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Palmitoylation-related gene ZDHHC22 as a potential diagnostic and immunomodulatory target in Alzheimer's disease: insights from machine learning analyses and WGCNA

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Abstract

Background The mechanism of palmitoylation in the pathogenesis of Alzheimer's disease (AD) remains unclear.

Methods This study retrieved AD data sets from the GEO database to identify palmitoylation-associated genes (PRGs). This study applied WGCNA along with three machine learning algorithms—random forest, LASSO regression, and SVM–RFE—to further select key PRGs (KPRGs). The diagnostic performance of KPRGs was evaluated using Receiver Operating Characteristic (ROC) curve analysis. Immune cell infiltration analysis was conducted to assess correlations between KPRGs and immune cell types, and a competing endogenous RNA (ceRNA) regulatory network was constructed to explore their potential regulatory mechanisms.

Results 17 PRGs were identified from the AD data sets, with 7 genes showing increased expression and 10 showing decreased expression. Through WGCNA and machine learning analyses, ZDHHC22 was selected as a KPRG. The ROC curve analysis demonstrated that ZDHHC22 had an area under the curve value of 0.659, indicating moderate diagnostic potential. Immune cell infiltration analysis revealed significant associations between ZDHHC22 expression and the infiltration of several immune cell types, including naïve B cells, CD8 + T cells, and M1 macrophages. In addition, 25 miRNAs and 55 lncRNAs were predicted to potentially target ZDHHC22, forming the basis for a lncRNA–miRNA–mRNA ceRNA network.

Conclusions This study is the first to use bioinformatics methods to identify ZDHHC22 as a key KPRG in AD, highlighting its potential role in disease diagnosis and immune regulation. The regulatory network of ZDHHC22 provides new insights into the molecular mechanisms of AD and lays the foundation for future targeted therapeutic strategies.

Keywords Alzheimer's disease, Palmitoylation, Machine learning, Weighted gene co-expression network analysis, Immunomodulatory

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder and the most prevalent form of dementia among older adults, accounting for approximately 60% to 70% of all dementia cases [1, 2]. As global aging accelerates, the prevalence of AD continues to rise, with projections estimating that the global AD population will exceed 150 million by 2050 [3, 4]. Currently, the etiology of AD remains incompletely understood, and effective treatment options are limited. Existing medications only alleviate symptoms but fail to halt or slow disease progression [5]. Therefore, investigating the pathogenesis of AD and identifying novel therapeutic targets have become focal points in neuroscience and biomedical research.

Palmitoylation is a post-translational modification in which a saturated fatty acid, palmitic acid, covalently attaches to cysteine residues of target proteins [6]. This modification plays a crucial role in regulating protein stability, localization, and interactions. Beyond influencing protein positioning within the cell membrane, palmitoylation is involved in various physiological processes, including signal transduction, neurotransmission, and immune response [7, 8]. Recently, there has been growing interest in the role of palmitoylation in neurodegenerative diseases, particularly in the pathogenesis of AD [9, 10].

Although the precise mechanisms underlying AD are still being unraveled, substantial evidence suggests that its pathological processes are closely linked to protein aggregation, such as the abnormal accumulation of β-amyloid and tau proteins [11, 12]. Palmitoylation may influence AD pathogenesis by modulating the stability and function of these key proteins [13]. For example, studies have shown that palmitoylation modifications can regulate the extracellular accumulation of β-amyloid, potentially affecting the progression of neurodegenerative lesions by altering its interactions with other cellular factors [14]. Thus, understanding the interplay between palmitoylation and AD mechanisms may not only shed light on AD pathogenesis but also provide potential targets for new diagnostic and therapeutic strategies.

To explore the potential role of palmitoylation in AD, this study employs multiple bioinformatic analysis methods, including LASSO regression, random forest, Support Vector Machine (SVM), and Weighted Gene Co-Expression Network Analysis (WGCNA). Using these approaches, we identified differentially expressed palmitoylation-related key enzymes from AD-related gene expression data sets. Further analysis of the roles of these key enzymes in AD pathogenesis offers a new perspective on the function of palmitoylation in AD and may inform future therapeutic targeting strategies (Fig. 1).

