

Gut microbiota may affect Alzheimer's disease through synaptic function mediated by CAMs pathway: A study combining Mendelian randomization and bioinformatics

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Abstract

Background: The association between gut microbes and Alzheimer's disease (AD) has not been entirely elucidated.

Objective: We aimed to demonstrate the association between gut microbes and AD and to further investigate the pathogenesis of microbes with a causal relationship to AD.

Methods: Mendelian randomization analyses were used to determine the significant causal relationship between gut microbes and AD. Protein-protein interaction (PPI) network was used to identify the hub genes. Functional enrichment analysis was used to reveal the pathogenesis theoretically between gut microbes and AD.

Results: In the present study, a total of 32 microbes were identified that were significantly associated with AD. Subsequently, DLGAP2, NRXN3, NEGR1, NTNAP2, MYH9, and SCN3A were identified as hub genes. The genes NRXN3, NEGR1, and NTNAP2 were enriched in the cell adhesion molecules (CAMs) signaling, and the taxons of gut microbes that corresponded to these were *Bifidobacterium adolescentis*, *Actinomycetales*, and *Intestinimonas massiliensis*.

Conclusions: *Bifidobacterium adolescentis*, *Actinomycetales*, and *Intestinimonas massiliensis* may promote the progression of AD through the regulation of the CAMs signaling pathway-mediated synaptic function. Hence, the in-depth study of gut microbes may increase the efficiency of screening and diagnosis of AD.

Keywords

Alzheimer's disease, bioinformatics, cell adhesion molecules signaling, gut microbes, mendelian randomization

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Introduction

Alzheimer's disease (AD) is a neurodegenerative encephalopathy caused by damage to neurons in the brain, leading to the deficits in language, movement, and thinking. The Alzheimer's Association (2024) announced that approximately 10 to 12 million people (>65 years old in America) will suffer from AD or other forms of cognitive disorders.¹ Between 2000 and 2021, the mortality of AD rose significantly and AD-related deaths doubled.² Some studies have reported that the life expectancy after a diagnosis of AD in older people aged 65 and over is generally four to eight years on average, with some lasting as long as 20 years.^{3–5} There was no doubt that the length of illness before death had a serious impact on patients, families, and even the social health care system, ultimately leading

to a heavy economic burden on families and society. Until now, there was no definitive prevention or cure for AD, which means that a broader and deeper understanding

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of AD was needed, including its etiology and how to prevent, manage, and cure it. The entire pathogenesis for AD was unclear, with the mainstream direction focus on neurofibrillary tangles and senile plaques.⁶

It is noteworthy that the central nervous system (CNS) appears to be a subtle link with the gut microbe, based on the concept of the gut-brain axis.⁷ Approximately 1000 species of microorganisms are involved in a variety of metabolic functions within the human gut.⁸ Due to the inter-individual variability in age, lifestyle, and environment, microbial diversity varies between individuals. Abnormalities in the gut microbe may contribute to an inflammatory response, which can result in damage to the intestinal mucosal barrier and the subsequent progression of inflammatory bowel disease.⁹ Previous studies have indicated that *Escherichia*, *Klebsiella*, *Haemophilus*, and *Proteus* are associated with this progression.^{10,11}

Furthermore, microbial metabolites have been demonstrated to contribute to host immunity and cerebral function. These include short-chain fatty acids, butyric acid, amino acids, and lipopolysaccharides (LPS).^{12–14} A noteworthy study suggested that tryptamine is a derivative of tryptophan, and that certain bacteria in the gut (such as *Clostridium* sp.) are capable of producing tryptamine. These bacteria contain NADH: ubiquinone reductase (NQR) sequences have been associated with AD. Elevated levels of tryptamine could induce the cytotoxicity and neurotoxicity before the onset of AD, which means that tryptamine in feces may serve as a potential early warning sign of AD.¹⁵ In summary, the gut-brain axis is involved in the pathways between the CNS, endocrine, metabolism, and the immune system.¹⁶ The health of the host is contingent upon the abundance and diversity of the gut microbe. Recent studies have suggested that gut microbial diversity may be an important factor in the pathogenesis of AD.^{17–20} In particular, the use of bioinformatics to explore common pathogenic mechanisms within the gut-brain axis system has become an increasingly established approach.

The MiBioGen study,²¹ which had 18,340 participants from 24 cohorts (across Europe, the Middle East, and East Asia), was a large-scale international scientific research cooperation project. The reporting of 211 microbial taxa for genome-wide association studies has frequently been employed to elucidate the influence of gut microbes on AD, and this subset of data has considerable research value. However, we elected not to utilize this particular subset of data, as the annotation of the alignment of their gut microbiota demonstrated considerable heterogeneity in microbial composition across cohorts. In order to maintain the racial consistency of the data, we elected to analyze the most recent gut microbial data available, with summary statistics for 473 microbial taxa by Mendelian randomization (MR). The combination of bioinformatics analysis with the aforementioned data provides compelling evidence for further in-depth analysis.

Methods

Study design

The detailed flowchart of this study was shown in Figure 1. First, the gut microbe was used as the exposure and AD as the outcome, and instrumental variables (IVs) were sought to explore the causal relationship between the two. Second, the gene set was built by matching the IVs and the National Center for Biotechnology Information (NCBI). Finally, the Gene Expression Omnibus (GEO) dataset was used to identify the differentially expressed genes (DEGs), and the overlaps were identified between DEGs and the gene set, which was further analyzed by protein-protein interaction (PPI) analysis and functional enrichment analysis. The study population was all European.

