

# Association of blood-based transcriptional risk scores with biomarkers for Alzheimer disease

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## Abstract

### Objective

To determine whether transcriptional risk scores (TRSs), a summation of polarized expression levels of functional genes, reflect the risk of Alzheimer disease (AD).

### Methods

Blood transcriptome data were from Caucasian participants, which included AD, mild cognitive impairment, and cognitively normal controls (CN) in the Alzheimer's Disease Neuroimaging Initiative (ADNI, n = 661) and AddNeuroMed (n = 674) cohorts. To calculate TRSs, we selected functional genes that were expressed under the control of the AD risk loci and were identified as being responsible for AD by using Bayesian colocalization and mendelian randomization methods. Regression was used to investigate the association of the TRS with diagnosis (AD vs CN) and MRI biomarkers (entorhinal thickness and hippocampal volume). Regression was also used to evaluate whether expression of each functional gene was associated with AD diagnosis.

### Results

The TRS was significantly associated with AD diagnosis, hippocampal volume, and entorhinal cortical thickness in the ADNI. The association of the TRS with AD diagnosis and entorhinal cortical thickness was also replicated in AddNeuroMed. Among functional genes identified to calculate the TRS, *CD33* and *PILRA* were significantly upregulated, and *TRAPPC6A* was significantly downregulated in patients with AD compared with CN, all of which were identified in the ADNI and replicated in AddNeuroMed.

### Conclusions

The blood-based TRS is significantly associated with AD diagnosis and neuroimaging biomarkers. In blood, *CD33* and *PILRA* were known to be associated with uptake of  $\beta$ -amyloid and herpes simplex virus 1 infection, respectively, both of which may play a role in the pathogenesis of AD.

### Classification of evidence

The study is rated Class III because of the case control design and the risk of spectrum bias.

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ADNI coinvestigators are listed in appendix 2 at the end of the article.

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## Glossary

**A $\beta$**  =  $\beta$ -amyloid; **AD** = Alzheimer disease; **ADAS-cog13** = Alzheimer's Disease Assessment Scale Cognitive Subscale 13; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **CN** = cognitively normal controls; **eQTL** = expression quantitative trait loci; **gB** = glycoprotein B; **GWAS** = genome-wide association study; **HSV-1** = herpes simplex virus 1; **ITIM** = immunoreceptor tyrosine-based inhibitory motif; **LD** = linkage disequilibrium; **MAF** = minor allele frequency; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **OR** = odds ratio; **QC** = quality control; **SMR** = summary data-based mendelian randomization; **SNP** = single nucleotide polymorphism; **SUV** = standardized uptake value; **TRS** = transcriptional risk score.

Alzheimer disease (AD) has a strong genetic component.<sup>1</sup> Previous studies suggest that the relative risk of AD for those with at least 1 first-degree relative with AD is 3.5 (95% confidence interval [CI] 2.6–4.6)<sup>2</sup> and possibly as high as 7.5 (95% CI 3.3–16.7) when 2 or more first-degree relatives are affected.<sup>2</sup> Large-scale genome-wide association studies (GWASs) have identified more than 20 AD risk loci.<sup>3,4</sup> However, it has been challenging to perform functional studies of AD risk loci to identify underlying molecular mechanisms.

It is known that trait-associated single nucleotide polymorphisms (SNPs) are likely to be expression quantitative trait loci (eQTL).<sup>5</sup> The risk SNPs identified by GWASs may contribute to the pathogenesis of disease by controlling expression of nearby genes, and the transcriptomic analysis to identify target genes regulated by the risk SNPs has been used to uncover molecular mechanisms.<sup>6</sup> Transcriptional risk scores (TRSs), a summation of polarized expression levels of functional genes that reflect the risk of disease, have been proposed and used to distinguish patients with Crohn disease from healthy subjects.<sup>6</sup>

Here, we calculated the TRS using blood-based transcriptomic profiles regulated by AD risk loci to investigate whether the TRS demonstrates an AD diagnosis group difference and is associated with AD-related neuroimaging biomarkers in 2 independent cohorts. In addition, we evaluated whether target genes selected to calculate the TRS are associated with AD diagnosis.

## Methods

### Participants

Data used in the study were obtained from Caucasian participants (AD, mild cognitive impairment [MCI], and cognitively normal controls [CN]) in the Alzheimer's Disease Neuroimaging Initiative (ADNI) and AddNeuroMed cohorts as discovery and replication samples, respectively. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Dr. Michael W. Weiner.<sup>7</sup> The primary goal of the ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to accurately

capture the progression of MCI and early AD. The AddNeuroMed is a cross European, public/private consortium developed for AD biomarker discovery.<sup>8</sup> AD was diagnosed clinically according to the NINCDS/ADRDA criteria for probable AD in ADNI and AddNeuroMed.<sup>9</sup> MCI was diagnosed when there was objective memory impairment but without meeting the criteria for dementia.<sup>7,8</sup> In ADNI, participants with MCI had a Mini-Mental State Examination (MMSE) score between 24 and 30, memory performance approximately 1 SD below expected education adjusted norms, and a Clinical Dementia Rating (CDR) score of 0.5. In AddNeuroMed, participants with MCI had an MMSE score between 24 and 30 and a CDR score of 0.5.