Materials and methods

Identification of palmitoylation-related genes (PRGs)

Gene expression data sets related to "Alzheimer's Disease" were retrieved from the GEO database to identify key genes. The data sets included in our analysis met the following criteria: (i) inclusion of whole-genome mRNA microarray data; (ii) samples collected from AD; (iii) data from human subjects only; and (iv) sufficient sample size to support statistical analysis. The

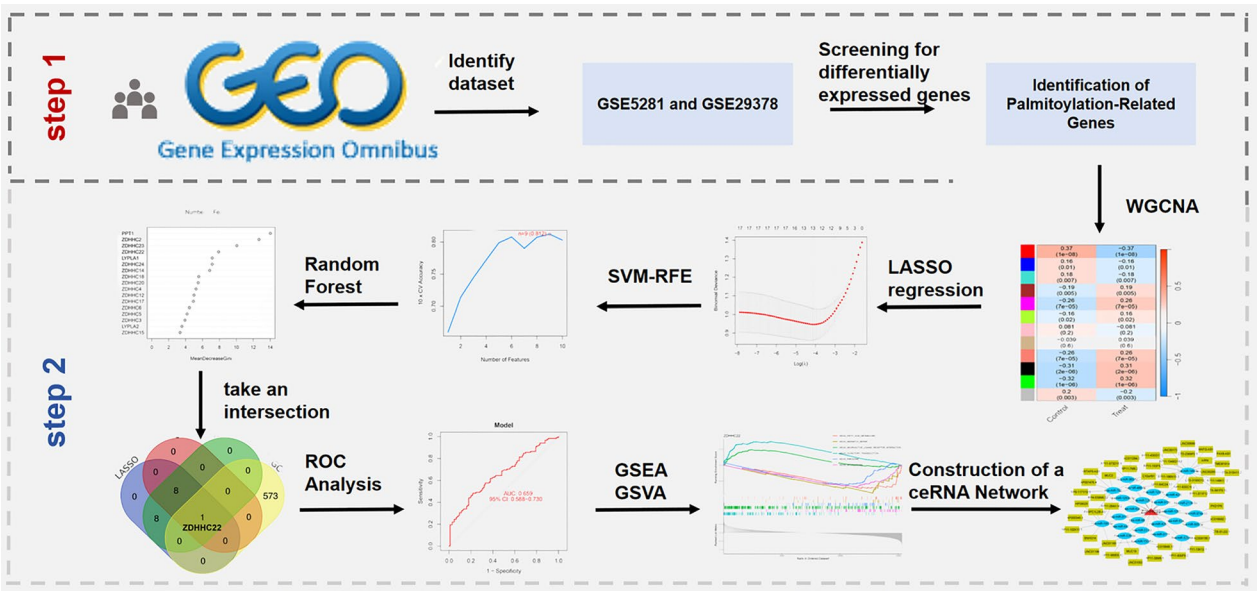

Fig. 1 Flow chart of the study

GSE5281 and GSE29378 data sets were selected for subsequent analysis. Using R software (version 4.2.1) and the "limma" package, differentially expressed genes (DEGs) were defined as those with a $p < 0.05$ and $|\log2FC| > 0.5$. Since the GEO database is a public resource, this study required no ethical approval. Based on published literature, 30 palmitoylation-related key enzymes (Supplementary Table 1) were selected for investigation [15, 16].

Construction of the WGCNA network

This study used the R package "WGCNA" to perform WGCNA, aiming to identify gene modules associated with AD and explore potential candidate biomarkers or therapeutic targets. First, the sample data were preprocessed, including the removal of outliers. Next, a correlation matrix was constructed using the "WGCNA" package, and the optimal soft-thresholding power (b) was selected to convert the correlation matrix into an adjacency matrix, ensuring a scale-free topology for the network. The Topological Overlap Matrix (TOM) was then computed, and genes with similar expression patterns were clustered into distinct modules using hierarchical clustering based on the TOM-based dissimilarity metric. Modules with an absolute correlation coefficient greater than 0.3 and statistical significance were prioritized for further analysis [17]. The relationship between module membership and gene importance was further explored to identify potential hub genes.

Screening of key genes using three machine learning algorithms

The Random Forest algorithm was implemented using the "Random Forest" package in R to rank genes by importance and construct a classifier. This method was chosen for its robustness in handling high-dimensional data and its ability to prevent overfitting while providing feature importance rankings. SVM–RFE, applied via the "e1071" package, uses support vector machine weights to rank genes by importance. This method was selected for its ability to capture non-linear relationships and its effectiveness in recursive feature elimination with tenfold cross-validation to ensure model stability. LASSO regression was conducted using the "glmnet" package to identify significant genes through L1 regularization [18, 19]. This method was chosen to reduce collinearity and overfitting while selecting the most relevant features in high-dimensional gene expression data.