Exposure and outcome data

The latest summary statistics data on gut microbe was selected for the present study. Exposure data source from a single large population-based cohort of 5959 genotyped individuals with matched gut microbial met genomes. A total of 473 genome-wide summary statistics were found in the NHGRI-EBI GWAS Catalog (<https://www.ebi.ac.uk/gwas/>) from accessions GCST90032172 to GCST90032644.²² The outcome data (ieu-b-5067) was selected as the AD dataset.

GEO dataset source

The AD GEO dataset selected for this study was obtained from the GEO database (<https://www.ncbi.nlm.nih.gov/geo/>). The following criteria were used to screen the dataset: (1) including cases and controls. (2) The minimum number of samples was 20. The GSE28146 of AD was selected to screen for DEGs, and the “GEO query” package of the R software (version 4.3.2, <http://rproject.org/>) was used to download the sample source from the GEO database. The dataset was downloaded from publicly available databases, and no additional ethical approval was required.

Data processing and differentially expressed gene screening

First, the data matrix of gene expression profiling was log2 transformed. Second, the “Limma” package in the R software was used to identify AD DEGs, which were defined as the $|\log_2FC| > (\text{mean}(\text{abs}(\log_2FC)) + 2 \times \text{sd}(\text{abs}(\log_2FC)))$ and $p\text{-values} < 0.05$. Third, to visualize the DEGs as heatmaps and volcano plots, the packages “ggplot2” and “pheatmap” were used, respectively.

Statistical analyses

The single nucleotide polymorphisms (SNPs) were used as IVs to perform the MR analysis. Three assumptions are

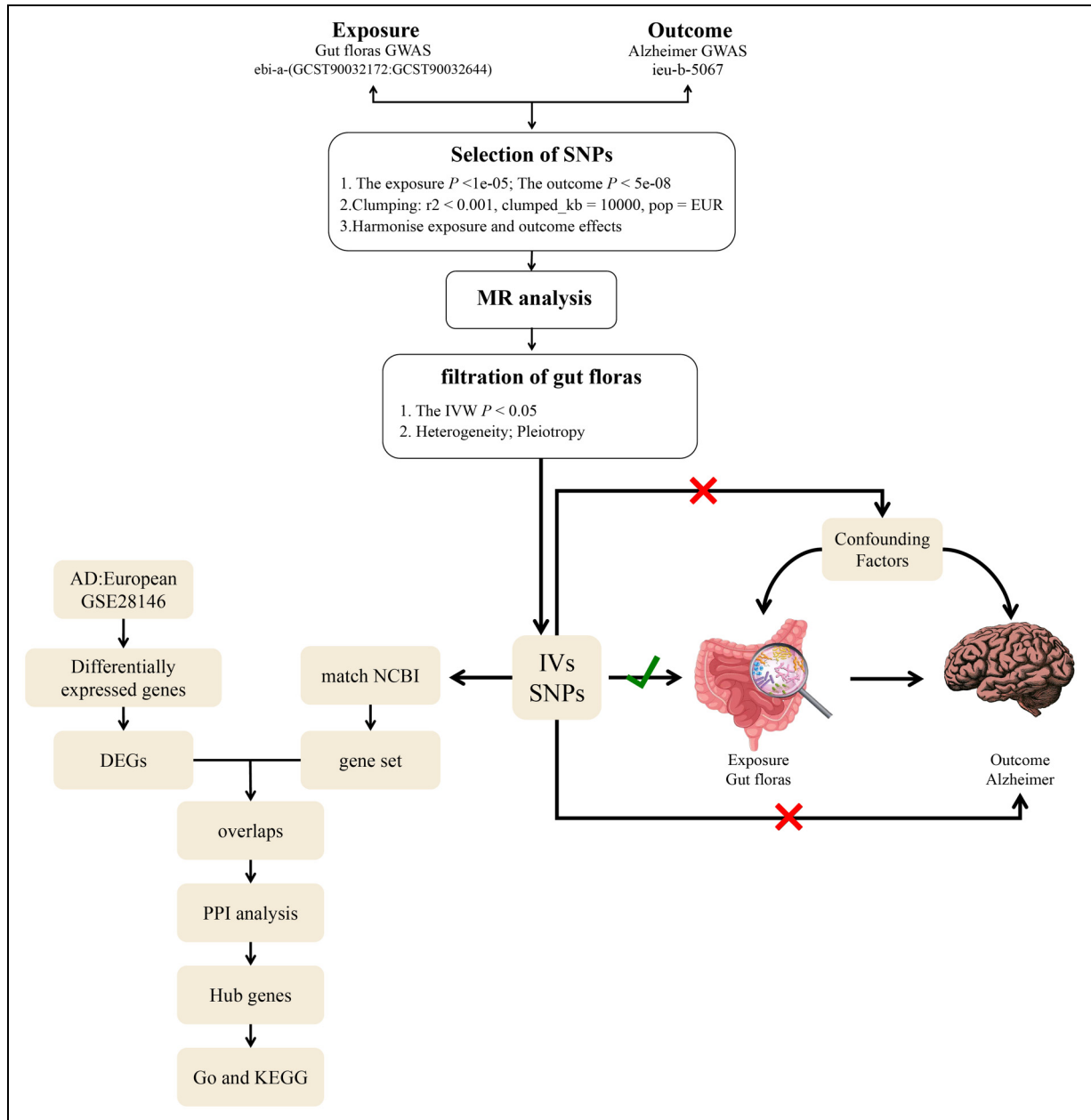


Figure 1. The detailed flowchart of the study.

