Genes & Diseases (2023) 10, 746–749

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RAPID COMMUNICATION

Exploration of the common gene and potential molecular mechanisms between Herpes simplex virus 1 infection and Alzheimer's disease

Herpes simplex virus 1 (HSV-1) is highly infectious. More than 70% of the world's population has been infected with HSV-1.[1] Most patients with HSV-1 have no obvious clinical symptoms. However, HSV-1 infection can lead to serious complications in people with an underlying genetic susceptibility, various causes of immunodeficiency, or immunocompromised populations.[2] HSV-1 has the property of activating periodically in neurons and is considered to be one of the risk factors for Alzheimer's disease (AD).[3] However, the underlying pathological mechanisms causing the development of AD induced by HSV-1 are not yet well established. With the spread of transcriptome sequencing and advances in bioinformatics technology, we can gain a deeper understanding of the underlying pathological mechanisms behind the occurrence of disease, which can help in clinical diagnosis and clinical treatment of diseases. In the present study, we used the Gene Expression Omnibus (GEO) database to obtain sequencing datasets related to HSV-1 and AD, explored the potential pathogenesis of HSV-1 leading to AD using various algorithms in bioinformatics, and combined with public databases to construct a potential competing endogenous RNAs (ceRNA) regulatory network for HSV-1 leading to AD (Fig. 1).

We searched the GEO database using the keywords "HSV-1" and "AD", respectively. The filtering criteria for this study were as follows[1]: The dataset's data type was mRNA transcriptome sequencing data.[2] The dataset compared transcriptomic data from patients and healthy individuals.[3] The tissue types used for sequencing should be consistent (neural progenitor cells). (4) The dataset should contain the expression matrix files of the samples. We obtained the HSV-1-related dataset GSE46042 and the AD-related dataset GSE117586. Both datasets were sequenced from neural progenitor cells (NPC).

GSEA was used to analyze GSE46042, and GSE117586 datasets screened in this study. The results showed that HSV-1-infected samples were mainly enriched in aminoacyl tRNA biosynthesis, cytosolic DNA sensing pathway, glycolysis gluconeogenesis, nucleotide excision repair, and tyrosine metabolism, whereas uninfected samples were mainly enriched in alpha-linolenic acid metabolism, linoleic acid metabolism, taste transduction, and sphingolipid metabolism (Fig. S1A). AD samples were mainly enriched in axon guidance, chemokine signaling pathway, melanogenesis, and Wnt signaling pathway, whereas normal human samples were mainly enriched in ABC transporters, glycosylphosphatidylinositol GPI anchor biosynthesis, galactose metabolism, beta-alanine metabolism, and primary immunodeficiency (Fig. S1B).

The 5000 genes with the most significant differences based on *p*-values were screened for gene clustering (Fig. S2A, B). We obtained 5 gene modules and 6 gene modules from the HSV-1 and AD datasets, respectively. Figure S2C and D showed the correlation of gene modules with HSV-1 and AD.

We intersected the "MEred" and "MEbrown" gene modules, which were most positively associated with HSV-1 and AD, and the "MEbrown" and "MEgreenyellow" gene modules, which were most negatively associated with HSV-1 and AD, to obtain 16 and 25 genes, respectively (Fig. S3A, B). These 41 intersecting genes were thought to be closely related to HSV-1 and AD and were defined as common genes (Table S1).

Peer review under responsibility of Chongqing Medical University.

