Key genes associated with Alzheimer's disease and periodontitis

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Research

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Abstract

Background: With increasing research on Alzheimer’s disease and periodontitis, many studies suggest a close correlation between Alzheimer’s disease and periodontitis, but the underlying pathophysiological mechanisms remain unclear. The aim of this study was to identify potential pivotal genes and pathways associated with both diseases by using a bioinformatics approach.

Materials/Methods: The GEO dataset GSE5281 for Alzheimer’s disease patients and normal controls was downloaded from the GEO database. The GSE10334 dataset for periodontitis patients and healthy controls was also obtained. Differentially expressed genes (DEGs) for the Alzheimer’s disease and periodontitis datasets were obtained, as well as genes common between them. Further GO and KEGG enrichment analyses were performed on the common genes. To determine the pathogenesis associated with Alzheimer’s disease and periodontitis, protein-protein interaction (PPI) networks were constructed. Finally, the diagnostic value of HUB genes in the Alzheimer’s disease and periodontitis datasets was analyzed separately using SPSS software.

Results: A total of 16 common genes were obtained for Alzheimer’s disease and periodontitis with a P value <0.05. 7 GO entries and 2 KEGG pathways were obtained. In addition, the first 6 central genes (CD4, KDR, CXCR4, CXCL12, JAK2 and PTPN11) were selected with a P<0.05.

Conclusion: The results of this study suggest that some novel genes play an important role in the development and progression of Alzheimer’s disease and periodontitis. More experimental studies and clinical trials are needed to validate our results.

Background

Alzheimer disease (AD) is a neurodegenerative disease characterized by progressive cognitive dysfunction and behavioral impairment. AD is the most common type of dementia in old age, accounting for more than 50% of all cases(Tahami Monfared, Byrnes, White, & Zhang, 2022). About 5% of people over the age of 65 have AD, and the prevalence increases with age, reaching 20% or more over the age of 85(Tahami Monfared et al., 2022). The prevalence of Alzheimer's disease has steadily increased in recent years. It is estimated that many older adults will be diagnosed with Alzheimer's disease in the next decade. For these reasons, there is an urgent need to identify the key molecules associated with Alzheimer's disease to improve clinical outcomes.

Amyloid-β (Aβ) is a 39–43 amino acid polypeptide produced from amyloid precursor protein by the proteolytic action of β- and γ-secretase. The most common isoforms of Aβ in humans are Aβ1–40 and Aβ1–42. Imbalance of Aβ production and clearance is the initiating factor in neuronal degeneration and dementia development, and induces a series of pathological processes such as tau protein hyperphosphorylation, inflammatory response, and neuronal death(Paumier et al., 2022). Aβ has been shown to be important in the development of Alzheimer’s disease, and although its exact pathogenesis is unclear, the inflammatory response plays an important role.
Periodontitis is a chronic inflammation of periodontal supporting tissues caused primarily by local factors, characterized by an immune response of the host to periodontal pathogens leading to destruction of the gingiva and tooth-supporting bone, with the age of onset being more common after 35 years of age. According to the World Health Organization, the prevalence of periodontitis in adults is about 50%, of which 10% suffer from severe periodontitis, and this prevalence increases sharply in adults over 65 years of age (Vu, Lee, & Kim, 2022). The inflammatory response also plays an important role in the pathogenesis of periodontitis.

In recent studies (Holmer, Eriksdotter, Schultzberg, Pussinen, & Buhlin, 2018), periodontitis has been shown to be an important risk factor for Alzheimer's disease. The results of cross-sectional and longitudinal studies have shown (Fu et al., 2022; Kaliamoorthy et al., 2022), periodontitis is strongly associated with cognitive impairment (CI) and Alzheimer's disease (AD). In addition, studies on AD patients from patients with periodontitis and human animal models have shown (Ilievski et al., 2018), Porphyromonas gingivalis (Pg) and/or its product gingival protease were transferred to the brain. The neuropathological features observed in this study strongly suggest that (Ilievski et al., 2018), low-grade chronic periodontal pathogen infection can lead to the development of neuropathology consistent with AD. Although partial progress has been made in the study of the relationship between Alzheimer's disease and periodontitis, relevant genetic studies are still limited and need to be further explored.