### Genotyping and imputation

Genotyping for the ADNI and AddNeuroMed was performed using blood DNA samples and a combination of Illumina GWAS array platforms (Illumina Human610-Quad BeadChip, Illumina HumanOmni Express BeadChip, and Illumina HumanOmni 2.5M BeadChip).<sup>10,11</sup> APOE genotyping was separately conducted using previously described standard methods to yield the APOE  $\epsilon$ 4 allele defining SNPs (rs429358, rs7412).<sup>10,11</sup> Using PLINK 1.9 (cog-genomics.org/plink2/),<sup>12</sup> we also performed standard quality control (QC) procedures for samples (sex inconsistencies and sample call rate < 95%) and SNPs (SNP call rate < 95%, Hardy-Weinberg  $p$  value <  $1 \times 10^{-6}$ , and minor allele frequency [MAF] < 1%) as described previously.<sup>13</sup> Then, to prevent spurious associations due to population stratification, we used multidimensional scaling analysis to select only non-Hispanic participants of European ancestry that clustered with HapMap CEU (Utah residents with Northern and Western European ancestry from the Centre d'Etude du Polymorphisme Humain collection) or Toscani in Italia populations.<sup>14,15</sup> After QC procedures, because the 2 cohorts used different genotyping platforms, we imputed ungenotyped SNPs separately in each platform using MaCH with the Haplotype Reference Consortium data as a reference panel.<sup>16,17</sup> Following the imputation, we imposed an  $r^2$  value of 0.30 as the threshold to accept the imputed genotypes.

### Blood-based RNA expression microarray profiling

The PAXgene Blood RNA Kit (Qiagen Inc., Valencia, CA) was used to purify total RNA from whole blood collected in a PAXgene Blood RNA Tube.<sup>10,18</sup> The Affymetrix Human

Genome U219 Array (Affymetrix, Santa Clara, CA) in the ADNI and the Illumina Human HT-12 v3 Expression BeadChips (Illumina Inc., San Diego, CA) in AddNeuroMed were used for expression profiling.<sup>10,18</sup> All probe sets were mapped and annotated to the human genome (hg19). Raw expression values were preprocessed using the robust multichip average normalization method and robust spline normalization method in the ADNI and AddNeuroMed, respectively.<sup>19,20</sup> We evaluated discrepancies between the reported sex and sex determined from sex-specific gene expression data, including *XIST* and *USP9Y*. We also determined whether SNP genotypes were matched with genotypes predicted from gene expression data.<sup>19</sup> After QC, the RNA expression profiles, which contained 21,150 probes in the ADNI and 5,141 probes in AddNeuroMed, were preadjusted with batch effects and RNA integrity number values using linear regression. Finally, if a gene contained more than 1 microarray probe, we selected only the probe with the greatest variance.

### Selection of AD-associated SNPs and candidate genes

To select AD-associated SNPs, we started by considering 29 SNPs that had genome-wide significant associations ( $p < 5 \times 10^{-8}$ ) in a recent AD GWAS meta-analysis<sup>3</sup> and 406 SNPs that were in strong linkage disequilibrium (LD) ( $r^2 > 0.8$ ) with them. Then, after pruning the 435 SNPs by removing SNPs in LD ( $r^2 > 0.1$ ) using LDlink 3.7 (ldlink.nci.nih.gov), we were left with 24 AD-associated SNPs. In addition, we selected SNPs (2,533, 3,288, 4,968, 9,909, 29,894, and 175,262 SNPs) that were associated with AD in the GWAS with  $p$  values less than  $1 \times 10^{-7}$ ,  $1 \times 10^{-6}$ ,  $1 \times 10^{-5}$ ,  $1 \times 10^{-4}$ ,  $1 \times 10^{-3}$ , and  $1 \times 10^{-2}$ , respectively.<sup>3</sup> After pruning, we had 92, 115, 188, 617, 3,237, and 20,978 AD-associated SNPs, respectively. Then, using the public blood eQTL database from CN (genenetwork.nl/bloodqtlbrowser), we identified candidate genes that are located within  $\pm 1$  Mbp of AD-associated and pruned SNPs that have a direct impact on gene expression (false discovery rate–corrected  $p < 0.05$  for eQTL).<sup>20,21</sup>

### Selection of target genes from AD-associated candidate genes using COLOC and summary data–based mendelian randomization

