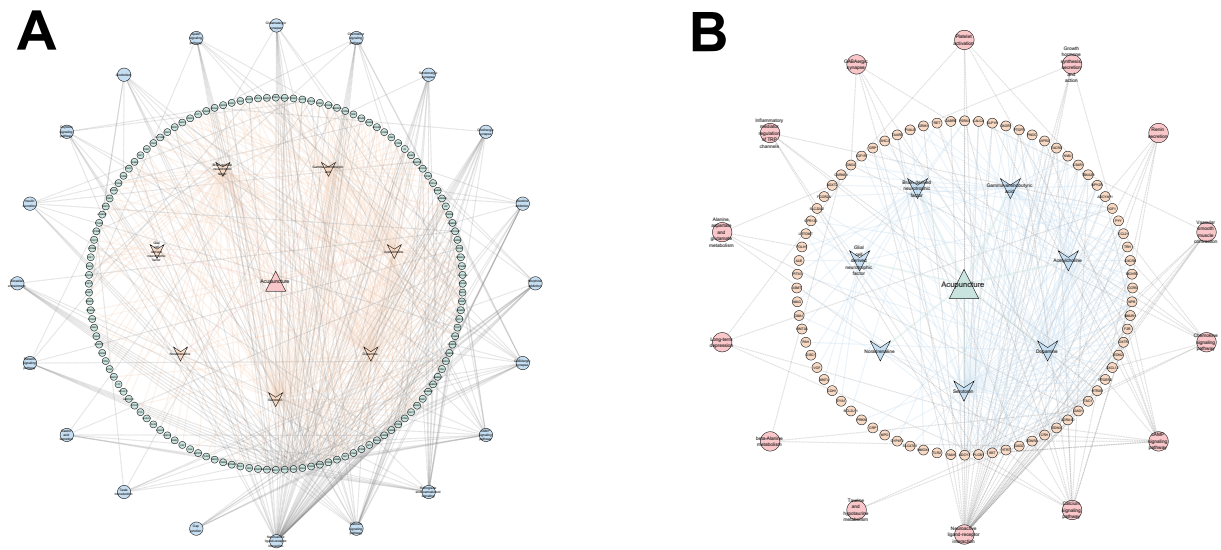


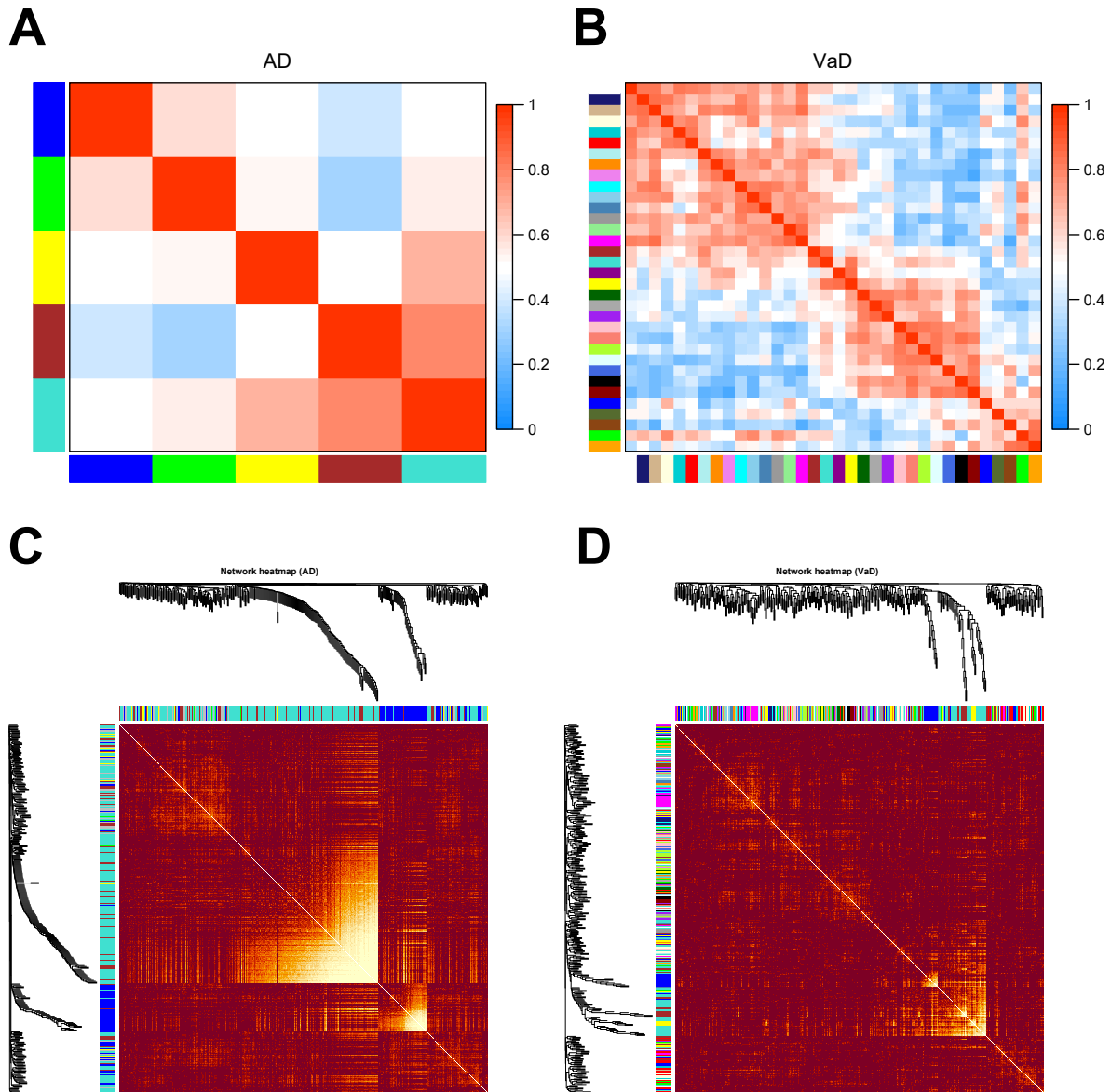
# Supplementary Material

## Acupuncture Therapy on Dementia: Explained with an Integrated Analysis on Therapeutic Targets and Associated Mechanisms