crucial for the validity of MR studies: (1) the SNPs must be significantly associated with the exposure; (2) the SNPs must be independent of confounding factors on the exposure and outcome; (3) the SNPs only related to the outcome by the exposure under study. Therefore, “ $p < 1e-05$ ” was used as a significant threshold for filtering out SNPs associated with the exposure. Then, this study used “ $R^2 = 0.001$ ” and “clump_kb = 10000” for linkage disequilibrium (LD) pruning. After excluding LD, the exposure data and outcome data were harmonized. To avoid potential weak instrumental variables, the F value

was used to filter out weak instrumental variables. If $F > 10$, the instrumental variables were considered strong enough to support the results of the MR analysis. Eventually, the results were analyzed using the methods of MR analysis, such as inverse variance weighted (IVW), MR Egger, weighted median, and weighted mode. In particular, the causal relationship between exposure and outcome was held for p-value of IVW less than 0.05, and further to detect the heterogeneity and horizontal pleiotropy. All statistical analyses were based on the Two-Sample MR package in the R software.

Hub genes identification

First, two datasets were built, named “gene set” and “AD DEGs”, respectively. The “gene set” was formed by matching the SNPs that supported the MR analyses with NCBI one by one. More specifically, we searched the rsID one by one on the NCBI (<https://www.ncbi.nlm.nih.gov/snp/>), identifying genes to form the “gene set”. The rsID was a kind of numbering form of the MR analysis results, which was based on the “BSgenome.Hsapiens.NCBI.GRCh38” package in the R version 4.4.0 software platform. The “AD DEGs” was built by using the “Limma package” in the R software. Second, the overlap between the “gene set” and the “AD DEGs” was obtained. Third, the hub genes were confirmed by using the K-means clustering to filter the overlaps. The K-means clustering was based on the STRING database (v 12.0, <https://string-db.org/>), and the PPI network was constructed with a confidence = 0.4.

Functional enrichment analysis

The Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed using the “Cluster Profiler” package in the R software. Dotplot function was used to visualize the results of the GO analysis, and the barplot function was used to visualize the results of the KEGG pathway. $p < 0.05$ was considered statistically significant.

Results

The associations between gut microbes and AD

The results of this study showed that a total of 32 microbes were identified from 473 microbial taxa as having a causal relationship with AD ($p < 0.05$). The 32 taxa included one phylum, one order, two families, 10 genera, and 18 species.