A significant association between an SNP and a gene from the aforementioned integration of AD GWAS summary statistics and the blood eQTL database does not necessarily imply that a gene is associated with AD. Therefore, to determine whether a gene regulated by an SNP is associated with AD, we estimated the colocalization of signals using COLOC and summary data–based mendelian randomization (SMR).<sup>6</sup> We applied both methods to distinguish target genes from candidate genes. COLOC uses a Bayesian framework that calculates posterior probabilities for hypotheses about the presence and sharing of causal SNPs by GWAS summary statistics and eQTL data.<sup>22</sup> We selected genes supporting the hypothesis of 1 causal SNP common to

both AD diagnosis (AD vs CN) and gene expression with 80% or greater posterior probability ( $H_4 > 80\%$ ).<sup>6</sup> The SMR combines GWAS summary statistics and eQTL data to identify target genes whose expression levels are associated with AD diagnosis (AD vs CN).<sup>23</sup> Multiple testing correction was performed using the Bonferroni method ( $p_{SMR} < 8.4 \times 10^{-6}$ ).

### Calculation of the TRS

We calculated the TRS using the following steps.<sup>6</sup> First, we transformed expression levels of each gene into a normal distribution with a mean of 0 and variance of 1. Then, we used the eQTL activity of AD-associated SNPs to infer the direction of risk at each gene selected for the TRS. The concept of high expression and low expression was used to denote whether an AD risk allele was associated with increased (high expression) or decreased (low expression) gene expression levels. In rare cases, genes were labeled as both high expression and low expression because the same gene could be associated with different SNPs in the eQTL data. Genes with both labels were excluded from the analysis. Next, we polarized gene expression levels by changing the sign of the expression levels ( $z$ -score) for genes labeled as low expression. Thus, elevated risk from gene expression, irrespective of the direction of risk, could be additively incorporated in the TRS. Finally, we calculated the TRS for each individual by summing the polarized  $z$ -scores over the corresponding genes.

### Statistical analysis

We performed logistic regression analysis to compare the TRS of AD with CN and made violin plots that included MCI. We then performed linear regression analysis to evaluate whether the TRS is associated with the following AD biomarkers: (1) hippocampal volume and entorhinal cortical thickness measured from T1-weighted brain MRI scans using FreeSurfer version 5.1 (surfer.nmr.mgh.harvard.edu),<sup>24</sup> (2) global cortical amyloid accumulation as mean standardized uptake values (SUVs) using preprocessed (coregistered, averaged, standardized image and voxel size, uniform resolution) [<sup>18</sup>F] florbetapir PET scans with a whole cerebellum reference region,<sup>25</sup> and (3) Alzheimer's Disease Assessment Scale Cognitive Subscale 13 (ADAS-cog13).<sup>26</sup> Covariates included age and sex. Intracranial volumes (ICV) and MRI field strength were also used as additional covariates for hippocampal volume and entorhinal cortical thickness. Educational level was also used as an additional covariate for ADAS-cog13. ADAS-cog13 and amyloid PET data were not available in AddNeuroMed. In addition, we also performed logistic regression analysis to evaluate whether the TRS is significantly different between patients with AD with positive amyloid PET (SUV ratio  $\geq 1.17$ ) and CN with negative amyloid PET (SUV ratio  $< 1.17$ ) in the ADNI.

Although we designated target genes as high expression and low expression based on the integration of GWAS summary statistics and the public blood eQTL database, expression levels of the target genes in the ADNI and AddNeuroMed may not be different between AD and CN. Therefore, for target genes used to calculate the TRS, we performed logistic

**Table 1** Demographics of study samples

Cohort	Diagnosis	N	Female, n (%)	Age at blood sample collection, mean (SD)	RIN, mean (SD)
ADNI (N = 661)	CN	213	107 (50)	76.4 (6.4)	6.91 (0.51)
	MCI	345	144 (42)	73.2 (7.9)	6.98 (0.55)
	AD	103	38 (37)	77.6 (7.8)	6.98 (0.64)
AddNeuroMed (N = 674)	CN	243	147 (60)	74.2 (6.6)	8.96 (0.73)
	MCI	208	120 (58)	75.5 (6.5)	8.50 (0.59)
	AD	223	146 (65)	76.8 (6.8)	8.43 (0.64)

Abbreviations: AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; CN = cognitively normal older adults; MCI = mild cognitive impairment; RIN = RNA integrity number.  
The mean and SD of age at onset in patients with AD in the ADNI were 75.5 and 7.83, respectively.  
The table was modified from a previous study.<sup>40</sup>

regression analysis of gene expression levels using the AD diagnosis group, with age and sex as independent variables and diagnosis as an outcome, to identify which genes are significantly upregulated or downregulated in AD compared with CN. We also used a heatmap to visualize the expression pattern across the participants. In this study, we used R version 3.6.0 (R-project.org) for analysis unless otherwise specified. The study is rated Class III because of the case control design and the risk of spectrum bias.

### Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained at the time of enrollment and included permission for analysis and data sharing. The protocol and informed consent forms were approved by the Institutional Review Board at each participating site. ClinicalTrials.

gov identifiers are NCT00106899, NCT01078636, and NCT01231971.