https://doi.org/10.1016/j.gendis.2022.10.012

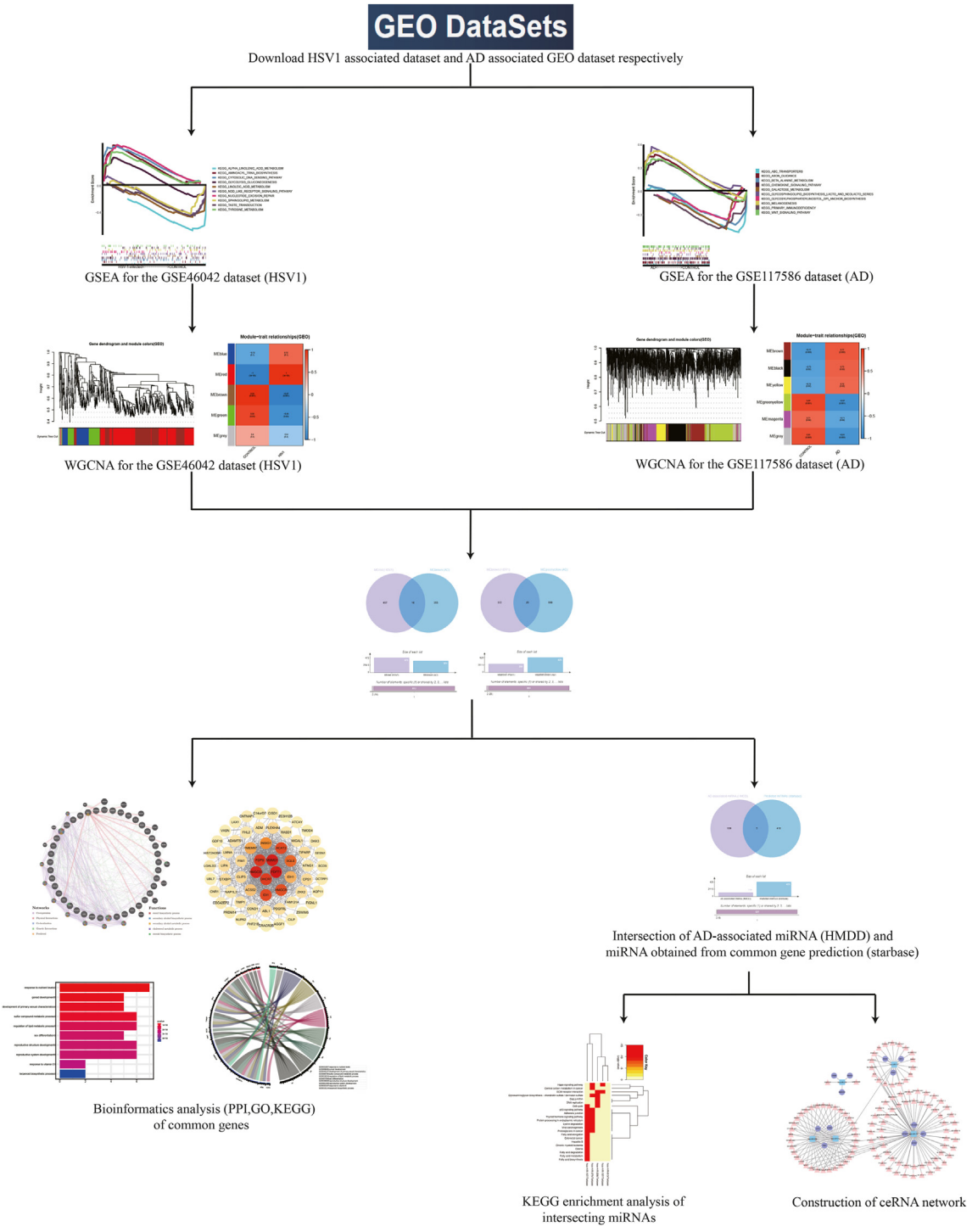

Figure 1 Flow chart.

The PPI network of common genes was constructed according to the operational guidelines of the GeneMANIA database (Fig. S3C and Table S2). The colored lines indicate the nodes' interrelationships, and the nodes' different colors indicate their enrichment in different Functions. Based on the PPI network, we found that common genes were enriched in Functions such as cholesterol metabolic process, sterol biosynthetic process, secondary alcohol biosynthetic process, steroid biosynthetic process, and secondary alcohol metabolic process. To find the core genes in the PPI network, we imported the node information of the PPI network into Cytoscape software. The CytoHubba plug-in calculated the degree values of the nodes, and the PPI network was visualized based on the degree values (Fig.

S3D). The color of the nodes was positively correlated with the degree of the nodes. FDPS, MSMO1, FDFT1, DHCR7, and HMGCS1 had the highest degree values, which may correlate with AD's occurrence and progression due to HSV-1.

GO and KEGG enrichment analyses were performed on 41 common genes using the "enrichGO" and "enrichKEGG" algorithms in R (Table S3, 4). GO enrichment analysis usually consists of 3 components of analysis, namely Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). BP enrichment analysis identified common genes enriched in response to nutrient levels, gonad development, sulfur compound metabolic process, regulation of lipid metabolic process, and sex differentiation (Fig. S4A). CC enrichment analysis identified common genes enriched in the synaptic membrane, presynaptic active zone, and collagen-containing extracellular matrix (Fig. S4C). MF enrichment analysis identified common genes enriched in receptor—ligand activity, amino acid binding, organic acid binding, glutamate binding, nucleoside-triphosphate diphosphatase activity, and AMP binding (Fig. S4E). KEGG enrichment analysis revealed that Terpenoid backbone biosynthesis, Carbon metabolism, Acute myeloid leukemia, p53 signaling pathway, Biosynthesis of amino acids, PPAR signaling pathway, and AMPK signaling pathway might be relevant to the mechanisms by which HSV-1 causes the onset and progression of AD (Fig. S4G). The R language "enrichplot" package was used to analyze the correlation between enrichment results (Fig. S4B, D, F, H). Finally, we used the "circlize" package in R to show the GO and KEGG enrichment analysis results against the corresponding genes (Fig. S5A—D).