Receiver operating characteristic (ROC) analysis

Genes identified by the three machine learning algorithms were intersected with those from the WGCNA analysis to define key palmitoylation-related genes (KPRGs). ROC curve analysis was then performed using the "ROCR" package in R to evaluate the sensitivity and specificity of KPRGs in the AD diagnostic model.

Gene set enrichment analysis (GSEA) and gene set variation analysis (GSVA)

GSEA was conducted using the "clusterProfiler" package in R to calculate the Normalized Enrichment Score (NES), assessing KPRG correlations with specific pathways ($NES > 0$ indicating a positive correlation). GSVA was also used to evaluate pathway enrichment levels of KPRGs across different AD samples, with significance determined by a False Discovery Rate (FDR) threshold of < 0.05.

Correlation between key genes and infiltrating immune cells

The CIBERSORT algorithm was applied to analyze the proportions of 22 types of infiltrating immune cells in AD patient tissues, with $p < 0.05$ considered significant. Pearson correlation analysis was conducted to assess the relationship between key genes and immune cell infiltration. The final results were visualized using the "reshape2" and "tidyverse" packages in R.

Construction of a ceRNA network for KPRGs

To investigate the regulatory mechanisms of KPRGs in AD, potential miRNAs and lncRNAs targeting KPRGs were predicted using TargetScan (http://www.targetscan.org/), miRDB (http://mirdb.org/), and miRanda (http://www.microrna.org/). The lncRNA–miRNA–mRNA competing endogenous RNA (ceRNA) network was constructed based on these predictions.

Results

Initial identification of 17 PRGs

A total of 732 differentially expressed genes (DEGs) were identified from the GSE5281 data set and 65 DEGs from the GSE29378 data set (Fig. 2A). The two data sets were subsequently integrated and normalized (Fig. 2B, C). From an initial list of 30 PRGs, 17 differentially expressed palmitoylation-related genes (DPRGs) were identified (Fig. 2D), among which 7 genes, including LYPLA1, were upregulated, and 10 genes, including ZDHHC3, were downregulated (Supplementary Table 2).

Identification of ZDHHC22 as the KPRG

WGCNA grouped the genes into 12 modules, with the red module showing the most significant correlation with the AD phenotype (Fig. 3A), comprising 574 genes. LASSO regression analysis identified 13 genes: ZDHHC2, ZDHHC4, ZDHHC5, ZDHHC12, ZDHHC14, ZDHHC18, ZDHHC20, ZDHHC22, ZDHHC23, ZDHHC24, PPT1, LYPLA1, and LYPLA2 (Fig. 3B).