### Data availability

Anonymized data used for this study are available from the corresponding authors on reasonable request.

## Results

In this study, a total of 1,335 participants were included from 2 independent cohorts (661 from the ADNI and 674 from Add-NeuroMed) (table 1). Using large-scale AD GWAS results and the public blood eQTL database, we selected candidate genes that are within  $\pm 1$  Mbp of AD-associated SNPs and have a direct impact on gene expression (table 2). Then, using COLOC and SMR (table 2), we identified target genes that have strong

**Table 2** Candidate genes under control of AD-associated SNPs ( $\pm 1$  Mbp) and target genes after applying COLOC and SMR

Criteria for selecting AD-associated SNPs	No. of candidate genes	Target genes identified using COLOC and SMR <sup>a</sup>
$p < 5 \times 10^{-8b}$	17	<i>B4GALT3<sup>c</sup>, BCKDK<sup>c</sup>, CD33, CR1<sup>c</sup>, EPHA1, MS4A2<sup>d</sup>, MS4A4A, MS4A6A, PILRA, STAG3<sup>c</sup>, and ZNF668</i>
$p < 1 \times 10^{-7}$	15	<i>B4GALT3<sup>c</sup>, CD33, KLC3<sup>d</sup>, PILRA, STAG3<sup>c</sup>, and TRAPPC6A</i>
$p < 1 \times 10^{-6}$	18	<i>B4GALT3<sup>c</sup>, CD33, KLC3<sup>d</sup>, PILRA, RTN2<sup>c</sup>, STAG3<sup>c</sup>, and TRAPPC6A</i>
$p < 1 \times 10^{-5}$	24	<i>B4GALT3<sup>c</sup>, CD33, CTSH, HSD3B7<sup>c</sup>, KLC3<sup>d</sup>, PILRA, RTN2<sup>c</sup>, STAG3<sup>c</sup>, TRAPPC6A, and ZNF668</i>
$p < 1 \times 10^{-4}$	47	<i>B4GALT3<sup>c</sup>, CD33, CTSH, HSD3B7<sup>c</sup>, KLC3<sup>d</sup>, PILRA, PLEKHA1<sup>c</sup>, RTN2<sup>c</sup>, SLC24A4<sup>d</sup>, STAG3<sup>c</sup>, TRAPPC6A, and ZNF668</i>
$p < 1 \times 10^{-3}$	171	<i>B4GALT3<sup>c</sup>, BCKDK<sup>c</sup>, CD33, CTSH, HSD3B7<sup>c</sup>, KLC3<sup>d</sup>, PILRA, PLEKHA1<sup>c</sup>, PTK2B, RTN2<sup>c</sup>, SIGLEC11<sup>c</sup>, SLC24A4<sup>d</sup>, STAG3<sup>c</sup>, TRAPPC6A, and ZNF668</i>
$p < 1 \times 10^{-2}$	536	<i>B4GALT3<sup>c</sup>, BCKDK<sup>c</sup>, CD33, CTSH, EPHA1, HSD3B7<sup>c</sup>, KLC3<sup>d</sup>, MS4A2<sup>d</sup>, MS4A6A, PILRA, PLEKHA1<sup>c</sup>, PPOX<sup>c</sup>, PRR14<sup>c</sup>, PTK2B, RTN2<sup>c</sup>, SIGLEC11<sup>c</sup>, SLC24A4<sup>d</sup>, STAG3<sup>c</sup>, TRAPPC6A, and ZNF668</i>

Abbreviations: AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; SMR = summary data-based mendelian randomization; SNP = single nucleotide polymorphism.

The microarray gene expression data for *MS4A2*, *SIGLEC11* and *STAG3* were not available in ADNI. The microarray gene expression data for *CR1*, *EPHA1*, *HSD3B7*, *KLC3*, *MS4A2*, *MS4A4A*, *PPOX*, *RTN2*, *SIGLEC11*, *SLC24A4*, *STAG3* and *ZNF668* were not available in AddNeuroMed.

<sup>a</sup> Unless otherwise specified, genes were identified by both COLOC and SM.

<sup>b</sup> SNPs in strong linkage disequilibrium ( $r^2 > 0.8$ ) with the SNPs that had genome-wide significant associations ( $p < 5 \times 10^{-8}$ ) were also included for analysis.

<sup>c</sup> These genes were identified by COLOC only.

<sup>d</sup> These genes were identified by SMR only.