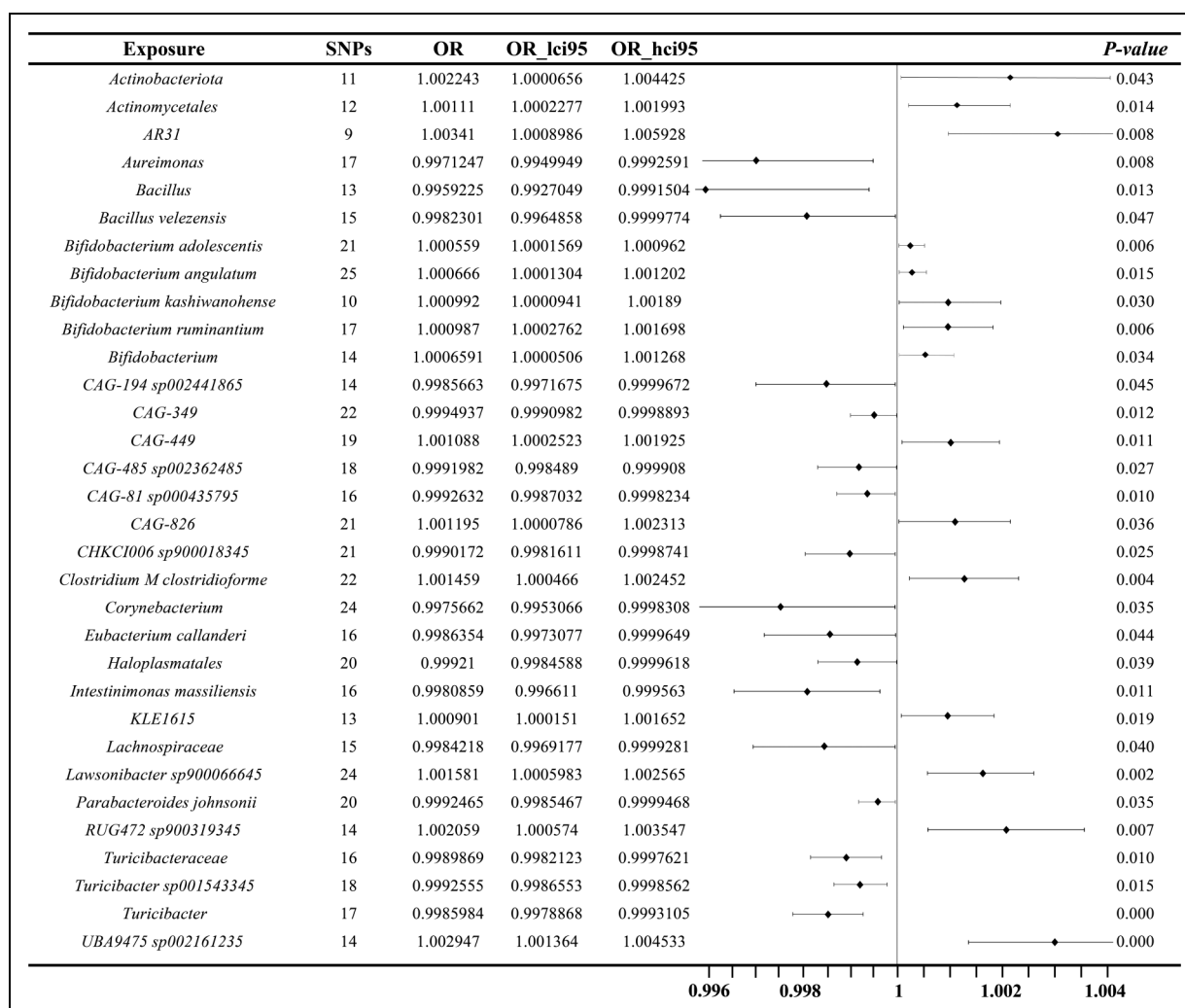


Figure 2. The associations between gut microbes and AD. The microbes were identified as weak protective factors by odds ratio > 1 , and the microbes were identified as weak risk factors by odds ratio > 1 .

The horizontal pleiotropy and heterogeneity effects were shown in Supplemental Table 1. The principal results are presented in Figure 2. A total of 16 microbes were identified as weak protective factors with odds ratios > 1 , and the reminding microbes were identified as weak risk factors with odds ratios < 1 . The weak protective factors included *Aureimonas*, *Bacillus*, *Bacillus Velezensis*, CAG-81 sp000435795, CAG-194, sp002441865, CAG-349, CAG-485 sp002362485, CHKCI006 sp900018345, *Corynebacterium*, *Eubacterium callanderi*, *Haloplasmales*, *Intestinimonas massiliensis*, *Lachnospiraceae*, *Parabacteroides johnsonii*, *Turicibacteraceae*, *Turicibacter*, *Turicibacter* sp001543345. The weak risk factors included *Actinobacteriota*, *Actinomycetales*, AR31, *Bifidobacterium*, *Bifidobacterium angulatum*, *Bifidobacterium adolescentis*, *Bifidobacterium ruminantium*, *Bifidobacterium kashiwanohense*, CAG-449, CAG-826, *Clostridium M clostridioforme*, KLE1615, *Lawsonibacter* sp900066645, RUG472 sp900319345, UBA9475 sp002161235.

Identification of two datasets

In the present study, two datasets were built. The first dataset of 1316 differentially expressed genes of GSE28146 was named “AD DEGs”. The visualization results were presented in Figure 3 by heatmap (3A) and volcano (3B). The second dataset of 314 genes, depicted in Figure 4(a), was matched by IVs and NCBI.

Identification of hub genes

A total of 14 overlaps of these datasets were identified and visualized by Venn diagram. The interactions of the 14 overlapping genes were further explored using the STRING database (v 12.0) (Figure 4(a)). The criterion confidence = 0.4 was used to filter out unconnected nodes, and two clusters were established by the K-means clustering. Cluster 1 had four nodes and five edges (Figure 4(b)), and cluster 2 had two nodes and one edge (Figure 4(c)). Finally, a total of six genes were confirmed as the hub genes and presented in Figure 4.

The associations between hub genes and chromosomes

The association between SNPs and various categories of gut microbes is visualized by a Manhattan plot (Figure 5). A total of 14 overlaps were clearly marked on the corresponding chromosomes, and cluster 1 and cluster 2 were marked in red and green tag. In addition, $1e-05$ and $5e-08$ were used as thresholds for marking in the Manhattan plot. The hub genes were mainly distributed in chr 1, chr 2, chr 7, chr 8, chr 14, and chr 22.

Enrichment analyses for hub genes

The six hub genes were used to perform GO analyses and KEGG pathway analyses. The top three in biological process (BP) were behavior, cell adhesion, and plasma membrane bounded cell projection organization. The top three in cell component (CC) were synapse, cell junction, and cell projection. The top three in molecular function (MF) were cell adhesion molecule binding, neuroligin family protein binding, and voltage-gated sodium channel activity. Cell adhesion molecules were the top KEGG pathway. The results were presented in Figure 6. A dotplot was used to visualize the results of the GO analysis (Figure 6(a)) and a barplot was used to visualize the results of the KEGG pathway (Figure 6(b)).

Correspondence between overlapped genes and microbes

We identified 32 microbial taxa with causal relationships with AD by Mendelian randomization, resulting in a total of 544 SNPs. We then searched NCBI for each of these SNPs and constrained a ‘gene set’ dataset. We then used bioinformatic analysis to identify 14 overlapping genes. Final, we matched genes with microbial taxa by identical rsIDs. The results showed that (*Actinobacteriota*, *Bifidobacterium*-DLGAP2), (*Actinomycetales*-NEGR1), (*Bifidobacterium adolescentis*-NRXN3), (CAG-449-TCF12), (*Actinomycetales*-TLDC2), and (*Bifidobacterium ruminantium*-CFAP46) showed risk factors for statistical significance ($P < 0.05$, $OR < 1$); (*Intestinimonas assiliensis*-CNTNAP2), (*Turicibacter* sp001543345-MYH9), (*Parabacteroides johnsonii*-SCN3A), (*Haloplasmales*, *Turicibacter* sp001543345, *Turicibacter*-SNX27), (*Lachnospiraceae*-UBE3C), (CAG-485 sp002362485-ATP10A), (*Corynebacterium*-ARHGEF3), and (*Eubacterium callanderi*-EIF1B-AS1) showed protective factors for statistical significance ($p < 0.05$, $OR > 1$). The results are shown in Table 1.

