Neurobiology of Aging 114 (2022) 27–37

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

Regular Article

Ethnic differences in the frequency of β-amyloid deposition in cognitively normal individuals

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ARTICLE INFO

Article history:
Received 4 April 2021
Revised 24 February 2022
Accepted 1 March 2022
Available online 7 March 2022

Keywords:
Alzheimer's disease
Cognitively normal
Genome-wide association study analyses
Ethnic differences

ABSTRACT

We investigated which factors might explain the differences between the frequencies of brain β-amyloid (Aβ) deposition in Korean and European cognitively normal individuals (CNs). We recruited 434 Korean CNs from the Samsung Medical Center (SMC) and 323 European CNs from the US Alzheimer's Disease Neuroimaging Initiative (ADNI). The Korean CNs showed lower education duration (11.8 $\pm$ 4.8 years vs. 16.8 $\pm$ 2.5 years, $p < 0.001$) than the European CNs. The frequency of Aβ (+) was higher in the European CNs (32.8%) than in the Korean CNs (20.0%; $p < 0.001$). In the SMC genome-wide association study (GWAS), 10 variants (including rs7481773 on chromosome 11, located near the brain-derived neurotrophic factor gene) exceeded the genome-wide significance level ($p < 5 \times 10^{-8}$). Especially, rs7481773 carriers showed more rapid decline in memory function than non–carriers ($p = 0.048$). However, this association was not observed in the ADNI GWAS. Our findings suggested that the different frequencies of Aβ (+) between CN Koreans and Europeans might be related to decreased cognitive reserve or genetic factors.

1. Introduction

Cerebral β-amyloid (Aβ) deposition is the earliest recognizable pathologic change in Alzheimer's disease (AD) (Bateman et al., 2012). In particular, the prevalence estimates of Aβ pathology and their related factors in cognitively normal (CN) individuals are required to understand the disease progression of AD and to design AD studies (Jansen et al., 2015).

The risk of AD dementia is substantially driven by cultural and genetic factors (Kunkle et al., 2019). Several factors related to cognitive reserve, including education (Stern et al., 2020) and socioeconomic status in childhood, may affect the development of dementia. The apolipoprotein E (*APOE*) ε4 allele is an important risk factor for the development of AD dementia. A recent genome-wide association study (GWAS) reported over 20 genetic loci that were associated with the development of AD (Jansen et al., 2019). Furthermore, specific genetic variants have exhibited different associations with AD in Europeans drawn from the US and other countries and Asians drawn from several countries in Asia (Han et al.,

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https://doi.org/10.1016/j.neurobiolaging.2022.03.001

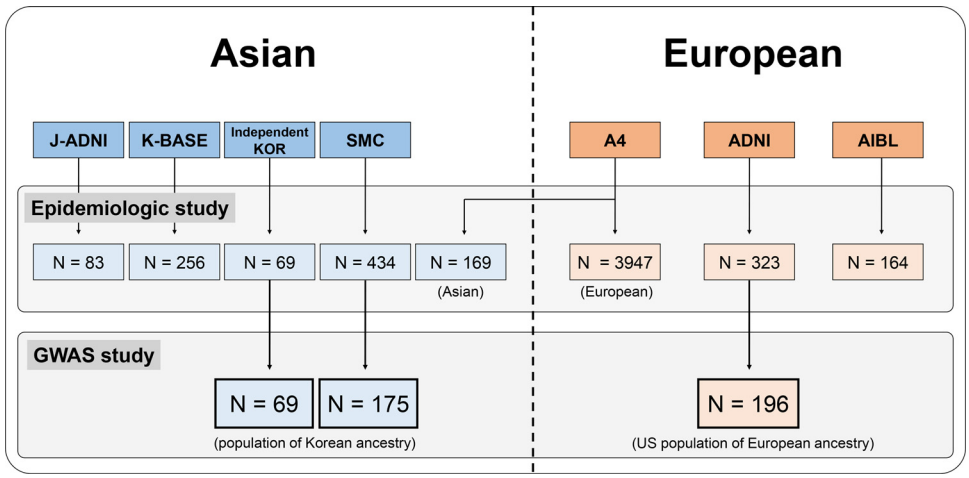

Fig. 1. Flow diagram showing the participants included in the study. Abbreviations: SMC, Samsung medical center; ADNI, Alzheimer's disease neuroimaging initiative; GWAS, genome-wide association study; KOR, Korean; US, United States.

2018; Han et al., 2019). Thus, it would be reasonable to expect genetic variants to exhibit associations with Aβ in specific populations, resulting differences in Aβ positivity among ethnic groups. In fact, differences have been observed in the frequency of amyloid positivity in CN across different populations despite including a relatively small number of non–European participants, including Asian individuals (Sperling et al., 2020).

In the present study, we compared the frequency of Aβ (+) in CN populations between a Korean, and a European cohort based on the Alzheimer's Disease Neuroimaging Initiative (ADNI). We investigated which factors, including age, sex, education level, and genetics, contributed to the difference in the frequency of Aβ (+) in CN populations between these 2 ethnically different cohorts.

2. Methods

2.1. Participants

A total of 494 CN individuals were recruited at the Samsung Medical Center (SMC), Seoul, Korea from September 2015 to December 2018. The data of normal controls recruited from our memory clinic were obtained to undergo comparisons with those of AD patients, including those of their CN spouses. Several participants complained of memory impairments but exhibited no abnormalities in their objective cognitive test results. All participants had to meet the ADNI CN criteria to be diagnosed as CN (http://adni.loni.usc.edu/methods/documents/) (Hahn et al., 2020; Kang et al., 2019): (1) Korean version of Mini-Mental State Examination score between 24 and 30 or greater than -1.5 standard deviations (SD) from the age-, sex-, and education-adjusted norms for those with fewer than 6 years of education; (2) greater than -1.0 SD from the age-, sex-, and education-adjusted norms on the Seoul Verbal Learning Test-Elderly's version for delayed recall; (3) absence of significant impairment in cognitive functions and greater than -2.0 SD from the age-, sex-, and education-adjusted norms on the Korean version of the Boston Naming Test, the Korean-Color Word Stroop test for color reading, and the Rey-Osterrieth Complex Figure Test copy; and (4) no history of other neurologic disorders. The screening was conducted by trained clinicians and clinical neuropsychologists. We excluded 46 participants younger than 55 years to match the age range of the sample with that of the ADNI data (Fig. 1).

The US population of European ancestry (European participants) comprised 383 CN individuals who were recruited from phases 2 and 3 of the ADNI. The complete inclusion and exclusion criteria are described in detail at http://adni.loni.usc.edu/methods/documents/. We excluded 60 participants of Hispanic and/or Latino, American Indian and/or Alaskan, Asian, or African American origin.

For the replication dataset, we analyzed the data from 69 CN individuals, including 25 CN individuals recruited from March to September 2020 at the SMC and 44 CN individuals of Korean ancestry recruited from the biobank of the Chronic Cerebrovascular Disease consortium from 2016 to 2018. The 2 cohorts used the same criteria to diagnose CN and the same standard of protocol suggested by the Korea National Institute of Health to recruit blood samples and extract DNA.

2.2. Standard protocol approvals, registration, and patient consents

All protocols were approved by the Institutional Review Board of each participating institution, and participants provided written informed consent at the time of enrollment. The authors obtained approval from the ADNI Data Sharing and Publications Committee for data use and publication.

2.3. Amyloid PET data acquisition and analysis

A total of 434 CN participants underwent ^{18}F-labeled amyloid PET: 227 ^{18}F-florbetaben (FBB) PET and 207 ^{18}F-flutemetamol (FMM) PET scan at the SMC. Scanning was performed using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI) in 3-dimensional scanning mode that examined 47 slices of 3.3 mm thickness spanning the entire brain, and 311.5 MBq FBB and 197.7 MBq FMM were injected prior to a 20-minutes emission PET scan using dynamic mode (consisting of 4 $\times$ 5 minutes frames).(Hahn et al., 2020) PET was performed 90 minutes after the injection. Three-dimensional PET images were reconstructed in a 128 $\times$ 128 $\times$ 48 matrix with a 2 $\times$ 2 $\times$ 3.27-mm voxel size using the ordered-subsets expectation maximization algorithm (^{18}FBB, iteration = 4 and subset = 20; ^{18}FMM, iteration = 4 and subset = 20) (Kim et al., 2021).

Participants were divided into Aβ-positive or negative groups using the Centiloid method for ^{18}F-florbetaben and ^{18}F-flutemetamol PET (Cho et al., 2020). The Centiloid cutoff was established by the value of low group 90th percentile Centiloid score derived from K-means clustering analysis in 527 participants

(Mormino et al., 2012). The optimal Centiloid cutoff value was set at 27.08.

PET images were co-registered to each participant's MR image, which were normalized to a T1-weighted MNI-152 template using SPM8 in Matlab 2014b (Mathworks, Natick, MA). We used cerebellar gray for FBB and pons for FMM as regions of interest to reference the uptake ratio (which is identical to the standardized uptake value ratio [SUVR]) using each reference region mask (Klunk et al., 2015). After standard space registration, we divided the gray matter into 116 regions using the Automated Anatomic Labeling atlas (Tzourio-Mazoyer et al., 2002). The global cerebral cortex amyloid retention ratios were assessed from the volume-weighted average SUVRs of 28 bilateral cerebral cortical volumes-of-interest (VOIs) (Jang et al., 2019). The cerebral cortical VOIs chosen for this study consisted of the following regions: bilateral frontal (superior and middle frontal gyri; medial part of the superior frontal gyrus; opercular part of the inferior frontal gyrus; triangular part of the inferior frontal gyrus; supplementary motor area; orbital part of the superior, middle, and inferior orbital frontal gyri; and rectus and olfactory cortex), posterior cingulate gyri, parietal (superior parietal, inferior parietal, supramarginal, and angular gyri, and precuneus), lateral temporal (superior, middle, and inferior temporal gyri, and Heschl's gyri), and occipital (superior, middle, and inferior occipital gyri; cuneus; calcarine fissure; and lingual and fusiform gyri).

When SUVR positivity was classified based on the SUVR cutoff value as calculated using the iterative outlier approach in different samples consisting of CN participants older than 55 years (Mormino et al., 2012), both the FBB and FMM showed high concordance rates between visual assessment and SUVR cutoff categorization for Aβ deposition (93.5% in FBB and 91.6% in FMM). From the ADNI dataset, we included CN participants who underwent 3.0T MRI scanning and ^{18}F-AV45 amyloid-PET (AV45, ADNI-2/3). The AV45 PET scans had previously been acquired using Siemens, GE, and Philips PET scanners according to a standard dynamic 50–70-minutes protocol following the intravenous injection of 370 $\pm$ 37 MBq of ^{18}F-AV45 amyloid-PET. Three-dimensional PET images were reoriented in a 160 $\times$ 160 $\times$ 96 matrix with 1.5 mm cubic voxels. We defined Aβ positivity as SUVR $>$1.11 (Landau et al., 2013).

2.4. Genetic analysis

A total of 179 Koreans were genotyped using the Illumina Asian Screening Array and 218 Europeans were genotyped using Illumina GWAS arrays (610-Quad, OmniExpress, or HumanOmni2.5-4v1) in the ADNI phase 2 and 3 datasets. We conducted an identical genotype quality control (QC) using PLINK 1.9 to eliminate any systematic errors that could lead to spurious associations and aligned genetic variants in each dataset to the GRCh37/hg19 assembly. We excluded samples with call rate less than 95%, sex mismatch, excess of heterozygosity ($\pm$5 SDs from the mean), or deviations from each population parameter, and excluded SNPs with call rate less than 98%, minor allele frequency (MAF) $<$1%, or genotype frequencies significantly deviated from Hardy-Weinberg equilibrium with $p < 10^{-6}$. Genome-wide imputation was performed in each dataset using Minimac4 software with all available reference haplotypes from HRC-r1.1 on the University of Michigan Imputation Server. Additionally, we performed post-imputation QC with a MAF $>$1% and high imputation quality with $r^2 > 0.8$ for imputed SNPs. After QC, 4,906,407 SNPs and 175 samples remained available for genetic association analyses in the SMC dataset and 7,117,161 SNPs and 196 samples remained in the ADNI dataset. To verify appropriate control for population structure, principal components (PCs) of ancestry were derived by EIGENSTRAT (Price et al., 2006) and used as covariates in regression analyses. We also conducted principal component analysis (PCA) for the 1000 Genomes Project samples and projected the SMC and ADNI samples to the PCA plot to confirm the ancestral distinction.

