

# Shared genes between Alzheimer's disease and ischemic stroke

Chang-Juan Wei<sup>1,2</sup> | Pan Cui<sup>1,2</sup> | He Li<sup>1,2</sup> | Wen-Jing Lang<sup>1,2</sup> | Gui-You Liu<sup>3</sup> |  
Xiao-Feng Ma<sup>1,2</sup>

<sup>1</sup>Department of Neurology, Tianjin Medical University General Hospital, Tianjin, China

<sup>2</sup>Tianjin Neurological Institute, Key Laboratory of Post-neurotrauma Neuro-repair and Regeneration in Central Nervous System, Ministry of Education, Tianjin, China

<sup>3</sup>School of Life Science and Technology, Harbin Institute of Technology, Harbin, China

## Correspondence

Gui-You Liu, School of Life Science and Technology, Harbin Institute of Technology, Harbin, China.

Email: liuguiyou1981@163.com and

Xiao-Feng Ma, Department of Neurology, Tianjin Medical University General Hospital, Tianjin, China.

Email: xfengma@tmu.edu.cn

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## Summary

**Aims:** Although converging evidence from experimental and epidemiological studies indicates Alzheimer's disease (AD) and ischemic stroke (IS) are related, the genetic basis underlying their links is less well characterized. Traditional SNP-based genome-wide association studies (GWAS) have failed to uncover shared susceptibility variants of AD and IS. Therefore, this study was designed to investigate whether pleiotropic genes existed between AD and IS to account for their phenotypic association, although this was not reported in previous studies.

**Methods:** Taking advantage of large-scale GWAS summary statistics of AD (17,008 AD cases and 37,154 controls) and IS (10,307 IS cases and 19,326 controls), we performed gene-based analysis implemented in VEGAS2 and Fisher's meta-analysis of the set of overlapped genes of nominal significance in both diseases. Subsequently, gene expression analysis in AD- or IS-associated expression datasets was conducted to explore the transcriptional alterations of pleiotropic genes identified.

**Results:** 16 AD-IS pleiotropic genes surpassed the cutoff for Bonferroni-corrected significance. Notably, *MS4A4A* and *TREM2*, two established AD-susceptibility genes showed remarkable alterations in the spleens and brains afflicted by IS, respectively. Among the prioritized genes identified by virtue of literature-based knowledge, most are immune-relevant genes (*EPHA1*, *MS4A4A*, *UBE2L3* and *TREM2*), implicating crucial roles of the immune system in the pathogenesis of AD and IS.

**Conclusions:** The observation that AD and IS had shared disease-associated genes offered mechanistic insights into their common pathogenesis, predominantly involving the immune system. More importantly, our findings have important implications for future research directions, which are encouraged to verify the involvement of these candidates in AD and IS and interpret the exact molecular mechanisms of action.

## KEYWORDS

Alzheimer's disease, gene expression analysis, gene-based analysis, genome-wide association studies, ischemic stroke, pleiotropic genes, Versatile Gene-based Association Study-2 version 2

Wei and Cui contributed equally to this work.

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## 1 | INTRODUCTION

Alzheimer's disease (AD) is the world's leading cause of dementia. The hallmarks of AD are extracellular amyloid- $\beta$  peptide (A $\beta$ ) accumulation and intracellular neurofibrillary tangles (NFTs), the latter of which is formed by hyperphosphorylated tau protein. Along with the notorious reputation as the second leading cause of mortality and disability worldwide,<sup>1,2</sup> stroke is another major cause of age-related cognitive decline and dementia.<sup>3</sup> As the most prevalent form, ischemic stroke (IS) accounts for ~85% of stroke incidents.<sup>3</sup> Collectively, AD and IS both exert a large burden on global public healthcare and clinical practice.

Growing evidence indicates that there are links between AD and IS. Firstly, emerging epidemiologic research shows that AD is associated with considerable increased risk of IS,<sup>4,5</sup> and vice versa.<sup>6</sup> Secondly, neuropathological studies show that cerebrovascular lesions frequently coexist with AD pathology.<sup>7</sup> The two mixed pathologies act synergistically in increasing the odds of clinical dementia.<sup>8</sup> Indeed, a handful of studies have reported that brain ischemia is a non-neglectable factor driving the development of AD through dysregulated expression of AD-associated genes, such as A $\beta$  precursor processing genes and tau protein gene.<sup>9,10</sup> Lastly, tau protein, a core hallmark of AD, can exacerbate brain injury in experimental IS through tau-mediated iron export and excitotoxicity.<sup>11,12</sup> Taken together, we hypothesized that there might be a shared genetic basis underlying these connections between AD and IS.