Discussion

In the present study, the most recent data on the gut microbiome, with summary statistics for 473 microbes, were selected for analysis. First, we identified 32 gut microbes that were statistically significant in the MR analyses, involving one phylum, one order, two families, 10 genera, and 18 species. Next, a total of 14 overlapping genes were identified, six of which were divided into two clusters and considered to be hub genes that interact with each other. The mechanisms of gut microbiota influence on AD were then revealed by molecular function and KEGG pathway enrichment. The pathway with the most enriched genes was the Cell Adhesion Molecules (CAMs) pathway,

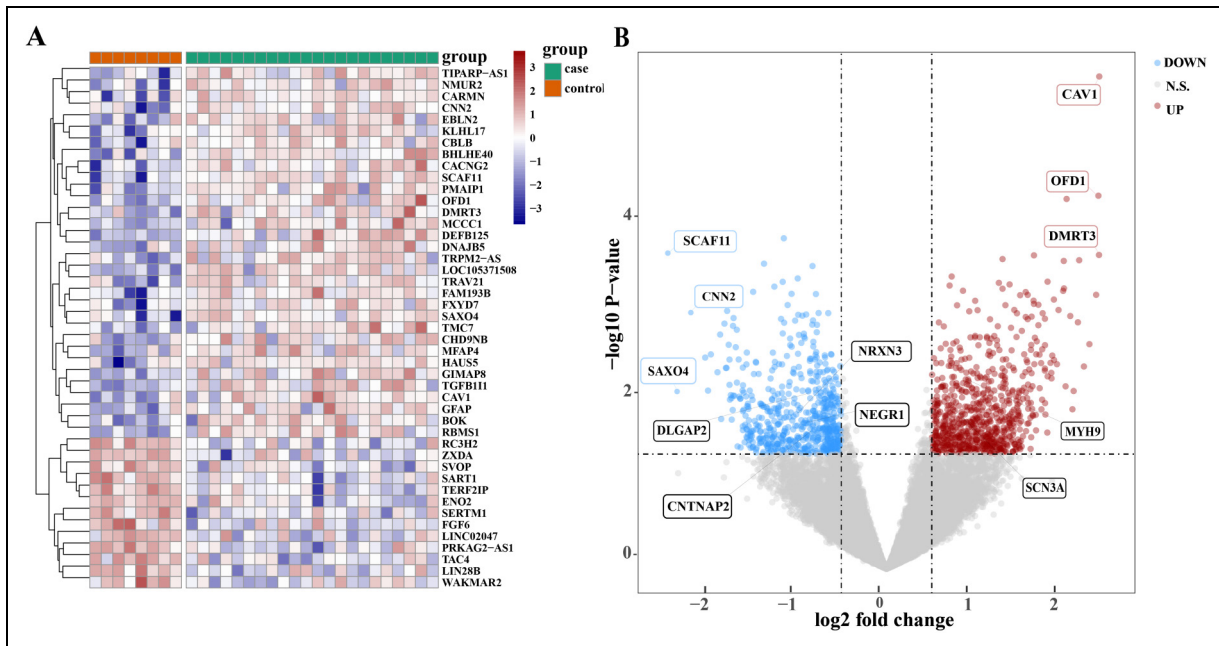


Figure 3. Visualization results of differential analyses on AD. (A) The heatmap of differentially expressed genes for AD. The clusters on the left y-axis mean the dendrogram on the cluster analysis of gene expression patterns. (B) The volcano of differentially expressed genes for AD. The genes in the blue and red boxes represent top genes, while the genes in the black box are the hub genes.

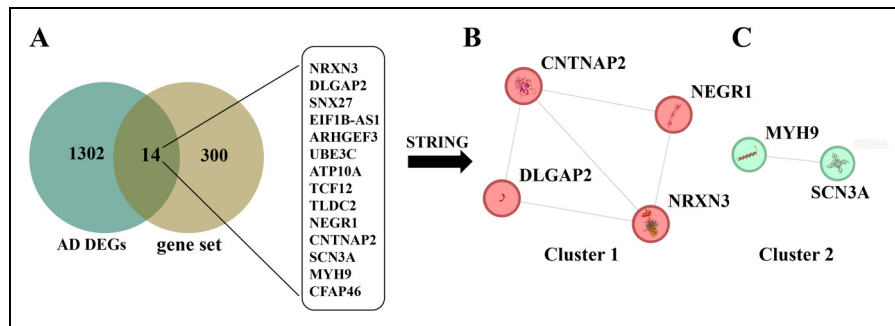


Figure 4. The PPI network of 14 overlapped DEGs, and the clusters based on the K-means clustering. (A) Two datasets overlapped a total of 14 DEGs. (B) Cluster 1 based on the K-means clustering. (C) Cluster 2 based on the K-means clustering.

including NRXN3, NEGR1, and CNTNAP2. The corresponding taxon of gut microbes was identified as *Bifidobacterium adolescentis*, *Actinomycetales*, and *Intestinimonas massiliensis*. Finally, we attempted to elucidate the relationships between hub genes, gut microbes, and AD.

