18</sup> F-2-fluoro-2-deoxy-D-glucose
PIB	<sup>11</sup> C-Pittsburgh compound B
MMSE	Mini-Mental State Examination
FAQ	Functional Assessment Questionnaire
CDR	Clinical Dementia Rating
CDR-SB	CDR-Sum of Boxes
ADAS-Cog	AD Assessment Scale-Cognitive Subscale
FDR	False discovery rate
HR	Hazard ratio
CI	Confidence interval

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13195-024-01414-x>.

**Additional file 1: Figure S1.** The excluded region around the *APOE* gene. We removed the *APOE* region, consisting of  $\pm$ 500 kb, from around the top-hit SNP rs1160985 (chr19:45403412) in our data. Each data point indicates GWAS *p* values from Jansen *et al.* [32] used as SNP weights in the PRS calculation. **Figure S2.** Associations between the PRS and covariates. Age at baseline examination and years of education were examined by Spearman correlation. Sex and doses of *APOE*  $\epsilon$ 4 and  $\epsilon$ 2 alleles were analysed by *t* tests or ANOVAs. CN = cognitively normal; MCI = mild cognitive impairment; ADD = Alzheimer's disease dementia. **Figure S3.** Associations between the PRS.adjLD and covariates. Age at examination and years of education were examined by Spearman correlations. Sex and dose of *APOE*  $\epsilon$ 4 and  $\epsilon$ 2 alleles were analysed by *t* tests or ANOVAs. **Figure S4.** Comparison of AD conversion between the *APOE*  $\epsilon$ 4 carriers and the *APOE*  $\epsilon$ 4 noncarriers with high PRS. Kaplan-Meier survival curves for conversion rates of MCI to AD in the *APOE*  $\epsilon$ 4 carriers and the *APOE*  $\epsilon$ 4 noncarriers with high PRS values. *p*-values were calculated by log-rank test. **Figure S5.** Age differences between the low- and high-PRS groups and between the nonconverters and converters. Baseline ages were compared between groups using the Wilcoxon rank-sum test. Each violin plot includes the kernel probability density of the data at different values and the box plots with the median value and the interquartile range.

### Additional file 2.

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are available at the website of the NBDC Human Database/the Japan Science and Technology Agency (JST).

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#### Authors' contributions

MK: Study design, analysis and interpretation of data, and manuscript draft. AM and NH: Genotyping analysis, interpretation of data, and manuscript revision. YS, SM, AK, HA: Provision of autopsy brains and manuscript revision. KK, KO, SN, RK, Tiwatsubo, and AN: Interpretation of data and manuscript revision. Tikeuchi: Study design, interpretation of data, and manuscript draft. All authors read and approved the final manuscript.

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#### Availability of data and materials

All the J-ADNI data except for the genome data and the reference genome data were obtained from the NBDC Human Database/the Japan Science and Technology Agency (JST) (<https://humandbs.biosciencedbc.jp/en/hum0043-v1>), (<https://humandbs.biosciencedbc.jp/en/hum0014-latest#JGAS000114rp>). GWAS statistics were obtained from the Center for Neurogenomics and

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The data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) ([adni.loni.usc.edu](http://adni.loni.usc.edu)). Thus, the investigators within the ADNI contributed to the design and implementation of the ADNI and/or provided data but did not participate in the analysis or the writing of this report. A complete listing of ADNI investigators can be found at [http://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf).

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#### Declarations

##### Ethics approval and consent to participate

This study was approved by the ethics committees of the University of Tokyo, Osaka University and Niigata University. For both ADNI and J-ADNI, ethics approval was obtained from the review boards of the participating institutions. Informed consent was obtained from every participant prior to enrolment.

##### Consent for publication

Consent for publication has been granted by J-ADNI administrators.

##### Competing interests

The authors declare no competing interests.

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