Week 1 – Paper Summary (Transcriptomics)

A. Title

Blood and brain transcriptome analysis reveals APOE genotype-mediated and immune-related pathways involved in Alzheimer disease

B. Overview

The ethiology of Alzheimer's disease (AD) has been linked to proteins such as amyloid plaques and neurofibrillary tau tangles in blood. Conditions like cerebrovascular amyloid angiopathy (CAA) which marks disruption in blood brain barrier have been identified as markers for amyloid-β (Aβ) accumulation and protein tau phosphorylation. The association with Apolipoprotein E (*APOE*) genotype has also been discussed. Loss of the ε4 allele proportional with the increase of AD risk as well as ε2 allele.

Study of both blood and brain from the same individual has not been done. Hence, this research aims to fill that gap. Transcription-wide study stratified by *APOE* genotype shared in blood and brain, to investigate gene expression change, biological pathway and gene networks in AD were done.

Objectives

- Identification of DEG shared between blood and brain tissues
- Analysis of gene set enrichment to identify important biological pathways
- Construction of co-expression networks to identify gene modules associated among APOE genotypes in AD for further identification of vascular injury traits

C. Contents

Samples

- Blood (576 ROSMAP+179): phenotype AD classification and RNA-seq
- Brain (576, RIN<5 excluded): prefrontal cortex RNA-seq, tissue lysate for immunoassay on vascular injury proteins (ICAM-1, VCAM-1, SAA)

1. Data origin

- Synapse portal: ROSMAP data
- FHS/ADRC
- Single Cell Portal: blood scRNA-seq

2. Data Processing

- FastQC: quality control & adapter trimming
- STAR: alignment to human reference genome
- RSEM and Bowtie2: gene and isoform levels quantification
- Trimmed Mean of M-values: normalization for between sample variability
- VOOM and LIMMA: DEG analysis
- CUMP (R package): combined DEG blood and brain using O'Brien's method
- MSigDB: gene set enrichment analysis
- WGCNA: co-expressed genes algorithm
- Association analyses of top-ranked genes in DEG: log-transformed FPKM values correlated with ICAM-1, VCAM-1, SAA proteins

Results

1. DEG in blood and brain

- Blood and brain significant genes: *HLA-DQA1* (↓), *INPP5D* (↑), *PIGHP1* (↑), *SPDYE3* (↓)
- Blood-only significant genes: *FRAS1* (↓)
- Brain-only significant genes: *BCKDK*, *TSPOAP1* (↓), *SIGLEC11* (↑)
- *FRAS1* and *PIGHP1* were novel DEG marker within *APOE* genotype groups
- *HLA-DQA1* and *INPP5D* were higher expressed in dendritic and monocytes
- *INPP5D* were the only brain cell specific, especially in microglia

2. Genotype-dependent pathway

- ε2/ε3: TNF-α signaling via NF-kB (↓)
- ε3/ε4: allograft rejection (↑), IFN-γ response (↑), peroxisome (↑), TNF-α signaling via NF-kB (↑)
- ε3/ε3: allograft rejection (↓), IFN-γ response (↓), peroxisome (↓)

3. Co-expression networks common to the brain and blood

- *NFKB1A* (NF-kB signaling pathway), *HLA-DRA* (allograft rejection), *INPP5D* (Fc gamma R-mediated phagocytosis and B cell receptor signaling), *C4B* (*Staph. aureu*s infection and systemic lupus erythematosus)
- VASP was associated with ICAM-1 and C4B was associated with ICAM-1, SAA, VCAM-1

Discussions

- *INPP5D* and *HLA-DQA1* were DEG both in brain and blood
- 10 pathways were specific for genotype people
- ε4 carrier were more enriched for AD genes compared to non-carriers
- Enriched pathways are associated with vascular injury proteins

Limitations

- Sample size related statistical power insufficiency especially in blood dataset
- Insufficiency of another blood type data
- No RIN (RNA quality) information in blood dataset
- Different expression profiles between tissues

D. Conclusion

- There was correlation between blood bio-markers with AD-related protein
- *APOE* genotype associated with AD-related pathology

E. Reference

Panitch, R., Hu, J., Xia, W., Bennett, D. A., Stein, T. D., Farrer, L. A., & Jun, G. R. (2022). Blood and brain transcriptome analysis reveals APOE genotype-mediated and immune-related pathways involved in Alzheimer disease. Alzheimer's Research & Therapy, 14(1). https://doi.org/10.1186/s13195-022-00975-z

F. Graphical Abstract