In this study, 1 gene expression profile for Alzheimer's disease and 1 gene expression profile for periodontitis were downloaded from the GEO database, an open access database that provides genetic information that can be used to identify novel disease targets by bioinformatics analysis (Ritchie et al., 2015). We identified differentially expressed genes (DEGs) in the disease and normal control groups of patients with Alzheimer's disease and periodontitis by bioinformatics analysis and obtained differentially expressed genes common to both diseases. HUB genes with multiple functions were searched for by clustering analysis, including gene ontology (GO) enrichment analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) and protein-protein interaction (PPI) network analysis. Thus, the identified HUB genes may become a new research hotspot, and the molecular mechanisms and signaling pathways obtained may also help to explain the relationship between Alzheimer's disease and periodontitis.

Materials And Methods

Microarray data acquisition

Gene microarray datasets for Alzheimer's disease, periodontitis, and normal controls were downloaded from the GEO database (http://www.ncbi.nlm.nih.gov/geo). The GSE5281 dataset contained gene expression profiles of 87 Alzheimer's patients and 74 normal controls. In the GSE10334 dataset, 183 patients with acute periodontitis and 64 healthy controls were included. Because these gene expression profiles were obtained from free and open databases available on the Internet, ethics committee approval was not required for our study.

Screening for differentially expressed genes (DEGs) in Alzheimer's disease and periodontitis
DEGs between Alzheimer's disease and normal controls, periodontitis patients and corresponding controls were identified using the LIMMA R package, a validated method of analysis in bioinformatics (Ritchie et al., 2015). The criteria selected in the Alzheimer's and periodontitis datasets were set to a P value < 0.05 and |log2FC| > 1. Using these screening conditions, we identified two sets of DEGs, and then placed these DEGs from both diseases into the online analysis tool VENN (http://bioinformatics.psb.ugent.be/WebTools/Venn/) to obtain their crossover genes. These intersecting common genes were used in subsequent analyses.

Functional enrichment analysis of common differential genes

Gene Ontology (GO) (Gene Ontology, 2006) Classification, including molecular function, biological processes and cellular components, and Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa, Sato, Kawashima, Furumichi, & Tanabe, 2016) Passage enrichment analysis was performed using the R package for intersecting common differential genes. p-value < 0.05 was defined as statistically significant.

Construction of a protein interaction (PPI) network and identification of HUB genes

To further explore the interactions between the common genes obtained above, we used the Search Tool for the Retrieval of Interacting Genes (STRING) 11.0 (http://string-db.org/) (Szklarczyk et al., 2015), a PPI network was constructed. The minimum interaction score required was considered high confidence (0.700) as a criterion for statistical significance. In the network results, nodes represent proteins, and lines represent interactions between proteins (Yang et al., 2017).

Statistical analysis

The subject operating characteristic (ROC) curves were constructed using SPSS 22.0 (SPSS, Inc, Chicago, IL, USA) and the area under the curve (AUC) for the HUB gene was calculated to compare the AUC as a model metric. These results show the validity of the genetic diagnosis. The area under the ROC curve has values between 0.5 and 1. The closer the AUC is to 1, the better the diagnosis, indicates better diagnosis. The AUC has low accuracy at 0.5 to 0.7, moderate accuracy at 0.7 to 0.9, and high accuracy at AUC above 0.9.

Result

Analysis of differential expression of genes common to Alzheimer's disease and periodontitis

In the Alzheimer's disease dataset GSE5281, we compared 87 Alzheimer's disease samples with 74 normal controls and screened 1277 differential genes. In the periodontitis dataset GSE10334, we compared 183 periodontitis samples with 64 normal controls and screened 175 differential genes. Figures 1 and 2 show the gene expression profiles for Alzheimer's disease and periodontitis, adjusted for P < 0.05, homogenized to 1277 and 175 differential genes, respectively. Differential genes were identified by |log2 Fc| > 1 and p < 0.05. Volcano plots were generated using the ggplot2 package for R, as shown in...
Figs. 3 and 4. Using the Venn diagram online tool, 16 intersecting common genes were obtained for both diseases, as shown in Fig. 5. Details of these common genes are also shown in Supplementary Table 1. Information on the entire study process is shown in Fig. 6.