2.5. Hippocampal volume measurement

To measure the hippocampal volume (HV), we used an automated hippocampus segmentation method using a graph-cut algorithm combined with an atlas-based segmentation and morphologic opening, as described in an earlier study (Kwak et al., 2013). To control for the brain size, we used the intracranial volume (ICV), using classified brain tissue information and a skull mask acquired from the T1-weighted image (Smith, 2002).

2.6. Statistical analysis

To compare the demographic and clinical data, a 2-sample t-test was used for continuous variables and a χ^2 test was used for categorical variables. To estimate the frequency of Aβ (+) according to age and *APOE* genotype in the SMC and ADNI groups, estimated probabilities and 95% confidence intervals (CIs) were generated from logistic regression analyses after adjusting for age (continuous), sex, education years, and *APOE* genotype.

We conducted a GWAS using a linear regression model with age, sex, education years, and the first 4 PCs of ancestry as covariates. To account for the non–normal distribution of each amyloid PET level and to ensure the robustness of our results, rank-based inverse normal transformation was applied to each amyloid PET level (FBB, FMM, and AV45). An inverse variance-weighted fixed-effects meta-analysis of the 2 sets of SMC Amyloid PET GWAS (FBB and FMM) results was performed using METAL (Willer et al., 2010).

We conducted a linear model analysis in each population to assess whether rs7481773, which was the most significant variant near the brain-derived neurotrophic factor (*BDNF*) gene in our GWAS, had a different effect on Aβ deposition between Koreans, and Europeans. The association between the rs7481773 allele carrier status and Aβ deposition was evaluated with a linear regression model including the study group (SMC or ADNI), age, sex, education years, *APOE* ε*4* carrier status (coded as 1 and 0 for carriers and non–carriers, respectively), rs7481773 carrier status, and study group $\times$ rs7481773 interaction term as covariates.

As a sensitivity analysis, we performed regression analyses in subgroups of *APOE* ε3 homozygote carriers or elderly participants (age $>$70 years) to determine whether the *APOE* ε4 allele and age affect the association of rs7481773 with Aβ (+).

We estimated the proportion of phenotypic variance explained by a particular SNP (Shim et al., 2015).

ANCOVA was performed to see if HV showed a significant difference between carriers of the rs7481773 variant and non–carriers, controlling for age, sex, *APOE* ε4 carrier status, and education. The longitudinal neuropsychological test data of 67 participants were analyzed using a linear mixed effects model. We entered the individual as a random effect component, while age, sex, *APOE* ε4 carrier status, education, group, time, and the interaction between group and time (group by time) were entered as fixed effect components.

We performed the genetic association study power analysis using a power calculation formula (https://genome.sph.umich.edu/wiki/Power_Calculations:_Quantitative_Traits).

All analyses were performed using PLINK 1.9 and R version 3.6.1 (R Project for Statistical Computing).

Table 1
Demographics of the study populations.

	SMC (n = 434)	ADNI (n = 323)	Independent KOR (n = 69)	KBASE[23] (n = 256)	J-ADNI[22] (n = 83)	A4 study[7] (n = 4,486)			AIBL[24] (n = 164)
						Total	Asian (n = 169)	European (n = 3,947)	
Age, mean (SD), y[a]	70.5 (7.3)[a]	72.6 (6.1)	70.3 (6.4)	68.7 (8.1)	67.9 (5.2)	71.3 (4.7)	71.7 (4.3)	71.3 (4.7)	71.4 (7.3)
Education, mean (SD), y	11.8 (4.8)[a]	16.8 (2.5)	9.6 (5.0)	11.9 (4.7)	13.9 (2.4)	16.6 (2.8)	16.1 (2.6)	16.7 (2.8)	12.4 (2.6)
Female, No. (%)	264 (60.8)	182 (56.3)	52 (55.1)	132 (51.6)	49 (59.0)	2,663 (59)	64 (37.9)	2,358 (59.7)	87 (53)
APOE ε4 carrier, No. (%)	103 (23.7)	96 (29.7)	11 (15.9)	47 (18.4)	22 (25.3)	1,550 (34.0)	37 (22.0)	1,393 (35.6)	70 (42.7)
MMSE, mean, (SD)	28.1 (1.8)[a]	29.1 (1.2)	27.5 (2.2)	26.9 (2.5)	29.2 (1.2)	28.2 (1.2)	28.3 (1.4)	28.8 (1.2)	28.8 (1.2)
Amyloid positivity (%)	20.0[a]	32.8	10.1	18.0	22.9	29.5	17.5	30.4	30.5

Abbreviations: SMC, Samsung Medical Center; ADNI, Alzheimer's Disease Neuroimaging Initiative; KOR, Korean; KBASE, Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's disease; J-ADNI, Japanese Alzheimer's Disease Neuroimaging Initiative; A4, Anti–Amyloid Treatment in Asymptomatic Alzheimer's disease; AIBL, Australian Imaging Biomarkers and Lifestyle; MMSE, Mini-Mental State Exam; *APOE*, apolipoprotein E.
[a] $p < 0.05$ between the SMC and ADNI datasets.

3. Results

3.1. Clinical and demographic characteristics of participants

The clinical and demographic characteristics of the participants are described in Table 1. The individuals in the SMC data showed younger ages (70.5 ± 7.3 years vs. 72.6 ± 6.1 years, $p < 0.001$) and lower education duration (11.8 ± 4.8 years vs. 16.8 ± 2.5 years, $p < 0.001$) than the ADNI data. The frequency of *APOE* ε4 carriers tended to be higher in the ADNI dataset (29.7%) than in the SMC dataset (23.7%) ($p = 0.064$). The frequency of Aβ (+) was higher in the ADNI dataset (32.8%) than in the SMC dataset (20.0%) ($p < 0.001$).

We combined SMC, independent KOR, J-ADNI, and A4 study (Asian) as Asian cohorts and ADNI, A4 study (European), and AIBL as European cohorts. The Asian cohorts showed *APOE* ε4 carriers in 21.8% of CN, whereas the European cohorts showed 35.2% CN (Supplementary Table S2). The frequencies of Aβ (+) were 18.0% in Asian cohorts and 30.6% in European cohorts (Supplementary Table S2).

3.2. Comparison of Aβ (+) frequency according to demographics and *APOE* ε4 genotype

The frequencies of Aβ (+) according to age, sex, education duration, and *APOE* ε4 carrier status in each dataset are shown in Fig. 2. In elderly participants (≥75 years), the ADNI data showed a higher prevalence of Aβ (+) individuals than in the SMC data (44.4% vs. 24.1%, $p < 0.001$). The frequency of Aβ (+) in females was higher in the ADNI dataset than in the SMC dataset (38.5% vs. 21.2%, $p < 0.001$). Moreover, the ADNI data showed a higher prevalence of Aβ (+) than the SMC dataset in the 13–15 years of education group (47.9% vs. 15.6%, $p = 0.003$), and the ≥ 16 years of education group (29.8% vs. 17.0%, $p = 0.003$). The frequency of Aβ (+) in the *APOE* ε3 homozygote group was significantly higher in the ADNI dataset than in the SMC dataset (23.9% vs. 11.1%, $p < 0.001$) (Fig. 2).

Both datasets showed a higher frequency of Aβ (+) in the older group than in the younger group (SMC: odds ratio [OR] 1.06, 95% CI 1.01–1.11; ADNI: OR 1.13, 95% CI 1.08–1.09). Lastly, *APOE* ε4 carriers showed a higher frequency of Aβ (+) than ε3 homozygotes in both the SMC and ADNI datasets (OR 8.6, 95% CI 5.0–14.9 for SMC and OR 5.6, 95% CI 3.1–10.1 for ADNI).

3.3. Genome-wide association analysis

Prior to GWAS, we conducted PCA for the 1000 Genomes Project samples and projected our samples to the PCA plot to clarify the ancestral distinction between SMC and ADNI. We confirmed that the ADNI samples overlapped with the 1000 Genomes European cluster, while the SMC samples overlapped with the East Asian cluster (Fig. 3).

For the SMC GWAS dataset, we performed a meta-analysis based on the GWAS results from FBB (99 samples), and FMM (76 samples) PET data. The association results for 4,906,407 variants are shown in Fig. 4A. We identified 10 variants on chromosome 11 that exceeded the genome-wide significance level ($p < 5 \times 10^{-8}$) (Table 3). Rs7481773 ($p = 3.05 \times 10^{-9}$), rs1491851 ($p = 3.94 \times 10^{-9}$), rs10002266, rs1552736 ($p = 6.63 \times 10^{-9}$), rs12803460, rs985205, rs17309958, rs1157659, rs17309951 ($P = 9.49 \times 10^{-9}$), and rs7482257 ($p = 2.12 \times 10^{-8}$) were in high linkage disequilibrium and located near *BDNF* as shown in Fig. 4E. At the suggestive level of association ($p < 1 \times 10^{-5}$), we identified rs66626994 (intergenic variant near *APOC1* and *APOC1P1*, $p = 3.61 \times 10^{-7}$) and rs429358 ($p = 4.33 \times 10^{-7}$) on chromosome 19 as the most significant variants in *APOE*. Other variants were located near genes that were previously related to AD risk, as summarized in Table 2.

In subgroup sensitivity analyses, we found that the minor allele of rs7481773 was positively associated with Aβ (+) (beta = 0.4171, standard error [SE] = 0.1341, $p = 0.0024$) in *APOE* ε3 homozygote carriers (n = 125). In the elderly participants (n = 95, age >70 years), rs7481773 was also positively associated with Aβ (+) (beta = 0.5131, SE = 0.1459, $p = 0.0007$).

For the ADNI dataset, we performed a GWAS using the ^{18}F-AV45 amyloid-PET data. The association results for 7,117,161 variants are shown in Fig. 4B. No SNPs passed the genome-wide significance level ($p < 5 \times 10^{-8}$). At the suggestive level of association ($p < 1 \times 10^{-5}$), we identified rs429358 (*APOE*, $p = 4.33 \times 10^{-7}$) as the most significant variant.