Genome-wide association studies (GWAS) have yielded new insights into the genetics of AD<sup>13,14</sup> and IS.<sup>15,16</sup> Shared genetic variants between AD and IS or its subtypes, have been first determined by Traylor et al.<sup>17</sup> They tested whether established genome-wide single nucleotide polymorphisms (SNPs) for AD or IS were significantly associated with the other disease. Yet no such variants have been found. Conventional GWAS methods just focus on significant SNPs judging by overly stringent criterion ( $P < 5.00E-08$ ) when exploring the genome. There is an emerging consensus that, however, complex diseases are mostly driven by the joint action of a large proportion of SNPs having modest effects well below genome-wide significance.<sup>18</sup> Alternatively, gene-based analysis can obtain more validated associations by combining the effects of all SNPs within corresponding genes, thus expand knowledge about genetic architectures of complex diseases.

Hence, in our present study, we performed gene-based association tests to identify potential candidate genes shared between AD and IS. Next, gene expression analyses were conducted to evaluate shared genes' expression alterations in AD and IS brains or peripheral blood versus matched controls. Furthermore, to further interpret the molecular mechanisms that underpin AD and IS, systematic dissection of individual genes' functionalities was conducted.

## 2 | MATERIALS AND METHODS

### 2.1 | Samples

The GWAS statistics data for AD and IS analyses were from the International Genomics of Alzheimer's Project (IGAP)<sup>13</sup> and the

METASTROKE consortium of the International Stroke Genetics Consortium,<sup>15</sup> respectively. Both GWAS datasets are based on populations of European descent imputed to the 1000 Genomes Project (1000G) reference panel. Poorly genotyped or imputed SNPs and SNPs with a minor allele frequency (MAF) of less than 0.01 were filtered out in both datasets.

IGAP is a large-scale, two-stage GWAS (for more details, see the research by Lambert et al<sup>13</sup>). In stage 1, a meta-analysis of four published GWAS samples comprising 17,008 AD cases and 37,154 controls was conducted. After quality control, 7,055,881 SNPs were available for analysis. In stage 2, 11,632 SNPs showing moderate evidence of association ( $P < 1.00E-03$ ) in stage 1 were genotyped and tested for replication in an independent sample totaling 8,572 cases and 11,312 controls. Lastly, a meta-analysis combining results from stages 1 and 2 was performed. For the present study, we used only summary data from stage 1.

The METASTROKE collaboration genotyped and imputed approximately 9 million SNPs from a meta-analysis of 12 independent GWAS comprising 10,307 IS cases and 19,326 controls. Differing from prior IS GWAS data imputed to the HapMap panel, which comprised up to 2.5 million SNPs with MAF more than 0.05, this expanded set of SNPs informed by 1000G project also included low-frequency variants (MAF 0.01-0.05) and totaled 8.3 million quality-controlled SNPs for analysis. For more detailed information, refer to the original study.<sup>15</sup>

### 2.2 | Statistical analyses

#### 2.2.1 | VEGAS2 method

Using the GWAS summary data for AD and IS, we performed a gene-based association test implemented in an updated version of Versatile Gene-based Association Study-2 version 2 (VEGAS2).<sup>19</sup> Among various methods of gene-based analysis, VEGAS2 is particularly feasible for analyzing GWAS summary statistics where individual-level genotypic and phenotypic data are unavailable. By uploading the individual SNPs' IDs and their association  $P$ -values, VEGAS2 sums the effects of all the SNPs within a gene and corrects for linkage disequilibrium (LD) referring to 1000G reference set and thus, generates a gene-based test statistic by doing simulations from the multivariate normal distribution. The simulation approach is computationally more efficient than other methods that rely on permutations, such as PLINK, minSNP.<sup>20</sup> The default "symmetric boundaries  $\pm 0$  kb outside gene and SNPs in LD above  $r^2 = 0.8$ " was chosen to define gene boundaries, which meant that the effects of SNPs within a gene, also outside of the gene with  $r^2 > 0.8$  with the ones in the gene, were considered to calculate gene-based  $P$ -values. This option both took account into the effects of nearby regulatory SNPs and reduced the non-specificity caused by large boundaries like  $\pm 50$  kb.

