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IDENTIFYING ENDOPLASMIC RETICULUM STRESS-RELATED KEY GENES OF VASCULAR DEMENTIA USING BIOINFORMATICS AND BIOLOGICAL EXPERIMENTS

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Background and aims: This research sought to uncover pivotal genes associated with endoplasmic reticulum stress (ERS), aiming to offer new insights into the underlying mechanisms and diagnostic approaches for vascular dementia (VaD).

Methods: Potential key ERS-related genes for the diagnosis of VaD were identified as hub genes using integrated bioinformatics and machine learning techniques. Moreover, hub genes were validated using an independent dataset. Immune cells with varying dysregulation were also studied. In animal experiments, cognitive functions were assessed at 30 d after chronic cerebral hypoperfusion using bilateral common carotid artery stenosis (BCAS) mouse model. The expression levels of hub genes in the BCAS mice were quantified through qRT- PCR and Western blotting analyses.

Results: We screened out 893 ERS-related genes in the combined ERS dataset, and 323 differentially expressed genes (DEGs) were examined through the GSE186798 dataset. Sixteen potential genes were found using differential gene analysis. Two potential core genes were identified by LASSO regression and random forest (RF) algorithms. The two hub genes, Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha (*PPARGC1A*) and SEC61 Translocon Subunit Gamma (*SEC61G*), showed a good diagnostic ability for VaD. Their high confidence levels were further established using an alternative dataset. MiRNA-hub genes, TFs-hub genes, and chemical-hub genes networks were built and immune cells with varying dysregulation were also observed. These results were validated in animals experiments.

Conclusions: This study highlights the significant role of *PPARGC1A* and *SEC61G* in VaD, suggesting its potential as biomarkers for early diagnosis and prognostic evaluation of this disease.

Conflict of interest: Yilong zhao: nothing to disclose