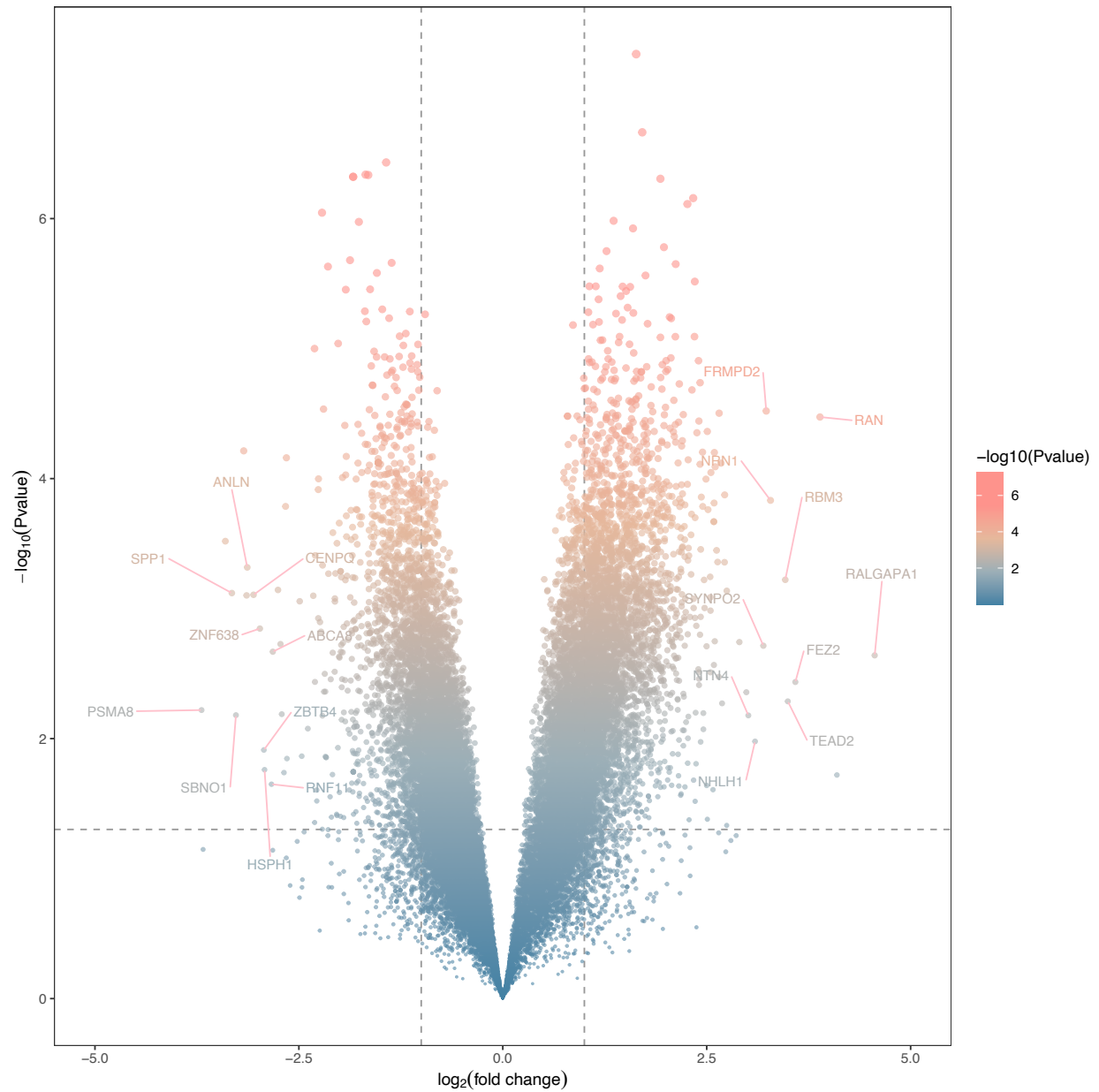
**Supplementary Figure 1.** Construction of integrative networks. A) Integrative network of acupuncture therapy (AT) on Alzheimer's disease. In this network, the information from the global network is summarized and integrated. B) Integrative network of AT on vascular dementia. In this network, the information from the global network is summarized and integrated.



**Supplementary Figure 2.** Correlations of modules and genes in the process of weighted gene co-expression network analysis (WGCNA). A) Correlation between diverse modules of Alzheimer's disease (AD). B) Correlation between diverse modules of vascular dementia (VaD). C) Topological overlap matrix (TOM) network heatmaps of genes associated with AD. D) TOM network heatmaps of genes associated with VaD.

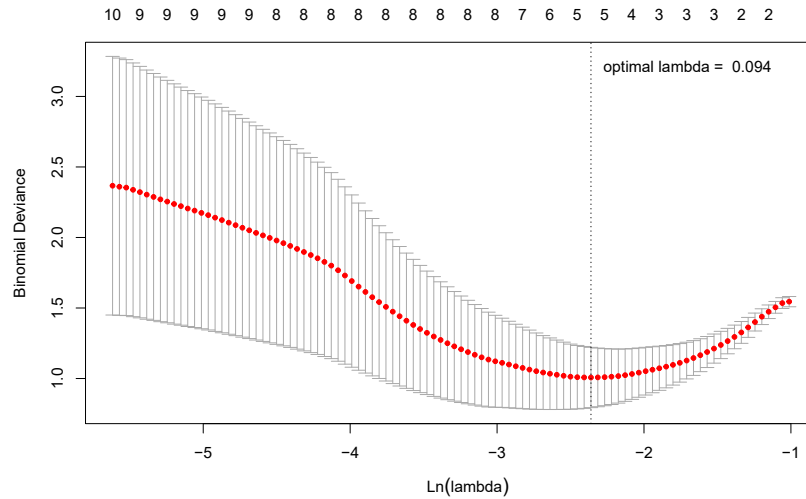


**Supplementary Figure 3.** Screening of differentially expressed genes (DEGs) from the validation dataset. Volcano plot that shows the DEGs between control group and AD group from the validation dataset.