To reduce the possibility of a single disease driving the cross-disease associations and uncover truly pleiotropic genes shared by AD and IS, we focused on shared genes that were nominally significant in each disease ( $P_{AD} < 0.05$  and  $P_{IS} < 0.05$ ).

**TABLE 1** Gene-based association results from gene-based meta-analyses of Alzheimer's disease (AD) and ischemic stroke (IS)

Region	Gene	AD			IS			$P_{\text{combined}}$
		P value	Top-SNP	Top-SNP P value	P value	Top-SNP	Top-SNP P value	
7q34	ZYX	<b>5.10E-04</b>	rs6464548	1.62E-06	<b>2.70E-05</b>	rs11772895	3.39E-06	2.63E-07
7q34-q35	EPHA1	1.00E-06	rs10808026	1.42E-11	3.64E-02	rs11762334	7.16E-05	6.60E-07
15q25.2	<b>EFTUD1</b>	<b>1.09E-04</b>	rs905450	2.82E-06	<b>8.24E-04</b>	rs151045855	2.17E-04	1.55E-06
11q12.2	MS4A4A	1.50E-05	rs55777218	3.94E-12	4.21E-02	rs115739426	5.29E-03	9.65E-06
22q11.21	YDJC	2.01E-04	rs2298428	7.28E-05	1.00E-02	rs3747093	2.87E-03	2.84E-05
22q11.21	UBE2L3	2.72E-04	rs12168746	8.82E-05	7.74E-03	rs738129	3.95E-03	2.96E-05
8q22.3	PABPC1	4.76E-03	rs1693547	9.19E-04	9.00E-04	rs3104313	1.94E-04	5.72E-05
16p12.2	RRN3P1	1.56E-03	rs12600118	3.92E-05	3.62E-03	rs4017431	8.17E-04	7.39E-05
15q25.2	FAM154B	2.56E-04	rs28522807	2.86E-04	2.56E-02	rs117388641	1.55E-03	8.48E-05
17q25.1	SLC16A5	7.22E-04	rs8078881	2.32E-04	1.23E-02	rs12943414	1.70E-03	1.12E-04
12q24.13	HECTD4	3.68E-02	rs147910225	2.31E-04	2.70E-04	rs10850034	2.49E-05	1.24E-04
5q31.3	ANKHD1-EIF4EBP3	8.61E-04	rs78028717	2.52E-04	1.27E-02	rs801459	1.39E-03	1.36E-04
8p23.1	PINX1	1.23E-03	rs7014168	3.60E-04	9.20E-03	rs12676417	6.40E-04	1.40E-04
22q11.23	SLC2A11	1.12E-03	rs5760076	3.91E-05	1.06E-02	rs73158776	2.17E-03	1.47E-04
12q24.13	OAS2	2.50E-04	rs1635142	4.27E-05	4.96E-02	rs929291	8.24E-03	1.52E-04
5q31.3	ANKHD1	1.18E-03	rs78028717	2.52E-04	1.06E-02	rs2108446	1.85E-03	1.54E-04
6p21.1	TREM2	1.52E-03	rs6933067	1.07E-03	9.50E-03	rs7748513	4.34E-03	1.75E-04

Top-SNP, most significant SNP from each gene. Significantly associated genes whose P-values in both phenotypes were below 0.001 were shown in bold.

## 2.2.2 | Meta-analysis using Fisher's method

We used Fisher's method to combine the  $P$ -values calculated by the VEGAS2 for each gene shared by AD and IS. For a given gene, the Fisher formula for meta-analysis is:

$$\chi^2 = -2 \sum_{i=1}^k \ln(P_i)$$

where  $P_i$  are the  $P$ -values of the genes in the  $i_{th}$  study and  $k$  is the total number of studies.  $\chi^2$  follows a chi-square distribution with  $2k$  degrees of freedom.<sup>21</sup> The gene-based meta-analysis was carried out using the R software package.