Previous studies have reported the associations between gut microbes and AD.^{23–25} For example, a sequencing study reported that there were significant differences in several gut microbes between the AD and control brains. In particular, *actinobacteria* showed a relatively higher proportion in the AD group.²⁶ The underlying mechanism may be that cerebral amyloid deposition, which could induce AD, was influenced by manipulation of gut microbes.²⁷ Also, inflammation and neurotoxicity were induced by gut microbes-mediated tau phosphorylation, such as *actinobacillus*,

tannerella forsythensis, and *helicobacter pylori*.²⁸ This evidence indicated that bacterial infections may be involved in the pathological processes of AD. In this study, *actinobacteria* and *actinomycetales* were weak risk factors for AD, which was consistent with the evidence mentioned above. In addition, *Bifidobacterium* and *Bifidobacterium adolescentis* in this study also showed weak risk factors for AD, which seemed to be in line with some recent research. For example, a systematic review of 11 studies reported that the abundance of *Proteobacteria*, *Bifidobacterium* and *Phascolarctobacterium* was higher in AD patients.²⁹ Moreover, some studies showed that the abundance of *Bifidobacterium* was higher in Parkinson's disease (PD) cases.^{30–34} A systematic review of 42 studies (26 PD and 16 AD) also shown that there were shared microbes serving between PD and AD, showing a higher

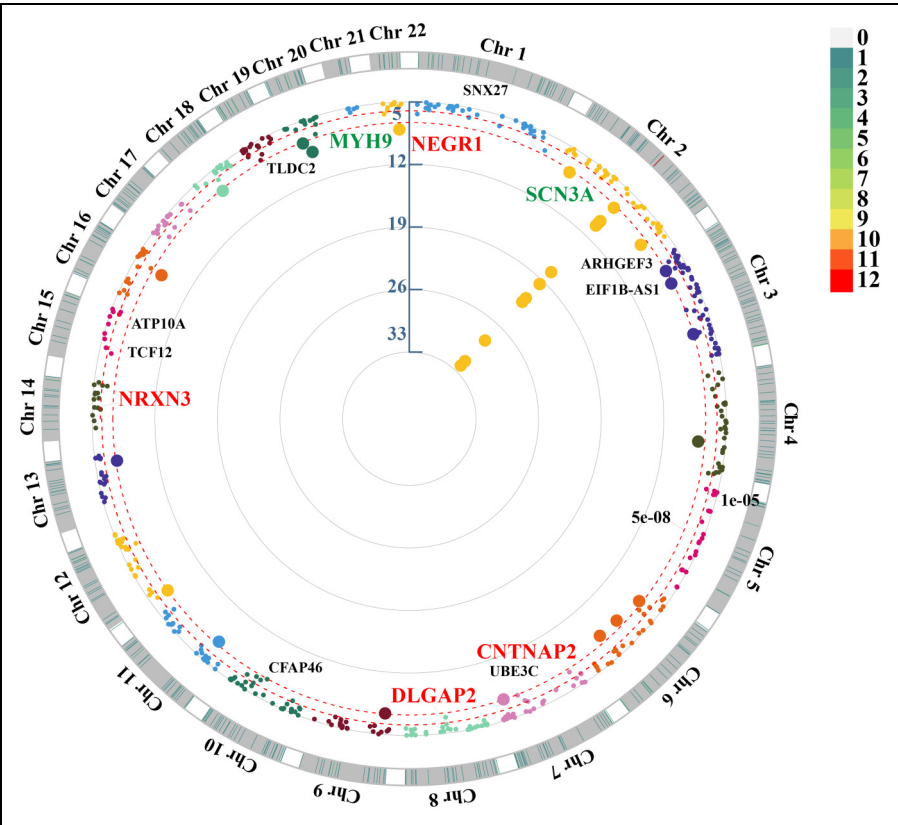


Figure 5. Manhattan plot showed the number of SNPs that associated with the various categories of gut microbes. The circumference was the x-axis, which was arranged from chromosomes 1 to 22. The radius was the y-axis, which represented the results of the relational degree by $-\log_{10}(p\text{-value})$.