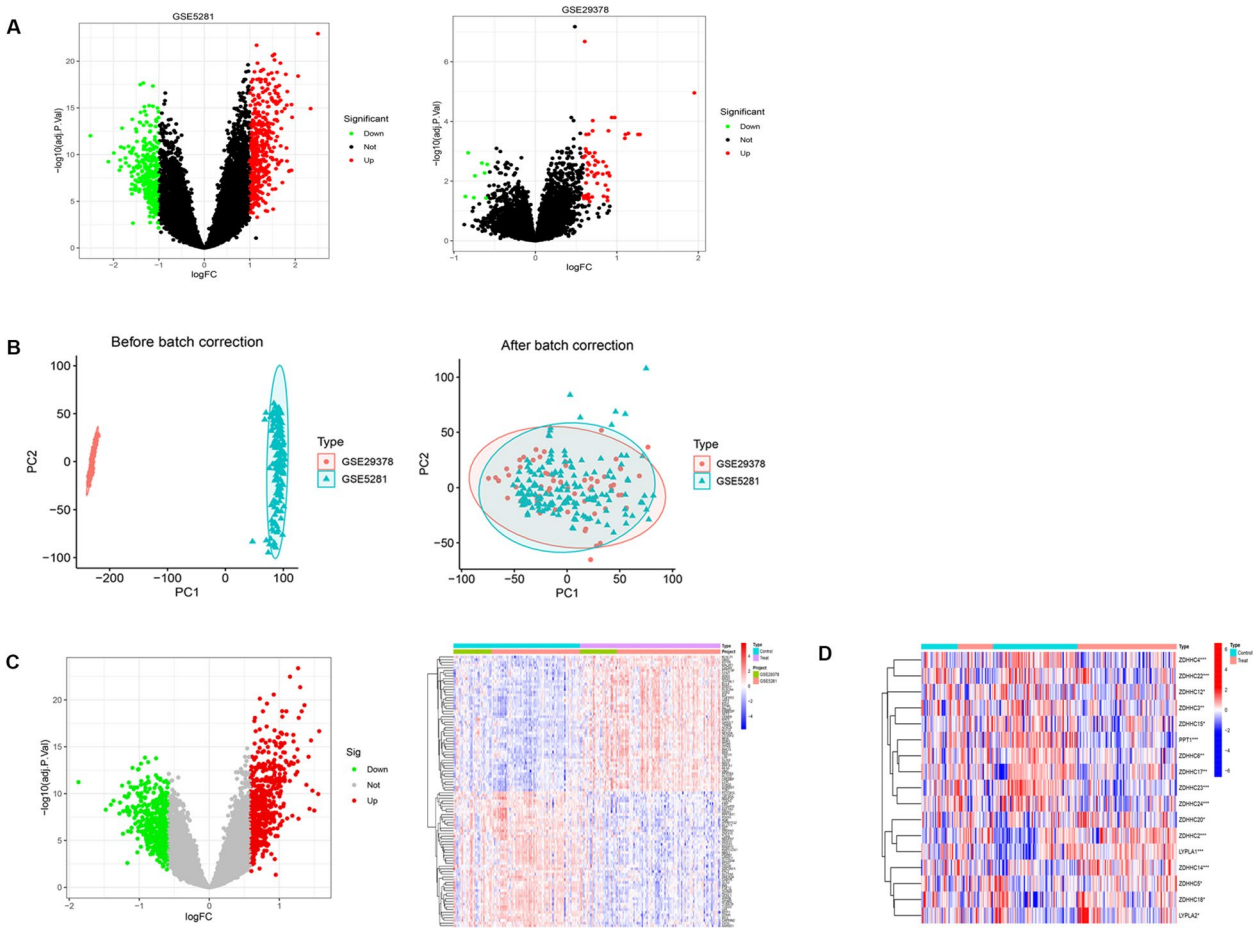

Fig. 2 Palmitoylation-related genes screened from the AD data set. **A** GSE5281 and GSE29378 were differentially expressed genes in two AD data sets. **B** Collate and merge the two databases**. C** Differentially expressed genes after merging two data sets. **D** 17 palmitoylation-related genes with different expression were initially screened

SVM–RFE analysis further screened 9 genes: ZDHHC2, ZDHHC14, ZDHHC23, PPT1, ZDHHC12, ZDHHC20, ZDHHC22, ZDHHC18, and ZDHHC3 (Fig. 3C). The random forest algorithm identified 17 genes (Fig. 3D). The intersection of genes identified by all three machine learning algorithms yielded 8 DPRGs: ZDHHC2, ZDHHC14, ZDHHC23, PPT1, ZDHHC12, ZDHHC20, ZDHHC22, and ZDHHC18. Ultimately, ZDHHC22 was identified as the key PRG (KPRG) from the intersection of WGCNA and machine learning results (Fig. 3E).

Diagnostic performance of ZDHHC22

ROC curve analysis indicated that ZDHHC22 has an area under the curve value of 0.659, suggesting moderate diagnostic potential (Fig. 3F).

Enrichment pathway analysis of ZDHHC22

GSEA revealed that ZDHHC22 is closely associated with pathways involving the spliceosome, ribosome, and fatty acid metabolism (Fig. 4A). GSVA further demonstrated that ZDHHC22 is significantly associated with pathways, such as ganglioside biosynthesis, mismatch repair, and propanoate metabolism (Fig. 4B) (Supplementary Table 3).

Correlation of ZDHHC22 with various immune cells

Immune cell infiltration analysis indicated that ZDHHC22 expression in AD tissues is significantly correlated with several immune cell types, including naïve B cells, memory B cells, resting CD4 + T cells, M1 macrophages, and resting mast cells (Fig. 4C). Specifically, high ZDHHC22 expression was associated with increased infiltration of naïve B cells, CD8 + T cells, and M1 macrophages, while the infiltration of resting dendritic cells and resting memory CD4 + T cells decreased, suggesting a critical role of ZDHHC22 in immune regulation (Fig. 4D, E).