To avoid false positive signals, we applied the stringent Bonferroni correction accounting for the number of genes and phenotypes tested, that is, the significance threshold was set at  $0.05/2N$ , where  $N$  represented the number of shared genes with nominal significance in both AD and IS.

## 2.2.3 | Gene expression analysis method

To explore the expression alterations of shared genes in each disease, we surveyed the expression datasets of AD and IS from the Gene Expression Omnibus (GEO) repository. Gene expression analysis was mainly restricted to brains and peripheral blood, as they are the most affected by AD- or IS-associated pathology.

Because AD-associated neuropathology shows regional specificity, expression profiles from discrete brain regions are more informative for discerning AD molecular signatures than analyses based on whole-brain expression data. Thus, we examined expression data from separate regions from postmortem human AD and control brains, including the dorsolateral prefrontal cortex (PFC) and hippocampus regions. The former (GSE44770) sampled 549 brains of 376 late-onset AD patients and 173 controls.<sup>22</sup> The latter (GSE48350) comprised 19 AD cases versus 43 matched controls.<sup>23</sup>

For IS, samples of brains and other tissues (eg spleen) from patients were generally not available. Considering that the core features of IS pathophysiology in rodents and humans are analogous, we included the expression data from peri-infarct brain areas of rats (GSE55260).<sup>24</sup> We also analyzed transcriptional data from peripheral blood collected within 24 hours of stroke onset in 39 IS patients and 24 controls (GSE16561).<sup>25</sup> Additionally, we explored transcriptional profiles from mouse spleens (GSE70841) as spleen is the major lymphoid organ involved in the inflammatory milieu secondary to brain ischemia. All gene aliases in rat or mouse were transformed to the official symbols corresponding to human genes.

If there were multiple transcripts within the same gene, the one with the smallest  $P$ -value was selected. Due to between-study heterogeneity, not all transcripts of AD-IS pleiotropic genes appeared in each dataset. The differential expression was determined by Bonferroni correction accounting for the number of shared genes present in each dataset ( $P = 0.05/n$ ,  $n \leq 16$ ).

## 3 | RESULTS

### 3.1 | Gene-based testing for risk genes of AD and IS

Firstly, the VEGAS2 method was applied to individual GWAS summary data from AD and IS. For AD, 34 genes exceeded gene-wide significance ( $P < 2.35E-6$  for 21,244 gene tests). Apart from 20 genes at 19q13.31-q13.32 harboring the well-known *APOE* locus, we confirmed 12 genes (*CD33*, *ABCA7*, *HLA-DRB6*, *MS4A2/MS4A6A*, *EPHA1*, *PICALM*, *CR1*, *CLU*, *MTCH2/SLC39A13*, and *BIN1*) within 10 established risk loci (*CD33*, *ABCA7*, *HLA-DRB5-DRB1* region, *MS4A* locus, *EPHA1*, *PICALM*, *CR1*, *CLU*, *CELF1*, and *BIN1*).<sup>13</sup> Considering the other 39 genes outside the *APOE* locus passing a loose significance threshold ( $P < 1.00E-4$ ), 23 genes belonged to the established risk loci, with 4 more loci validated (*CD2AP*, *PTK2B*, *SORL1*, and *SLC24A4*).<sup>13</sup> The well-replicated results showed the good performance of VEGAS2 for gene-based analysis. For the full results, see Supporting Information Table S1.

For IS, no genes of gene-wide significance were recognized ( $P < 2.28E-06$  for 21,913 gene tests), while two genes surpassed a loose significance threshold ( $P < 1.00E-04$ ): *ZYX* ( $P = 2.70E-05$ ) and *NCR3LG1* ( $P = 7.30E-05$ ).

### 3.2 | Gene-based testing for shared genes between AD and IS

After overlapping 1915 AD genes and 1288 IS genes with nominal significance, 130 shared genes remained for further Fisher's meta-analysis. We identified 17 genes reaching the significance threshold at  $P_{combined} < 1.92E-4$  [ $0.05/(2*130)$ ] (Table 1), some of which were located in adjacent positions, that is, *ZYX/EPHA1* at 7q34-7q35, *EFTUD1/FAM154B* at 15q25.2, *YDJC/UBE2L3* and *SLC2A11* at 22q11, *HECTD4/OAS2* at 12q24.13, and *ANKHD1-EIF4EBP3/ANKHD1* at 5q31.3. The latter was regarded as one gene as they were likely to arise from the same SNPs signals as *ANKHD1-EIF4EBP3* is a fusion transcript of *ANKHD1* and its downstream *EIF4EBP3*. It's worth noting that *ZYX* and *EFTUD1* even reached  $P < 0.001$  in both AD and IS datasets. For the full results, refer to Supporting Information Table S2.