**Table 3** Difference of the TRS between CN (N = 213) and AD (N = 103) according to various criteria for selecting AD-associated SNPs in ADNI

Criteria for selecting SNPs	TRS using all candidate genes, mean (SD)			TRS using target genes from COLOC, mean (SD)			TRS using target genes from SMR, mean (SD)		
	CN	AD	OR of the TRS (95% CI, <i>p</i> value)	CN	AD	OR of the TRS (95% CI, <i>p</i> value)	CN	AD	OR of the TRS (95% CI, <i>p</i> value)
$p < 5 \times 10^{-8a}$	-0.477 (5.05)	1.10 (4.13)	1.06 (1.01–1.13, $3.02 \times 10^{-2}$ )	-0.467 (4.92)	1.39 (3.86)	1.08 (1.02–1.15, $6.03 \times 10^{-3}$ )	-0.238 (3.56)	0.807 (2.92)	1.08 (1.00–1.17, $5.01 \times 10^{-3}$ )
$p < 1 \times 10^{-7}$	-0.264 (4.40)	1.11 (4.05)	1.08 (1.02–1.14, $1.33 \times 10^{-2}$ )	-0.209 (2.69)	0.881 (2.33)	1.18 (1.07–1.31, $1.19 \times 10^{-3}$ )	-0.0973 (2.39)	0.809 (2.23)	1.18 (1.06–1.33, $2.58 \times 10^{-3}$ )
$p < 1 \times 10^{-6}$	-0.324 (4.90)	1.40 (4.71)	1.08 (1.02–1.14, $4.77 \times 10^{-3}$ )	-0.122 (2.58)	0.771 (2.35)	1.15 (1.05–1.28, $5.20 \times 10^{-3}$ )	-0.0973 (2.39)	0.809 (2.23)	1.18 (1.06–1.33, $2.58 \times 10^{-3}$ )
$p < 1 \times 10^{-5}$	-0.339 (6.04)	1.67 (5.18)	1.06 (1.02–1.11, $7.45 \times 10^{-3}$ )	-0.140 (3.23)	1.25 (2.86)	1.14 (1.05–1.24, $1.44 \times 10^{-3}$ )	-0.139 (3.03)	1.16 (2.63)	1.16 (1.06–1.27, $1.34 \times 10^{-3}$ )
$p < 1 \times 10^{-4}$	-0.644 (7.80)	1.64 (6.21)	1.04 (1.00–1.07, $3.31 \times 10^{-2}$ )	-0.0544 (3.00)	1.11 (2.78)	1.14 (1.05–1.24, $3.28 \times 10^{-3}$ )	-0.0961 (2.75)	1.04 (2.46)	1.16 (1.06–1.28, $2.20 \times 10^{-3}$ )
$p < 1 \times 10^{-3}$	-0.314 (13.5)	1.47 (11.5)	1.01 (0.988–1.03, $4.89 \times 10^{-1}$ )	-0.228 (3.91)	1.54 (3.39)	1.13 (1.05–1.21, $7.03 \times 10^{-4}$ )	-0.189 (3.22)	1.26 (2.92)	1.15 (1.06–1.25, $8.73 \times 10^{-4}$ )
$p < 1 \times 10^{-2}$	1.07 (24.5)	2.95 (23.4)	1.00 (0.994–1.01, $4.84 \times 10^{-1}$ )	-0.282 (5.38)	1.92 (4.73)	1.08 (1.03–1.14, $2.88 \times 10^{-3}$ )	-0.257 (3.89)	1.47 (3.44)	1.12 (1.05–1.21, $1.15 \times 10^{-3}$ )

Abbreviations: AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; CI = confidence interval; CN = cognitively normal older adults; OR = odds ratio; SNP = single nucleotide polymorphism; TRS = transcriptional risk score.

ORs and 95% CIs of the TRS were derived from the logistic regression analysis with adjustment of age and sex.

<sup>a</sup> SNPs in strong linkage disequilibrium ( $r^2 > 0.8$ ) with the SNPs that had genome-wide significant associations ( $p < 5 \times 10^{-8}$ ) were also included for analysis.