3.4. Replication of the association between variants on chromosome 11 and Aβ deposition

We performed a linear regression analysis in an independent Korean cohort (n = 69) to replicate the SMC GWAS results on chromosome 11 ($p < 5 \times 10^{-8}$). We found that the minor alleles of all 10 variants identified in the SMC GWAS were positively associated

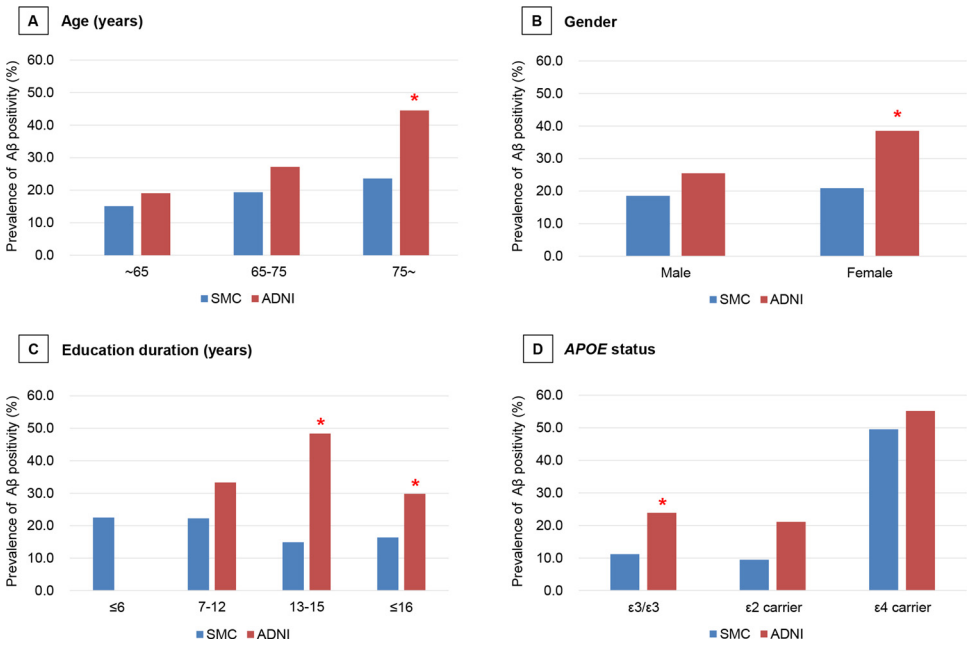

Fig. 2. Comparison of the prevalence of amyloid positivity according to characteristics in each study group.
*$p < 0.05$ between the SMC and ADNI datasets. Abbreviations: ADNI, Alzheimer's disease neuroimaging initiative; SMC, Samsung medical center.

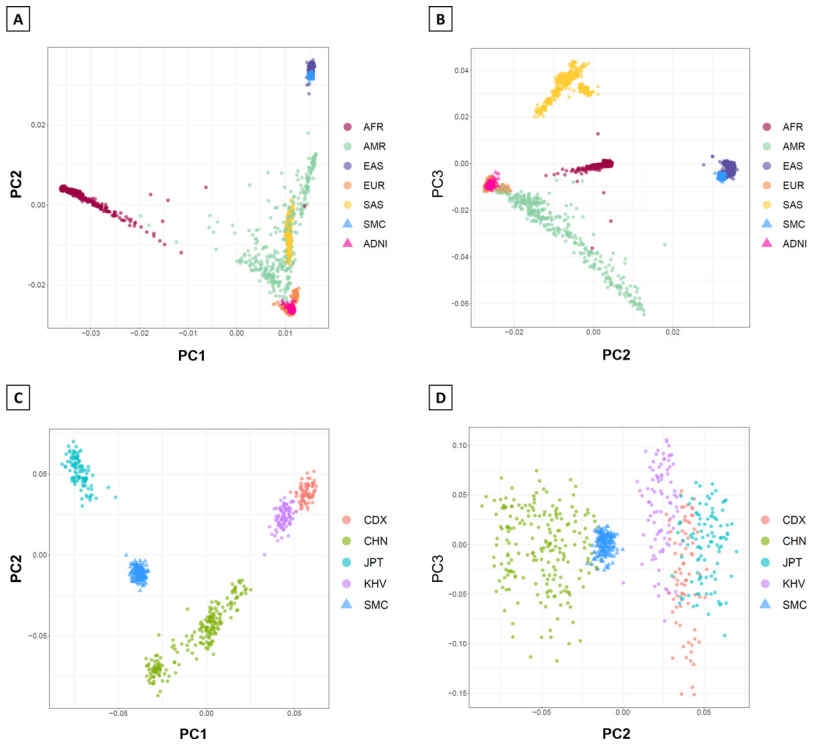

Fig. 3. PCA plots of SMC and ADNI with the 1000 genomes project samples. Abbreviations: PCA, principal component analysis; PC, principal component; SMC, Samsung medical center; ADNI, Alzheimer's disease neuroimaging initiative; AFR, African; AMR, American; EAS, East Asian; EUR, European; SAS, South Asian; CDX, Chinese Dai in Xishuangbanna, China; CHN, Han Chinese in Beijing, China; JPT, Japanese in Tokyo, Japan; KHV, Kinh in Ho Chi Minh City, Vietnam.

with Aβ deposition in the replication data ($p < 0.05$) and showed similar effect sizes to the discovery data. The results are shown in Table 3.

3.5. Power estimation

We estimated the genetic association study power using 175 samples (N), 0.05/1,000,000 for alpha (genome-wide significance level), and 60% for the heritability (H^2) of amyloid levels (Ertekin-Taner et al., 2001). Resultantly, this experimental setting was estimated to achieve a statistical power of approximately 99.9% in the discovery set. Moreover, we achieved a statistical power of approximately 99.9% (69 samples (N), and 0.05/10 for alpha (number of replicated SNPs)) in the replication set.

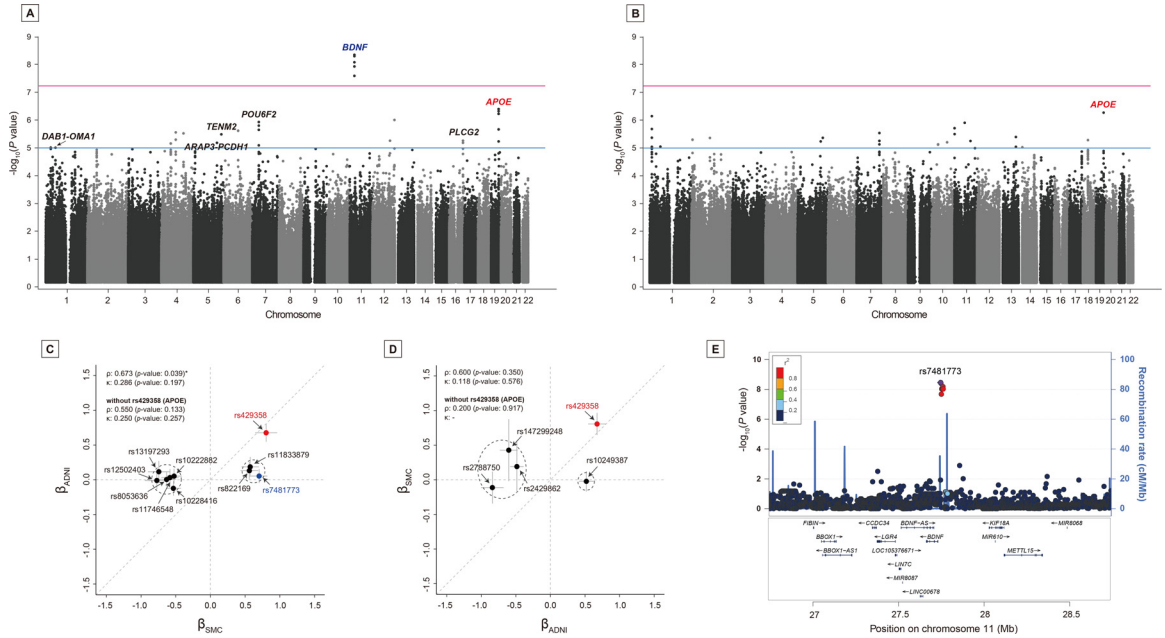

Fig. 4. Genome-wide association analyses of Aβ deposition. (A) Manhattan plot of the GWAS meta-analysis for Aβ deposition in cognitively normal Korean subjects; (B) Manhattan plot of the GWAS analysis for Aβ deposition in cognitively normal ADNI subjects; (C) Scatter plot comparing the effect size of the Korean GWAS significant SNPs ($p < 1 \times 10^{-5}$) between the 2 study groups; (D) Scatter plot comparing the effect size of the ADNI GWAS significant SNPs ($p < 1 \times 10^{-5}$) between the 2 study groups; (E) Regional plot for rs7481773 associated with Aβ deposition in cognitively normal Korean subjects. Abbreviations: β, coefficient of each SNP estimated by linear regression; ρ, Spearman's correlation coefficient; κ, Cohen's kappa coefficient; ADNI, Alzheimer's disease neuroimaging initiative; GWAS, genome-wide association study.

3.6. Comparing genetic variations between populations

rs429358, one of the SNPs that determines *APOE* ε4 status, showed significant associations, based on the suggestive threshold ($p < 1 \times 10^{-5}$), in both the SMC GWAS (beta = 0.8046, SE = 0.1592, $p = 4.33 \times 10^{-7}$), and ADNI GWAS (beta = 0.6751, SE = 0.1295, $p = 4.88 \times 10^{-7}$). The most significant SNP near *BDNF* was not significant in the ADNI GWAS (rs7481773, $p = 0.59$). Additionally, we confirmed that the interaction term between rs7481773, and each population was significantly associated with Aβ deposition ($p = 0.0125$) in the multivariate linear regression analysis. The proportion of Aβ deposition variance as explained by the *BDNF* rs7481773 variant also differed between the 2 cohorts (16.6% in the SMC dataset and 0.1% in the ADNI dataset), while that of the *APOE* rs429358 variant was similar (12.7% in the SMC dataset and 12.2% in the ADNI dataset). Moreover, we compared the effect size (beta) of significant SNPs at the suggestive level ($p < 1 \times 10^{-5}$) detected in each GWAS. The correlation of effect size and agreement for effect direction between the 2 cohorts were weak overall (Fig. 4C and D).

3.7. Hippocampal volume and memory decline of the rs7481773 variant carriers

The HV was measured in 154 CN participants in the SMC dataset (Supplementary Table S1). There were no statistically significant differences in HV between carriers of the rs7481773 variant (n = 68) and non–carriers (n = 86) (4.6 ± 0.6, 4.8 ± 0.5, HV/ICV x 10^3, $p = 0.14$) (Fig. 5A).

We also collected the longitudinal data of detailed neuropsychological tests in 67 CN participants in the SMC dataset (Supplementary Table S1). rs7481773 carriers showed more rapid decline in memory function (Seoul Verbal Learning Test delayed recall) than rs7481773 non–carriers ($p = 0.048$) (Fig. 5B).

4. Discussion

We compared the frequency of Aβ (+) in CN individuals between Korean and European participants and investigated which factors explained the difference in these frequencies according to ethnicity. The major findings of our study are as follows. First, the frequency of Aβ (+) in CN individuals was significantly lower in Korean participants than in European participants. The Korean CNs showed lower education duration, which is generally considered an index of lower cognitive reserve (Stern et al., 2020), than the European CNs. Second, the effects of *APOE* ε4 on Aβ (+) in CN individuals between the Korean, and European groups were similar. Finally, *BDNF* polymorphisms were significantly correlated with Aβ uptake in the Korean participants, but not in the European participants. The effects of *BDNF* polymorphisms on Aβ uptake differed between the 2 ethnicities. Cumulatively, our findings suggest that cognitive reserve or genetic factors may explain the different frequencies of Aβ (+) between CN Koreans, and Europeans.

Our first major finding was that the frequency of Aβ (+) of CN was significantly lower in Asians than in Europeans. Our findings are consistent with those of other studies (Dang et al., 2018; Donohue et al., 2014; Iwatsubo et al., 2018; Moon et al., 2019; Sperling et al., 2020). Another study reported that the prevalence of Aβ (+) in CN Korean individuals was 18.0% (Table 1) (Moon et al., 2019). The Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) also showed that the prevalence of Aβ (+) in the CN Japanese population was 23% (Iwatsubo et al., 2018). However, the Australian Imaging Biomarkers, and Lifestyle (AIBL) study showed a 30.5% Aβ (+) prevalence in European CN populations (Dang et al., 2018; Donohue et al., 2014). Furthermore, our findings are also supported by the Anti–Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) study's finding that the prevalence of Aβ (+) in CN Europeans was 30.4%, although it was only 17.5% in Asians (Sperling et al., 2020). Our observations of lower frequency of Aβ (+) in CN Korean participants might be related to

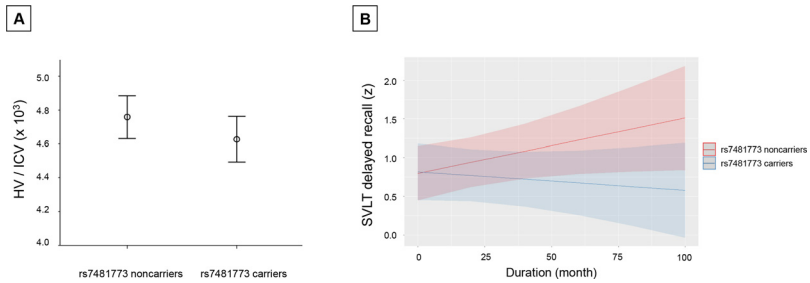

Fig. 5. (A) Hippocampal volumes of rs7481773 variant non–carriers and rs7481773 variant carriers among cognitively normal participants at SMC ($p = 0.14$). (B) Cognitive trajectories of rs7481773 variant non–carriers and rs7481773 variant carriers among cognitively normal participants of SMC ($p = 0.048$).
Abbreviations: HV, hippocampal volume; ICV, intracranial volume; SMC, Samsung medical center; SVLT, Seoul verbal learning test.

