Supplementary Material

Potential Novel Genes for Late-Onset Alzheimer's Disease in East-Asian Descent Identified by *APOE*-Stratified Genome-Wide Association Study

GARD Cohort

The GARD (Gwangju Alzheimer's & Related Dementias) cohort is a group recruiting local Korean senior citizens aged 60 years or older that has been tracked since 2010 for research on Alzheimer's disease and dementia. Most of the subjects were recruited at the Early Dementia Examination Center in Gwangju's Bitgoeul Senior Health Town, Republic of Korea to verify basic personal information, academic background, medical history, family history, and relevant drug treatment; and to conduct biometric (EEG, PPG, impedance) and K-MMSE (Korean Mini-Mental State Examination) tests to determine whether the subject suffered from dementia. Among the subjects whose K-MMSE assessment had been completed, those whose MMSE score were greater than 27 were selected. Thus, a cohort of 16,002 subjects was recruited for the present study. An additional thorough clinical examination was conducted for those who wished to have one conducted and those who agreed to the study after conducting the basic examination. Clinical evaluation was conducted through brain imaging information of subjects using the Seoul Neuropsychological Screening Battery (SNSB) [1] test and 3T MRI (Skyra, Siemens Healthineers Ltd., Seoul, Republic of Korea) single scanner. ^{18}F-Florbetaben (FBB) beta-amyloid positron emission tomography (PET) was performed those who agreed. All diagnoses were evaluated by dementia specialists in neurology and psychiatry at Chosun University Hospital, Gwangju, Republic of Korea and Chonnam National University Hospital, Gwangju, Republic of Korea. Blood tests (complete blood count, cholesterol, blood sugar, and thyroid function tests) and CSF tests were carried out on the diagnosed subjects. Genomic DNA was extracted from peripheral

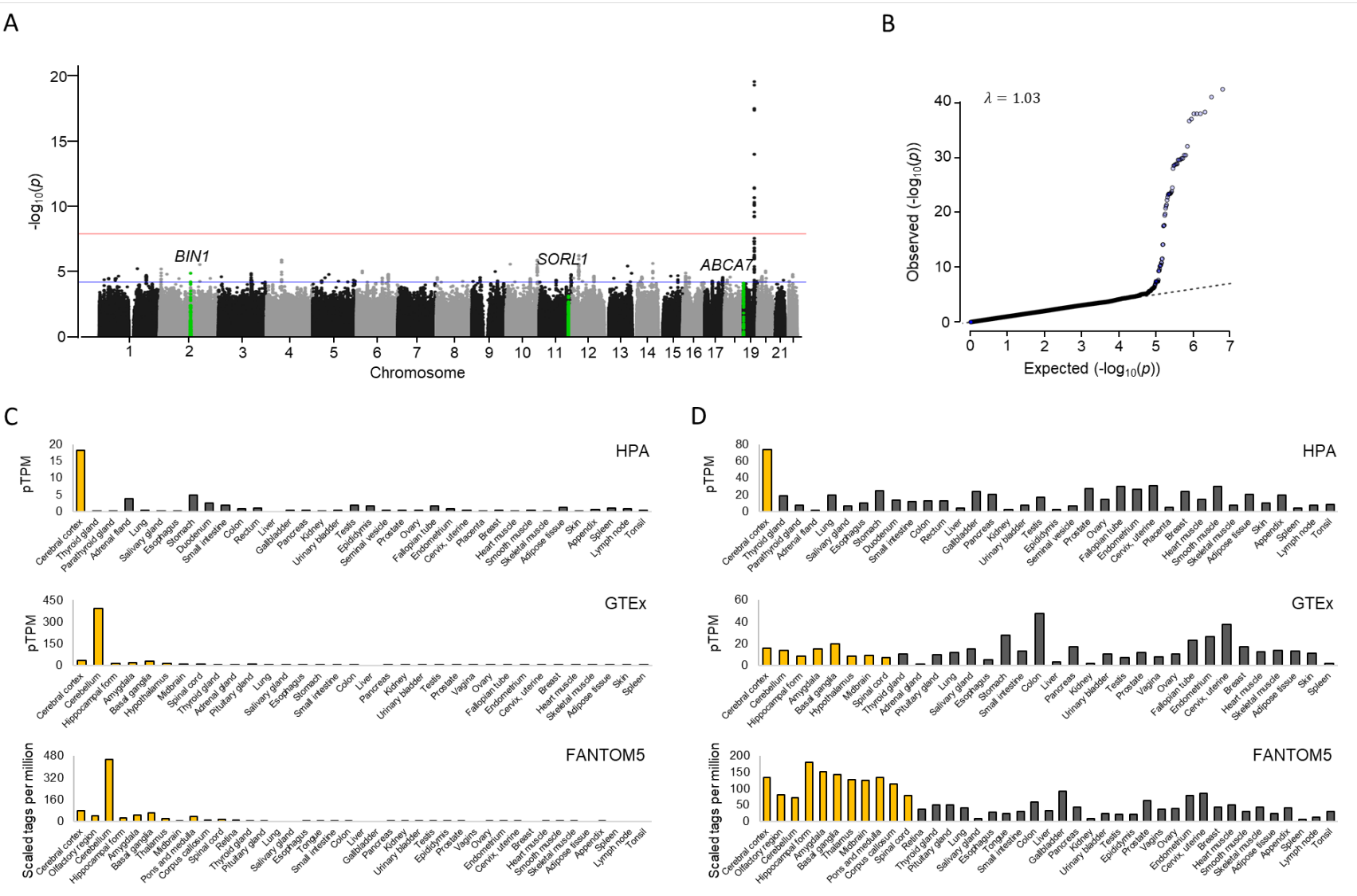
blood leukocytes that were isolated from whole blood collected in collection tube containing EDTA. Cognitively normal (CN) subjects had no evidence of neurological disorders and impairment in cognitive function or routine activities. Excluded subjects included those who had less than three years of education, a history of brain disease and poor mental health, were undergoing relevant medical treatment and consuming high levels of alcohol or diagnosed with depression. The clinical diagnosis of probable AD was determined on the basis of NINCDS/ADRDA criteria [2]. A portion of AD blood specimens were from other major hospitals in Korea, including Seoul National University Hospital, Kyungpook National University Hospital, Inha University Hospital, and Pusan National University Hospital. The use of these blood samples was approved by the IRB of Chosun University Hospital, Gwangju, Republic of Korea.