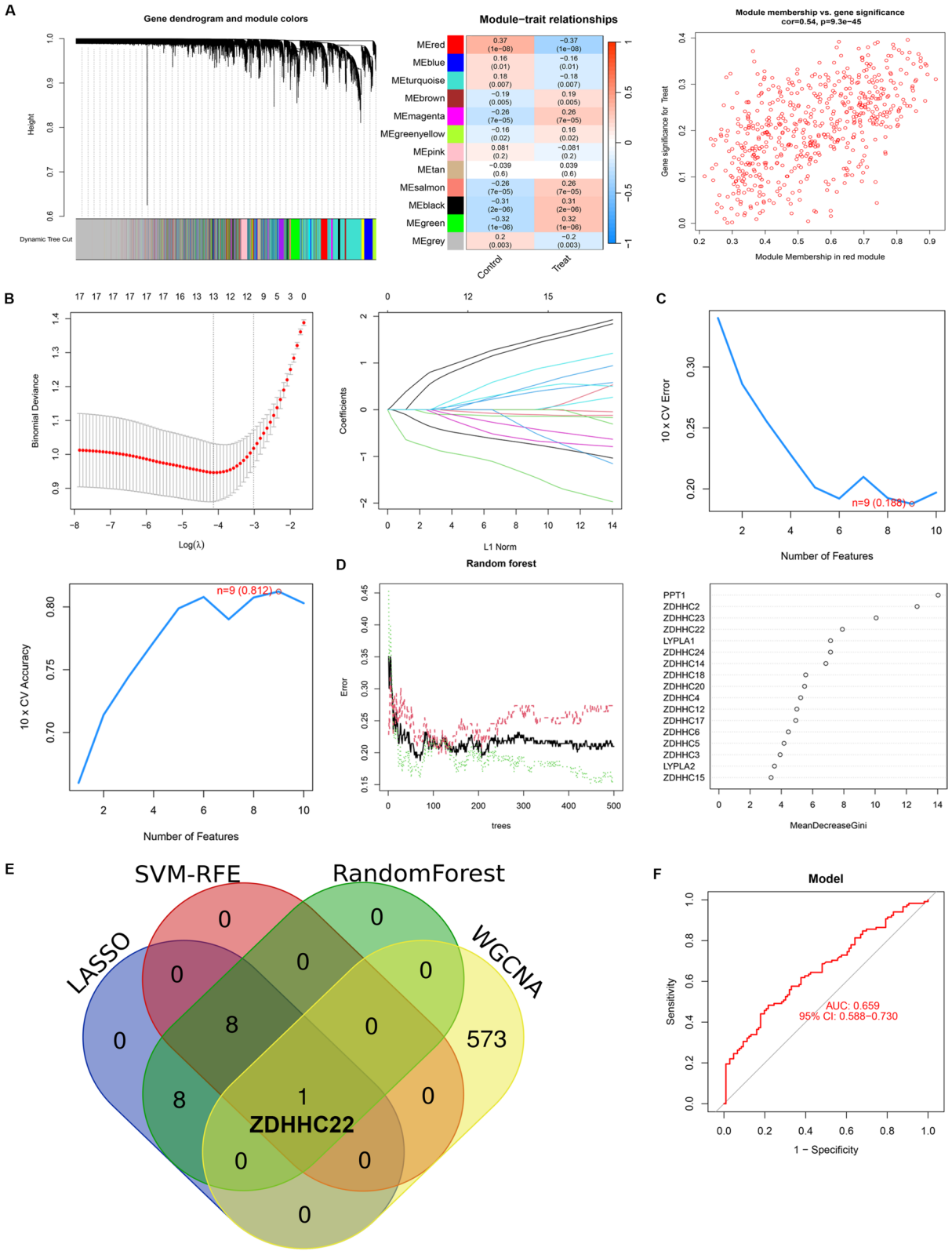

Fig. 3 ZDHHC22 was identified as a key palmitoylation genes (KPRGs). **A** Screening of 574 genes strongly associated with AD using WGCNA. **B** 13 genes associated with AD were screened using Lasso regression. **C** Nine genes associated with AD were screened using SVM–RFE analysis. **D** 17 genes associated with AD were screened using random forest. **E** ZDHHC22 was obtained by taking the intersection of WGCNA with the genes obtained from the three machine learning analyses. **F** ROC curve analysis indicated that ZDHHC22 has an area under the curve value of 0.659

