**(Cary et al., 2024)Method**

**RNA mapping**

For each sample, paired‐end FASTQ reads were aligned to the GRCh38 reference genome (Ensembl release-106 annotation, Homo\_sapiens.GRCh38.106.gtf) using HISAT2 v2.2.1, which employs a hierarchical graph FM index for spliced alignment. The alignments (SAM) were sorted directly into BAM format with Samtools v1.20 . Gene‐level quantification was performed by featureCounts v2.0.2 in paired‐end, stranded mode assigning reads to exonic features based on the Ensembl GTF. Post‐processing involved extracting gene IDs and raw counts, sorting by gene identifier, and joining to a pre‐compiled Ensembl gene ID–to–gene name mapping (release 106).

**GSVA Enrichment Score Generation**

All analyses were conducted in R 4.4.0 (2024-04-24). Pathway enrichment scores were computed using the GSVA algorithm (Hänzelmann et al., 2013)(Bioconductor v3.21, GSVA v2.3.1) via Bioconductor. Gene sets were loaded from the MSigDB “c5.go.v2023.1.Hs.symbols.gmt” file using getGmt() from the GSEABase package (v3.21) . The raw count matrix (counts) was coerced to a numeric matrix via as.matrix(), and GSVA parameters were specified with gsvaParam(). Single‐sample enrichment scores were then calculated by gsva(), yielding a gene‐set (row) and sample (column) matrix.

**Alzheimer’s Disease Biological Domain Definition**

The biological domains and their constituent Gene Ontology (GO) term lists were taken directly from (Cary et al., 2024) with the full GO ID collections provided in Supplementary Table S2 . We extracted each domain’s GO IDs from Table S2 and converted them into R gene‐set objects via the GSEABase package (v3.21) using getGmt() and custom parsing . These GO IDs were then programmatically mapped to human gene symbols with GO.db (v3.21.0) and AnnotationDbi (v1.69.0) to ensure reproducible, updatable definitions. By anchoring domain membership to the exhaustive GO term expansions in Table S2, this strategy remains objective, fully automatable, transparent, and communally modifiable. The resulting per‐domain gene lists served as the gene‐set inputs for GSVA enrichment scoring.

**Result**

We aggregate the GSVA score of each bidomain, the AD group and the Control show significant difference on biodomain xxx, xxx,xxx. The AD+ R-drug would have significant recsure effect on biodomain xxx,

Reference:

Cary, G. A., Wiley, J. C., Gockley, J., Keegan, S., Amirtha Ganesh, S. S., Heath, L., Butler, R. R., Mangravite, L. M., Logsdon, B. A., Longo, F. M., Levey, A., Greenwood, A. K., & Carter, G. W. (2024). Genetic and multi‐omic risk assessment of Alzheimer’s disease implicates core associated biological domains. *Alzheimer’s & Dementia : Translational Research & Clinical Interventions*, *10*(2), e12461. https://doi.org/10.1002/trc2.12461

Hänzelmann, S., Castelo, R., & Guinney, J. (2013). GSVA: Gene set variation analysis for microarray and RNA-Seq data. *BMC Bioinformatics*, *14*(1), 7. https://doi.org/10.1186/1471-2105-14-7