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RESEARCH ARTICLE

Ethnic-specific effects of the *LILRB2–LILRB5* locus and newly identified risk loci for Alzheimer's disease in the East Asian population

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Abstract

INTRODUCTION: Genome-wide association studies have identified numerous Alzheimer's disease (AD) susceptibility loci in European populations. However, the genetic architecture of AD in non-European populations remains underinvestigated.

METHODS: We performed a genetic association study in East Asians ($N = 8514$) to validate known AD loci and identify new susceptibility loci.

RESULTS: We identified *LILRB2–LILRB5* as an AD susceptibility locus with ethnic-specific effects between Europeans and East Asians. The lead variant, rs587709-T, was associated with decreased AD risk and increased *LILRB5* expression in Europeans. Conversely, in East Asians, the same allele was associated with increased AD risk and increased *LILRB2* expression. Furthermore, genome-wide analysis identified *TTC3* and *FAM135A* as candidate susceptibility loci for AD or cognition.

DISCUSSION: The results establish *LILRB2–LILRB5* as a cross-ancestry AD-associated locus with ethnic-specific genetic mechanisms and reveal new susceptibility loci, extending the understanding of the genetic etiology of AD.

KEYWORDS
cognitive decline, genome-wide association studies, paired immunoglobulin-like receptors B, quantitative trait loci, trans-ethnic

Highlights

- Known Alzheimer's disease (AD) risk loci from Europeans are thoroughly investigated in East Asians.
- The *LILRB2–LILRB5* locus exerts ethnic-specific effects on AD.
- The AD-associated genetic variant affects *LILRB2* and *LILRB5* expression differently across ethnic populations.
- Both LILRB2 and LILRB5 proteins are associated with biomarkers of AD pathologies.
- *TTC3* and *FAM135A* are newly identified candidate risk loci for AD or cognitive decline.

1 | BACKGROUND

Alzheimer's disease (AD) is the most prevalent form of dementia and a leading cause of death in the elderly population.[1] AD has a strong genetic basis, with an estimated heritability of ≈ 70%.[2] Genetic studies of familial AD have identified critical disease-causing mutations in amyloid beta (Aβ) pathway genes, such as amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*).[3] However, these mutations are rare and account for only a small fraction of AD cases.[4] The genetic etiology of most AD cases is complex and involves numerous common single-nucleotide polymorphisms (SNPs) with small risk effects that collectively contribute to the genetic risk of AD.[5] A recent genome-wide association study (GWAS) identified 75 AD risk loci, including 42 new loci,[6] highlighting the crucial role of genetic variants in the pathogenesis of AD.

AD genetic studies have predominantly focused on populations of European descent,[6–9] which limits our understanding about the genetic architecture of AD. Among the 75 AD risk loci identified in the European population,[6] only a few of them, such as apolipoprotein E (*APOE*),[10] *ABCA7*,[11,12] and *SORL1*,[13] have been validated in other populations. However, the effects of many AD risk loci, particularly the 42 loci newly identified in a recent GWAS,[6] are still not well understood in non-European populations. Moreover, the risk effects of specific genetic variants on AD can vary among populations.[14] For instance, the odds ratios of *APOE* ε4, the most significant AD risk SNP, range from 2.11 to 5.46 across global populations.[15] This highlights the importance of studying AD risk genetic variants in non-European populations to comprehensively understand the genetic risk factors of AD. In addition, the distinct genetic backgrounds of ethnic groups offer opportunities to discover new AD risk loci in non-European populations.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed literature from PubMed. While genome-wide association studies identify numerous Alzheimer's disease (AD) susceptibility loci in European populations, the genetic architecture of AD in non-European populations remains underinvestigated. This study reviews relevant genetic studies and includes some prior data in the meta-analysis.
2. **Interpretation**: The results establish *LILRB2–LILRB5* as an AD susceptibility locus in European and East Asian populations. Notably, the same AD-associated allele at this locus confers opposing effects on AD risk and differently affects *LILRB2* and *LILRB5* expression between populations, suggesting an ethnic-specific genetic mechanism. Furthermore, *TTC3* and *FAM135A* were identified as new candidate susceptibility loci for AD or cognitive decline, extending the understanding of genetic etiology of AD.
3. **Future directions**: The ethnic-specific genetic regulation of the *LILRB2–LILRB5* locus requires mechanistic insight. Future studies should use functional genomics to elucidate the molecular basis of this locus across diverse populations.

Given that most AD risk genetic variants identified by GWASs are in non-coding regions,[6] it is important to investigate their regulatory effects on gene expression.[16] Advances in high-throughput transcriptomic and proteomic profiling technologies have enabled the establishment of robust associations between genetic variants and the expression of genes or proteins.[17,18] Quantitative trait loci (QTL) analysis, including gene expression QTL (eQTL) and protein QTL (pQTL), has revealed significant roles of AD-associated genetic variants in regulating the expression of genes related to amyloid and tau pathologies as well as immune pathways.[6,19] As such, these findings have substantially deepened our knowledge about the molecular mechanisms underlying AD.

Accordingly, in this study, we performed a comprehensive genetic analysis to identify genetic risk factors in the East Asian population and elucidate their regulatory effects on gene expression. First, we analyzed 75 known AD risk loci in the East Asian population (1029 cases vs. 1316 controls for discovery; 2013 cases vs. 2114 controls for replication). We identified significant associations between AD and two known AD risk loci: *SORL1* and *LILRB2–LILRB5*. Notably, we observed different effects of the lead AD-associated SNP in the *LILRB2–LILRB5* locus, rs587709-T, on AD risk between Europeans and East Asians. Specifically, rs587709-T was associated with decreased AD risk in Europeans but increased AD risk in East Asians. Meanwhile, the regulatory effect of rs587709-T on its flanking genes also differed between populations: it was associated with elevated LILRB5 in Europeans and elevated LILRB2 in East Asians, indicating that both *LILRB2* and *LILRB5* are candidate AD risk genes. Interestingly, we showed that higher cerebrospinal fluid (CSF) LILRB2 was associated with elevated CSF phosphorylated tau-181 (p-tau181) while higher CSF LILRB5 was associated with elevated CSF Aβ42. These findings implicate both LILRB2 and LILRB5 in AD pathogenesis, providing insights into the genetic mechanisms underlying the *LILRB2–LILRB5* locus. Furthermore, our genome-wide association analysis identified *TTC3* and *FAM135A* as new candidate risk loci for AD and dementia.

2 | METHODS

2.1 | Cohort recruitment

For the Hong Kong Chinese cohort, we recruited 3091 participants from the Prince of Wales Hospital, Queen Elizabeth Hospital, Tuen Mun Hospital, United Christian Hospital, and Ruttonjee & Tang Shiu Kin Hospitals. All participants (≥ 60 years old) underwent the Montreal Cognitive Assessment (MoCA)[20] and were diagnosed according to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.[21] These clinically diagnosed participants included 1006 cognitively normal controls (NCs), 852 patients with mild cognitive impairment (MCI), 934 patients with AD, and 299 patients with dementia (e.g., vascular dementia, mixed dementia, dementia with Lewy bodies, and unclassified dementia). We also recruited 1670 elderly volunteers from Haven of Hope Christian Service and the Community CareAge Foundation and examined their cognitive performance using the MoCA. We then used different MoCA score cutoffs to classify these volunteers into NC (MoCA ≥ 25, $n = 678$), MCI (MoCA 21–24, $n = 425$), and dementia (MoCA ≤ 20, $n = 567$) groups (Table S1 in supporting information). This study was approved by the clinical research and ethics committees of the Joint Chinese University of Hong Kong–New Territories East Cluster for Prince of Wales Hospital (CREC ref. no. 2015.461), the Kowloon Central Cluster/Kowloon East Cluster for Queen Elizabeth Hospital (KC/KE-15-0024/FR-3), and the Human Participants Research Panel of the Hong Kong University of Science and Technology (CRP#180 and CRP#225). All participants provided written informed consent for both study enrollment and sample collection.