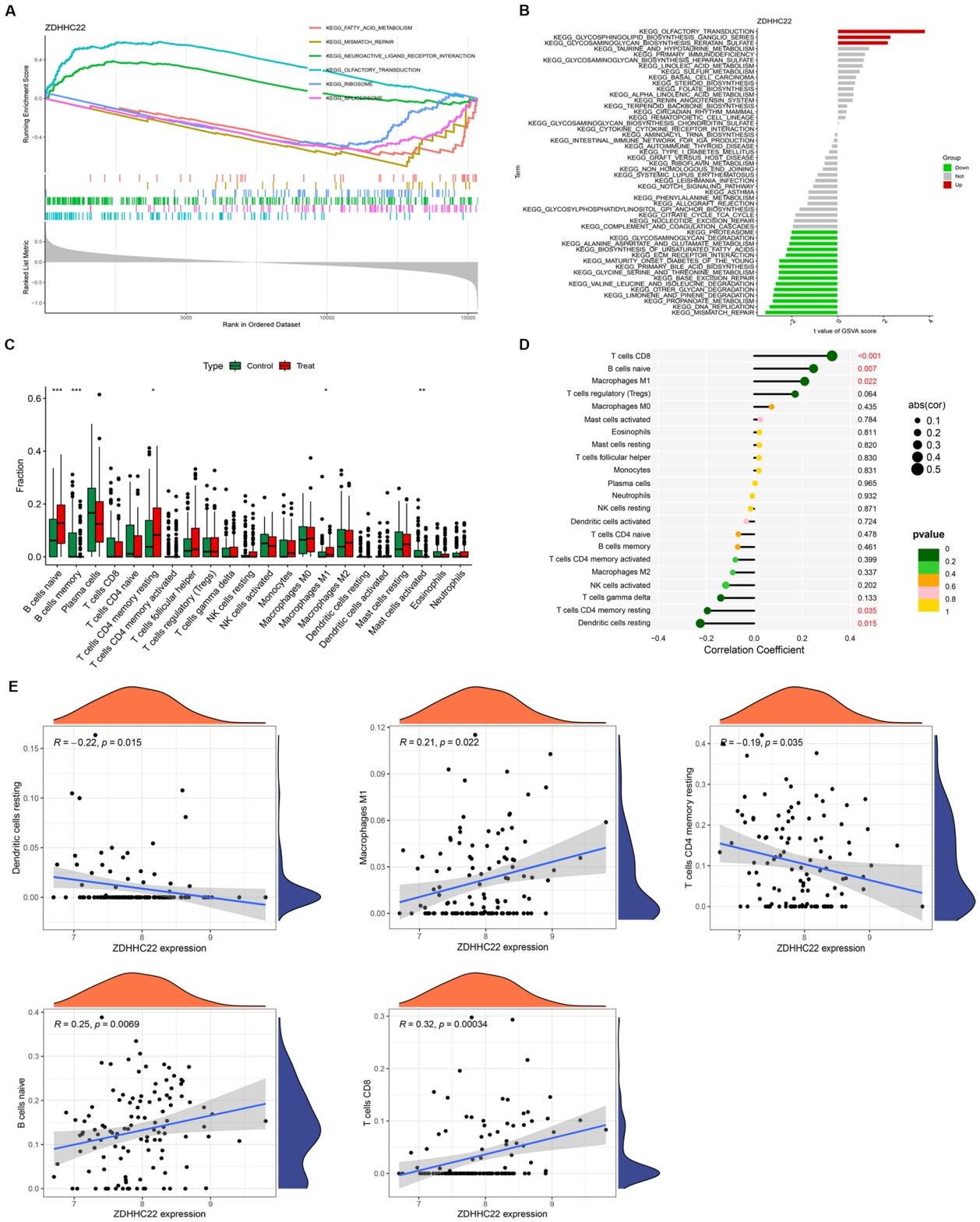

Fig. 4 Pathway enrichment analysis and immune cell infiltration analysis of ZDHHC22. **A**, **B** GSEA and GSVA analysis of ZDHHC22. **C** Differences in the infiltration of 22 types of immune cells in AD. **D**, **E** Analysis of ZDHHC22-associated immune cell infiltration

Construction of the ceRNA network for ZDHHC22

Using three miRNA-target prediction tools, 25 miRNAs, including miR-149-3p and miR-22-5p, were predicted to regulate ZDHHC22. In addition, 55 lncRNAs, including C10orf91 and LINC01002, were identified as potential targets of these 25 miRNAs. The lncRNA–miRNA–ZDHHC22 ceRNA network was constructed based on these predictions (Fig. 5).

Discussion

In this study, 17 PRGs were identified, with 7 showing increased expression and 10 showing decreased expression, suggesting that palmitoylation-related genes may have bidirectional regulatory roles in AD. Palmitoylation is an essential modification in the nervous system, impacting protein localization, stability, and function, and it plays a critical role in synaptic plasticity and signal transduction. Previous studies have associated abnormal palmitoylation with neurodegenerative diseases [20, 21]. Specifically, in AD, aberrant palmitoylation may lead to abnormal processing of amyloid precursor protein, exacerbating Aβ aggregation [14, 22]. Therefore, these 17 PRGs may participate in AD pathogenesis by modulating protein palmitoylation.