Table 2
Genetic variants associated with Aβ deposition in the meta-analysis of the Korean population ($p < 1 \times 10^{-5}$).

Peak SNP	Chr	Position	A1	A2	SNPs (N)[a]	Nearby genes	Region	SMC CN					ADNI CN				
								Beta	SE	*p* value	MAF	EASMAF[b]	Beta	SE	*p* value	MAF	Non–FinnishEUR MAF[b]
rs7481773	11	27751390	G	A	10	*BDNF*	Intergenic	0.7033	0.1191	3.50E–09	0.2486	0.2869	0.0537	0.0994	5.90E–01	0.5128	0.5087
rs429358	19	45411941	T	C	18	*APOE*	Exonic	0.8046	0.1592	4.33E–07	0.1114	0.0885	0.6751	0.1295	4.88E–07	0.1531	0.1486
rs3825100	12	131623101	G	A	1	*ADGRD1*	Intronic	-1.3779	0.2807	9.17E–07	0.0371	0.0713	-	-	–	-	0.0005
rs10228416	7	39303261	T	C	7	*POU6F2*	Intronic	-0.5332	0.1094	1.09E–06	0.3886	0.3844	-0.1227	0.1057	2.47E–01	0.5026	0.4655
rs13196777	6	86988003	A	G	2	*SNHG5, HTR1E*	Intergenic	-0.7436	0.1574	2.31E–06	0.1143	0.0720	0.1972	0.1524	1.97E–01	0.1199	0.1035
rs10222882	4	86292692	T	G	1	*WDFY3-AS2, ARHGAP24*	Intergenic	-0.5232	0.1114	2.65E–06	0.4829	0.4657	0.0528	0.1074	6.24E–01	0.5000	0.5247
rs74902001	4	132482544	C	T	1	*LINC02479, SNHG27*	Intergenic	-0.8327	0.1780	2.88E–06	0.1057	0.0224	-	-	–	-	0.0035
rs11746548	5	167329808	C	G	1	*TENM2*	Intronic	-0.5824	0.1249	3.13E–06	0.3486	0.5084	0.0320	0.1232	7.96E–01	0.2219	0.2608
rs8053636	16	81931362	C	T	2	*PLCG2*	Intronic	-0.6307	0.1386	5.39E–06	0.2057	0.2147	0.0045	0.1062	9.66E–01	0.3214	0.3341
rs11833879	12	105196755	T	C	1	*SLC41A2*	Down stream	0.5747	0.1263	5.39E–06	0.2486	0.2272	0.1859	0.1439	1.98E–01	0.1327	0.1544
rs151079266	5	141197132	C	T	1	*ARAP3, PCDH1*	Intergenic	1.5880	0.3521	6.48E–06	0.0229	0.0173	-	-	–	-	0.0001
rs12503448	4	56571962	T	C	6	*NMU, LOC644145*	Intergenic	0.7719	0.1716	6.86E–06	0.1029	0.0770	0.0008	0.1240	9.95E–01	0.2270	0.2474
rs61766358	1	30716230	G	A	1	*LINC01648, MATN1*	Intergenic	-0.5178	0.1171	9.72E–06	0.2743	0.2142	-	-	–	-	0.0078
rs822169	1	58912438	A	G	1	*DAB1, OMA1*	Intergenic	0.5625	0.1272	9.85E–06	0.2429	0.2108	0.1312	0.1237	2.90E–01	0.2526	0.2532

Abbreviations: SMC, Samsung Medical Center; ADNI, Alzheimer's Disease Neuroimaging Initiative; CN, cognitively normal participants; Chr, chromosome; A1, major allele; A2, minor allele (effect allele); MAF, minor allele frequency; SE, standard error; EAS, East Asian; EUR, European.
[a] The number of significant SNPs ($p < 1 \times 10^{-5}$) of SMC GWAS in each locus
[b] Minor allele frequency for East Asian and non–Finnish European samples from the Genome Aggregation Database (gnomAD version 2.1.1, https://gnomad.broadinstitute.org).

Table 3
Discovery and replication of the association between rs429358 and variants near *BDNF* with Aβ deposition in the Korean population

SNP	Chr	Position	A1	A2	SMC CN (n = 175)		Independent CN (n = 69)[a]				Meta (n = 244)		Meta adjustedfor *APOE* ε4	
					MAF	Beta	*p* value	MAF	Beta	*p* value	Beta	*p* value	Beta	*p* value
rs429358	19	45411941	C	T	0.1114	0.8046	4.33E–07	0.0725	0.8117	0.0648	0.8055	6.85E–08	-	-
rs7481773	11	27751390	G	A	0.2486	0.7033	3.50E–09	0.2536	0.7435	0.0056	0.7103	5.21E–11	0.5768	2.48E-07
rs1491851	11	27752763	T	C	0.2600	0.6832	3.94E–09	0.2609	0.7632	0.0032	0.7140	2.11E–11	0.5759	7.78E-08
rs1002266	11	27764612	G	T	0.2629	0.6772	6.63E–09	0.2536	0.8964	0.0011	0.6976	3.33E–11	0.5906	5.38E-08
rs1552736	11	27763277	A	G	0.2629	0.6772	6.63E–09	0.2536	0.8964	0.0011	0.7049	4.11E–11	0.5906	5.38E-08
rs12803460	11	27760058	C	T	0.2600	0.6719	9.49E–09	0.2319	0.8679	0.0015	0.7049	4.11E–11	0.5811	9.24E-08
rs985205	11	27758992	A	T	0.2600	0.6719	9.49E–09	0.2319	0.8679	0.0015	0.7049	4.11E–11	0.5811	9.24E-08
rs17309958	11	27765787	T	C	0.2600	0.6719	9.49E–09	0.2319	0.8362	0.0017	0.7140	2.11E–11	0.5823	6.98E-08
rs1157659	11	27757622	A	G	0.2600	0.6719	9.49E–09	0.2319	0.8679	0.0015	0.7049	4.11E–11	0.5811	9.24E-08
rs17309951	11	27764932	C	A	0.2600	0.6719	9.49E–09	0.2319	0.8679	0.0015	0.7006	4.56E–11	0.5811	9.24E-08
rs7482257	11	27755298	T	C	0.2657	0.6603	2.12E–08	0.2899	0.8488	0.0011	0.6953	6.37E–11	0.5706	1.49E-07

Abbreviations: SMC, Samsung Medical Center; CN, cognitively normal; Chr, chromosome; A1, major allele; A2, minor allele (effect allele); MAF, minor allele frequency; SE, standard error.
[a] Linear regression model: A$\beta \sim$ age + sex + education years + PCs (1-4) + PET ligand type (FBB or FMM) + SNP.

the lower frequency of *APOE* $\varepsilon 4$ in Koreans than in Europeans, as *APOE* $\varepsilon 4$ is an important risk factor for Aβ (+). A previous study showed that the frequency of Aβ (+) in CN individuals was likely to be lower in Asians than in Europeans, suggesting that it might be related to the lower prevalence of *APOE* $\varepsilon 4$ carriers in Asians than in Europeans (Sperling et al., 2020). However, in the present study, the differences in the frequency of Aβ (+) CN between the 2 cohorts were prominently seen in *APOE* $\varepsilon 3$ homozygotes. Interestingly, Koreans had a lower frequency of Aβ (+) than Europeans in females, but not in males. Further studies are needed to determine whether ethnicity might modify the relationships between sex and Aβ (+) in CN.

In the present study, the difference in the frequency of Aβ (+) CN between the 2 groups was more prominent in the older group ($\geq$75 years) than in the younger group. Korean participants aged 55–90 years were born between 1925–1960. Considering that the cultural influences during our elderly participants' childhood were substantially different from those in the ADNI elderly participants, it is possible that the lower frequency of Aβ (+) CN in Koreans might be explained by several cultural factors. The elderly participants included survivors of a society in transition from an exploited colony of the Japanese Empire (1910–1945) to a modern developed nation (Booth and Deng, 2017). Education before 1960 provided different educational experiences in students from Korea and North America. Moreover, adult literacy rates in 1938 differed between Korea (22%) and North America (>90%). As members of a Japanese colony, most Koreans completed no more than 4 years at school and received only poor-quality food in restricted amounts. Japanese land lords controlled agricultural production, and workers were mostly involuntary laborers. Additionally, nutritious food produced was forcibly extracted to mainland Japan (Booth and Deng, 2017). Previous studies have shown that childhood stress is associated with increased AD risk (Radford et al., 2017), and differences in socioeconomic status during childhood have been associated with cognitive function in old age (Everson-Rose et al., 2003). It would therefore be reasonable to expect that older-generation Koreans have acquired fewer protective factors against amyloid β pathologies and are more vulnerable to cognitive impairments than are CN European elderly participants. In fact, the incidence of AD in Koreans (Park et al., 2019) (13.0 per 1000 person-years) seemed to be higher than that in Europeans (Niu et al., 2017) (11.1 per 1000 person-years). Further studies are needed to investigate the effects of cultural differences in childhood on the frequency of Aβ (+) CN.

Our second major finding was that the effects of *APOE* $\varepsilon 4$ on Aβ (+) between Korean (OR = 6.0) and European CN groups (OR = 5.6) were similar. This finding was also supported by our GWAS analysis showing that effect sizes were comparable between the 2 cohorts (the beta value of rs429358 was 0.8046 and 0.6751 in the SMC and ADNI datasets, respectively). To our knowledge, the effects of *APOE* $\varepsilon 4$ on Aβ (+) have not yet been extensively investigated in different ethnic groups. However, it was previously shown that there might be differences in the effects of *APOE* $\varepsilon 4$ on the development of dementia by ethnicity (Heffernan et al., 2016). Specifically, the effect of the *APOE* $\varepsilon 4$ allele on AD dementia in Europeans (OR for $\varepsilon 3/\varepsilon 4$ = 3.2 and OR for $\varepsilon 4/\varepsilon 4$ = 14.9) was weaker than that in Japanese (OR for $\varepsilon 3/\varepsilon 4$ = 5.6 and OR for $\varepsilon 4/\varepsilon 4$ = 33.1) (Farrer et al., 1997; Heffernan et al., 2016). Therefore, further studies with larger sample sizes are needed to determine whether the effects of *APOE* $\varepsilon 4$ on Aβ (+) in CN individuals differ between ethnicities.