For the Singapore cohort, we included 283 participants recruited from National University Hospital and St. Luke's Hospital (Table S1). All participants (≥ 50 years old) underwent comprehensive neuropsychological assessment and were diagnosed according to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition for dementia and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) criteria for AD.[22,23] This study was approved by the National Healthcare Group Domain-Specific Review Board (NHG DSRB reference numbers: 2018/01098 and 2010/00017). All participants or their legal representatives provided written informed consent for both study enrolment and sample collection.

2.2 | DNA extraction and genotyping

We collected 6 mL whole blood samples from the study participants using ethylenediaminetetraacetic acid (EDTA) tubes (Greiner Bio-One) to prevent blood coagulation. We centrifuged the EDTA tubes at 2000 × g for 15 minutes at 4°C. We then stored the separated plasma and cell pellet at −80°C. We performed DNA extraction from 400 µL blood cell pellets using a QIAamp DNA Blood Mini Kit (Qiagen) on a QIAcube Connect (Qiagen). We eluted the extracted DNA twice using 50 and 60 µL AE buffer, respectively, which yielded ≈ 100 µL DNA samples. We evaluated the concentration and quality control metrics (i.e., A260/280 and A260/230) of the DNA samples using a BioDrop Duo+ spectrophotometer (Biochrom).

We genotyped the DNA samples using a NeuroBooster Array BeadChip (Illumina). We processed 200 ng DNA per sample according to the Illumina Infinium LCG Assay protocol. We imaged BeadChips on an iScan System with iScan Control Software (Illumina). We input raw data files into GenomeStudio (v2010.2) to call genotypes with a GenCall threshold of 0.15. We subsequently used the BCFtools (v1.11) gtc2vcf plugin to generate VCF from GTC files.[24,25] The genomic DNA samples were randomized, and the researcher performing the genotyping assay was blinded to the groups. Both the Hong Kong Chinese and Singapore cohorts were genotyped at the same center in Hong Kong following the same protocol.

2.3 | Genetic data quality control and genotype imputation

We used PLINK (v2.0) to infer sex from genetic data and excluded samples with inconsistent genetic sex and clinical records (n = 20).[26] All individuals showed a genotype call rate > 99% with an inbreeding coefficient |F| < 0.15. We estimated the pairwise KING kinship coefficient among participants using PLINK (v2.0) and excluded duplicate (n = 197) or related individuals with a second-degree or closer relationship (kinship coefficient > 0.088, n = 392).[26] We then used the bigsnpr (v1.12.2) R package to compute genetic principal components (PCs) by projecting the genetic data to the 1000 Genomes Project reference panel.[27,28] We excluded participants of non-East Asian ancestry (n = 48; Figure S1 in supporting information). To obtain genetic PCs for association analysis, we used the bigsnpr (v1.12.2) R package to perform second-round PC analysis using all unrelated participants of East Asian ancestry.[27]

We performed quality control on genetic variants using PLINK (v2.0).[26] Specifically, we excluded variants with only reference calls (n = 747,692), variants with a call rate < 95% (n = 7623), duplicate or multi-allelic genetic variants (n = 41,749), non-autosomal variants (n = 59,739), and variants significantly deviating from Hardy–Weinberg equilibrium ($P \leq 5 \times 10^{-8}$, n = 3392) or the frequency in 1000 Genomes unrelated East Asian samples ($P \leq 5 \times 10^{-8}$, χ^2 test, n = 121,080). After quality control, we included 1,023,096 high-quality genetic variants for phasing and imputation using Eagle (v2.4.1)[29] and Minimac4,[30] with the high-coverage 1000 Genomes Project reference panel.[28] We kept 5,425,154 common variants (i.e., minor allele frequency > 0.05) with high imputation quality (i.e., R^2 > 0.6) for genome-wide association analysis. All variant calling and imputation analysis were based on the GRCh38 reference genome. The specific numbers of genetic variants and samples included in each quality control step are provided in Table S2 in supporting information.

2.4 | Replication cohorts

For replication analysis, we used a Japanese clinical cohort from Niigata University. Probable AD cases (n = 1874) were ascertained on the basis of the criteria of the NINCDS/ADRDA.[31] The Mini-Mental State Examination, Clinical Dementia Rating, and/or Function Assessment Staging were primarily used to evaluate cognitive impairment. Elders living in an unassisted manner in the local community with no signs of dementia were used as controls (n = 1969). The clinical cohort was further jointly analyzed with the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) cohort.[32] J-ADNI enrolled cognitively unimpaired participants (n = 145), participants with late MCI (n = 220), and patients with mild AD dementia (n = 139) using criteria consistent with those of the North American Alzheimer's Disease Neuroimaging Initiative (ADNI).[33] As the cognition test results of the Niigata cohort are not available to the researchers, we did not use this cohort for the replication analysis of the cognition-associated SNPs.

We also obtained summary statistics from a Japanese AD GWAS by Shigemizu et al. through the NBDC database (https://humandbs.dbcls.jp/en/hum0237-v1).[34] As this dataset does not include the known AD-associated SNPs in the *LILRB2–LILRB5* locus (i.e., rs587709 and its proxy SNPs), we did not include it in the replication analysis of the *LILRB2–LILRB5* locus. Moreover, as the Niigata cohort partially overlaps with the study cohort of Shigemizu et al., we only included the non-overlapping subset of the Niigata cohort (n = 1039 patients with AD and 1167 NCs) in the meta-analysis of both the Niigata cohort and the cohort of Shigemizu et al.

2.5 | Replication analysis of known AD risk loci

To replicate the AD associations of known AD risk loci identified in the European population, we queried genome-wide significant loci and their lead AD-associated genetic variants reported in Bellenguez et al.[6] We used MAGMA (v1.10) to perform gene-level analysis of known AD risk loci.[35] For each locus, we selected all common genetic variants residing within the 35 kb upstream and 10 kb downstream window. We used the "MULTI" model implemented in MAGMA to perform the association analysis in each cohort, adjusting for age, sex, and the first three PCs. We performed a meta-analysis of the statistics from different study cohorts using MAGMA. To examine the associations between individual genetic variants and AD, we used PLINK (v2.0) to perform logistic regression, adjusting for age, sex, the first three PCs, and genotyping center (if more than one).[26] For the *LILRB2–LILRB5* locus in particular, we also performed conditional analysis on rs587709 to

examine the independent effects of genetic variants on AD in the East Asian population. We performed meta-analysis of the statistical results from different cohorts using the fixed-effect model in METASOFT (v2.0.0).[36] We applied the Benjamini–Hochberg procedure to calculate the false discovery rate (FDR) of known AD-associated loci/genetic variants by using the p.adjust function in R.

2.6 | Genome-wide association analysis

We used the same analytical methods as those used for the replication analysis above to examine the genome-wide associations between AD and genetic variants. To analyze cognitive performance, we first applied rank-based, inverse normal transformation to MoCA scores using the RNOmni (v0.6.0) R package.[37] We then performed linear regression on the normalized MoCA scores, adjusting for age, sex, and the first three PCs, using PLINK (v2.0) and MAGMA (v1.10) for variant- and gene-level analysis, respectively. We also used the same methods as above to perform meta-analysis. We used Bonferroni adjusted *P* values to determine significant loci in gene-level and genome-wide association analysis. We performed power analysis for genetic variants with a range of effect sizes and minor allele frequencies (see Methods in supporting information). The power calculations are shown in Figure S2 in supporting information.