Among the PRGs, ZDHHC22 was identified as a key gene through WGCNA and multiple machine learning algorithms. ROC curve analysis of ZDHHC22 demonstrated an AUC value of 0.659, indicating modest diagnostic potential in AD. However, since the AUC did not reach 0.7, the sensitivity and specificity of ZDHHC22 alone as a diagnostic biomarker are limited. Combining ZDHHC22 with other PRGs or traditional biomarkers may enhance diagnostic efficiency. A multi-marker approach combining β-amyloid and tau proteins has been shown to significantly improve the early diagnosis of AD [23, 24]. We speculate that combining tau protein or neuroinflammation-related markers with ZDHHC22 in the future may improve the diagnostic accuracy of AD, and also allow further exploration of the therapeutic potential of palmitoylation in clinical practice.

ZDHHC22 is a significant palmitoyl transferase involved in the palmitoylation of various neuronal proteins, thereby contributing to synaptic transmission and the construction of neuronal signaling networks

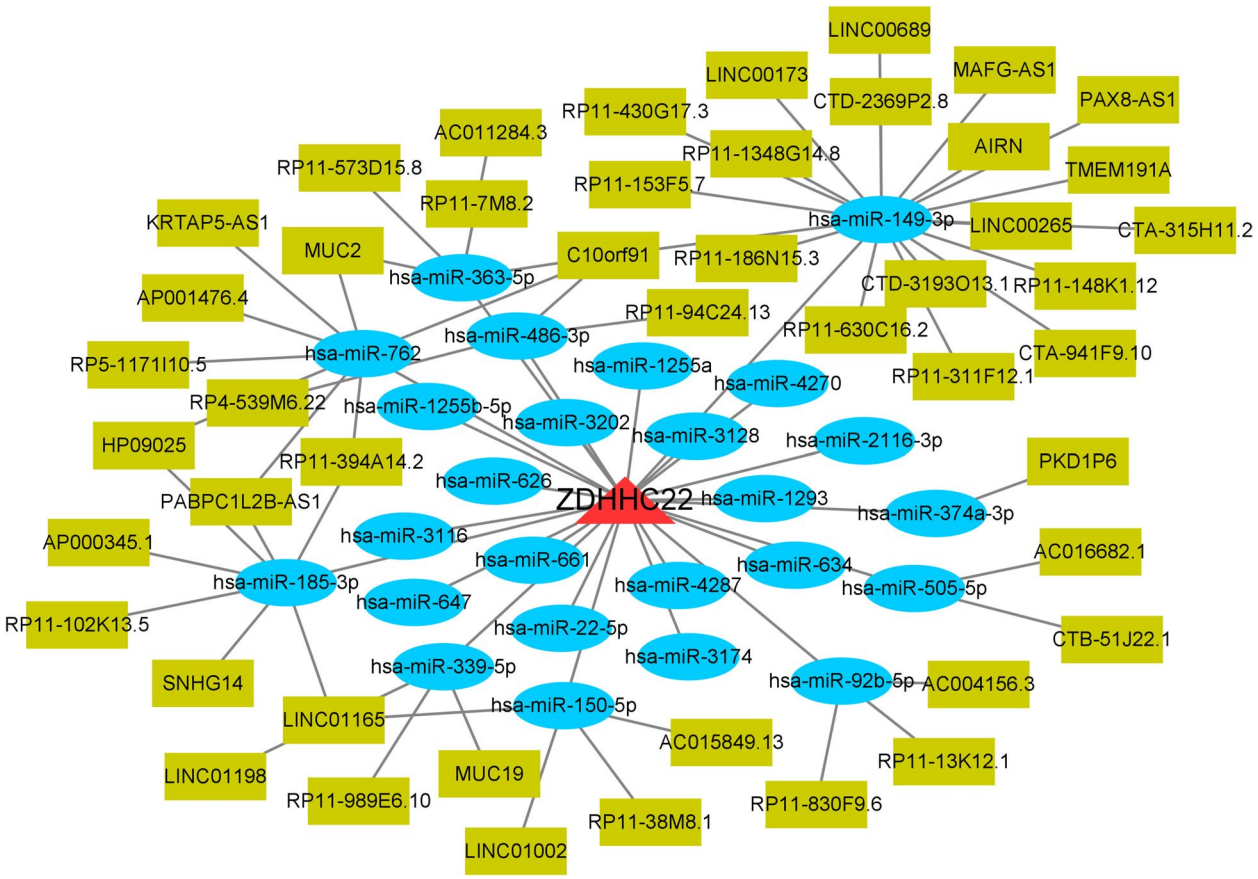

Fig. 5 ceRNA network of miRNAs and LncRNAs was established based on ZDHHC22

[25]. Palmitoylation modification is considered to be an important mechanism for regulating cellular functions, especially in neurons and immune cells, where palmitoylation influences many key processes, such as cell signaling, synaptic plasticity, cell membrane stability and immune responses [26]. Studies have shown that ZDHHC22 plays a vital role in synaptic plasticity and neuronal survival and may be involved in cognitive dysfunction in the brain [27]. In the context of AD, palmitoylation may influence neuroinflammation, synaptic function, and neurodegeneration by modulating neuronal membrane proteins, receptors, and signaling pathways [28]. Based on the above, we speculate that ZDHHC22 may further influence AD by affecting neuroinflammatory responses and immune cell functions. This could involve regulating the activity of immune cells, such as microglia and T cells, thereby driving the progression of AD, although this remains unverified at present [29]. In addition, ZDHHC22 may impact synaptic dysfunction in AD by regulating the palmitoylation of several neurotransmitter receptors, with palmitoylation being a potential mechanism underlying synaptic dysfunction in AD [30, 31].

Immune cell infiltration analysis showed that ZDHHC22 expression correlates significantly with immune cells, such as naïve B cells, CD8 + T cells, and M1 macrophages. The immune system plays a crucial role in AD pathogenesis, with the activation of microglia and macrophages being widely studied. ZDHHC22 expression may modulate the activation and infiltration of these immune cells, influencing AD progression through changes in the inflammatory microenvironment [32]. In particular, the elevated expression of M1 macrophages is closely associated with neuroinflammation, while the infiltration of B and T cells reflects systemic immune dysregulation, further supporting the potential role of ZDHHC22 in immune cells [33].