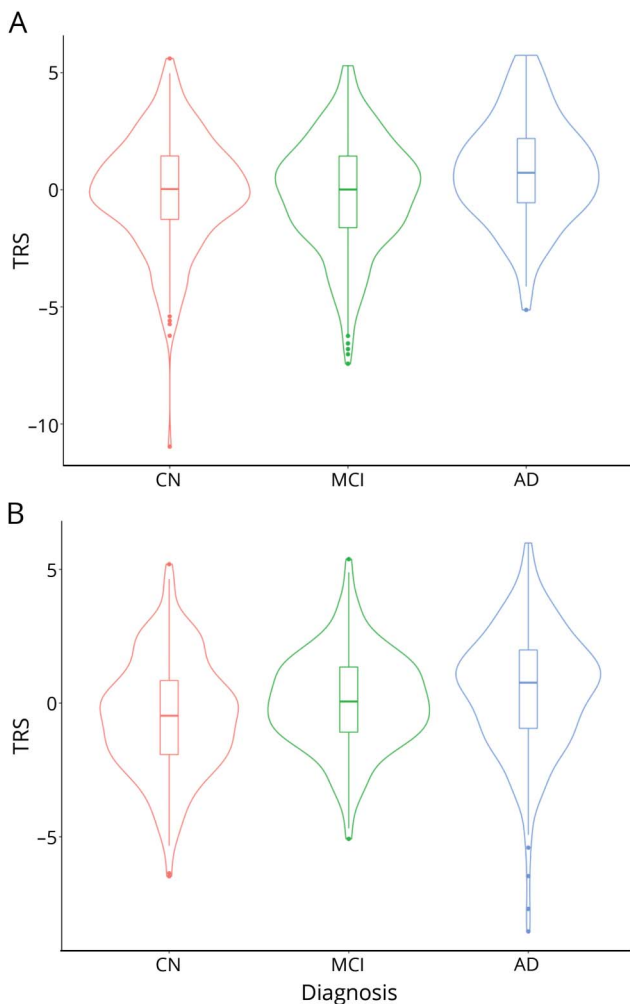
evidence for colocalization of association signals. When genome-wide significant SNPs ( $p < 5 \times 10^{-8}$ ) were selected to identify candidate AD-associated genes, the TRS of the candidate genes without the colocalization step was significantly different between AD and CN in the ADNI (odds ratio [OR] 1.06, 95% CI 1.01–1.13) (table 3). However, when the TRS was calculated only from target genes identified by COLOC, the diagnosis group difference of the TRS was slightly larger (OR 1.08, 95% CI 1.02–1.15). As shown in table 3 and figure 1, when AD-associated SNPs with  $p < 1 \times 10^{-7}$  were selected to identify candidate genes, the diagnosis group difference of the TRS for target genes identified by COLOC or SMR was the largest (OR 1.18, 95% CI 1.07–1.31 for COLOC; OR 1.18, 95% CI 1.06–1.33 for SMR) (table 3 and figure 1). The result remained significant when the TRS was compared between patients with AD with positive amyloid PET and CN with negative amyloid PET (OR 1.21, 95% CI 1.07–1.39 for COLOC; OR 1.24, 95% CI 1.08–1.43 for SMR). In AddNeuroMed, the TRS was also significantly different between AD and CN (table e-1, links.lww.com/NXG/A321). Furthermore, the diagnosis group difference of the TRS for target genes identified by COLOC or SMR was the largest (OR 1.20, 95% CI 1.12–1.30 for COLOC; OR 1.23, 95% CI 1.13–1.35 for SMR) after AD-associated SNPs were selected with  $p < 1 \times 10^{-7}$  or  $1 \times 10^{-6}$  (figure 1).

The TRS of target genes identified by COLOC or SMR was associated with MRI-based imaging biomarkers (hippocampal volume and entorhinal cortical thickness), cortical amyloid

accumulation and ADAS-cog13 in the ADNI (tables e-2 to e-5; figures e-1 and e-2, links.lww.com/NXG/A321). In AddNeuroMed, the TRS of target genes identified by COLOC or SMR was also associated with entorhinal cortical thickness (figure e-1 and table e-6). There was no significant association between the TRS and the hippocampal volume in AddNeuroMed.

Among 6 target genes identified by COLOC and SMR from AD-associated SNPs with  $p < 1 \times 10^{-7}$ , 2 genes (*CD33* and *PILRA*) and 4 genes (*B4GALT3*, *KLC3*, *STAG3*, and *TRAPPC6A*) were labeled as high expression and low expression, respectively. In the ADNI, expression levels of 2 genes (*CD33* and *PILRA*) were significantly increased, whereas 1 gene (*TRAPPC6A*) was significantly decreased in AD compared with CN, which was consistent with the prediction based on the integration of GWAS and the public blood eQTL database (figure 2, figure e-3 and table e-7, links.lww.com/NXG/A321). Expression levels of the remaining 3 genes in ADNI were not significantly different between AD and CN. In AddNeuroMed, expression levels of 2 genes (*CD33* and *PILRA*) were significantly increased, and 2 genes (*B4GALT3* and *TRAPPC6A*) were significantly decreased in AD compared to CN, as predicted by the GWAS and the eQTL database (figure 2, figure e-3 and table e-7). Expression levels of the remaining 2 genes in AddNeuroMed were not significantly different between AD and CN. Thus, the diagnosis group difference and directionality of gene expression levels of *CD33*, *PILRA*, and *TRAPPC6A* that were identified in ADNI were replicated in AddNeuroMed.

**Figure 1** Violin plots for the TRS between CN, MCI, and AD



Target genes identified from SMR at  $p$  value of AD-associated SNPs less than  $1 \times 10^{-7}$  were used to calculate the TRS. The violin plot shows the probability density of the TRS data as well as median and interquartile ranges in ADNI (A) and AddNeuroMed (B). AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; CN = cognitively normal older adults; MCI = mild cognitive impairment; SMR = summary data-based mendelian randomization; TRS = transcriptional risk score.