2.7 | Collection of proteomic datasets

To examine the associations between genetic variants and plasma proteins, we used Olink Proximity Extension Assay technology to measure 1160 plasma proteins in 406 participants in the Hong Kong cohort as described previously.[38,39] We also retrieved the genetic and proteomic data of the European INTERVAL study cohort, which includes 3622 plasma proteins measured by the SOMAscan platform in 3301 participants.[18] We also obtained genetic and CSF proteomic profiles from the ADNI dataset.[40] Furthermore, we predicted the plasma levels of LILRB2 and LILRB5 in the ADNI dataset using genetic score models obtained from the OmicsPred database (LILRB2: OPGS000075, LILRB5: OPGS000006).[41] The genetic scores of LILRB2 and LILRB5 are strongly correlated with the actual plasma protein levels of LILRB2 (r = 0.677) and LILRB5 (r = 0.849), respectively.[41] We normalized all protein levels and genetic scores by rank-based, inverse normal transformation using the RNOmni (v0.6.0) R package.[37]

2.8 | Association analysis of proteomic data

To examine the associations of the plasma levels of LILRB2 and LILRB5 with genetic variants, we performed linear regression using the lm function in R, adjusting for age, sex, and the first three PCs. We also performed linear regression to examine the associations of the CSF levels of LILRB2 and LILRB5 with their predicted plasma protein scores and genetic variants in the ADNI dataset, adjusting for age, sex, the first three PCs, and years of education. We included years of education as a covariate because of the high prevalence of participants with a high education level in the ADNI dataset.[42] To examine the associations between AD and the CSF levels of LILRB2 and LILRB5 in the ADNI dataset, we performed logistic regression using the glm function in R, adjusting for age, sex, the first three PCs, and years of education. We also performed linear regression to examine the associations of the CSF levels of LILRB2 and LILRB5 with AD pathological biomarkers in the ADNI dataset, including the CSF levels of p-tau181 and Aβ42. As the CSF levels of LILRB2 and LILRB5 were positively correlated (β = 0.184, $P = 2.3 \times 10^{-7}$), we simultaneously fit LILRB2, LILRB5, and their interaction term in the regression models, adjusting for age, sex, the first three PCs, and years of education. We applied the Holm–Bonferroni method to correct the results of statistical tests among multiple proteins by using the p.adjust function in R.

2.9 | Data visualization

We generated Manhattan and quantile–quantile (Q–Q) plots using the qqman package (v0.1.9)[43] in R and generated regional plots using LocusZoom (v1.4).[44] We used the car package (v3.1) in R to generate all added-variable plots.[45] We generated all bar and box plots using GraphPad Prism (v8.0.2). For box plots, boxes extend from the 25th to 75th percentiles, and whiskers mark the 10th and 90th percentiles.

3 | RESULTS

3.1 | Replication analysis of known AD-associated loci in the East Asian population

We used the Illumina NeuroBooster microarray to genotype 5044 participants. After genetic data quality control, we included 4387 unrelated participants of East Asian ancestry for genetic analysis (Figure S1), comprising 1316 NCs, 1266 participants with MCI, 1029 participants with AD, and 776 participants with dementia (Table S1). To replicate known AD-associated loci, we conducted gene-level analysis (1029 AD vs. 1316 NC) on the 75 AD risk loci (excluding *APOE*) identified in a recent European AD GWAS (Table S3 in supporting information).[6] We observed nominally significant associations between AD and several loci, including *SORL1* ($P = 5.8 \times 10^{-4}$), *MYO15A* ($P = 6.4 \times 10^{-3}$), *PRKD3* ($P = 6.9 \times 10^{-3}$), and *LILRB2* ($P = 1.1 \times 10^{-2}$; Figure 1A). In particular, the association between *SORL1* and AD remained significant after multiple test correction (FDR = 4.3×10^{-2}), corroborating the previous association between AD and the *SORL1* locus in the East Asian population.[13,46,47]

To investigate the AD risk effects of genetic variants in these loci across ethnic groups, we analyzed the 83 independent AD-associated SNPs from the 75 AD risk loci identified in the European population.[6] Among the 83 reported SNPs, 13 were not genotyped in our study cohort because of their low prevalence in the East Asian population (n = 12; Figure S3 and Table S4 in supporting information) or their loca-

(A)

Locus	Chr	Start	End	No. of variants	*P*	*FDR*
SORL1	11	121417203	121643762	317	5.8×10^{-4}	4.4×10^{-2}
MYO15A	17	18073706	18190225	189	6.4×10^{-3}	1.7×10^{-1}
PRKD3	2	37240502	37359772	198	6.9×10^{-3}	1.7×10^{-1}
LILRB2	19	54263812	54316178	193	1.1×10^{-2}	2.1×10^{-1}

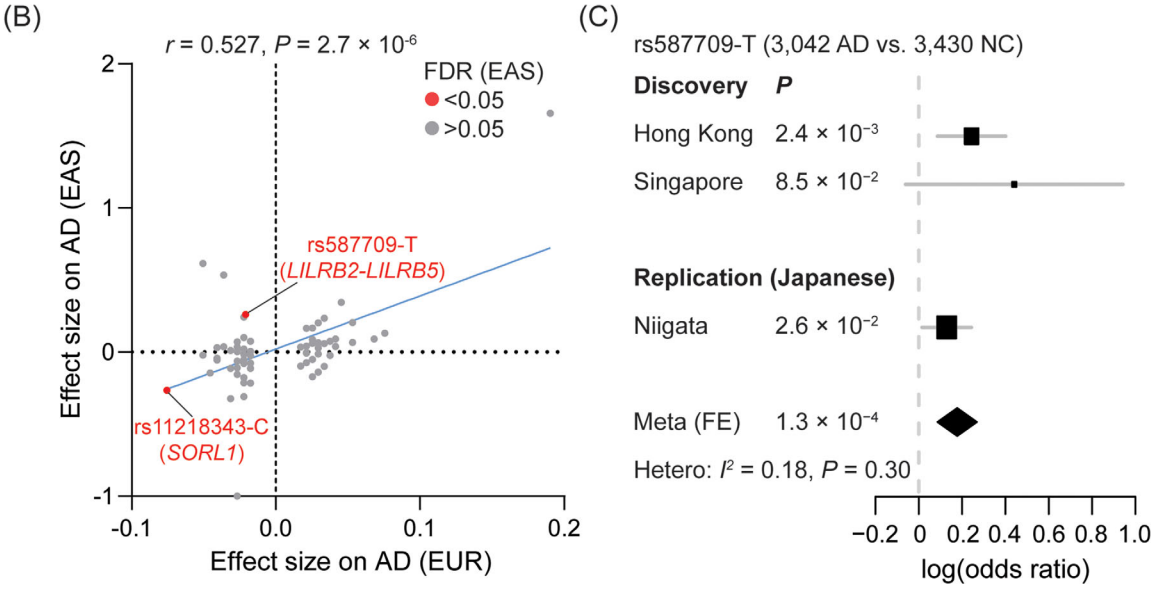

FIGURE 1 Replication analysis of known AD-associated loci in the East Asian population. A, Gene-level replication analysis of known AD-associated loci in the EAS. B, Correlations of the effect sizes of genetic variants on AD between the EAS and EUR. *r*, Pearson's correlation coefficient. C, Meta-analysis of the association between the rs587709-T allele and AD in the EAS. AD, Alzheimer's disease; EAS, East Asian population; EUR, European population; FDR, false discovery rate; FE, fixed-effect meta-analysis.

tion within the complex *IGH* locus ($n = 1$). We then compared the effects of the remaining 70 SNPs on AD between populations (1029 patients with AD vs. 1316 NCs in the East Asian population). Overall, the AD risk/protective effects of these SNPs in the East Asian population were positively correlated with those reported in the European population ($r = 0.527$, $P = 2.7 \times 10^{-6}$; Figure 1B). This indicates that most AD-associated loci identified in the European population exhibit a similar trend of effects on AD risk in the East Asian population. In particular, rs11218343-C in the *SORL1* locus exerted significant AD protective effects in the East Asian population after multiple test correction ($\beta = -0.265$, FDR = 0.033; Figure 1B, Table S4), which is concordant with its effect in the European population and in previous studies in the East Asian population.[13,48]

Of note, one genetic variant exerted different effects on AD risk between the European and East Asian populations. Specifically, rs587709-T, the lead AD-associated variant residing in the intergenic region between *LILRB2* and *LILRB5*, was associated with decreased AD risk in the European population ($\beta = -0.021$, $P = 3.6 \times 10^{-11}$) and increased AD risk in the East Asian population ($\beta = 0.261$, $P = 6.5 \times 10^{-4}$, FDR = 0.033; Figure 1B, Table S4), indicating an ethnic-specific effect of this locus. To validate this finding, we performed replication analysis in a Japanese AD cohort from Niigata University ("Niigata cohort" hereafter; $n = 2013$ patients with AD and 2114 NCs). Accordingly, we identified an AD risk effect of rs587709-T in the Niigata cohort ($\beta = 0.129$, $P = 2.6 \times 10^{-2}$; Figure 1C), which was concordant with that in the discovery East Asian cohorts. Furthermore, meta-analysis confirmed a significant AD risk effect of rs587709-T in the East Asian population ($\beta = 0.177$, $P = 1.3 \times 10^{-4}$; Figure 1C). In addition, there was no significant interaction between rs587709-T and other known AD risk factors, such as sex ($P = 0.102$) or *APOE* ε4 genotype ($P = 0.586$), in the East Asian population. Therefore, these results collectively identify the *LILRB2–LILRB5* locus as an AD-associated locus in the East Asian population that exerts a different effect on AD risk compared to that in the European population.