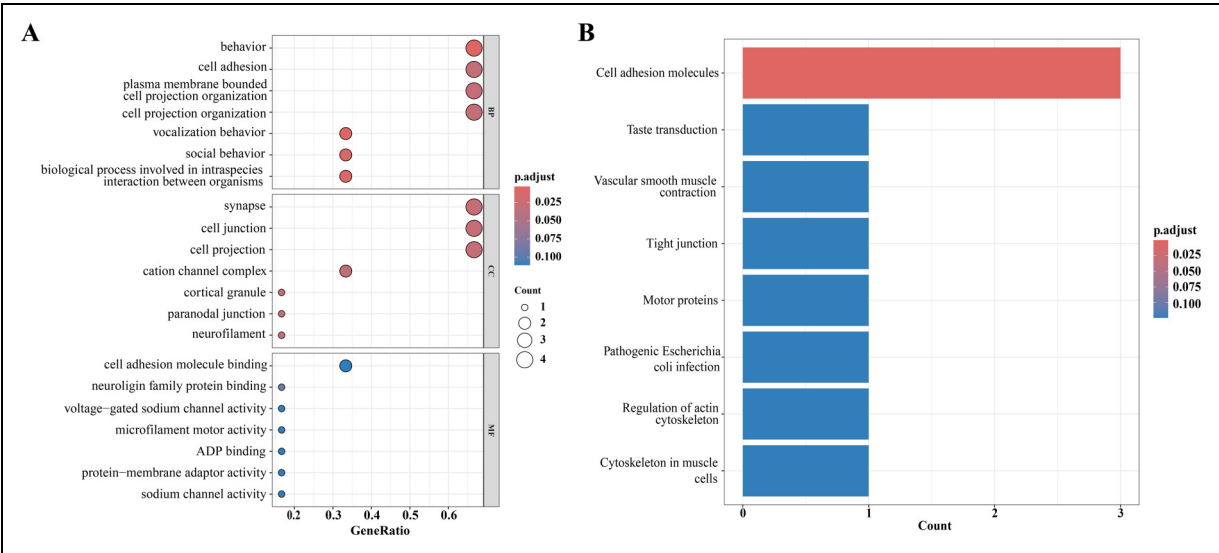


Figure 6. Enrichment analyses for hub genes by GO analyses and KEGG pathway analyses. (A) The GO enrichment analysis of hub genes. (B) The KEGG pathway enrichment analysis of hub genes.

abundance of which included *Bifidobacterium*, *Lachnospiraceae*, and *Proteobacteria*. As PD and AD are both belonged to neurodegenerative diseases, these overlapped microbes meant the possibility of shared pathogenic mechanisms, which required to be explored in depth.³⁵

Table 1. The correspondence between overlapped genes and microbes.

Overlapped genes	SNP	Gut microbes	OR	OR_ici95	OR_uci95
Cluster 1					
DLGAP2	rs2158787	<i>Actinobacteriota</i>	1.002243	1.0000656	1.004425
		<i>Bifidobacterium</i>	1.0006591	1.0000506	1.001268
CNTNAP2	rs73170308	<i>Intestinimonas assiliensis</i>	0.9980859	0.996611	0.999563
NEGR1	rs17091560	<i>Actinomycetales</i>	1.00111	1.0002277	1.001993
NRXN3	rs716064	<i>Bifidobacterium adolescentis</i>	1.000559	1.0001569	1.000962
Cluster 2					
MYH9	rs117155525	<i>Turicibacter_sp001543345</i>	0.9980859	0.996611	0.999563
SCN3A	rs1899014	<i>Parabacteroides johnsonii</i>	0.9992465	0.9985467	0.9999468
Unconnected					
SNX27	rs72692745	<i>Haloplasmatales</i>	0.99921	0.9984588	0.9999618
		<i>Turicibacter_sp001543345</i>	0.9992555	0.9986553	0.9998562
		<i>Turicibacter</i>	0.9985984	0.9978868	0.9993105
UBE3C	rs57210743	<i>Lachnospiraceae</i>	0.9984218	0.9969177	0.9999281
ATP10A	rs117094938	<i>CAG-485_sp002362485</i>	0.9991982	0.998489	0.999908
TCF12	rs76014583	<i>CAG-449</i>	1.001088	1.0002523	1.001925
TLDC2	rs116897774	<i>Actinomycetales</i>	1.00111	1.0002277	1.001993
CFAP46	rs10870212	<i>Bifidobacterium ruminantium</i>	1.000987	1.0002762	1.001698
ARHGEF3	rs76907118	<i>Corynebacterium</i>	0.9975662	0.9953066	0.9998308
EIF1B-AS1	rs11712107	<i>Eubacterium callanderi</i>	0.9986354	0.9973077	0.9999649

However, some contradictory results have also been reported. Several animal experiments showed that the cognitive dysfunction of A β -mediated AD model mice could be regulated by *Bifidobacterium breve* strain A1, and inflammation and immune response gene were also inhibited.³⁶ *Bifidobacterium longum* NK46 was reported to be associated with LPS, and the cognitive dysfunction of 5xFAD-transgenic mice could be regulated by targeting at the LPS-mediated NF- κ B activation.³⁷ A randomized controlled trial investigating the effect of probiotic on cognition showed that MMSE scores improved significantly with *Bifidobacterium intervention*.³⁸ In addition, *Bifidobacterium* belongs to the *Actinobacteria*, both of which have been reported to be less abundant in people with AD.³⁹ In another meta-analysis of randomized controlled trials, cognitive function was not significantly different between AD cases and controls in the *Bifidobacterium* and *Lactobacillus interventions*, meaning that there was no benefit of *Bifidobacterium* for AD.⁴⁰ Such conflicting evidence suggested that more research was needed to confirm the influence of *Bifidobacterium* on AD.