### 3.3 | Gene expression analyses of shared genes

To validate the relevance of the 16 AD-IS genes, we evaluated their expressions in brains or peripheral blood of AD or IS cases versus controls. Importantly, *MS4A4A* and *TREM2*, two established AD-susceptibility genes, showed remarkable alterations in the spleens and brains afflicted by IS, respectively. A comparison of differentially expressed genes in each dataset was presented in Table 2.

AD-associated expression profiles from the PFC region (Supporting Information Table S3A) revealed that 8 genes were differentially expressed, with *MS4A4A*, *UBE2L3*, *TREM2*, and *HECTD4* being the most significant, while just 3 genes' expression

**TABLE 2** Expression changes of shared genes in distinct expression datasets for Alzheimer's disease (AD) and ischemic stroke (IS)

Gene	AD		IS		
	GSE44770	GSE48350	GSE55260	GSE16561	GSE70841
	PFC	Hippocampus	Brain	Peripheral blood	Spleen
ZYX	2.41E-01	2.13E-01	<b>8.43E-04</b>	<b>3.38E-04</b>	8.08E-02
EPHA1	6.12E-01	4.26E-02	9.48E-01	<b>1.22E-03</b>	9.23E-01
EFTUD1	2.48E-01	4.15E-02	4.79E-02	5.31E-02	8.60E-02
MS4A4A	<b>1.08E-24</b>	3.87E-03**	—	<b>2.73E-05</b>	<b>1.57E-05*</b>
YDJC	—	<b>1.14E-04</b>	7.58E-03	2.17E-01	4.61E-01
UBE2L3	<b>3.24E-20</b>	4.45E-01	7.32E-01	5.68E-02	<b>1.83E-03</b>
PABPC1	<b>1.90E-11</b>	<b>2.99E-04</b>	<b>4.17E-05*</b>	7.40E-02	5.27E-01
RRN3P1	—	2.69E-01	—	—	—
FAM154B	—	3.14E-01	5.54E-02	8.80E-01	2.55E-01
SLC16A5	<b>4.93E-10</b>	3.15E-01	1.16E-01	3.47E-02	—
HECTD4	<b>8.74E-16</b>	<b>5.17E-05</b>	—	—	—
ANKHD1-EIF4EBP3	4.30E-01	2.05E-01	9.75E-02	4.15E-02	—
PINX1	<b>2.46E-04</b>	3.13E-01	2.03E-01	8.44E-01	—
SLC2A11	<b>1.41E-11</b>	5.39E-03	—	<b>2.55E-03</b>	—
OAS2	1.13E-01	1.46E-01	1.29E-01	2.04E-01	—
TREM2	<b>6.80E-20</b>	1.34E-01	<b>9.29E-06*</b>	5.37E-01	7.10E-01
Significance threshold	3.85E-03	3.13E-03	3.85E-03	3.57E-03	5.56E-03

GEO accession, GSE44772, GSE48350, GSE55260, GSE16561 and GSE70841; PFC, dorsolateral prefrontal cortex; “—”, (no data) meant that the transcripts of this gene did not exist in corresponding datasets. Bolded *P*-values of genes achieved Bonferroni-corrected significance, adjusted for the number of shared genes present in each expression dataset (0.05/*n*, *n* ≤ 16).

\*Gene expression level showing more than 2 folds upregulation or downregulation compared to controls.

\*\*Genes near the significance threshold.

levels (*HECTD4*, *YDJC*, and *PABPC1*) were altered in the hippocampal regions compared with control brains (Supporting Information Table S3B). In peri-infarcted rat brains (Supporting Information Table S4A), we observed expression changes of 4 genes (*TREM2*, *PABPC1*, *ZYX*, and *YDJC*). Notably, *TREM2* showed nearly 4-fold upregulation versus controls (log<sub>2</sub>-fold change = 1.99). Transcriptional changes of four genes (*MS4A4A*, *ZYX*, *EPHA1* and *SLC2A11*) were present in the peripheral blood of IS patients (Supporting Information Table S4B). Particularly, differential expression of *MS4A4A* was even more evident in mouse spleens, with over 5-fold increase (log<sub>2</sub>-fold change = 2.37; Supporting Information Table S4C). It's necessary to point out that, however, the transcriptional data from rat brains and mouse spleens were not compelling enough due to the small sample size. More robust transcriptional datasets are needed to further validate the candidate genes.