Our final major finding was that *BDNF* polymorphisms significantly correlated with amyloid accumulation in Koreans but not in Europeans. There were interactions between *BDNF* polymorphisms and ethnicities in Aβ uptake. Previous studies have shown that *BDNF* is essential for maintaining adult cortical neurons in the entorhinal cortex, which is related to short-term memory function in AD (Giuffrida et al., 2018; Nagahara et al., 2009). Furthermore, studies have shown that *BDNF* polymorphisms are associated with Aβ-related cognitive decline in preclinical AD (Lim et al., 2013; Lim et al., 2015). In the AIBL study based on the European population, the $BDNF^{Val66Met}$ polymorphism showed no relationship with the amount of Aβ or with the rate of Aβ accumulation in healthy adults (Lim et al., 2013). However, in the same AIBL study group, $A\beta^{+}\varepsilon 4^{+}/BDNF^{Met}$ individuals are expected to show significant memory dysfunction after 3 years from baseline neuropsychological (NP) testing, whereas $A\beta^{+}\varepsilon 4^{+}/BDNF^{Val/Val}$ individuals are expected to show a similar degree of dysfunction after 10 years from baseline NP testing (Lim et al., 2015). Our finding might be supported by a previous study showing that in Koreans, polymorphisms in *BDNF* may be associated with a vulnerability in brain structure ne2rks (Park et al., 2017). This results in a rapid decrease in cognitive function in the amyloid positive population and leads to a lower Aβ (+) prevalence in CN individuals than in Europeans.

We also found that significant variants at suggestive levels in the SMC GWAS, rs10228415 (*POU6F2*), rs11746548 (*TENM2*), rs8053636 (*PLCG2*), rs151079266 (*ARAP3, PCDH1*), and rs822169 (*DAB1, OMA1*), were reportedly associated with AD or Aβ deposition in previous genetic studies (Bastias-Candia et al., 2015; Chouraki et al., 2014; Cuchillo-Ibanez et al., 2013; Cuchillo-Ibanez et al., 2016; Furney et al., 2011; Hoe et al., 2006; Homayouni et al., 1999; Lempriere, 2019; Li et al., 2015; Magno et al., 2019; Shulman et al., 2011; Sims et al., 2017; Tessarin et al., 2019; van der Lee et al., 2019). However, the findings that these SNPs potentially contribute to Aβ deposition in CN East Asians need to be investigated using meta-analyses in independent East Asian populations in further studies.

To explain our finding of lower frequency of Aβ (+) in CN Koreans than in CN Europeans participants, we hypothesized that Aβ (+) CN might more rapidly progress to cognitive impairments in Koreans than in Europeans. There are potential mechanisms to explain our hypotheses. First, considering that education levels refer to a proxy of cognitive reserve (Stern et al., 2022; Stern et al., 2020), it is possible to expect that CN Koreans might have lower cognitive reserve than in CN Europeans because CN Koreans had lower education levels than CN Europeans. Alternatively, the differences in the effects of BDNF polymorphisms on Aβ uptake between the 2 ethnicities might explain our hypothesis. In fact, relative to non–carriers, rs7481773 variant carriers showed more rapid decline in memory function. However, we did not find statistically significant differences in hippocampal volume, which is a proxy of brain reserve, between carriers, and non–carriers. To test whether genetic differences between the 2 ethnicities might have an effect on different frequencies of Aβ (+) through brain reserve hypothesis, further studies with a larger number should be needed.

4.1. Strengths and limitations

The strengths of our study are the relatively large sample size and the carefully standardized phenotyping of CN participants. However, there are some limitations to our study. First, the difference between the SNP microarray panels used for the GWAS of each population might have affected our analyses. These discrepancies might be addressed by performing QC and imputation using an identical pipeline for the 2 datasets, as we have observed that the same variant (rs429358 near *APOE*) has shown significant associations in both GWAS. Second, we did not identify any other significant GWAS variants other than the polymorphisms near *BDNF*, implying insufficient statistical power for GWAS given our sample size. Third, CN individuals in the SMC dataset underwent 2 different 18F-labeled amyloid PETs or different methods in evaluating

Aβ positivity. However, this limitation might be mitigated by the Centiloid methods in evaluating Aβ positivity (Cho et al., 2020; Morris et al., 2016; Ng et al., 2007). Fourth, there might be differences between SMC and ADNI in relationships between cognitive test scores and amyloid β deposition in CN. Recently, we developed the Preclinical Amyloid Sensitive Composite (PASC) model to predict Aβ (+) in CN (Hahn et al., 2020). The items of cognitive tests in the PASC are similar to those of the cognitive tests included in the Preclinical Alzheimer Cognitive Composite for ADNI CN. Fifth, in our analysis, we didn't control for detailed socioeconomic factors such as life stressors, and other factors that may vary between the cohorts. Further studies are needed to add socioeconomic data and information about possible aging-related health disparities to investigate the differences between Korean and European samples. Sixth, another effector, responder, or modifier to *BDNF* may be present that may explain the discrepancy between the 2 ethnicities which is not sufficiently explained by the *BDNF* SNP. We did not perform functional studies of the effects of SNPs on *BDNF* in the present study. Thus, further studies are needed to investigate the effects of SNPs on *BDNF*. Lastly, we were unable to access the genetic dataset from J-ADNI, KBASE, AIBL, and the A4 study. Future studies with larger populations are needed using the genetic dataset.

5. Conclusions

In conclusion, our results showed differences in the frequencies of Aβ (+) between Koreans and Europeans and in the clinical and genetic factors related to Aβ (+) in Koreans and Europeans. Our findings suggest that the effects of *APOE* ε4 on Aβ (+) between Korean and European CN cohorts are similar, while *BDNF* variants are associated with Aβ uptake in Korean, but not in European CN cohorts. Therefore, our findings will encourage clinicians to consider ethnic differences including prevailing cultures in their childhood, and genetic factors for the prevention of dementia progression.

Author contributions

Jaeho Kim: study concept and design, acquisition, analysis, and interpretation of data; Sang-Hyuk Jung: study concept and design, acquisition, analysis, and interpretation of data; Yeong Sim Choe: analysis of data; Soyeon Kim: analysis of data; Beomsu Kim: analysis of data; Hang-Rai Kim: acquisition of data, critical revision of manuscript; Sang Joon Son: acquisition of data; Chang Hyung Hong: acquisition of data; Duk L. Na: acquisition of data, critical revision of manuscript; Hee Jin Kim: acquisition of data, critical revision of manuscript; Soo-Jin Cho: critical revision of manuscript; Hong-Hee Won: study concept and design, acquisition, analysis and interpretation of data, and critical revision of manuscript for intellectual content; Sang Won Seo: study concept and design, acquisition, analysis and interpretation of data, and critical revision of manuscript for intellectual content.

Funding

This research was supported by the Korea Health Technology R&D Project grant through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI19C1132, HU20C0111, and HU21C0111), the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (NRF-2018R1A1A3A04079255, NRF-2019R1A5A2027340), Institute of Information & communications Technology Planning & Evaluation (IITP) grant funded by the Korea government (MSIT) (No.2021-0-02068, Artificial Intelligence Innovation Hub), Future Medicine 20*30 Project of the Samsung Medical Center [#SMX1220021], and the "National Institute of Health" research project (2021-ER1006-01).

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2022.03.001.

References

Bastias-Candia, S., Braidy, N., Zolezzi, J.M., Inestrosa, N.C., 2015. Teneurins and Alzheimer's disease: a suggestive role for a unique family of proteins. Medical Hypotheses 84 (4), 402–407.

Bateman, R.J., Xiong, C., Benzinger, T.L., Fagan, A.M., Goate, A., Fox, N.C., Marcus, D.S., Cairns, N.J., Xie, X., Blazey, T.M., Holtzman, D.M., Santacruz, A., Buckles, V., Oliver, A., Moulder, K., Aisen, P.S., Ghetti, B., Klunk, W.E., McDade, E., Martins, R.N., Masters, C.L., Mayeux, R., Ringman, J.M., Rossor, M.N., Schofield, P.R., Sperling, R.A., Salloway, S., Morris, J.C., 2012. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N. Engl. J. Med 367 (9), 795–804.

Booth, A., Deng, K., 2017. Japanese colonialism in comparative perspective. J. World Hist 28, 61–98.

Cho, S.H., Choe, Y.S., Kim, H.J., Jang, H., Kim, Y., Kim, S.E., Kim, S.J., Kim, J.P., Jung, Y.H., Kim, B.C., Baker, S.L., Lockhart, S.N., Na, D.L., Park, S., Seo, S.W., 2020. A new Centiloid method for (18)F-florbetaben and (18)F-flutemetamol PET without conversion to PiB. Eur J Nucl Med Mol Imaging 47 (8), 1938–1948.

Chouraki, V., De Bruijn, R.F., Chapuis, J., Bis, J.C., Reitz, C., Schraen, S., Ibrahim-Verbaas, C.A., Grenier-Boley, B., Delay, C., Rogers, R., Demiautte, F., Mounier, A., Fitzpatrick, A.L., Berr, C., Dartigues, J.F., Uitterlinden, A.G., Hofman, A., Breteler, M., Becker, J.T., Lathrop, M., Schupf, N., Alperovitch, A., Mayeux, R., van Duijn, C.M., Buee, L., Amouyel, P., Lopez, O.L., Ikram, M.A., Tzourio, C., Lambert, J.C., 2014. A genome-wide association meta-analysis of plasma Abeta peptides concentrations in the elderly. Mol Psychiatry 19 (12), 1326–1335.

Cuchillo-Ibanez, I., Balmaceda, V., Botella-Lopez, A., Rabano, A., Avila, J., Saez-Valero, J., 2013. Beta-amyloid impairs reelin signaling. PloS one 8 (8), e72297.

Cuchillo-Ibanez, I., Mata-Balaguer, T., Balmaceda, V., Arranz, J.J., Nimpf, J., Saez-Valero, J., 2016. The beta-amyloid peptide compromises Reelin signaling in Alzheimer's disease. Sci Rep 6, 31646.

Dang, C., Harrington, K.D., Lim, Y.Y., Ames, D., Hassenstab, J., Laws, S.M., Yassi, N., Hickey, M., Rainey-Smith, S., Robertson, J., Sohrabi, H.R., Salvado, O., Weinborn, M., Villemagne, V.L., Rowe, C.C., Masters, C.L., Maruff, P., 2018. Relationship between amyloid-beta positivity and progression to mild cognitive impairment or dementia over 8 years in cognitively normal older adults. J Alzheimers Dis 65 (4), 1313–1325.

Donohue, M.C., Sperling, R.A., Salmon, D.P., Rentz, D.M., Raman, R., Thomas, R.G., Weiner, M., Aisen, P.S., 2014. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. JAMA Neurol 71 (8), 961–970.

Ertekin-Taner, N., Graff-Radford, N., Younkin, L.H., Eckman, C., Adamson, J., Schaid, D.J., Blangero, J., Hutton, M., Younkin, S.G., 2001. Heritability of plasma amyloid beta in typical late-onset Alzheimer's disease pedigrees. Genetic Epidemiol 21 (1), 19–30.

Everson-Rose, S.A., Mendes de Leon, C.F., Bienias, J.L., Wilson, R.S., Evans, D.A., 2003. Early life conditions and cognitive functioning in later life. Am. J. Epidemiol. 158 (11), 1083–1089.

Farrer, L.A., Cupples, L.A., Haines, J.L., Hyman, B., Kukull, W.A., Mayeux, R., Myers, R.H., Pericak-Vance, M.A., Risch, N., van Duijn, C.M., 1997. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer disease meta analysis consortium. Jama 278 (16), 1349–1356.

Furney, S.J., Simmons, A., Breen, G., Pedroso, I., Lunnon, K., Proitsi, P., Hodges, A., Powell, J., Wahlund, L.O., Kloszewska, I., Mecocci, P., Soininen, H., Tsolaki, M., Vellas, B., Spenger, C., Lathrop, M., Shen, L., Kim, S., Saykin, A.J., Weiner, M.W., Lovestone, S., 2011. Genome-wide association with MRI atrophy measures as a quantitative trait locus for Alzheimer's disease. Mol Psychiatry 16 (11), 1130–1138.

Giuffrida, M.L., Copani, A., Rizzarelli, E., 2018. A promising connection between BDNF and Alzheimer's disease. Aging 10 (8), 1791–1792.

Hahn, A., Kim, Y.J., Kim, H.J., Jang, H., Cho, H., Choi, S.H., Kim, B.C., Park, K.W., Na, D.L., Chin, J., Seo, S.W., 2020. The preclinical amyloid sensitive composite to determine subtle cognitive differences in preclinical Alzheimer's disease. Sci Rep 10 (1), 13583.