In the present study, *Turicibacter_sp001543345*, *Parabacteroides johnsonii*, and *intestinimonas massiliensis* were identified as weak protective factors for AD. Although these microbes have not been directly linked to AD, and the abundance of which had some significant differences at the genus level. The results of 16S rRNA sequencing showed a decrease in *Turicibacter* in AD individuals,³⁹ and similar results were also observed in an animal study, further indicating that three species of *Turicibacter* were evidently less abundant in the 5xFAD mice model.⁴¹ It was notable that a similarity of 98% sequence was demonstrated between *Parabacteroides johnsonii* and *Parabacteroides merdae*,⁴² both of which

belong to the genus *Parabacteroides* and have been associated with cardiovascular damage,⁴³ metabolic syndrome, and inflammatory bowel disease.⁴⁴ Although there was no experimental evidence of an association between *Parabacteroides* and AD, a multivariable MR indicated a causal relationship between *Parabacteroides* and AD, and alanine serums mediated the causal effect of *Parabacteroides* on AD.⁴⁵ Some studies have also shown that *Parabacteroides* was a common bacterial genus among PD, stroke and multiple sclerosis,⁴⁶ and a decreased abundance of *Parabacteroides* has been shown in PD cases,⁴⁷ as it may block off the effects of Levodopa medication.⁴⁸ Additionally, it also had an effect on tyrosine metabolism, which has been shown to be an effective intervention in stroke.⁴⁹ We tended to guess that *Parabacteroides* may promote the development of AD, based on the findings mentioned above, but this needed further verification. Similarly, no direct evidence seemed to have been searched to support the findings of our study with *Intestinimonas*. A study exploring the interactions between microbes and host immune responses in Huntington's disease was considered the most relevant literature to explain this finding, the results of which showed that *Intestinimonas* was positively associated with IL-4,⁵⁰ meaning that the anti-inflammatory effect associated with neurodegenerative diseases may be benefited by *Intestinimonas*. However, this hypothesis needed further verification.

Some evidence suggested these hub genes may be employed in the development of AD. A recent study showed that DLGAP2 was a regulator for AD dementia, mainly showing differential expression in declining cognition, AD diagnosis, and neuropathology of multiple cerebral regions.⁵¹ And the expression of DLGAP2 may be

elevated in the brain and served in the process of neuronal cells signaling and molecular organization of synapses.⁵² In addition, a number of studies indicated that NRXN3,^{53,54} NEGR1,^{55,56} and CNTNAP2⁵⁷ were associated with the neural cell communication and synapse function, which were the main genes of enrichment in the CAMs signaling pathway. Numerous studies have demonstrated that the CAMs played a crucial role in the pathogenesis and development of AD.^{55,58}

It was worth mentioning that NEGR1 has been shown to target the same signaling pathways (such as ERK and AKT signaling) synergistically with FGFR2.⁵⁹ And more than one study has demonstrated that the ERK and the AKT signaling served a crucial role in AD neuroprotection.^{60–62} For the genes in cluster 2 in this paper, although there was no direct evidence of regulatory action in AD, numerous studies have shown that MYH9 also targets the ERK and the AKT pathways.^{63,64} And SCN3A has been reported to be involved in PD.⁶⁵ Remarkably, there is no direct experimental evidence of the targeting relationship between these microbes and hub genes, which needs to be further explored.

In the present study, we used the Mendelian randomization to avoid the confounding factors, particularly environmental exposures and lifestyle habits. This approach provided direct evidence of a potential causal link between the gut microbes and AD, combining with bioinformatics analysis, and further identifying the hub genes linked to AD. These findings served as evidence for unraveling potential therapeutic targets. However, there were several limitations in this paper. The pathogenesis of AD was complex, involving the variation and interaction of multiple genes, and it was difficult to fully explain the variation of a single gene or SNP. Although we have identified hub genes, their specific functions and mechanisms within the context of AD were still unclear, what's more, the available data are hard to support the relationship between the gut microbes and AD completely, further functional validation and rigorous experimental exploration were needed. In addition, the availability of high-quality, large-scale genome-wide association study data, and the consistency across genetic variations and phenotypic profiles in Mendelian randomization analyses, these two both limited the depth and accuracy of study. These limitations underscore the vast potential for future study.

In conclusion, the hub genes (including DLGAP2, NRXN3, NEGR1, CNTNAP2, MYH9, and SCN3A) were identified to associate with AD. The taxons of gut microbes that corresponded to these were *Actinobacteriota*, *Actinomycetales*, *Bifidobacterium*, *Bifidobacterium adolescentis*, *Intestinimonas massiliensis*, *Turicibacter_sp001543345*, and *Parabacteroides johnsonii*. Especially, NRXN3 (*Bifidobacterium adolescentis*), NEGR1 (*Actinomycetales*) and CNTNAP2 (*Intestinimonas massiliensis*) may promote the progress of AD through regulating the CAMs pathway-mediated synaptic function.

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Statements and declarations

Author contributions

Ji-yun Liu (Data curation; Formal analysis; Methodology; Writing – original draft); Cong-yan Tan (Data curation; Methodology; Visualization); Li Luo (Data curation; Formal analysis; Methodology); Xuan Yin (Conceptualization; Project administration; Supervision; Writing – review & editing).

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Declaration of conflicting interests

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Data availability

The GWAS data of the gut microbes supporting the findings of this study are openly available in the NHGRI-EBI GWAS Catalog. These data were derived from the following resources available in the public domain: [accessions GCST90032172 to GCST90032644 from <https://www.ebi.ac.uk/gwas/>]. The GWAS data of the AD supporting the findings of this study are openly available in the IEU OPEN GWAS. This data was derived from the following resource available in the public domain: [accession “ieu-b-5067” from <https://gwas.mrcieu.ac.uk/>]. The GSE28146 dataset of AD supporting the findings of this study are openly available in the Gene Expression Omnibus (GEO) database (<https://www.ncbi.nlm.nih.gov/geo/>).

Supplemental material

Supplemental material for this article is available online.

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