REFERENCES

[1] Kang Y, Na D, Hahn S (2003) *Seoul Neuropsychological Screening Battery*. Human Brain Research & Consulting Co, Incheon.

[2] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-939.

Supplementary Figure 1. The results of genome-wide association analysis for AD and gene expression analysis for novel genes. Manhattan plot (A) and Q-Q plot (B) show the significance for all SNPs from the GWAS result using all samples. The previously reported genes (*BIN1*, *SORL1*, and *ABCA7*) are highlighted in green. (Supplementary: https://drive.google.com/file/d/1hu0DLFJnlXolwPoOQTFBwY8Uqeiuqk D_/view?usp=sharing). The RNA expression and distribution of *CACNA1A* (C) and *LRIG1* (D) in brain region (yellow bar) among normal human tissues. C) Data from HPA dataset showing highest mRNA expression of the *CACNA1A* gene in the cerebral cortex at 18.2 protein-coding transcripts per million (pTPM). The expression of the *CACNA1A* gene was highest in the cerebellum at 394.1 pTPM in GTEx, 453.4 scaled-tags per million reported by FANTOM5. D) The expression levels of *LRIG1* were high in the cerebral cortex at 74.1 pTPM in HPA, 16.0 pTPM reported by GTEx. Data from FANTOM5 dataset showing highest mRNA expression of the *LRIG1* gene in hippocampal formation at 179.9 scaled-tags per million. (Data available from https://www.proteinatlas.org/ENSG00000141837-CACNA1A/tissue and https://www.proteinatlas.org/ENSG00000144749-LRIG1/tissue)


A
-log10(p)
BIN1
SORL1
ABCA7
Chromosome
B
λ = 1.03
Observed (-log10(p))
Expected (-log10(p))
C
HPA
GTEx
FANTOM5
pTPM
Scaled tags per million
D
HPA
GTEx
FANTOM5
pTPM
Scaled tags per million