Han, Z., Qu, J., Zhao, J., Zou, X., 2018. Analyzing 74,248 Samples confirms the association between CLU rs11136000 polymorphism and Alzheimer's disease in caucasian but not Chinese population. Sci Rep 8 (1), 11062.

Han, Z., Wang, T., Tian, R., Zhou, W., Wang, P., Ren, P., Zong, J., Hu, Y., Jin, S., Jiang, Q., 2019. BIN1 rs744373 variant shows different association with Alzheimer's disease in Caucasian and Asian populations. BMC Bioinformatics 20 (Suppl 25), 691.

Heffernan, A.L., Chidgey, C., Peng, P., Masters, C.L., Roberts, B.R., 2016. The neurobiology and age-related prevalence of the epsilon4 allele of apolipoprotein E in Alzheimer's disease cohorts. J Mol Neurosci 60 (3), 316–324.

Hoe, H.S., Tran, T.S., Matsuoka, Y., Howell, B.W., Rebeck, G.W., 2006. DAB1 and Reelin effects on amyloid precursor protein and ApoE receptor 2 trafficking and processing. J Biol Chem 281 (46), 35176–35185.

Homayouni, R., Rice, D.S., Sheldon, M., Curran, T., 1999. Disabled-1 binds to the cytoplasmic domain of amyloid precursor-like protein 1. J Neurosci 19 (17), 7507–7515.

Iwatsubo, T., Iwata, A., Suzuki, K., Ihara, R., Arai, H., Ishii, K., Senda, M., Ito, K., Ikeuchi, T., Kuwano, R., Matsuda, H., Sun, C.K., Beckett, L.A., Petersen, R.C., Weiner, M.W., Aisen, P.S., Donohue, M.C., 2018. Japanese and North American Alzheimer's disease neuroimaging initiative studies: harmonization for international trials. Alzheimers Dement 14 (8), 1077–1087.

Jang, H., Jang, Y.K., Kim, H.J., et al., 2019. Clinical significance of amyloid β positivity in patients with probable cerebral amyloid angiopathy markers. Eur J Nucl Med Mol Imaging 46, 1287–1298.

Jansen, I.E., Savage, J.E., Watanabe, K., Bryois, J., Williams, D.M., Steinberg, S., Sealock, J., Karlsson, I.K., Hagg, S., Athanasiu, L., Voyle, N., Proitsi, P., Witoelar, A., Stringer, S., Aarsland, D., Almdahl, I.S., Andersen, F., Bergh, S., Bettella, F., Bjornsson, S., Braekhus, A., Brathen, G., de Leeuw, C., Desikan, R.S., Djurovic, S., Dumitrescu, L., Fladby, T., Hohman, T.J., Jonsson, P.V., Kiddle, S.J., Rongve, A., Saltvedt, I., Sando, S.B., Selbaek, G., Shoai, M., Skene, N.G., Snaedal, J., Stordal, E., Ulstein, I.D., Wang, Y., White, L.R., Hardy, J., Hjerling-Leffler, J., Sullivan, P.F., van der Flier, W.M., Dobson, R., Davis, L.K., Stefansson, H., Stefansson, K., Pedersen, N.L., Ripke, S., Andreassen, O.A., Posthuma, D., 2019. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat Genet 51 (3), 404–413.

Jansen, W.J., Ossenkoppele, R., Knol, D.L., Tijms, B.M., Scheltens, P., Verhey, F.R., Visser, P.J., Aalten, P., Aarsland, D., Alcolea, D., Alexander, M., Almdahl, I.S., Arnold, S.E., Baldeiras, I., Barthel, H., van Berckel, B.N., Bibeau, K., Blennow, K., Brooks, D.J., van Buchem, M.A., Camus, V., Cavedo, E., Chen, K., Chetelat, G., Cohen, A.D., Drzezga, A., Engelborghs, S., Fagan, A.M., Fladby, T., Fleisher, A.S., van der Flier, W.M., Ford, L., Forster, S., Fortea, J., Foskett, N., Frederiksen, K.S., Freund-Levi, Y., Frisoni, G.B., Froelich, L., Gabryelewicz, T., Gill, K.D., Gkatzima, O., Gomez-Tortosa, E., Gordon, M.F., Grimmer, T., Hampel, H., Hausner, L., Hellwig, S., Herukka, S.K., Hildebrandt, H., Ishihara, L., Ivanoiu, A., Jagust, W.J., Johannsen, P., Kandimalla, R., Kapaki, E., Klimkowicz-Mrowiec, A., Klunk, W.E., Kohler, S., Koglin, N., Kornhuber, J., Kramberger, M.G., Van Laere, K., Landau, S.M., Lee, D.Y., de Leon, M., Lisetti, V., Lleo, A., Madsen, K., Maier, W., Marcusson, J., Mattsson, N., de Mendonca, A., Meulenbroek, O., Meyer, P.T., Mintun, M.A., Mok, V., Molinuevo, J.L., Mollergard, H.M., Morris, J.C., Mroczko, B., Van der Mussele, S., Na, D.L., Newberg, A., Nordberg, A., Nordlund, A., Novak, G.P., Paraskevas, G.P., Parnetti, L., Perera, G., Peters, O., Popp, J., Prabhakar, S., Rabinovici, G.D., Ramakers, I.H., Rami, L., Resende de Oliveira, C., Rinne, J.O., Rodrigue, K.M., Rodriguez-Rodriguez, E., Roe, C.M., Rot, U., Rowe, C.C., Ruther, E., Sabri, O., Sanchez-Juan, P., Santana, I., Sarazin, M., Schroder, J., Schutte, C., Seo, S.W., Soetewey, F., Soininen, H., Spiru, L., Struyfs, H., Teunissen, C.E., Tsolaki, M., Vandenberghe, R., Verbeek, M.M., Villemagne, V.L., Vos, S.J., van Waalwijk van Doorn, L.J., Waldemar, G., Wallin, A., Wallin, A.K., Wiltfang, J., Wolk, D.A., Zboch, M., Zetterberg, H., 2015. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. Jama 313 (19), 1924–1938.

Kang, S.H., Park, Y.H., Lee, D., Kim, J.P., Chin, J., Ahn, Y., Park, S.B., Kim, H.J., Jang, H., Jung, Y.H., Kim, J., Lee, J., Kim, J.S., Cheon, B.K., Hahn, A., Lee, H., Na, D.L., Kim, Y.J., Seo, S.W., 2019. The Cortical Neuroanatomy Related to Specific Neuropsychological Deficits in Alzheimer's Continuum. Dement Neurocogn Disord 18 (3), 77–95.

Kim, H.R., Choe, Y.S., Moon, S.H., Kim, H.J., Jang, H., Na, D.L., Park, S.B., Seo, S.W., 2021. Finding the optimal cutoff value for amyloid β positivity using the iterative outlier method and concordance rate. Precis Future Med 5 (2), 83–89.

Klunk, W.E., Koeppe, R.A., Price, J.C., Benzinger, T.L., Devous M.D., Sr., Jagust, W.J., Johnson, K.A., Mathis, C.A., Minhas, D., Pontecorvo, M.J., Rowe, C.C., Skovronsky, D.M., Mintun, M.A., 2015. The Centiloid project: standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement 11 (1) 1-15.e11-14.