GO and KEGG enrichment analysis

Functional enrichment and KEGG pathway analysis of 16 common genes in patients with Alzheimer's disease and periodontitis were performed with a P value < 0.05 as the threshold. Changes in GO biological processes (BP) mainly included the organization of the intermediate filament cytoskeleton and responses to various chemicals (e.g. morphine, isoquinoline alkaloids), as shown in Fig. 7. In Fig. 8, the changes in molecular function (MF) were mainly focused on the structural components of the cytoskeleton, and G-protein α-subunit binding. In addition, changes in the KEGG pathway focus on the inflammatory response (leukocyte transendothelial migration), the tumor necrosis factor signaling pathway (TNF signaling pathway), and the interaction of viral proteins with cytokines and cytokine receptors, as shown in Fig. 9.

PPI network analysis and HUB gene selection

To distinguish HUB genes from common genes, a PPI network was constructed. As shown in Fig. 10, CD4, KDR, CXCR4, CXCL12, JAK2, PTPN11, CXCL1, PECAM1, SOCS3, CXCR1, CXCR2 and JAK1 proteins interacted with other proteins > 5, which are the central nodes of the protein interaction network. Figure 11 shows the specific scores of these key genes. Finally, we selected the top 6 genes for further study.

Validation of the diagnostic value of the HUB gene

To validate the diagnostic value of the first 6 HUB genes obtained from the above analysis, we constructed ROC curves and calculated the corresponding area under the curve (AUC) for the expression levels of these genes in the Alzheimer's and periodontitis datasets. Figure 12 shows the results for Alzheimer's disease, with AUC values of 0.542 (95% confidence interval, 0.451–0.633), 0.612 (95% confidence interval, 0.524-0.700), and 0.851 (95% confidence interval, 0.792–0.909), 0.673 (95% confidence interval, 0.588–0.759), 0.464 (95% confidence interval, 0.374–0.554); and 0.517 (95% CI, 0.423–0.612) for CD4, KDR, CXCR4, CXCL12, JAK2, and PTPN11 for Alzheimer's disease patients and normal controls respectively (Table 1). Figure 13 shows the ROC curves for patients with periodontitis and normal controls with AUC values of 0.808 (95% CI, 0.743–0.874), 0.881(95% CI, 0.831–0.932), 0.866 (95% CI, 0.812–0.920), 0.765 (95% CI, 0.697–0.833), 0.650 (95% CI, 0.573–0.727), and 0.767 (95% CI, 0.699–0.834)) for CD4, KDR, CXCR4, CXCL12, JAK2, and PTPN11 respectively (Table 2).

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Discussions
Alzheimer's disease and periodontitis are highly prevalent diseases worldwide. A previous study showed (Holmer et al., 2018) that periodontitis is strongly associated with cognitive impairment (CI) and Alzheimer's disease (AD) and is one of the important risk factors for Alzheimer's disease. The risk increases progressively as the disease progresses, making it necessary to explore the molecular mechanisms of both diseases and to find early targets to prevent disease progression.

In this study, by searching the datasets of Alzheimer's disease and periodontitis in GEO, we identified 16 common differential genes between these two diseases. We also performed GO and KEGG pathway enrichment analysis and constructed a PPI network to identify the top 6 HUB genes from the differential genes. We also validated the diagnostic value of these 6 HUB genes for patients with Alzheimer's disease and periodontitis. The results suggest that these 6 HUB genes may be important in predicting the risk of Alzheimer's disease and periodontitis.

The CD4 molecule is expressed primarily on the surface of mature CD4 cells. This gene encodes the CD4 membrane glycoprotein of T lymphocytes. CD4 antigen acts as a co-receptor with the T cell receptor on T lymphocytes to recognize antigens displayed by antigen presenting cells in the class II MHC molecular environment (J. Chen et al., 2022). The CD4 antigen is also the primary receptor for human immunodeficiency virus entry through interaction with the HIV Env gp120 subunit. The gene is expressed not only in T lymphocytes, but also in B cells, macrophages, granulocytes, and various regions of the brain. The protein functions to initiate or enhance the early stages of T-cell activation and may act as an important mediator of indirect neuronal injury in infectious and immune-mediated diseases of the central nervous system (Chen, Barr, Zuk, Gorman, & Colgan, 2022). Diseases associated with CD4 include immunodeficiency 79 and Okt4 epitope defects (Dong et al., 2022). No studies have yet shown a relationship between CD4 and Alzheimer's disease and periodontitis.