## 4 | DISCUSSION

Different from conventional SNP-based GWAS studies, our research used VEGAS2 gene-based association test to detect pleiotropic genes jointly associated with AD and IS. To avoid the problem of joint effects arising from a dominant association with

one single disease, we focused on shared genes with nominal significance in both AD and IS (*P* < 0.05). By this criterion, 16 genes survived the stringent Bonferroni correction. Next, they were screened for differential expression in AD and IS cases versus controls. To search for supportive evidence for their relevance to AD and IS, we paid extra attention to the molecular functions of these genes.

### 4.1 | ZYX and EPHA1 gene at 7q34-7q35

Zyxin (*ZYX*) encodes a zinc-binding adaptor protein that translocates from focal adhesions to the nucleus to conduct signal transduction and modulate gene expression. Recently, zyxin has been identified as a novel target of Aβ metabolism in AD.<sup>26</sup> Besides, Zyxin is a novel interacting partner of SIRT1<sup>27</sup> that is protective against aging-associated pathologies like AD<sup>28</sup> and IS.<sup>29</sup> Here, *ZYX* was jointly associated with AD and IS (*P*<sub>combined</sub> = 2.63E-07) with *P* < 0.001 in each disease. Of note was that *ZYX* showed the most significant association (*P* = 2.70E-05) in the gene-based analysis of IS.

*EPHA1* is an established risk locus of AD, and our gene-based analysis confirmed its gene-wide association with AD (*P* = 1.00E-06). Ephrin type-A receptor 1 (*EPHA1*) belongs to the eph receptor subfamily that is the largest family of receptor tyrosine kinases, mediating axonal guidance, synaptic plasticity, and

cell-to-cell communication in the central nervous system (CNS).<sup>30,31</sup> Moreover, *EPHA1* can modulate leukocyte extravasation, chemotaxis, and inflammatory cell migration.<sup>32–34</sup> Indeed, ample evidence has implicated the involvement of *EPHA1*, as well as *MS4A4A* and *TREM2* listed below, in the immune module of AD.<sup>22,35,36</sup> As previously described,<sup>37</sup> we observed no aberrant *EPHA1* expression in the PFC region of AD patients, neither in the hippocampus.

#### 4.2 | *MS4A4A* gene at 11q12.2

*MS4A4A* is a strong AD candidate gene<sup>38</sup> within the membrane-spanning 4-domains subfamily A (*MS4A*) gene cluster, an established risk locus for AD.<sup>13,39,40</sup> It is predominantly expressed in immune cells, including resident microglia in the CNS. Following microglial activation, *MS4A4A* shows increased expression.<sup>41</sup> Similarly, *MS4A4A* is upregulated in activated dendritic cells (DCs) and M1 macrophages, while not detected in immature DCs and M2 macrophages.<sup>42</sup> Here, *MS4A4A* showed significantly altered expression in the PFC region of AD brains ( $P = 1.08E-24$ ), yet displayed an expression alteration of suggestive evidence in the hippocampal region ( $P = 3.87E-03$ ).

Notably, *MS4A4A* was also differentially expressed in peripheral blood of IS patients ( $P = 2.73E-05$ ) and in mouse spleens after IS with over 5-fold upregulation ( $P = 1.57E-05$ ; log<sub>2</sub>-fold change = 2.37). Following IS, increased incidence of infections occurs, mainly in the form of pneumonia and urinary tract infections.<sup>43,44</sup> The underlying mechanism is insufficient antigen-presentation of monocytes/macrophages and DCs in peripheral immune organs, resulting from downregulation of MHC class II and co-stimulatory molecules and remarkable reduction of proinflammatory cytokines.<sup>45</sup> Herein, we speculated that the pronounced upregulation of *MS4A4A* in the spleen following IS might reflect a phenotypic switch of monocytes from the proinflammatory M1 phenotype to the anti-inflammatory M2 phenotype.