Kunkle, B.W., Grenier-Boley, B., Sims, R., Bis, J.C., Damotte, V., Naj, A.C., Boland, A., Vronskaya, M., van der Lee, S.J., Amlie-Wolf, A., Bellenguez, C., Frizatti, A., Chouraki, V., Martin, E.R., Sleegers, K., Badarinarayan, N., Jakobsdottir, J., Hamilton-Nelson, K.L., Moreno-Grau, S., Olaso, R., Raybould, R., Chen, Y., Kuzma, A.B., Hiltunen, M., Morgan, T., Ahmad, S., Vardarajan, B.N., Epelbaum, J., Hoffmann, P., Boada, M., Beecham, G.W., Garnier, J.G., Harold, D., Fitzpatrick, A.L., Valladares, O., Moutet, M.L., Gerrish, A., Smith, A.V., Qu, L., Bacq, D., Denning, N., Jian, X., Zhao, Y., Del Zompo, M., Fox, N.C., Choi, S.H., Mateo, I., Hughes, J.T., Adams, H.H., Malamon, J., Sanchez-Garcia, F., Patel, Y., Brody, J.A., Dombroski, B.A., Naranjo, M.C.D., Daniilidou, M., Eiriksdottir, G., Mukherjee, S., Wallon, D., Uphill, J., Aspelund, T., Cantwell, L.B., Garzia, F., Galimberti, D., Hofer, E., Butkiewicz, M., Fin, B., Scarpini, E., Sarnowski, C., Bush, W.S., Meslage, S., Kornhuber, J., White, C.C., Song, Y., Barber, R.C., Engelborghs, S., Sordon, S., Voijnovic, D., Adams, P.M., Vandenberghe, R., Mayhaus, M., Cupples, L.A., Albert, M.S., De Deyn, P.P., Gu, W., Himali, J.J., Beekly, D., Squassina, A., Hartmann, A.M., Orellana, A., Blacker, D., Rodriguez-Rodriguez, E., Lovestone, S., Garcia, M.E., Doody, R.S., Munoz-Fernadez, C., Sussams, R., Lin, H., Fairchild, T.J., Benito, Y.A., Holmes, C., Karamujic-Comic, H., Frosch, M.P., Thonberg, H., Maier, W., Roshchupkin, G., Ghetti, B., Giedraitis, V., Kawalia, A., Li, S., Huebinger, R.M., Kilander, L., Moebus, S., Hernandez, I., Kamboh, M.I., Brundin, R., Turton, J., Yang, Q., Katz, M.J., Concari, L., Lord, J., Beiser, A.S., Keene, C.D., Helisalmi, S., Kloszewska, I., Kukull, W.A., Koivisto, A.M., Lynch, A., Tarraga, L., Larson, E.B., Haapasalo, A., Lawlor, B., Mosley, T.H., Lipton, R.B., Solfrizzi, V., Gill, M., Longstreth Jr., W.T., Montine, T.J., Frisardi, V., Diez-Fairen, M., Rivadeneira, F., Petersen, R.C., Deramecourt, V., Alvarez, I., Salani, F., Ciaramella, A., Boerwinkle, E., Reiman, E.M., Fievet, N., Rotter, J.I., Reisch, J.S., Hanon, O., Cupidi, C., Andre Uitterlinden, AG, Royall, DR, Dufouil, C, Maletta, RG, de Rojas, I, Sano, M, Brice, A, Cecchetti, R, George-Hyslop, PS, Ritchie, K, Tsolaki, M, Tsuang, DW, Dubois, B, Craig, D, Wu, CK, Soininen, H, Avramidou, D, Albin, RL, Fratiglioni, L, Germanou, A, Apostolova, LG, Keller, L, Koutroumani, M, Arnold, SE, Panza, F, Gkatzima, O, Asthana, S, Hannequin, D, Whitehead, P, Atwood, CS, Caffarra, P, Hampel, H, Quintela, I, Carracedo, A, Lannfelt, L, Rubinsztein, DC, Barnes, LL, Pasquier, F, Frolich, L, Barral, S, McGuinness, B, Beach, TG, Johnston, JA, Becker, JT, Passmore, P, Bigio, EH, Schott, JM, Bird, TD, Warren, JD, Boeve, BF, Lupton, MK, Bowen, JD, Proitsi, P, Boxer, A, Powell, JF, Burke, JR, Kauwe, JSK, Burns, JM, Mancuso, M, Buxbaum, JD, Bonuccelli, U, Cairns, NJ, McQuillin, A, Cao, C, Livingston, G, Carlson, CS, Bass, NJ, Carlsson, CM, Hardy, J, Carney, RM, Bras, J, Carrasquillo, MM, Guerreiro, R, Allen, M, Chui, HC, Fisher, E, Masullo, C, Crocco, EA, DeCarli, C, Bisceglio, G, Dick, M, Ma, L, Duara, R, Graff-Radford, NR, Evans, DA, Hodges, A, Faber, KM, Scherer, M, Fallon, KB, Riemenschneider, M, Fardo, DW, Heun, R, Farlow, MR, Kolsch, H, Ferris, S, Leber, M, Foroud, TM, Heuser, I, Galasko, DR, Giegling, I, Gearing, M, Hull, M, Geschwind, DH, Gilbert, JR, Morris, J, Green, RC, Mayo, K, Growdon, JH, Feulner, T, Hamilton, RL, Harrell, LE, Drichel, D, Honig, LS, Cushion, TD, Huentelman, MJ, Hollingworth, P, Hulette, CM, Hyman, BT, Marshall, R, Jarvik, GP, Meggy, A, Abner, E, Menzies, GE, Jin, LW, Leonenko, G, Real, LM, Jun, GR, Baldwin, CT, Grozeva, D, Karydas, A, Russo, G, Kaye, JA, Kim, R, Jessen, F, Kowall, NW, Vellas, B, Kramer, JH, Vardy, E, LaFerla, FM, Jockel, KH, Lah, JJ, Dichgans, M, Leverenz, JB, Mann, D, Levey, AI, Pickering-Brown, S, Lieberman, AP, Klopp, N, Lunetta, KL, Wichmann, HE, Lyketsos, CG, Morgan, K, Marson, DC, Brown, K, Martiniuk, F, Medway, C, Mash, DC, Nothen, MM, Masliah, E, Hooper, NM, McCormick, WC, Daniele, A, McCurry, SM, Bayer, A, McDavid, AN, Gallacher, J, McKee, AC, van den Bussche, H, Mesulam, M, Brayne, C, Miller, BL, Riedel-Heller, S, Miller, CA, Miller, JW, Al-Chalabi, A, Morris, JC, Shaw, CE, Myers, AJ, Wiltfang, J, O'Bryant, S, Olichney, JM, Alvarez, V, Parisi, JE, Singleton, AB, Paulson, HL, Collinge, J, Perry, WR, Mead, S, Peskind, E, Cribbs, DH, Rossor, M, Pierce, A, Ryan, NS, Poon, WW, Nacmias, B, Potter, H, Sorbi, S, Quinn, JF, Sacchinelli, E, Raj, A, Spalletta, G, Raskind, M, Caltagirone, C, Bossu, P, Orfei, MD, Reisberg, B, Clarke, R, Reitz, C, Smith, AD, Ringman, JM, Warden, D, Roberson, ED, Wilcock, G, Rogaeva, E, Bruni, AC, Rosen, HJ, Gallo, M, Rosenberg, RN, Ben-Shlomo, Y, Sager, MA, Mecocci, P, Saykin, AJ, Pastor, P, Cuccaro, ML, Vance, JM, Schneider, JA, Schneider, LS, Slifer, S, Seeley, WW, Smith, AG, Sonnen, JA, Spina, S, Stern, RA, Swerdlow, RH, Tang, M, Tanzi, RE, Trojanowski, JQ, Troncoso, JC, Van Deerlin, VM, Van Eldik, LJ, Vinters, HV, Vonsattel, JP, Weintraub, S, Welsh-Bohmer, KA, Wilhelmsen, KC, Williamson, J, Wingo, TS, Woltjer, RL, Wright, CB, Yu, CE, Yu, L, Saba, Y, Pilotto, A, Bullido, MJ, Peters, O, Crane, PK, Bennett, D, Bosco, P, Coto, E, Boccardi, V, De Jager, PL, Lleo, A, Warner, N, Lopez, OL, Ingelsson, M, Deloukas, P, Cruchaga, C, Graff, C, Gwilliam, R, Fornage, M, Goate, AM, Sanchez-Juan, P, Kehoe, PG, Amin, N, Ertekin-Taner, N, Berr, C, Debette, S, Love, S, Launer, LJ, Younkin, SG, Dartigues, JF, Corcoran, C, Ikram, MA, Dickson, DW, Nicolas, G, Campion, D, Tschanz, J, Schmidt, H, Hakonarson, H, Clarimon, J, Munger, R, Schmidt, R, Farrer, LA, Van Broeckhoven, C, COD, M, DeStefano, AL, Jones, L, Haines, JL, Deleuze, JF, Owen, MJ, Gudnason, V, Mayeux, R, Escott-Price, V., Psaty, B.M., Ramirez, A., Wang, L.S., Ruiz, A., van Duijn, C.M., Holmans, P.A., Seshadri, S., Williams, J., Amouyel, P., Schellenberg, G.D., Lambert, J.C., Pericak-Vance, M.A., 2019. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Abeta, tau, immunity and lipid processing. Nat Genet 51 (3), 414–430.

Kwak, K., Yoon, U., Lee, D.K., Kim, G.H., Seo, S.W., Na, D.L., Shim, H.J., Lee, J.M., 2013. Fully-automated approach to hippocampus segmentation using a graph-cuts algorithm combined with atlas-based segmentation and morphological opening. Magn. Reson. Imaging 31 (7), 1190–1196.

Landau, S.M., Lu, M., Joshi, A.D., Pontecorvo, M., Mintun, M.A., Trojanowski, J.Q., Shaw, L.M., Jagust, W.J., 2013. Comparing positron emission tomography imaging and cerebrospinal fluid measurements of beta-amyloid. Ann Neurol 74 (6), 826–836.

Lempriere, S., 2019. Genetic variant cuts risk of multiple forms of dementia. Nat Rev Neurol. 15 (8), 436.

Li, Q.S., Parrado, A.R., Samtani, M.N., Narayan, V.A., 2015. Variations in the FRA10AC1 fragile site and 15q21 are associated with cerebrospinal fluid Abeta1-42 level. PloS one 10 (8), e0134000.

Lim, Y.Y., Villemagne, V.L., Laws, S.M., Ames, D., Pietrzak, R.H., Ellis, K.A., Harrington, K.D., Bourgeat, P., Salvado, O., Darby, D., Snyder, P.J., Bush, A.I., Martins, R.N., Masters, C.L., Rowe, C.C., Nathan, P.J., Maruff, P., 2013. BDNF Val66Met, Abeta amyloid, and cognitive decline in preclinical Alzheimer's disease. Neurobiol Aging 34 (11), 2457–2464.

Lim, Y.Y., Villemagne, V.L., Laws, S.M., Pietrzak, R.H., Snyder, P.J., Ames, D., Ellis, K.A., Harrington, K., Rembach, A., Martins, R.N., Rowe, C.C., Masters, C.L., Maruff, P., 2015. APOE and BDNF polymorphisms moderate amyloid beta-related cognitive decline in preclinical Alzheimer's disease. Mol Psychiatry 20 (11), 1322–1328.

Magno, L., Lessard, C.B., Martins, M., Lang, V., Cruz, P., Asi, Y., Katan, M., Bils-