KDR (kinase insertion domain receptor) is a protein-coding gene. Its related pathways include GPCR pathway and Hippo-Merlin signaling dysregulation. An important paralog of this gene is FLT1. tyrosine protein kinase that acts as a cell surface receptor for VEGFA, VEGFC, and VEGFD and plays an important role in the regulation of angiogenesis, vascular development, vascular permeability, and embryonic hematopoiesis by promoting the proliferation, survival, migration, and differentiation of endothelial cells and facilitating the reorganization of the actin cytoskeleton (Chamnanya et al., 2022; Fagbohun et al., 2022; Modak & Saha, 2022; Saoud, Aflouk, Ben Afia, Gaha, & Bel Hadj Jrad, 2022). Diseases associated with KDR include hemangiomas, infantile capillary hemangiomas, and cluster hemangiomas (X. Li et al., 2017; Y. Li, Xia, & Jin, 2007).

CXCR4 encodes a CXC chemokine receptor specific for stromal cell-derived factor-1. The protein has seven transmembrane regions and is located on the cell surface. It acts with the CD4 protein to support HIV entry into cells and is also highly expressed in breast cancer cells (Kotb, Ibrahim, Mostafa, & Shahin, 2022; L. Li, Chen, Yu, Zhang, & Chen, 2022). Diseases associated with CXCR4 include WHIM (warts, hypogammaglobulinemia, infection and osteomyelitis) syndrome and macroglobulinemia (Garcia-Cuesta et al., 2022; Luo, De Pascali, Richmond, Khojah, & Benovic, 2022). Recent studies have also shown that
CXCR4 is associated with periodontitis, for example, CXCR4 antagonists inhibit periodontal bone loss due to periodontitis (McIntosh & Hajishengallis, 2012), CXCR4 signaling contributes to alveolar bone resorption in Porphyromonas gingivalis-induced periodontitis in mice (McIntosh & Hajishengallis, 2012), CXCR4 signaling in macrophages contributes to periodontal mechanical hypersensitivity in Porphyromonas gingivalis-induced periodontitis in mice (Nagashima et al., 2017).

CXCL12 is a protein-coding gene that encodes an endocrine family of stromal cell-derived alpha chemokines submembers. The encoded protein acts as a G protein-coupled receptor, chemokine (C-X-C motif) receptor4 ligands that function in many different cellular functions, including embryogenesis, immune surveillance vision, inflammatory response, tissue homeostasis, and tumor growth and metastasis (Barinov et al., 2017; B. Li et al., 2018; Ruscher et al., 2013). CXCL12 is associated with the diseases include human immunodeficiency virus type 1 and ischemia (Bachelerie, 2010; Riek-Burchardt et al., 2010). There are also recent studies showing an association between CXCL12 associated with periodontitis, for example: in a mouse model of Pseudomonas gingivalis-induced periodontitis, CXCL12 in expression is upregulated in Pseudomonas aeruginosa infection in periodontitis (Hernandez et al., 2011). CXCL12 promoter DNA methylation status in periodontal play an important role in the development of disease (Grdovic et al., 2016).

JAK2 encodes a non-receptor tyrosine kinase that plays a central role in cytokine and growth factor signaling enzymes. Mutations in this gene are associated with many myeloproliferative disorders, malignancies, true erythropoietic disorders, thrombocytosis, and JAK2 was one of the first diagnostic markers for the diagnosis of myeloproliferative disorders (Van Egeren et al., 2022; Zhang, Tu, Sha, & Qian, 2022). The V617F mutation is the most clinically relevant variant, seen in approximately half of all myeloproliferative disorders. This variant is a known activating mutation, and activated JAK2 is sufficient to drive myeloproliferative disease in mouse models. V617F, although the most common, is not the only mechanism by which JAK2 is activated in patients. The gene is also a downstream target of the cytokine IL6, which is produced by B cells, T cells, dendritic cells, and macrophages to generate an immune response or inflammation (Feng et al., 2022; Zhou, Chen, Yao, & Gu, 2022). Dysregulation of the IL6/JAK2/STAT3 signaling pathway leads to abnormal proliferation of hematopoietic stem cells and myeloproliferative neoplasms (Jin et al., 2022).