#### 4.3 | *UBE2L3*, *YDJC* and *SLC2A11* genes at 22q11

Ubiquitin-conjugating enzyme E2 L3 (*UBE2L3*) and *YDJC* are located at 22q11.21. The genetic relationship between the 22q11.21 region and multiple autoimmune diseases has been extensively elucidated.<sup>46–48</sup> Besides, SNPs near *YDJC* are suggested to be a pleiotropic locus between AD and Crohn disease.<sup>49</sup> Lately, *UBE2L3* has been identified as a hub gene in the gene regulatory networks of AD.<sup>50</sup>

*UBE2L3* encodes an E2 ubiquitin-conjugating enzyme. Through its action on ubiquitination in NF- $\kappa$ B signaling, *UBE2L3* promotes NF- $\kappa$ B activation, thus mediates its link with numerous autoimmune diseases.<sup>51–53</sup> Moreover, *UBE2L3* modulates pro-IL-1 $\beta$  processing and mature IL-1 $\beta$  secretion,<sup>54</sup> the deregulation of which pronouncedly intensifies neuronal damage in both AD and IS.<sup>55,56</sup> In addition, *UBE2L3* directly interacts with the parkin protein, a ubiquitin-protein ligase that is protective against not only neurodegenerative diseases,<sup>57–59</sup> but also cerebral ischemia-reperfusion injury.<sup>60</sup> Nonetheless, there is no conclusive evidence to date demonstrating a causative link between *UBE2L3* and AD or IS. The function of *YDJC* remains largely obscure. Solute-carrier 2A

family member 11 (*SLC2A11*) encodes GLUT11, a fructose-transporting protein that might participate in fructose consumption in the CNS.<sup>61</sup>

#### 4.4 | *PABPC1* gene at 8q22.3

Poly(A) binding protein cytoplasmic 1 (*PABPC1*), one type of RNA-binding proteins, is a central component of cytoplasmic stress granules comprising proteins and mRNAs stalled at the translation initiation step.<sup>62</sup> Pathological stress granules play crucial roles in neurodegenerative disorders,<sup>63,64</sup> also in brain ischemia.<sup>65</sup> Moreover, abnormal cytoplasmic inclusions of *PABPC1* have been observed in human ALS spinal cord neurons.<sup>66,67</sup> In the present work, *PABPC1* was differentially expressed in both the PFC ( $P = 1.90E-11$ ) and hippocampal regions ( $P = 2.99E-04$ ) of AD. Evidently in IS brains, its expression was significantly enhanced (log<sub>2</sub>-fold change = 1.19) compared to control subjects (Supporting Information Table S4A).

#### 4.5 | *HECTD4* and *OAS2* gene at 12q24

Mounting GWAS studies have demonstrated the pleiotropic effects of 12q24 locus on type 1 diabetes,<sup>68,69</sup> celiac disease,<sup>70</sup> coronary artery disease<sup>71–73</sup> and a number of cardiovascular risk factors, including hypertension,<sup>72,74,75</sup> cholesterol levels,<sup>72,76</sup> waist-hip ratio,<sup>77</sup> and glycemia.<sup>78</sup> Importantly, the 12q24 region has been suggested to be a risk locus of IS.<sup>79</sup> Recently, SNPs near *HECTD4* are shown to be associated with memory performance.<sup>80</sup> HECT domain E3 ubiquitin-protein ligase 4 (*HECTD4*) is a E3 ubiquitin-protein ligase. HECT-type E3s can function with *UBE2L3* discussed above in the ubiquitin system.<sup>81</sup> Here, *HECTD4* was differentially expressed in both AD's PFC ( $P = 8.74E-16$ ) and hippocampal ( $P = 1.73E-03$ ) regions compared to controls. Regrettably, the transcripts of *HECTD4* were not detected in any expression datasets of IS. 2'-5'-oligoadenylate synthetase 2 (*OAS2*) gene, together with neighboring *OAS1* and *OAS3* gene, encodes enzymes participating in innate immunity response to viral infection.<sup>82</sup>