3.2 | Association between AD and the *LILRB2–LILRB5* locus in the European and East Asian populations

The distinct effects of rs587709 on AD risk in the European and East Asian populations highlight a noteworthy ethnic difference in

the *LILRB2–LILRB5* locus. Therefore, we examined the AD associations in this locus in both populations. While rs587709 was identified as the lead AD-associated variant in the European population (Figure 2A), in the East Asian population, rs141869975 ($P = 1.6 \times 10^{-4}$) exhibited a slightly stronger association with AD than rs587709 ($P = 6.5 \times 10^{-4}$; Figure 2B). Nonetheless, conditional analysis showed that rs141869975 was not associated with AD after controlling for rs587709 ($P = 0.06$; Figure S4 in supporting information), indicating that the association between rs141869975 and AD also depends on rs587709 in the East Asian population. Hence, we focused on the effects of rs587709 in downstream genetic analysis between the East Asian and European populations. Interestingly, the prevalence and AD association of rs587709 varied between populations. Specifically, in the European population, rs587709-T was the major allele (allele frequency [AF] = 67.5%) and was associated with decreased AD risk ($\beta = -0.021$, $P = 3.6 \times 10^{-11}$; Table S4). However, in the East Asian population, rs587709-T was the minor allele (AF = 26.5%) and was associated with increased AD risk ($\beta = 0.261$, $P = 6.5 \times 10^{-4}$; Table S4). These findings suggest that rs587709 may modulate AD risk in the European and East Asian populations via different genetic mechanisms.

3.3 | Associations of rs587709 with *LILRB2* and *LILRB5* expression in the European and East Asian populations

The rs587709 variant resides in the intergenic region between *LILRB2* and *LILRB5*, which encode leukocyte immunoglobulin-like receptors that play critical roles in maintaining immune homeostasis.[49] Therefore, we subsequently investigated the regulatory effects of rs587709 by analyzing its associations with blood LILRB2 and LILRB5 protein levels using the proteomic dataset from the European INTERVAL study and the Hong Kong Chinese study cohort.[18,50] Interestingly, in the European population, rs587709-T was nominally associated with increased LILRB2 levels ($\beta = 0.085$, adjusted $P = 9 \times 10^{-3}$; Figure 2C and Table S5 in supporting information) and significantly associated with increased LILRB5 levels, passing the genome-wide threshold ($\beta = 0.456$, adjusted $P = 1.0 \times 10^{-66}$; Figure 2D, Table S5). This indicates that rs587709 confers stronger regulatory effects on LILRB5 than LILRB2 in the European population. In contrast, in the East Asian population, rs587709-T was only associated with increased LILRB2 levels ($\beta = 0.642$, adjusted $P = 8.4 \times 10^{-24}$; Figure 2E) without affecting LILRB5 levels (adjusted $P = 0.51$; Figure 2F, Table S5). We also examined the effects of rs587709-T on *LILRB2* and *LILRB5* transcript levels using RNA sequencing data from the Genotype-Tissue Expression (GTEx) dataset and the Hong Kong Chinese study cohort.[17,51] The rs587709-T allele was associated with increased expression of *LILRB5* in the European population ($\beta = 0.220$, adjusted $P = 1.6 \times 10^{-2}$; Table S6 in supporting information) and *LILRB2* in the East Asian population ($\beta = 0.251$, adjusted $P = 2.1 \times 10^{-7}$; Table S6). These results align with the aforementioned genotype–protein associations.

To further investigate the regulatory effects of rs587709 on LILRB2 and LILRB5 in the brain, we retrieved the genomic and CSF proteomic profiles of individuals of European descent from the ADNI dataset.[40] We found that in the European population, rs587709-T was only associated with an increased CSF level of LILRB5 ($\beta = 0.529$, adjusted $P = 8.4 \times 10^{-21}$) and not LILRB2 (Figure 2G,H; Table S5), again suggesting that rs587709 predominantly affects LILRB5 in the European population. To understand the correlation between the genetic regulation of LILRB2 and LILRB5 protein levels in plasma and CSF, we used genetic score models from OmicsPred to predict plasma LILRB2 and LILRB5 levels in the ADNI dataset.[41] The predicted plasma LILRB2 and LILRB5 were positively correlated with the CSF LILRB2 ($r = 0.411$, $P = 3.6 \times 10^{-36}$; Figure 2I) and LILRB5 ($r = 0.720$, $P = 1.3 \times 10^{-94}$; Figure 2J), respectively, suggesting that their protein expressions in plasma and CSF have similar genetic control. These results collectively indicate that rs587709 confers ethnic-specific regulatory effects on LILRB2 and LILRB5 protein expression in the East Asian and European populations, respectively, suggesting that both LILRB2 and LILRB5 are associated with AD.

3.4 | Associations of LILRB2 and LILRB5 with AD pathologies

To investigate the roles of LILRB2 and LILRB5 in AD pathogenesis, we examined their associations with AD and related endophenotypes. Although the plasma levels of LILRB2 and LILRB5 were not associated with AD (adjusted $P \geq 0.19$, Hong Kong Chinese cohort; Figure 3A,B), patients with AD had higher CSF LILRB2 levels ($\beta = 0.331$, adjusted $P = 9.2 \times 10^{-3}$, ADNI dataset; Figure 3C) and lower CSF LILRB5 levels ($\beta = -0.274$, adjusted $P = 4.9 \times 10^{-2}$, ADNI dataset; Figure 3D) compared to NCs. Therefore, we examined the associations of the CSF levels of LILRB2 and LILRB5 with two AD pathological biomarkers—CSF Aβ42 and p-tau181—using the ADNI dataset (Table S7 in supporting information). Accordingly, higher CSF LILRB2 levels were correlated with increased CSF p-tau181 levels ($r = 0.189$, adjusted $P = 1.2 \times 10^{-4}$; Figure 3E,F), indicating more severe tau accumulation in brain tissues. In contrast, higher CSF LILRB5 levels were correlated with higher CSF Aβ42 levels ($r = 0.130$, adjusted $P = 1.4 \times 10^{-3}$; Figure 3G,H), indicating less amyloid plaque deposition in the brain. Given that *APOE ε4* is the most significant genetic risk factor for AD, we performed additional analyses adjusting for *APOE ε4* genotypes to control for potential confounding. Both CSF LILRB2 and LILRB5 remained significantly associated with increased CSF p-tau181 levels ($r = 0.169$, adjusted $P = 4.3 \times 10^{-5}$) and Aβ42 levels ($r = 0.170$, adjusted $P = 4.0 \times 10^{-5}$), respectively. These results collectively illustrate that increased CSF LILRB2 levels and decreased CSF LILRB5 levels are associated with higher AD risk and more severe AD pathologies; in turn, this suggests that both LILRB2 and LILRB5 are involved in AD pathogenesis and may therefore account for the AD risk effects of the *LILRB2–LILRB5* locus.

