Broadening Gene Discovery for Alzheimer's Disease

Incorporating Cerebrovascular Risk Factors and Examining Multi-Omics Profiles to Unravel Mechanisms and Causal Pathways

Zhengwei Song, Zuoqiao Cui, Annie J. Lee*

[1,2]Columbia University Mailman School of Public Health, [3]Columbia University Department of Neurology

COLUMBIA
COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

BACKGROUND

- Cardiovascular risk factors (CVRFs) increase the risk of cerebrovascular disease and clinical Alzheimer's Disease (AD), and over 30% of the patients with AD coincident cerebrovascular pathology.
- We previously found that FMNL2 interacts with CVRFs (p=6.6x10-7) by altering the normal astroglial-vascular mechanisms that underly amyloid clearance[1]. Identify additional genes that contribute to the interaction between CVRFs and AD will provide greater insight into the genetic factors associated with AD, which can help understand the **multifactorial etiology of AD.**

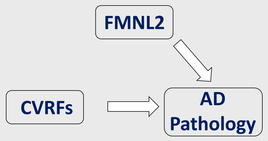

Figure 1. FMNL2 interacts with CVRFs altering mechanisms that underly amyloid clearance1

OBJECTIVES & DATA

Objectives: Gene Discovery with Mechanisms and causal pathways

- Using **multi-omics** data can provide a comprehensive perspective on disease mechanisms, which helps to understand the complexity of AD at the molecular level

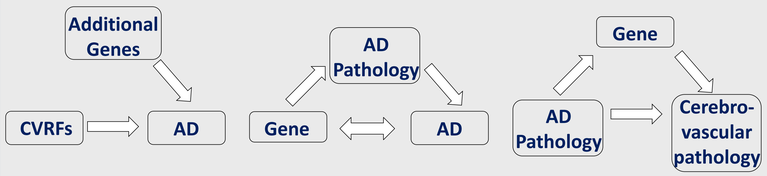

Figure 2. Studying the relationship between CVRFs, cerebro-vascular pathology, AD and its pathology

Data Overview

- Frontal Cortex Data from Religious Orders Study/Memory and Aging Project (ROSMAP)[2], with eight multi-ethnic study batches
  - **Genotype**: 11,480,632 SNPs, with 530 AD patients, 503 controls, and 861 others
  - **Proteomics**: 7,737 proteins, with 184 AD patients, 134 controls, and 82 others
  - **Bulk RNA sequencing**: 18,629 genes, with 688 AD patients and 404 controls
  - **Phenotype**: 19,028 variables, with 688 AD patients and 404 controls
- Quality Control
  - Omics count data Normalization by TMM
  - Regressed each omics feature out by age, sex and 11 processing factors, and used residual as the final omics value
  - Technical factors adjustment by extracting correlation matrix between 20 Principal Components (PCs) from the previous residuals and technical variables including study batch. In addition, a forward selection approach using the voom/limma pipeline is to verify technical factors.

METHODS

- **CVRF score** was created from the first principal component of self-reported history of hypertension, diabetes, and heart disease, and measured BMI
- **Genome-wide gene-CVRF score (GxE)** interaction analysis for AD
- Gene-based interaction by the **adaptive gene-environment interaction (aGE) test**, results were summarized using a meta-analysis
  - aGE Model: Phenotype ~ SNP + GxE + SNP*GxE + Age + Sex, adjusted by top 3 genotype PCs
- **Trait Analysis**: Tested the association between pathological AD, amyloid-β, tangles deposition (tau), and 45 brain infarction regions with gene and protein expression from the frontal cortex. Age and sex were adjusted in all models.
  - AD ~ Omics (Transcript/Protein)
  - Omics (Transcript/Protein) ~ AD Pathology (amyloid/tau) in AD patients
  - Infarction Region ~ Omics (Transcript/Protein) *AD Pathology (amyloid/tau)
  - Infarction Region ~ Omics (Transcript/Protein) in all sample and AD patients
  - AD ~ Infarction Region * Omics (Transcript/Protein)
- **Causal Mediation Analysis**
  - Omics (Transcript/protein) → AD Pathology (amyloid/tau) → AD
  - AD Pathology (amyloid/tau) → Omics (Transcript/Protein) → Infarction Region