#### 4.6 | *PINX1* gene at 8p23.1

PIN2 (TERF1) interacting telomerase inhibitor 1 (*PINX1*) protein is a potent telomerase inhibitor,<sup>83</sup> and a microtubule-binding protein essential for chromosome segregation in mitosis.<sup>84</sup> In addition to its biological significance in various cancers,<sup>85</sup> *PINX1* gene is associated with subclinical cardiovascular events like carotid intima media thickness,<sup>86</sup> blood lipids,<sup>87,88</sup> and involved in AD as a potential interactor of A $\beta$ .<sup>89</sup>

#### 4.7 | *TREM2* gene at 6p21.1

Triggering receptor expressed on myeloid cells-2 (*TREM2*) is highly expressed on microglia as an innate immune receptor involved in phagocytosis, clearance of damaged neurons, and inhibition of the microglial proinflammatory response.<sup>90</sup> Mutation of rare variants in *TREM2* confers a substantial increase in AD risk,<sup>91–93</sup> which has been

experimentally proved.<sup>94,95</sup> *TREM2* has been indicated to be upregulated and participate in ischemic brain damage by modulating microglial phenotypes despite conflicting findings.<sup>96-100</sup> Here, *TREM2* was shared by AD and IS with individual  $P = 0.0015$  and  $P = 0.0095$ , respectively. Since rare variants (MAF < 0.01) were excluded from the GWAS panels of both AD and IS, we assumed that the true joint association signal of *TREM2* with AD and IS might be stronger than we observed. *TREM2* transcriptional changes were observed in the PFC region ( $P = 6.80E-20$ ) of AD, and in rat peri-infarcted brains ( $P = 9.29E-06$ ). Expectedly, the latter showed nearly 4-fold increased expression for *TREM2* (log2-fold change = 1.99; Supporting Information Table S4A).

#### 4.8 | Others

Though we found that the following genes (ie *EFTUD1/FAM154B* at 15q25.2, *RRN3P1*, *SLC16A5*, and *ANKHD1-EIF4EBP3*) were common association signals for AD and IS in terms of bioinformatics, less is known about their biological roles due to lack of overwhelming evidence related to AD or IS.

Based on the concise discussion about their biological significance, partial pleiotropic genes underlying AD and IS were prioritized, including *ZYX*, *EPHA1*, *MS4A4A*, *UBE2L3*, *PABPC1*, *HECTD4*, *PINX1*, and *TREM2*. Consistent with our previous findings from the pathway-oriented perspective,<sup>101</sup> we once again highlighted the critical roles of neuroinflammation in the development and progression of AD and IS, since half of them (*EPHA1*, *MS4A4A*, *UBE2L3* and *TREM2*) were engaged in immune signaling.

Although gene-based tests increase the power to detect disease-associated genes harboring multiple associated variants, they do have limitations. Firstly, the VEGAS test is prone to underestimating effects of low-frequency SNPs correlated with few SNPs in LD blocks,<sup>102</sup> but may be unable to distinguish the truly causal genes from several adjacent ones colocalizing in one significant locus. Secondly, genes revealed by positional proximity to significant variants are not necessarily the causal ones for disease pathogenesis. In complex diseases, significant variants are mostly located in intronic/intergenic areas, presumably regulating gene expression, including acting on distant genes. Next, we leveraged the GEO dataset to estimate the expression alteration of candidate genes in disease-related tissues, the reliability of which largely relied on the raw data, for instance, the size of tissue samples in the original studies. Further powerful approaches and sophisticated functional interpretation analyses are warranted to prioritize causal genes. Moreover, being pathologically and genetically heterogeneous,<sup>103</sup> IS has different etiological subtypes (ie large vessel disease, cardioembolic stroke, and small vessel disease, undetermined and other). Here, we just surveyed the genetic link between AD and overall IS.

## 5 | CONCLUSIONS

We presented a gene-based strategy that corroborates shared candidate genes between AD and IS, with gene expression analysis ensued,

which provided a typical example of how genetic studies could add to biological understanding of cross-trait etiology. Literature mining supported the potential association of partial novel candidate genes with both AD and IS. Our findings yielded mechanistic insights into the common pathogenesis underlying AD and IS, predominantly involving the immune system, and might suggest common intervention targets. More importantly, our findings should encourage more studies to verify the involvement of these candidates in AD and IS and interpret the exact molecular mechanisms of action.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

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

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