land, J., Lashley, T., Chakrabarty, P., Golde, T.E., Whiting, P.J., 2019. Alzheimer's disease phospholipase C-gamma-2 (PLCG2) protective variant is a functional hypermorph. Alzheimer's Res. Ther 11 (1), 16.
Moon, S.W., Byun, M.S., Yi, D., Lee, J.H., Jeon, S.Y., Lee, Y., Kee, B.S., Lee, D.Y., 2019. The ankle-brachial index is associated with cerebral beta-amyloid deposition in cognitively normal older adults. J Gerontol A Biol Sci Med Sci 74 (7), 1141–1148.
Mormino, E.C., Brandel, M.G., Madison, C.M., Rabinovici, G.D., Marks, S., Baker, S.L., Jagust, W.J., 2012. Not quite PIB-positive, not quite PIB-negative: Slight PIB elevations in elderly normal control subjects are biologically relevant. NeuroImage 59 (2), 1152–1160.
Morris, E., Chalkidou, A., Hammers, A., Peacock, J., Summers, J., Keevil, S., 2016. Diagnostic accuracy of (18)F amyloid PET tracers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 43 (2), 374–385.
Nagahara, A.H., Merrill, D.A., Coppola, G., Tsukada, S., Schroeder, B.E., Shaked, G.M., Wang, L., Blesch, A., Kim, A., Conner, J.M., Rockenstein, E., Chao, M.V., Koo, E.H., Geschwind, D., Masliah, E., Chiba, A.A., Tuszynski, M.H., 2009. Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. Nat Med 15 (3), 331–337.
Ng, S., Villemagne, V.L., Berlangieri, S., Lee, S.T., Cherk, M., Gong, S.J., Ackermann, U., Saunder, T., Tochon-Danguy, H., Jones, G., Smith, C., O'Keefe, G., Masters, C.L., Rowe, C.C., 2007. Visual assessment versus quantitative assessment of 11C-PIB PET and 18F-FDG PET for detection of Alzheimer's disease. J. Nucl. Med 48 (4), 547–552.
Niu, H., Álvarez-Álvarez, I., Guillén-Grima, F., Aguinaga-Ontoso, I., 2017. Prevalence and incidence of Alzheimer's disease in Europe: a meta-analysis. Neurologia 32 (8), 523–532.
Park, C.-h., Kim, J., Namgung, E., Lee, D.-W., Kim, G.H., Kim, M., Kim, N., Kim, T.D., Kim, S., Lyoo, I.K., Yoon, S., 2017. The BDNF Val66Met polymorphism affects the vulnerability of the brain structural network. Front Hum Neurosci 11, 400.
Park, J.E., Kim, B.S., Kim, K.W., et al., 2019. Decline in the Incidence of All-Cause and Alzheimer's Disease Dementia: a 12-Year-Later Rural Cohort Study in Korea. J Korean Med Sci. 34 (44), e293 Published 2019 Nov 18.
Price, A.L., Patterson, N.J., Plenge, R.M., Weinblatt, M.E., Shadick, N.A., Reich, D., 2006. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet 38 (8), 904–909.
Radford, K., Delbaere, K., Draper, B., Mack, H.A., Daylight, G., Cumming, R., Chalkley, S., Minogue, C., Broe, G.A., 2017. Childhood stress and adversity is associated with late-life dementia in aboriginal Australians. Am J Geriatr Psychiatry 25 (10), 1097–1106.
Shim, H., Chasman, D.I., Smith, J.D., Mora, S., Ridker, P.M., Nickerson, D.A., Krauss, R.M., Stephens, M., 2015. A multivariate genome-wide association analysis of 10 LDL subfractions, and their response to statin treatment, in 1868 Caucasians. PloS one 10 (4), e0120758.
Shulman, J.M., Chipendo, P., Chibnik, L.B., Aubin, C., Tran, D., Keenan, B.T., Kramer, P.L., Schneider, J.A., Bennett, D.A., Feany, M.B., De Jager, P.L., 2011. Functional screening of Alzheimer pathology genome-wide association signals in Drosophila. Am J Hum Genet 88 (2), 232–238.
Sims, R., van der Lee, S.J., Naj, A.C., Bellenguez, C., Badarinarayan, N., Jakobsdottir, J., Kunkle, B.W., Boland, A., Raybould, R., Bis, J.C., Martin, E.R., Grenier-Boley, B., Heilmann-Heimbach, S., Chouraki, V., Kuzma, A.B., Sleegers, K., Vronskaya, M., Ruiz, A., Graham, R.R., Olaso, R., Hoffmann, P., Grove, M.L., Vardarajan, B.N., Hiltunen, M., Nothen, M.M., White, C.C., Hamilton-Nelson, K.L., Epelbaum, J., Maier, W., Choi, S.H., Beecham, G.W., Dulary, C., Herms, S., Smith, A.V., Funk, C.C., Derbois, C., Forstner, A.J., Ahmad, S., Li, H., Bacq, D., Harold, D., Satizabal, C.L., Valladares, O., Squassina, A., Thomas, R., Brody, J.A., Qu, L., Sanchez-Juan, P., Morgan, T., Wolters, F.J., Zhao, Y., Garcia, F.S., Denning, N., Fornage, M., Malamon, J., Naranjo, M.C.D., Majounie, E., Mosley, T.H., Dombroski, B., Wallon, D., Lupton, M.K., Dupuis, J., Whitehead, P., Fratiglioni, L., Medway, C., Jian, X., Mukherjee, S., Keller, L., Brown, K., Lin, H., Cantwell, L.B., Panza, F., McGuinness, B., Moreno-Grau, S., Burgess, J.D., Solfrizzi, V., Proitsi, P., Adams, H.H., Allen, M., Seripa, D., Pastor, P., Cupples, L.A., Price, N.D., Hannequin, D., Frank-Garcia, A., Levy, D., Chakrabarty, P., Caffarra, P., Giegling, I., Beiser, A.S., Giedraitis, V., Hampel, H., Garcia, M.E., Wang, X., Lannfelt, L., Mecocci, P., Eiriksdottir, G., Crane, P.K., Pasquier, F., Boccardi, V., Henandez, I., Barber, R.C., Scherer, M., Tarraga, L., Adams, P.M., Leber, M., Chen, Y., Albert, M.S., Riedel-Heller, S., Emilsson, V., Beekly, D., Braae, A., Schmidt, R., Blacker, D., Masullo, C., Schmidt, H., Doody, R.S., Spalletta, G., Longstreth Jr., W.T., Fairchild, T.J., Bossu, P., Lopez, O.L., Frosch, M.P., Sacchinelli, E., Ghetti, B., Yang, Q., Huebinger, R.M., Jessen, F., Li, S., Kamboh, M.I., Morris, J., Sotolongo-Grau, O., Katz, M.J., Corcoran, C., Dunstan, M., Braddel, A., Thomas, C., Meggy, A., Marshall, R., Gerrish, A., Chapman, J., Aguilar, M., Taylor, S., Hill, M., Fairen, M.D., Hodges, A., Vellas, B., Soininen, H., Kloszewska, I., Daniilidou, M., Uphill, J., Patel, Y., Hughes, J.T., Lord, J., Turton, J., Hartmann, A.M., Cecchetti, R., Fenoglio, C., Serpente, M., Arcaro, M., Caltagirone, C., Orfei, M.D., Ciaramella, A., Pichler, S., Mayhaus, M., Gu, W., Lleo, A., Fortea, J., Blesa, R., Barber, I.S., Brookes, K., Cupidi, C., Maletta, R.G., Carrell, D., Sorbi, S., Moebus, S., Urbano, M., Pilotto, A., Kornhuber, J., Bosco, P., Todd, S., Craig, D., Johnston, J., Gill, M., Lawlor, B., Lynch, A., Fox, N.C., Hardy, J., Albin, R.L., Apostolova, L.G., Arnold, S.E., Asthana, S., Atwood, C.S., Baldwin, C.T., Barnes, L.L., Barral, S., Beach, T.G., Becker, J.T., Bigio, E.H., Bird, T.D., Boeve, B.F., Bowen, J.D., Boxer, A., Burke, J.R., Burns, J.M., Buxbaum, J.D., Cairns, N.J., Cao, C., Carlson, C.S., Carlsson, C.M., Carney, R.M., Carrasquillo, M.M., Carroll, S.L., Diaz, C.C., Chui, H.C., Clark, D.G., Cribbs, D.H., Crocco, E.A., DeCarli, C., Dick, M., Duara, R., Evans, D.A., Faber, K.M., Fallon, K.B., Fardo, D.W., Farlow, M.R., Ferris, S., Foroud, T.M., Galasko, D.R., Gearing, M., Geschwind, D.H., Gilbert, J.R., Graff-Radford, N.R., Green, R.C., Growdon, J.H., Hamilton, R.L., Harrell, L.E., Honig, L.S., Huentelman, M.J., Hulette, C.M., Hyman, B.T., Jarvik, G.P., Abner, E., Jin, L.W., Jun, G., Karydas, A., Kaye, J.A., Kim, R., Kowall, N.W., Kramer, J.H., LaFerla, F.M., Lah, J.J., Leverenz, J.B., Levey, A.I., Li, G., Lieberman, A.P., Lunetta, K.L., Lyketsos, C.G., Marson, D.C., Martiniuk, F., Mash, D.C., Masliah, E., McCormick, W.C., McCurry, S.M., McDavid, A.N., McKee, A.C., Mesulam, M., Miller, B.L., Miller, C.A., Miller, J.W., Morris, J.C., Murrell, J.R., Myers, A.J., O'Bryant, S., Olichney, J.M., Pankratz, V.S., Parisi, J.E., Paulson, H.L., Perry, W., Peskind, E., Pierce, A., Poon, W.W., Potter, H., Quinn, J.F., Raj, A., Raskind, M., Reisberg, B., Reitz, C., Ringman, J.M., Roberson, E.D., Rogaeva, E., Rosen, H.J., Rosenberg, R.N., Sager, M.A., Saykin, A.J., Schneider, J.A., Schneider, L.S., Seeley, W.W., Smith, A.G., Sonnen, J.A., Spina, S., Stern, R.A., Swerdlow, R.H., Tanzi, R.E., Thornton-Wells, T.A., Trojanowski, J.Q., Troncoso, J.C., Van Deerlin, V.M., Van Eldik, L.J., Vinters, H.V., Vonsattel, J.P., Weintraub, S., Welsh-Bohmer, K.A., Wilhelmsen, K.C., Williamson, J., Wingo, T.S., Woltjer, R.L., Wright, C.B., Yu, C.E., Yu, L., Garzia, F., Golamaully, F., Septier, G., Engelborghs, S., Vandenberghe, R., De Deyn, P.P., Fernadez, C.M., Benito, Y.A., Thonberg, H., Forsell, C., Lilius, L., Kinhult-Stahlbom, A., Kilander, L., Brundin, R., Concari, L., Helisalmi, S., Koivisto, A.M., Haapasalo, A., Dermecourt, V., Fievet, N., Hanon, O., Dufouil, C., Brice, A., Ritchie, K., Dubois, B., Himali, J.J., Keene, C.D., Tschanz, J., Fitzpatrick, A.L., Kukull, W.A., Norton, M., Aspelund, T., Larson, E.B., Munger, R., Rotter, J.I., Lipton, R.B., Bullido, M.J., Hofman, A., Montine, T.J., Coto, E., Boerwinkle, E., Petersen, R.C., Alvarez, V., Rivadeneira, F., Reiman, E.M., Gallo, M., O'Donnell, C.J., Reisch, J.S., Bruni, A.C., Royall, D.R., Dichgans, M., Sano, M., Galimberti, D., St George-Hyslop, P, Scarpini, E, Tsuang, DW, Mancuso, M, Bonuccelli, U, Winslow, AR, Daniele, A, Wu, CK, Peters, O, Nacmias, B, Riemenschneider, M, Heun, R, Brayne, C, Rubinsztein, DC, Bras, J, Guerreiro, R, Al-Chalabi, A, Shaw, CE, Collinge, J, Mann, D, Tsolaki, M, Clarimon, J, Sussams, R, Lovestone, S, O'Donovan, MC, Owen, MJ, Behrens, TW, Mead, S, Goate, AM, Uitterlinden, AG, Holmes, C, Cruchaga, C, Ingelsson, M, Bennett, DA, Powell, J, Golde, TE, Graff, C, De Jager, PL, Morgan, K, Ertekin-Taner, N, Combarros, O, Psaty, BM, Passmore, P, Younkin, SG, Berr, C, Gudnason, V, Rujescu, D, Dickson, DW, Dartigues, JF, DeStefano, AL, Ortega-Cubero, S, Hakonarson, H, Campion, D, Boada, M, Kauwe, JK, Farrer, LA, Van Broeckhoven, C, Ikram, MA, Jones, L, Haines, JL, Tzourio, C, Launer, LJ, Escott-Price, V, Mayeux, R, Deleuze, JF, Amin, N, Holmans, PA, Pericak-Vance, MA, Amouyel, P, van Duijn, CM, Ramirez, A, Wang, LS, Lambert, JC, Seshadri, S, Williams, J, Schellenberg, GD, 2017. Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. Nat Genet 49 (9), 1373–1384.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum Brain Mapp 17 (3), 143–155.
Sperling, R.A., Donohue, M.C., Raman, R., Sun, C.K., Yaari, R., Holdridge, K., Siemers, E., Johnson, K.A., Aisen, P.S., 2020. Association of factors with elevated amyloid burden in clinically normal older individuals. JAMA neurology 77 (6), 735–745.
Stern, Y., Albert, M., Barnes, C., Cabeza, R., Pascual-Leone, A., Rapp, P., 2022. Reserve and Resilience Accessed from: https://reserveandresilience.com/framework/. Accessed 2 Feb. 2022.
Stern, Y., Arenaza-Urquijo, E.M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W.S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., 2020. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimers Dement 16 (9), 1305–1311.
Tessarin, G.W.L., Michalec, O.M., Torres-da-Silva, K.R., Da Silva, A.V., Cruz-Rizzolo, R.J., Goncalves, A., Gasparini, D.C., Horta-Junior, J.A.C., Ervolino, E., Bittencourt, J.C., Lovejoy, D.A., Casatti, C.A., 2019. A putative role of Teneurin-2 and its related proteins in astrocytes. Front Neurosci 13, 655.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15 (1), 273–289.
van der Lee, S.J., Conway, O.J., Jansen, I., Carrasquillo, M.M., Kleineidam, L., van den Akker, E., Hernandez, I., van Eijk, K.R., Stringa, N., Chen, J.A., Zettergren, A., Andlauer, T.F.M., Diez-Fairen, M., Simon-Sanchez, J., Lleo, A., Zetterberg, H., Nygaard, M., Blauwendraat, C., Savage, J.E., Mengel-From, J., Moreno-Grau, S., Wagner, M., Fortea, J., Keogh, M.J., Blennow, K., Skoog, I., Friese, M.A., Pletnikova, O., Zulaica, M., Lage, C., de Rojas, I., Riedel-Heller, S., Illan-Gala, I., Wei, W., Jeune, B., Orellana, A., Then Bergh, F., Wang, X., Hulsman, M., Beker, N., Tesi, N., Morris, C.M., Indakoetxea, B., Collij, L.E., Scherer, M., Morenas-Rodriguez, E., Ironside, J.W., van Berckel, B.N.M., Alcolea, D., Wiendl, H., Strickland, S.L., Pastor, P., Rodriguez Rodriguez, E., Boeve, B.F., Petersen, R.C., Ferman, T.J., van Gerpen, J.A., Reinders, M.J.T., Uitti, R.J., Tarraga, L., Maier, W., Dols-Icardo, O., Kawalia, A., Dalmasso, M.C., Boada, M., Zettl, U.K., van Schoor, N.M., Beekman, M., Allen, M., Masliah, E., de Munain, A.L., Pantelyat, A., Wszolek, Z.K., Ross, O.A., Dickson, D.W., Graff-Radford, N.R., Knopman, D., Rademakers, R., Lemstra, A.W., Pijnenburg, Y.A.L., Scheltens, P., Gasser, T., Chinnery, P.F., Hemmer, B., Huisman, M.A., Troncoso, J., Moreno, F., Nohr, E.A., Sorensen, T.I.A., Heutink, P., Sanchez-Juan, P., Posthuma, D., Clarimon, J., Christensen, K., Ertekin-Taner, N., Scholz, S.W., Ramirez, A., Ruiz, A., Slagboom, E., van der Flier, W.M., Holstege, H., 2019. A nonsynonymous mutation in PLCG2 reduces the risk of Alzheimer's disease, dementia with Lewy bodies and frontotemporal dementia, and increases the likelihood of longevity. Acta neuropathologica 138 (2), 237–250.
Willer, C.J., Li, Y., Abecasis, G.R., 2010. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 26 (17), 2190–2191.