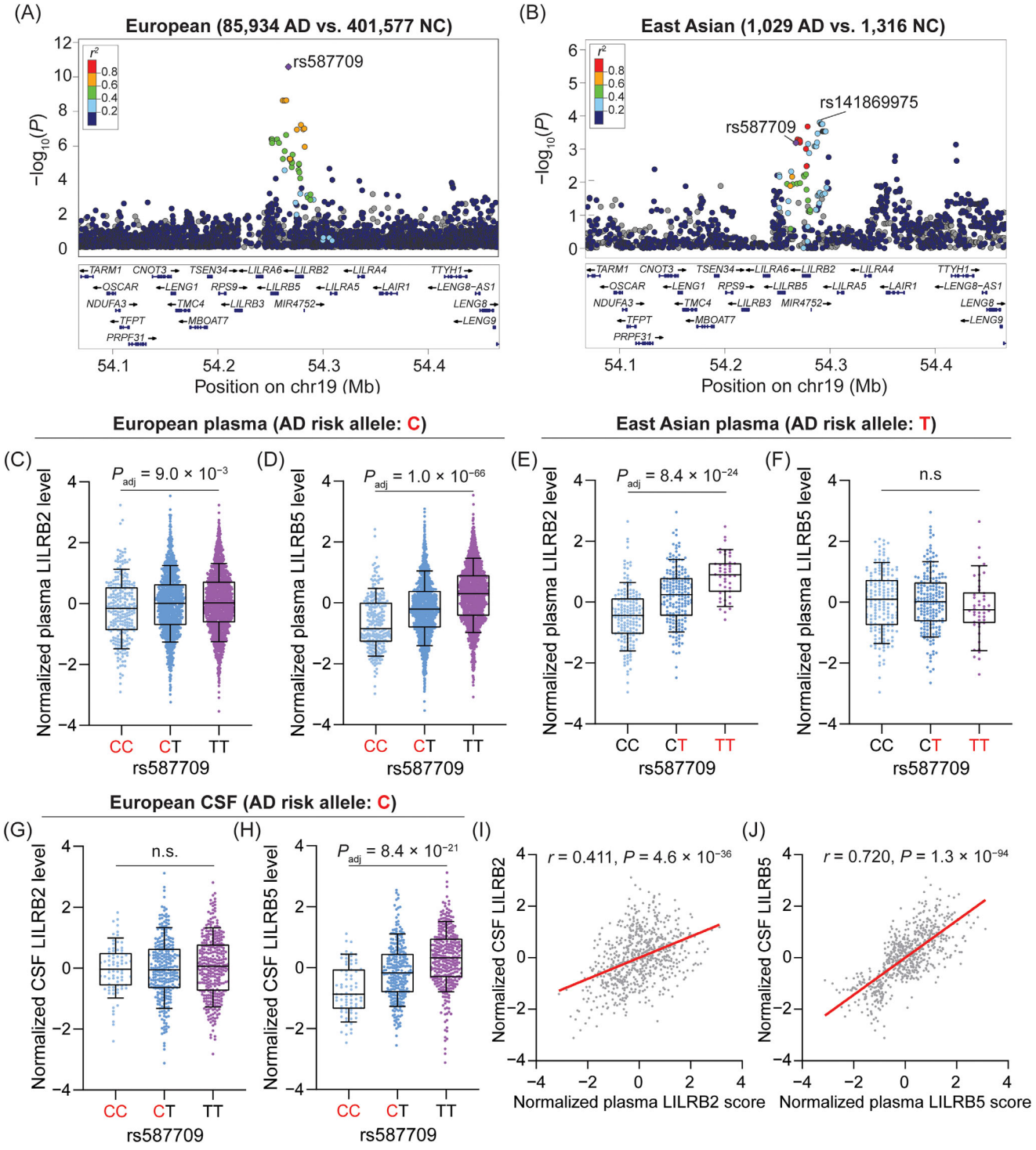

FIGURE 2 Associations of the *LILRB2–LILRB5* locus with AD risk and gene expression in the European and East Asian populations. A, B, Associations between the *LILRB2–LILRB5* locus and AD in the European (A) and East Asian populations (B). Colors denote linkage disequilibrium between rs587709 and other variants. Logistic regression. Mb, megabase pairs. C, D, Effects of rs587709 on plasma LILRB2 (C) and LILRB5 (D) protein levels in the European population. E, F, Effects of rs587709 on plasma LILRB2 (E) and LILRB5 (F) protein levels in the East Asian population. G, H, Effects of rs587709 on CSF LILRB2 (G) and LILRB5 (H) protein levels in the European population. I, J, Correlations between the plasma and CSF protein levels of LILRB2 (I) and LILRB5 (J) in the European population. Plasma protein levels were predicted using genetic score models from the OmicsPred database (LILRB2: OPGS000075, LILRB5: OPGS000006). *r*, Pearson's correlation coefficient. Linear regression was used in (C–J). n.s., not significant; P_{adj}, *p*-values adjusted by the Holm–Bonferroni method for multiple test correction. AD, Alzheimer's disease; CSF, cerebrospinal fluid.

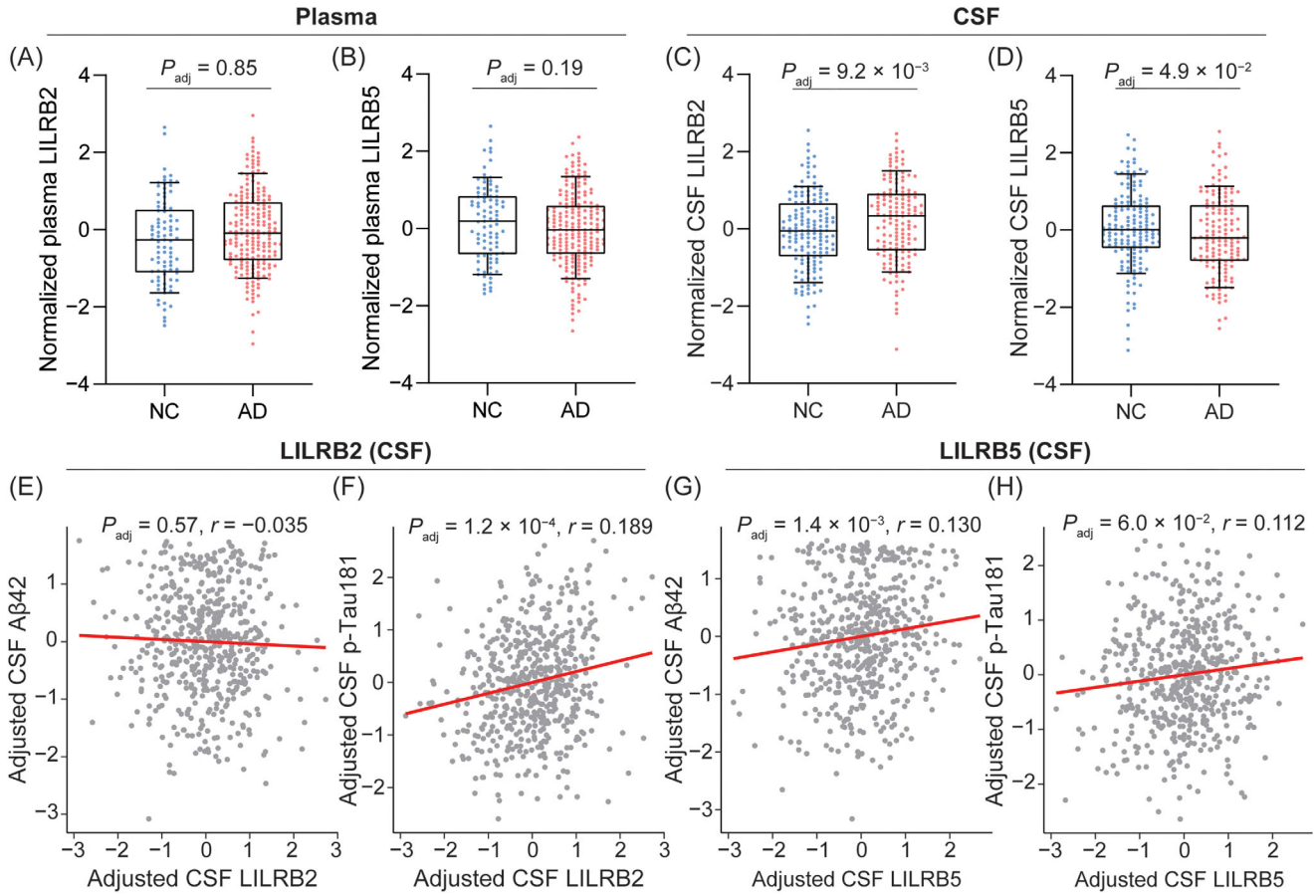

FIGURE 3 Associations of LILRB2 and LILRB5 protein levels with AD and related pathological biomarkers. A, B, Associations between AD and plasma LILRB2 (A) and LILRB5 (B) protein levels in the Hong Kong Chinese cohort. C, D, Associations between AD and CSF LILRB2 (C) and LILRB5 (D) protein levels in the ADNI dataset. E, F, Added-variable plots illustrating the associations of CSF LILRB2 protein levels with CSF Aβ42 levels (E) and CSF p-tau181 levels (F). G, H, Added-variable plots illustrating the associations between CSF LILRB5 protein levels and CSF Aβ42 levels (G) and p-tau181 levels (H). Linear regression was used for all analyses. P_{adj}, *p*-values adjusted by the Holm–Bonferroni method for multiple test correction; *r*, Pearson's correlation coefficient. Aβ, amyloid beta; AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CSF, cerebrospinal fluid; NC, normal control; p-tau, phosphorylated tau.