Through the prediction of miRNA and lncRNA interactions, a ceRNA network centered on ZDHHC22 was constructed. The ceRNA network may play a crucial role in multilayer gene regulation and is significant in the molecular regulatory mechanisms of AD. Recent studies indicate that miRNAs, such as miR-22, are involved in AD pathology and exert protective effects by interfering with inflammatory pathways and amyloid deposition [34, 35]. The ceRNA network of ZDHHC22 reveals potential interactions with miRNAs and lncRNAs, suggesting that ZDHHC22 may regulate AD-related gene expression through ceRNA mechanisms, thereby influencing disease progression.

This study has several limitations. Although ZDHHC22 shows certain diagnostic potential, its relatively low AUC value limits its effectiveness as an independent diagnostic biomarker. The moderate diagnostic accuracy suggests that ZDHHC22 may be more useful in combination with other biomarkers, rather than as a standalone indicator. In addition, this study relies solely on publicly available data sets, which, while valuable, can introduce biases depending on the data quality and the heterogeneity of the sample populations. More importantly, this study lacks experimental validation of the bioinformatics findings, which is a crucial step for confirming the biological relevance of ZDHHC22 in AD. Therefore, future studies should include functional validation, such as knockdown or overexpression studies of ZDHHC22 in neuronal models, to better understand its role and confirm its potential as a therapeutic target or diagnostic biomarker. Only through experimental confirmation can the findings be considered for practical clinical application.

Conclusion

This study employed WGCNA and multiple machine learning algorithms to identify key palmitoylation-related genes associated with AD, enhancing the accuracy and reliability of the results. Immune cell infiltration analysis and ceRNA network construction further revealed the potential roles of ZDHHC22 in immune regulation and gene regulatory networks, providing new insights into AD mechanisms.

Abbreviations

AD	Alzheimer's disease
KPRG	Key palmitoylation-related gene
GEO	Gene expression omnibus
WGCNA	Weighted gene co-expression network analysis
ROC	Receiver operating characteristic
AUC	Area under the curve
ceRNA	Competing endogenous RNA
DEG	Differentially expressed gene
NES	Normalized enrichment score
GSEA	Gene set enrichment analysis
GSVA	Gene set variation analysis
SVM–RFE	Support vector machine–recursive feature elimination
LASSO	Least absolute shrinkage and selection operator
miRNA	MicroRNA
lncRNA	Long non-coding RNA

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02277-0.

Supplementary material 1.

Supplementary material 2.

Supplementary material 3.

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Author contributions

Sanying Mao (Writing—original draft; Writing –review & editing); Xiyao Zhao and Lei Wang (Writing—original draft;); Yilong Man and Kaiyuan Li (Writing –review & editing).

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Data availability
Data for GSE5281 and GSE29378 can be downloaded from the GEO public database (https://www.ncbi.nlm.nih.gov/geo/).

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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