The protein encoded by the PTPN11 gene is a member of the protein tyrosine phosphatase (PTP) family. PTP is known to be a signaling molecule that regulates a variety of cellular processes, including cell growth, differentiation, mitotic cycle, and oncogenic transformation (Macia et al., 2022). This PTP is widespread in most tissues. This PTP is widely expressed in most tissues and plays a regulatory role in a variety of cellular signaling events important for many cellular functions, such as mitotic activation, metabolic control, transcriptional regulation, and cell migration (Liu et al., 2016; Wang et al., 2009). Mutations in this gene are the cause of Noonan syndrome and acute myeloid leukemia (Fobare et al., 2022; Wang et al., 2009).
We also evaluated relevant gene biological functions and pathways, such as GO enrichment analysis of the tumor necrosis factor signaling pathway, inflammatory response and immune system disease pathways, reported to be closely associated with both diseases.

**Conclusion**

In the present study, 1 Alzheimer’s disease dataset and 1 periodontitis dataset were downloaded from GEO. After data selection, patient samples were compared with normal samples, and 16 crossover genes were obtained from these datasets. The biological functions and pathways associated with inflammation were obtained by GO and KEGG analysis. The HUB genes CD4, KDR, CXCR4, CXCL12, JAK2, and PTPN11 were screened by constructing a PPI network and their diagnostic value was verified by SPSS data analysis. Our findings may provide potential targets for the prevention and treatment of Alzheimer’s disease and periodontitis.

However, there are some limitations to our study. First, DEGs screened by bioinformatics methods can predict the occurrence of Alzheimer’s disease and periodontitis, and our research team is conducting in vivo and in vitro experiments and confirming these results with clinical cases, which will be published in the near future. Second, for samples from different races and groups, the results may not be applicable to all populations and will need to be studied in other populations. Finally, our sample size is relatively small and a large sample, multicenter study is needed.

**Declarations**

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**Author contributions**

Laboratory experiments, data analysis and manuscript writing were accomplished by KZ and LJW; part of experimental design and data analysis were accomplished by LBW; part of experiment were accomplished by QW and LZ; guidance of experimental design and manuscript writing was accomplished by XY and DL. All authors have read and approved the final manuscript.

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Availability of data and materials

All data in the article can be requested from the corresponding author.

Ethics approval and consent to participate

This study does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References


Tables

Table 1: Specific values of diagnostic efficiency of the top 6 HUB genes in Alzheimer’s disease.
<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>Predicted ending</th>
<th>Area under the curve (AUC)</th>
<th>Confidence interval (CI)</th>
</tr>
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<td>JAK2</td>
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<td>0.464</td>
<td>0.374-0.554</td>
</tr>
<tr>
<td>PTPN11</td>
<td>Reference group vs. experimental group</td>
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<td>0.423-0.612</td>
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</table>

Table 2: Specific values of diagnostic efficiency of the top 6 HUB genes for periodontitis.

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Figures
Figure 1

Heat map showing changes in Alzheimer's expression. group1 - control; group2 - Alzheimer's.
Figure 2

Heat map showing changes in periodontitis expression. group1 - control; group2 - periodontitis.
Figure 3

Volcano map of genes in the Alzheimer's disease dataset.
**Figure 4**

Volcano map of genes in the periodontitis dataset.
Figure 5

Cross Venn diagram of common genes identified by differential genes in Alzheimer's disease and periodontitis.
Figure 6
Flow chart of the study.
Figure 7

GO analysis of biological processes (BP)

Biological process

intermediate filament-based process
intermediate filament cytoskeleton organization
response to morphine
response to isoquinoline alkaloid
intermediate filament organization

GeneRatio

Molecular function

structural constituent of cytoskeleton
G-protein alpha-subunit binding

GeneRatio
**Figure 8**

GO analysis of molecular function (MF)

![Diagram of GO analysis](image)

**Figure 9**

KEGG enrichment analysis of common genes

![KEGG enrichment analysis](image)

**Figure 10**

PPI network structure and key genes in different colors

![PPI network structure](image)
Figure 11

Scores for key genes
Figure 12

Diagnostic value of the top 6 HUB genes of the ROC curve in Alzheimer's disease.

- CD4 (AUC = 0.808)
- KDR (AUC = 0.881)
- CXCR4 (AUC = 0.866)
- CXCL12 (AUC = 0.765)
- JAK2 (AUC = 0.650)
- PTPN11 (AUC = 0.767)
Figure 13

Diagnostic value of the top 6 HUB genes of the ROC curve for periodontitis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
• SupplementaryData.docx