3.5 | Genome-wide association analysis of AD in the East Asian population

The different genetic background between the East Asian and European populations provides opportunities to discover new AD risk loci in the East Asian population. Therefore, we performed genome-wide association analysis of AD in the East Asian population (1029 patients with AD vs. 1316 NCs). We identified genome-wide significant signals in the *APOE* locus (Figure 4A) without observing genomic inflation (λ = 1.007; Figure 4B). Outside the *APOE* locus, no individual genetic variants passed the genome-wide significance threshold (Figure 4A). Nonetheless, gene-level analysis considering the aggregate effects of genetic variants within the same locus revealed significant associations between the *TTC3* locus and AD (Bonferroni adjusted $P = 0.023$; Figure 4C) without genomic inflation ($\lambda = 0.974$; Figure 4D), suggesting *TTC3* as a candidate AD risk locus.

To validate the association between AD and the *TTC3* locus, we performed replication analysis of the top AD-associated SNP, rs56167027 (Figure 4E), using additional East Asian AD cohorts. Interestingly, a Japanese AD GWAS by Shigemizu et al. reports a nominally significant association between this SNP and decreased AD risk ($\beta = -0.097$, $P = 1.6 \times 10^{-2}$; examined using the proxy SNP, rs2835569-T, $r^2 = 0.94$, $D' = 0.98$; Figure 4F).[34] We observed a similar trend of an AD protective effect in the Niigata cohort ($\beta = -0.063$, $P = 0.413$; Figure 4F). Meta-analysis of these two Japanese replication cohorts indicated a nominally significant association between rs56167027-T and AD ($\beta = -0.090$, $P = 1.2 \times 10^{-2}$; Figure 4F), which supports the AD protective effects of rs56167027 observed in the discovery cohorts ($\beta = -0.315$,

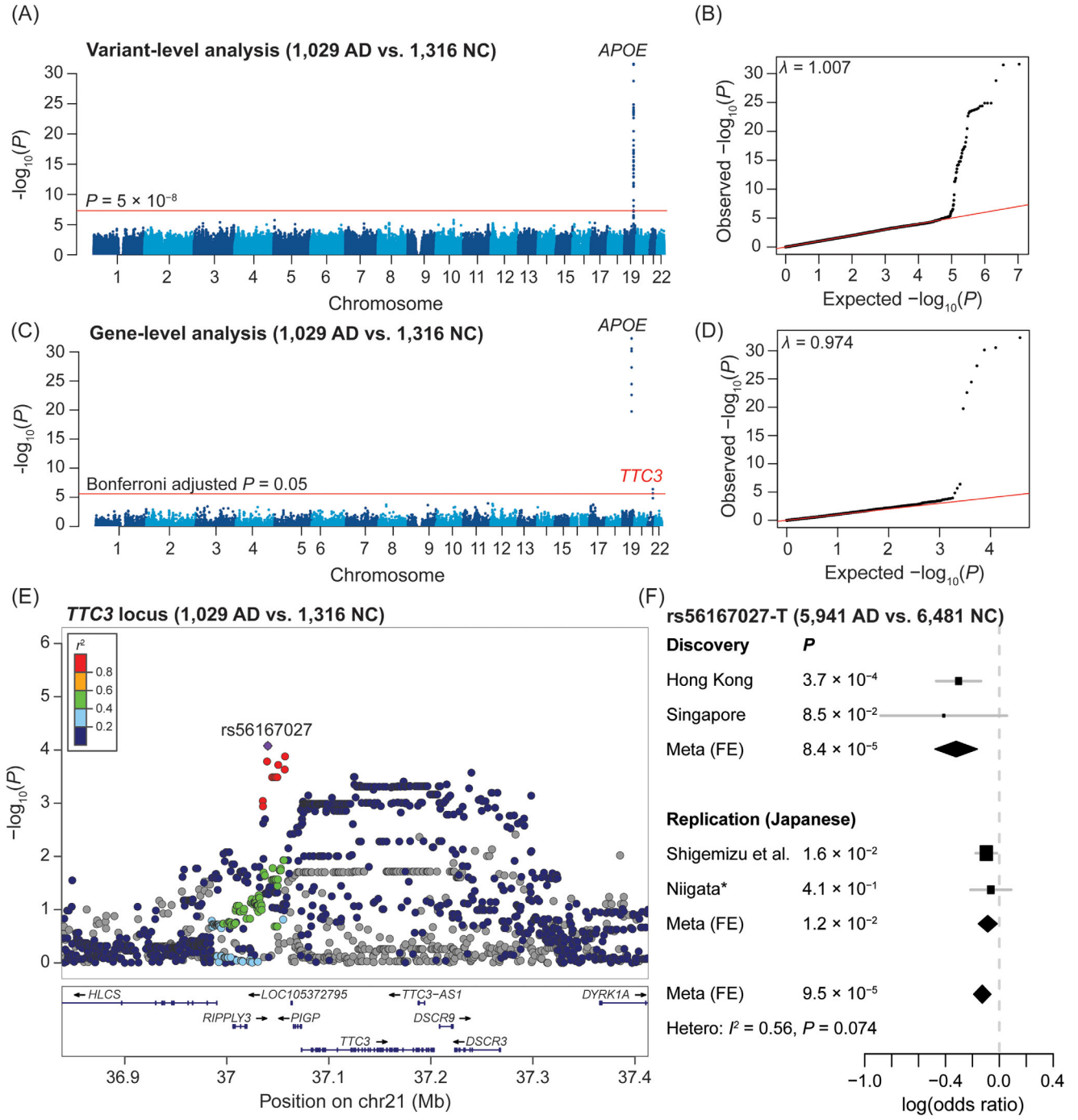

FIGURE 4 Genome-wide association analysis between common genetic variants and AD in the East Asian population. A, Associations between AD and common (i.e., minor allele frequency > 5%) SNPs. The red line indicates the cutoff for genome-wide significance (i.e., 5×10^{-8}). B, Q–Q plot illustrating the genomic inflation observed in genome-wide association analysis. C, Gene-level associations between AD and common SNPs. The red line indicates Bonferroni adjusted $P = 0.05$. D, Q–Q plot illustrating the genomic inflation observed in gene-level analysis. E, Association between the *TTC3* locus and AD. The purple point indicates the top AD-associated SNP. Colors denote linkage disequilibrium between the top SNP and other SNPs. F, Meta-analysis of the association between rs56167027-T and AD in the East Asian population. *The association analysis in the Niigata cohort excluded samples overlapping with those in the study by Shigemizu et al. λ, genomic inflation factor; AD, Alzheimer's disease; FE, fixed-effect meta-analysis; Mb, megabase pair; NC, normal control; Q–Q, quantile–quantile; SNP, single nucleotide polymorphism.

$P = 8.4 \times 10^{-5}$; Figure 4F). Hence, genome-wide association analysis suggests *TTC3* as a candidate AD-associated locus in the East Asian population.