## Discussion

In this study, we selected candidate AD-associated genes by integrating large-scale AD GWAS summary statistics with the public blood eQTL database. Candidate genes were prioritized using COLOC and SMR to identify the target genes. Then, the TRS was calculated using blood-based transcriptome profiles of the target genes from 2 independent cohorts (ADNI and AddNeuroMed). The TRS was not only significantly different between AD and CN but also significantly associated with entorhinal cortical thickness in both of the cohorts. When AD-associated SNPs were selected from GWAS summary statistics with  $p$  values less than  $1 \times 10^{-7}$ , the TRS showed the largest associations with diagnosis and AD biomarkers in general. In addition, we found that expression levels of 2 genes (*CD33* and *PILRA*) were significantly increased, and 1 gene

(*TRAPPC6A*) was significantly decreased in AD compared with CN in the ADNI and AddNeuroMed, which was consistent with the prediction based on the GWAS and the public blood eQTL database. The expression of these genes in peripheral blood may be associated with the corresponding AD-associated SNPs and have an impact on the pathophysiology of AD.

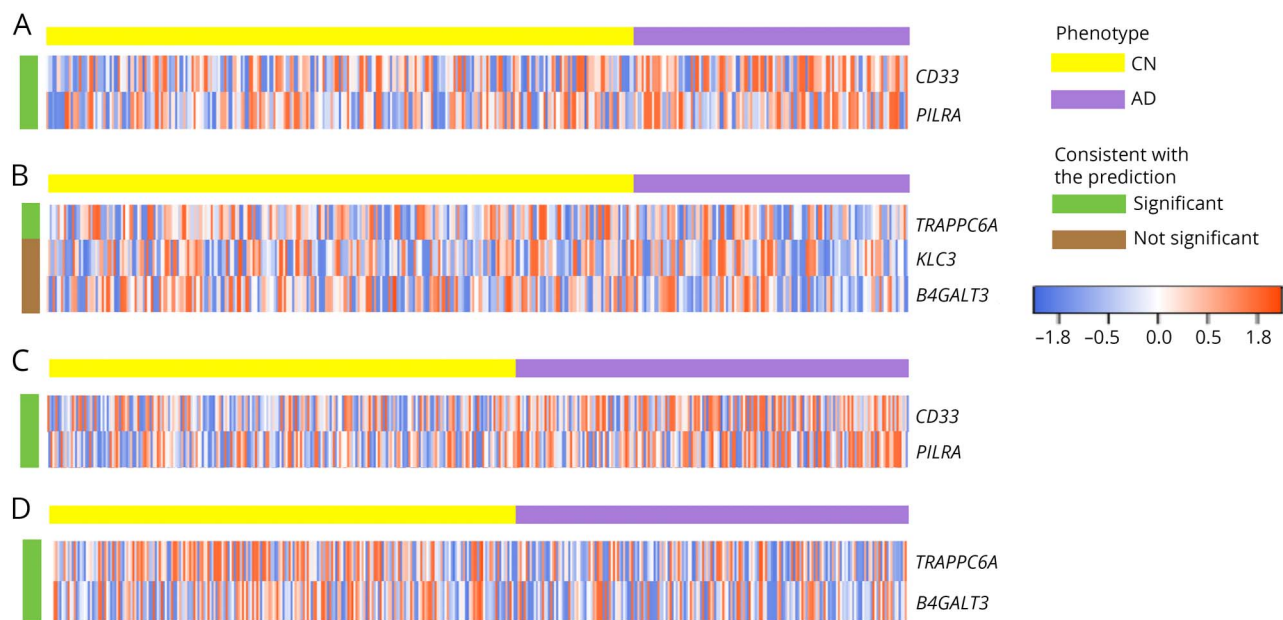
*CD33* encodes a sialic acid-binding transmembrane glycoprotein expressed on the surface of immune cells<sup>27</sup> and is one of the top-ranked AD risk genes identified by the GWAS.<sup>3</sup> It contains immunoreceptor tyrosine-based inhibitory motifs (ITIMs) that inhibit cellular activity such as phagocytosis.<sup>27</sup> As demonstrated in this study, the C (risk) allele of rs3865444 (rs3865444<sup>C</sup>) is known to be associated with increased expression levels of *CD33* on peripheral blood monocytes.<sup>28</sup> Although overall phagocytic activity of peripheral monocytes is reported to increase in subjects with positive amyloid PET scans compared with subjects with negative amyloid PET scans,<sup>29</sup> rs3865444<sup>C</sup> was found to be associated with reduced uptake of  $\beta$ -amyloid ( $A\beta$ ) on peripheral blood monocytes.<sup>28</sup> This suggests that increased expression levels of *CD33* by rs3865444<sup>C</sup> may interfere with peripheral uptake of  $A\beta$ , which could play a role in the pathogenesis of AD.