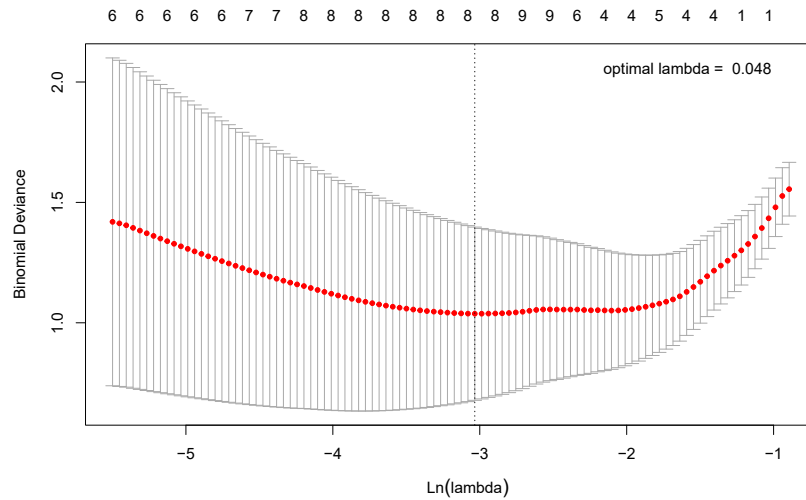


**Supplementary Figure 4.** Identification of core targets for AT on AD and VaD. A) Least absolute shrinkage and selection operator (LASSO) regression for the identification of core targets for AT on AD from crucial targets with ten-fold cross-validation using minimum mean of binomial deviance values to detect optimal lambda. B) LASSO regression for the identification of core targets for AT on VaD from crucial targets with ten-fold cross-validation using minimum mean of binomial deviance values to detect optimal lambda.

**A**



**B**



**Supplementary Table 1.** Differentially expressed genes (DEGs) of Alzheimer's disease (AD) and vascular dementia (VaD). A total of 1,906 DEGs of AD were identified, including 805 upregulated and 1,101 downregulated DEGs, labeled as “up” and “down”, respectively. A total of 1,692 DEGs of VaD were identified, including 844 upregulated and 848 downregulated DEGs, labeled as “up” and “down”, respectively. See Excel file.

**Supplementary Table 2.** Molecular targets of acupuncture therapy (AT) active components. The 1,048 molecular targets of AT active components were screened and acquired from Similarity Ensemble Approach, STITCH5.0, and SwissTargetPrediction. See Excel file.

**Supplementary Table 3.** Acupuncture therapeutic targets on Alzheimer's disease (AD) and vascular dementia (VaD). By comparing the differentially expressed genes (DEGs) of AD and VaD against the molecular targets of acupuncture therapy (AT) active components, 132 and 76 acupuncture therapeutic targets on AD and VaD were identified, and 58 and 24 crucial targets were further screened. See Excel file.

**Supplementary Table 4.** Functional enrichment analysis. Results of Gene Ontology (GO) (biological process, cellular component, and molecular function) and KEGG functional enrichment analysis of acupuncture therapeutic targets on Alzheimer's disease (AD) and vascular dementia (VaD). See Excel file.

**Supplementary Table 5.** Degree value for targets of acupuncture therapy (AT) in protein-protein interaction (PPI) network. The 118 interacting targets in PPI network out of 132 acupuncture therapeutic targets on Alzheimer's disease (AD) were identified. According to the increasing degree value from 1.00 to 57.00, the interaction intensity on targets was correspondingly enhanced. The 66 interacting targets in PPI network out of 76 acupuncture therapeutic targets on vascular dementia (VaD) were identified. According to the increasing degree value from 1.00 to 38.00, the interaction intensity on targets was correspondingly enhanced. See Excel file.

**Supplementary Table 6.** Differentially expressed genes (DEGs) of Alzheimer's disease (AD) in the validation dataset. A total of 13,536 significant DEGs ( $p < 0.05$ ) of AD were identified, and 5,741 remained notably regulated when controlling for  $|\log_2(\text{fold change})| > 1$  in the validation dataset. See Excel file.