3.6 | Genome-wide association analysis of cognitive performance in the East Asian population

Cognitive decline is an important AD-related phenotype that is strongly correlated with disease progression.[52] Accordingly, to identify genetic variants associated with AD progression, we performed genome-wide association analysis of cognitive performance assessed by the MoCA ($n = 4346$, including all diagnostic groups). We observed a genome-wide significant association between the *APOE* locus and cognitive performance in both variant-level ($\lambda = 1.021$; Figure 5A,B) and gene-level ($\lambda = 0.999$; Figure 5C,D) genome-wide association analysis. Beyond the *APOE* locus, variant-level analysis also identified a significant cognition-associated signal near the *FAM135A* locus (Figure 5A,E). In particular, rs150786294-C, the top SNP of this locus, was associated with increased cognitive performance that passed the genome-wide significance threshold ($\beta = 0.267$, $P = 3.4 \times 10^{-8}$; Figures 5E,F and S5 in supporting information). Interestingly, the prevalence of rs150786294-C differs substantially among populations (Figure 5G). Although this SNP is common in both the East Asian population (AF = 5.6%) and admixed American population (AF = 5.3%), its frequency is very low in European and other populations (AF < 0.2%). This highlights the importance of performing GWASs in non-European populations to achieve a comprehensive representation of AD genetic risk factors.

4 | DISCUSSION

GWASs have identified numerous AD-associated loci primarily in populations of European descent. However, it is largely unclear whether these loci confer similar effects on AD in non-European populations. In this study, we performed a comprehensive genetic analysis of known AD risk loci in the East Asian population and showed that the *SORL1* and *LILRB2–LILRB5* loci are significantly associated with AD. Interestingly, the *LILRB2–LILRB5* locus exhibited ethnic-specific effects on AD risk between the European and East Asian populations. Specifically, rs587709-T, the lead AD-associated SNP in this locus, was associated with increased AD risk in East Asians but decreased AD risk in Europeans. Subsequent pQTL analysis revealed that rs587709-T differently affects the protein expressions of LILRB2 and LILRB5 in blood in the East Asian and European populations, which may contribute to the underlying mechanism of the ethnic-specific AD risk associations of this variant. The associations of the CSF levels of LILRB2 and LILRB5 with Aβ and tau pathological biomarkers also suggest the involvement of both LILRB2 and LILRB5 protein in AD pathogenesis. Furthermore, our genome-wide association analysis in the East Asian population identified *TTC3* and *FAM135A* as new candidate risk loci for AD and cognition, respectively. Collectively, these findings extend our understanding of the genetic etiology of AD.

The lack of ethnic diversity of research participants is a major limitation of genetics studies of human diseases.[14] More than 90% of GWASs focus on European populations.[53] The effects of genetic variants on diseases can vary among ethnic populations owing to varying allele frequencies and linkage disequilibrium.[14,54] Therefore, to comprehensively understand the genetic etiology of AD, it is crucial to identify AD-associated genetic variants in diverse populations other than populations of European descent. Genetic analysis of known AD risk loci in non-European populations represents an important first step toward this goal. In this study, we validated the significant association between AD and *SORL1*, which has been reported in multiple studies of both European and East Asian populations.[13,47,48] Furthermore, we identified a significant association between AD and the *LILRB2–LILRB5* locus in the East Asian population. This AD risk locus was identified by GWASs in the European population[6] but had not been replicated in a non-European population until this study. Notably, although most lead AD-associated genetic variants were not significantly associated with AD in the East Asian population, their effects on AD were positively correlated with those in the European population (Figure 1B). This suggests that the genetic etiology of AD is at least partially shared between the European and East Asian populations despite population-specific effect sizes. Nevertheless, further studies with larger sample sizes are required to validate the effects of the remaining loci in the East Asian and other non-European populations.

Given the complex pathogenic mechanism of AD, the effects of its risk genes can be context dependent, affected by factors such as disease stage[55] and genetic background.[15] Interestingly, we show that *LILRB2–LILRB5* is one such locus that has different AD protective/risk effects between the European and East Asian populations. The *LILRB2–LILRB5* locus, which encodes receptors for highly polymorphic human leukocyte antigens,[56,57] exhibits significantly different haplotype frequencies between the East Asian and European populations,[58] which likely results in the different prevalence of rs587709-T between the East Asian population (AF = 26.5%) and European population (AF = 67.5%). Indeed, the distinct regulatory effects of rs587709 on LILRB2 and LILRB5 expression in the East Asian and European populations suggest an ethnic-specific genetic control mechanism in this locus. By analyzing genetic variants within candidate regulatory regions (Table S8 in supporting information), we show that rs587709 is in linkage disequilibrium with different candidate regulatory variants in the European population (i.e., rs12984029 and rs3170522; $r^2 \geq 0.644$) and East Asian population (i.e., rs12459843, rs60728668, and rs452717; $r^2 \geq 0.585$), suggesting that rs587709 tags different regulatory haplotypes between populations. This ethnic-specific genetic regulation warrants further investigation through functional genomics studies. Nonetheless, the current findings highlight the importance of integrating trans-ethnic GWASs and QTL analysis to clarify critical genes that are regulated by AD-associated genetic variants within identified risk loci.

Functional studies of LILRB2 and its murine ortholog, paired immunoglobulin-like receptors B (PirB), show that LILRB2 (as a recep-