*PILRA* encodes paired immunoglobulin-like type 2 receptor alpha that is a cell surface inhibitory receptor with ITIM on immune cells.<sup>30</sup> The A (protective) allele of rs1859788 (rs1859788<sup>A</sup>) is a missense mutation that causes a conformational change of *PILRA* by a glycine-to-arginine substitution near the sialic acid-binding pocket and inhibits the binding of ligands to *PILRA*.<sup>31</sup> One of the ligands for *PILRA* is glycoprotein B (gB) of herpes simplex virus 1 (HSV-1), which is important for HSV-1 to enter the cells.<sup>30</sup> The transfected cells with rs1859788<sup>A</sup> had reduced binding of *PILRA* with HSV-1 gB and decreased levels of HSV-1 infection.<sup>31</sup> In addition to the conformational change of *PILRA*, our study suggests that rs1859788<sup>A</sup> is associated with reduced expression of *PILRA* in blood. Considering that the HSV-1 infection causes the accumulation of  $A\beta$  and phosphorylated tau,<sup>32</sup> altered expression of *PILRA* by rs1859788<sup>A</sup> may be protective for AD due to decreased reactivation of HSV-1.

*TRAPPC6A* encodes trafficking protein particle complex 6A. Although it is not clear how it affects the pathogenesis of AD, genetic variation of *TRAPPC6A* is reported to be associated with nonverbal reasoning.<sup>33</sup>

Given that we identified candidate and target genes from the public blood eQTL database and calculated the TRS using blood transcriptome data from the ADNI and AddNeuroMed cohorts, mechanisms that were identified in this study were observed in peripheral blood. Although AD is viewed primarily as a neurodegenerative CNS disease, many systemic manifestations have suggested that AD is a multifactorial disease that affects both the brain and the periphery.<sup>34</sup> In general, the systemic manifestations parallel the progressive

**Figure 2** Heatmaps of gene expression between CN and AD



Two genes (*CD33* and *PILRA*) that were predicted to have increased expression in patients with AD from the integration of GWAS summary statistics and eQTL data showed significantly increased expression in patients with AD in ADNI (A). Among 3 genes predicted to have decreased expression in patients with AD, 1 gene (*TRAPPC6A*) showed significantly decreased expression in patients with AD in ADNI (B). In AddNeuroMed, the expression level of two genes (*CD33* and *PILRA*) was significantly increased in patients with AD (C), whereas the expression level of two genes (*B4GALT3* and *TRAPPC6A*) was significantly decreased in patients with AD (D). The gene expression values were transformed into a normal distribution with mean 0 and variance 1. AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; CN = cognitively normal older adults; eQTL = expression quantitative trait locus; GWAS = genome-wide association study.

functional decline associated with neurodegeneration.<sup>34</sup> However, some systemic manifestations are also observable before the presence of CNS symptoms of AD.<sup>35</sup> Because blood interacts with all organs in the body, including the brain, blood-based profiles might provide an accessible and effective tool for evaluating the complex interplay between the brain and the periphery in the pathogenesis of AD.<sup>36</sup>

The present study has some limitations. First, we used the public blood eQTL database generated from CN, not from patients with AD. As the relationship between gene expression levels and SNPs may be different in normal subjects and patients with AD, it would be better to use a blood eQTL database including patients with AD. However, there is no public blood eQTL database generated from cohorts including patients with AD. Further study using the eQTL database including patients with AD is needed to identify pathogenic genes more precisely. Second, the ADNI participants may not be representative of the general population of older adults. To generalize our findings, we need to validate our findings in larger community-based prospective cohort studies. Third, blood-based transcriptomic profiles could be influenced by confounding factors such as medication, as well as blood collection, processing, and storage procedures.<sup>36,37</sup> The transcriptome samples in the ADNI and AddNeuroMed were collected, processed, and stored following the standard protocols to minimize these risks. Fourth, transcriptome profiling was performed on different microarray platforms in

the ADNI and AddNeuroMed. Therefore, in this study, we did not perform a mega-analysis but calculated the TRS in the ADNI and AddNeuroMed separately. Finally, we analyzed cross-sectionally collected gene expression data. Our findings thus represent association not causality. Longitudinal studies are needed to understand the role of altered transcriptome profiles in the onset of AD as well as cause-and-effect relationships.

In conclusion, we selected genes to calculate the TRS by integrating AD GWAS summary statistics with the public blood eQTL database, and we demonstrated that the blood-based TRS was significantly associated with AD biomarkers by using the transcriptomic database from the ADNI and AddNeuroMed cohorts. Looking toward the future, given the extensive omics data generated by various studies with better integrative approaches, it will likely become easier to determine the relation to relevant pathophysiologic mechanisms and discover novel biomarkers for clinical use.<sup>38</sup> With more omics data and sophisticated integrative approaches for analysis, multilayer omics data are likely to become useful for predicting, diagnosing, and personalizing treatment for AD.<sup>39</sup>

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## Disclosure

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## Association of blood-based transcriptional risk scores with biomarkers for Alzheimer disease

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