We investigated the HMDD database with the keyword "Herpes simplex virus 1" and found no relevant miRNAs, while the keyword "Alzheimer's disease" revealed 114 relevant miRNAs (Table S5). The miRNAs associated with common genes were predicted using the starbase database (Table S6). The predicted miRNAs were intersected with 114 AD-related miRNAs to obtain a total of 5 miRNAs, and we defined these miRNAs as common miRNAs (Fig. S6A and Table S7). KEGG enrichment analysis of common miRNAs identified the Hippo signaling pathway, Central carbon metabolism in cancer, ECM-receptor interaction, Gap junction, DNA replication, Cell cycle, and p53 signaling pathway as possible mechanisms involved in the onset of AD due to HSV-1 (Fig. S6B and Table S8). By comparing the results of the KEGG enrichment analysis of common genes and common miRNAs, we found an overlapping pathway, the p53 signaling pathway.

Predictions of lncRNAs associated with common miRNAs were made by utilizing the starbase database. The regulatory information of miRNA-RNA and lncRNA-miRNA was imported into Cytoscape software for visualization (Fig. S7). Red triangles, blue squares, and purple circles represent lncRNAs, miRNAs, and genes. The ceRNA network constructed in this study may be relevant to the potential mechanisms by which HSV-1 contributes to the onset and progression of HSV-1-caused AD.

This study used bioinformatics algorithms to analyze mRNA sequencing data from HSV-1 and AD samples. The analysis results revealed potential molecular mechanisms underlying the onset and progression of AD caused by HSV-1 and provided multiple validated biomarkers and therapeutic targets for patients with HSV-1-induced AD, which may be useful for basic research, clinical diagnosis, and treatment of AD caused by HSV-1.

Conflict of interest

The authors declare no competing interests.

Funding

The study was supported by Joint Funds for the innovation of science and Technology, Fujian province (China) (No. 2018Y9064). Shenzhen Science and Technology Program (No. RCBS20210706092409017), Shenzhen University Program (China) (No. 827000615).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2022.10.012.

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Weizheng Liang [b,1], Xiushen Li [c,d,1], Hao Wang [c,d,1], Shuangqing Wang [e,1], Qingxue Meng [b], Ruoqing Feng [c], Jingbo Zhai [f], Mengzhou Xue [g,**], Chunfu Zheng [a,h,*]

[a] *Institute of Animal Health, Guangdong Academy of Agricultural Sciences, Key Laboratory of Livestock Disease Prevention of Guangdong Province, Scientific Observation and Experiment Station of Veterinary Drugs and Diagnostic Techniques of Guangdong Province, Ministry of Agriculture and Rural Affairs, Guangzhou, Guangdong 510640, China*
[b] *Central Laboratory, The First Affiliated Hospital of Hebei North University, Zhangjiakou, Hebei 075000, China*
[c] *Department of Obstetrics and Gynecology, Shenzhen University General Hospital, Shenzhen, Guangdong 518055, China*
[d] *Shenzhen Key Laboratory, Shenzhen University General Hospital, Shenzhen, Guangdong 518055, China*
[e] *Department of Neurology, Shenzhen University General Hospital, Shenzhen University, Shenzhen, Guangdong 518055, China*
[f] *Key Laboratory of Zoonose Prevention and Control at Universities of Inner Mongolia Autonomous Region, Tongliao, Mongolia 028000, China*

[1] These authors contributed equally to this work.

[g] *Department of Cerebrovascular Diseases, The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450001, China*
[h] *Department of Microbiology, Immunology and Infectious Diseases, University of Calgary, Calgary, Alberta T2N 1N4, Canada*

*Corresponding authors. Institute of Animal Health, Guangdong Academy of Agricultural Sciences, Key Laboratory of Livestock Disease Prevention of Guangdong Province, Scientific Observation and Experiment Station of Veterinary Drugs and Diagnostic Techniques of Guangdong Province, Ministry of Agriculture and Rural Affairs, Guangzhou 510640, China.

**Corresponding author.
E-mail addresses: xuemengzhou@zzu.edu.cn (M. Xue), zheng.alan@hotmail.com (C. Zheng)

17 August 2022
Available online 9 November 2022