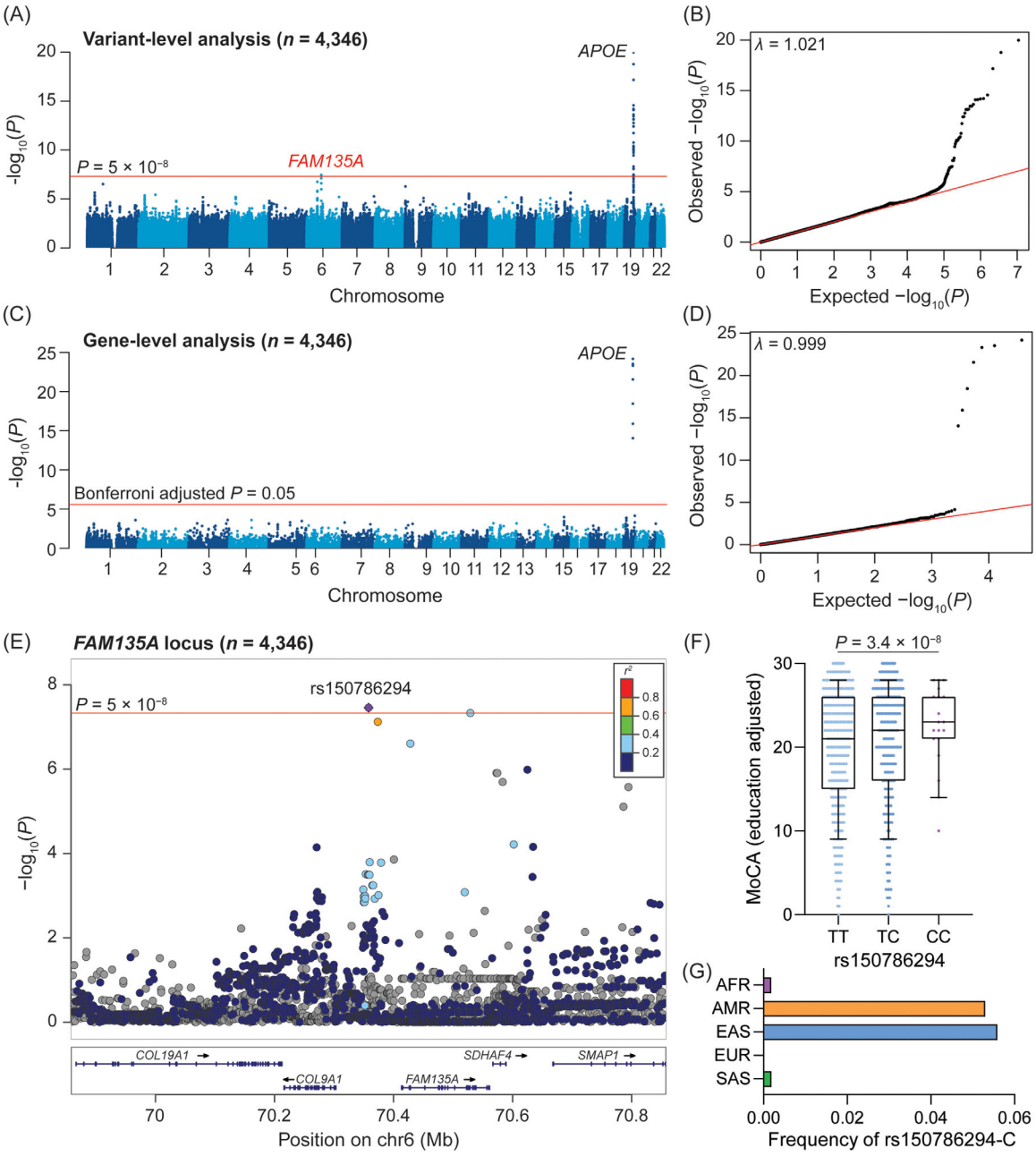

FIGURE 5 Genome-wide association analysis between common genetic variants and cognitive performance in the East Asian population. A, Associations between cognitive performance and common (i.e., minor allele frequency > 5%) SNPs. The red line indicates the cutoffs for genome-wide significance (i.e., 5×10^{-8}). B, Q–Q plot illustrating the genomic inflation observed in genome-wide association analysis. C, Gene-level associations between cognitive performance measured by the MoCA and common SNPs. The red line indicates Bonferroni adjusted $P = 0.05$. D, Q–Q plot illustrating the genomic inflation observed in gene-level analysis. E, Associations between SNPs residing in the *FAM135A* locus and cognitive performance. The purple point indicates the top cognitive performance-associated SNP. Colors denote linkage disequilibrium between the top SNP and other SNPs. F, Association between rs150786294 and cognitive performance. Linear regression. G, Frequency of the rs150786294-C allele in diverse populations. Allele frequencies were obtained from gnomAD. λ, genomic inflation factor; AD, Alzheimer's disease; AFR, African; AMR, admixed American; EAS, East Asian; EUR, European (non-Finnish); Mb, megabase pair; MoCA, Montreal Cognitive Assessment; Q–Q, quantile–quantile; SAS, South Asian; SNP, single nucleotide polymorphism.

tor on myeloid cells) interacts with Aβ oligomers and regulates synaptic plasticity in AD transgenic mouse models.[59–61] Blocking LILRB2 with a monoclonal antibody mitigates the neurotoxic effects of Aβ,[62,63] enhancing triggering receptor expressed on myeloid cells 2 signaling and leading to increased microglial phagocytosis and clustering around Aβ plaques.[64] Moreover, the interaction between LILRB2 and C4d, a high-affinity ligand, drives synaptic pruning in cortical pyramidal neurons.[65] Given the crucial role of LILRB2 in AD pathogenesis, it was prioritized as the primary AD risk gene in the *LILRB2–LILRB5* locus in the previous AD GWAS.[6] Nonetheless, our current findings indicate

that the lead AD-associated SNP in this locus affects the expression of LILRB2 and LILRB5 in the East Asian and European populations, respectively (Figure 2). Moreover, the associations of the CSF levels of LILRB2 and LILRB5 with AD pathological biomarkers suggest that both proteins may be involved in AD pathogenesis. Collectively, these findings indicate that both LILRB2 and LILRB5 are potential AD risk genes that account for the AD association of this locus. Hence, our study suggests that in addition to the well-studied *LILRB2* gene, *LILRB5* is a novel candidate risk gene for AD.

In addition, by performing a GWAS involving both AD diagnosis and cognitive performance, we identified candidate dementia-associated signals near the *TTC3* and *FAM135A* loci. Interestingly, while one *TTC3* rare coding mutation is reported to be associated with AD,[66] our study shows that common genetic variants in the *TTC3* locus are also associated with AD, supporting the AD risk effects of this locus. The *TTC3* gene encodes an E3 ubiquitin ligase that regulates ubiquitination and plays a role in the Akt signaling pathway,[67] which is an important signaling pathway in AD pathogenesis.[68] Therefore, both the genetic associations and biological function of *TTC3* suggest its involvement in AD pathogenesis. Regarding the *FAM135A* locus, although we identified genome-wide significant associations between cognitive performance and SNPs near *FAM135A* (Figure 5), the limited brain QTL resources based on the East Asian population make it difficult to determine the genes affected by those SNPs in disease-relevant tissues. Meanwhile, the scarcity of cognitive performance data in the Japanese AD cohort limited replication analysis of the *FAM135A* locus. Therefore, future studies are required to validate the *FAM135A* locus in additional cohorts and clarify the gene(s) regulated by AD-associated genetic variants within this locus.

In summary, our trans-ethnic genetic analysis sheds light on ethnic-specific genetic mechanisms that underlie the *LILRB2–LILRB5* locus and provides new candidate AD risk loci for further investigation. This highlights the importance of including non-European populations in future genetic studies of AD.

AUTHOR CONTRIBUTIONS

H.C., X.Z., A.K.Y.F., and N.Y.I. conceived of the study; F.C.F.I., H.Y.W., Y.C., T.C.Y.K., V.C.T.M., L.C.W.L., A.L.T.C., R.M.N.L., B.W.Y.W., and E.Y.L.C. organized patient recruitment and sample collection for the Hong Kong Chinese cohort; C.C. and J.R.C. contributed to the Singapore cohort; M.K., A.M., and T.I. contributed to the Niigata cohort; E.Y.L.C. performed the experiments; H.C. and Z.Z. set up the data processing pipelines; H.C., Z.Z., X.Z., M.K., M.S., J.H., K.Y.M., A.K.Y.F., and N.Y.I. analyzed the data; H.C., A.K.Y.F., and N.Y.I. wrote the manuscript with input from all authors.

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CONFLICT OF INTEREST STATEMENT

F.C.F.I. is a co-founder of Cognitact. J.H. has served as a consultant for Eli Lilly and Eisai. The remaining authors declare no competing interests. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

The summary statistics of the Hong Kong Chinese cohort are available on GWAS Catalog (https://www.ebi.ac.uk/gwas/) under accession number GCST90727420 and GCST90727421. The summary statistics of the European AD GWAS are available on GWAS Catalog under accession number GCST90027158. The summary statistics of the Japanese AD GWAS by Shigemizu et al. are available through the NBDC database (https://humandbs.dbcls.jp/en/) under accession number hum0237.v1. The European proteomic dataset is available on European Genotype Archive (https://ega-archive.org/) under accession number EGAS00001002555. The ADNI dataset is accessible to qualified researchers upon application submission via the official ADNI website (https://adni.loni.usc.edu/data-samples/access-

data/). The GTEx data are available through the GTEx Portal (https://gtexportal.org/home/).

CODE AVAILABILITY STATEMENT

We used publicly available software for data analysis in this study. The software is described in the Methods section along with citations.

CONSENT STATEMENT

Regarding the individual genetic, transcriptomic, and proteomic data of the Hong Kong Chinese cohort, the consent form signed by each participant states that the research content will remain private under the supervision of the hospital and research team. Therefore, these data will only be made available and shared in the context of a formal collaboration. Applications for data sharing and project collaboration will be processed and reviewed by a review panel hosted at the Hong Kong University of Science and Technology. Researchers may contact sklneurosci@ust.hk for further details on project collaboration and the sharing of data from this study. For the Singapore cohort, data will only be made available and shared in the context of a formal collaboration. Researchers may contact phccclh@nus.edu.sg for further details on project collaboration and the sharing of data from this study. For the Japanese cohorts, individual genetic data are available only within the framework of formal research collaborations. Researchers interested in accessing these data may contact kikuchi@bri.niigata-u.ac.jp for further information.

ETHICS STATEMENT

This study was approved by the Clinical Research & Ethics Committees of the Joint Chinese University of Hong Kong–New Territories East Cluster for the Prince of Wales Hospital (CREC ref. no. 2015.461), the Human Participants Research Panel of the Hong Kong University of Science and Technology (CRP#180 and CRP#225), and National Healthcare Group Domain-Specific Review Board (NHG DSRB reference numbers: 2018/01098 and 2010/00017). All participants provided written informed consent for both study enrolment and sample collection.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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