RESULTS

- The previous **interaction of CVRF score with FMNL2 on AD** ($p=3.64x10^{-7}$) **was strengthened** and **additional genes were identified including BRINP1** ($p=2.45x10^{-6}$), **CFAP99** ($p=3.30x10^{-6}$), and **PRG3** ($p=3.71x10^{-6}$).
- FMNL2 encodes a formin-related protein important in regulating actin and microtubules.
- **FMNL2** and **BRINP1** gene expressions were **higher in the brains of patients with brain infarcts** (p = 0.025 and p = 0.006).
- protein expression was associated with pathological AD (p=0.0002) and wasBRINP1 higher in the brains of patients with brain infarcts (p = 0.022).
- **51 candidate genes detected** from aGE test (FDR<0.05); **Amyloid-β fully mediates between BRINP1, TPR, PTPRF and AD**, respectively (FDR<0.05); **Tangles Deposition fully mediates TPR, PTPRF and AD**, respectively (FDR<0.05), and **partially mediates between TPR, PTPRF and AD**, respectively (FDR<0.05).
- **BRINP1, SCIN,PTPRF fully mediates between Amyloid-β & Tangles Deposition and some of 7 Infarction Regions**. (FDR<0.05)

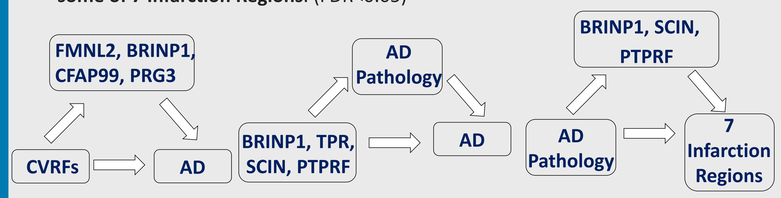

Figure 3. Result for the relationship between CVRFs, cerebro-vascular pathology, AD and its pathology

CONCLUSIONS

- The **four novel genes (FMNL2, BRINP1, CFAP99, PRG3)** are likely to be involved in the complex **interaction between Alzheimer's disease pathology** (amyloid and phosphorylated tau deposition) **and cerebrovascular pathology** at the glia-vascular interface during AD progression. Understanding how these genes interfere with the mechanisms in brain will be essential.
- **Pathway Mediation by Amyloid-β**: The relationship between three novel genes (BRINP1, TPR, PTPRF) and AD is fully explained by the role of Amyloid-β.
- **Pathway Mediation by Tangles Deposition**: The effect of two novel genes (TPR, PTPRF) on AD is entirely channeled through Tangles Deposition. Furthermore, it partially mediates between TPR, PTPRF, and AD, suggesting that Tangles Deposition is a significant but not the sole pathway of influence.
- **Gene & Protein Mediation Impacting Infarction Regions**: The genes BRINP1, SCIN, and PTPRF are complete mediators between Amyloid-β & Tangles Deposition and some of the 7 Infarction Regions identified. This indicates a direct pathway where these genes mediate the effects of Amyloid-β and Tangles Deposition on specific brain regions affected by infarction.

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REFERENCES

- 1. Lee, A. J., Raghavan, N. S., Bhattarai, P, et al. (2022). FMNL2 regulates gliovascular interactions and is associated with vascular risk factors and cerebrovascular pathology in Alzheimer's disease. Acta neuropathologica, 144(1), 59–79. https://doi.org/10.1007/s00401-022-02431-6
- 2. Bennett, D. A., Buchman, A. S., Boyle, P. A., Barnes, L. L., Wilson, R. S., & Schneider, J. A. (2018). Religious Orders Study and Rush Memory and Aging Project. Journal of Alzheimer's disease : JAD, 64(s1), S161–S189. https://doi.org/10.3233/JAD-179939