Fine-Mapping Estrogen Receptor Variants to Elucidate Sex-Specific Genetic Risk in Late-Onset Alzheimer's Disease

literature review:

To date, no preventive or disease-modifying treatments exist for Alzheimer's disease (AD). In the brain, AD pathology can be recognized by extracellular amyloid-β (Aβ) plaques as well as intracellular microgliosis, astrocytosis and neurofibrillary tangles. [1]But the cause of AD is unclear. AD is divided by two categories based on the onset time. Early-onset AD is mainly associated with amyloid-β precursor protein *(APP)*, presenilin 1 (*PSEN1*), and presenilin 2 *(PSEN2*), which are the pivotal pathogenic cause of early-onset AD [2]. While late-onset AD is more intricate and polygenic. Apolipoprotein ε4 allele homozygotic carriers *(APOE4)* increase 50% risk of late-onset AD [3]. Another study indicated that LOAD patients who didn't carry Apolipoprotein ε4 allele had significant variant in *AKT1 IGF2R GSR XDH MSH3* genes. [4] More analyses have to conduct to verify the causal genes to LOAD.

Genome-wide association studies (GWASs) has conducted with around 20500 AD patients and discovered approximately 75 genetic loci related to AD [5]. Empirically, more analysis needs to be performed for validation. Roque et al. (2024) carried out additional staticstic analyses with these 75 loci related to AD and found out that a small fraction of hits can't explain confidently. It is vital to interpret GWAS data correctly. With the genome fine mapping method [6], we could interpret genome data precisely by finemapping. Finemapping carries on by using the PLINK [7] to capture the region around ±5Mb of target genes. Then, conduct GCTA to search out lead SNPs and investigate the causal SNPs with FINEMAP software. [8]

Recent studies indicate that sex plays an important role in pathogenesis of late-onset AD [9]. To explore sex impact on the AD, research discovered that female and disease-associated microglia (FDAMic) are classified together by their transcriptomic and pathological profiles after T-SNE classification. After investigation, it indicated that estrogen receptor 1 and 2 were expressed less in FDAMic. This causes the whole metabolic changes of cells including afterward signal transduction and rho GTPase signaling. [11] Therefore, I aim to fine-map genomic variants in estrogen receptor genes ESR1 and ESR2 and their downstream signaling pathways to identify sex-specific genetic contributors to late-onset Alzheimer's disease. This approach may help uncover causal variants that explain female-biased disease risk and guide future therapeutic development.

Method

WGS and RNA-Seq data will be obtained from the AMP-AD RNAseqReprocessing Study (Synapse ID: syn9702085). Based on Differential expression gene data (DEG), utilize the PLINK to select the region within ±5 megabases (Mb) vicinity to these genes. After that, discover lead SNPs signals that has credibility ($p<10^{-5}$) with GCTA. Ran FINEMAP v.1.3 at each locus with --n-causal-snps given as the number of independent SNPs determined by GCTA. For FINEMAP, we excluded variants with an MAF < 0.2%. For regions with multiple association signals, we applied GCTA's --cojo-cond to perform conditional analysis on each independently associated SNP identified earlier, and we retained SNPs located within 500 kb of any of these conditionally independent SNPs.

To reduce potential confounding from linkage disequilibrium (LD), SNPs will be further validated using Bayes Factor calculations in the GCTA software. For control the false discovery rate, the Benjamini-Hochberg correction will be applied to GWAS. To analyze causal variants, use FINDMAP to find most important causal configurations of the region.

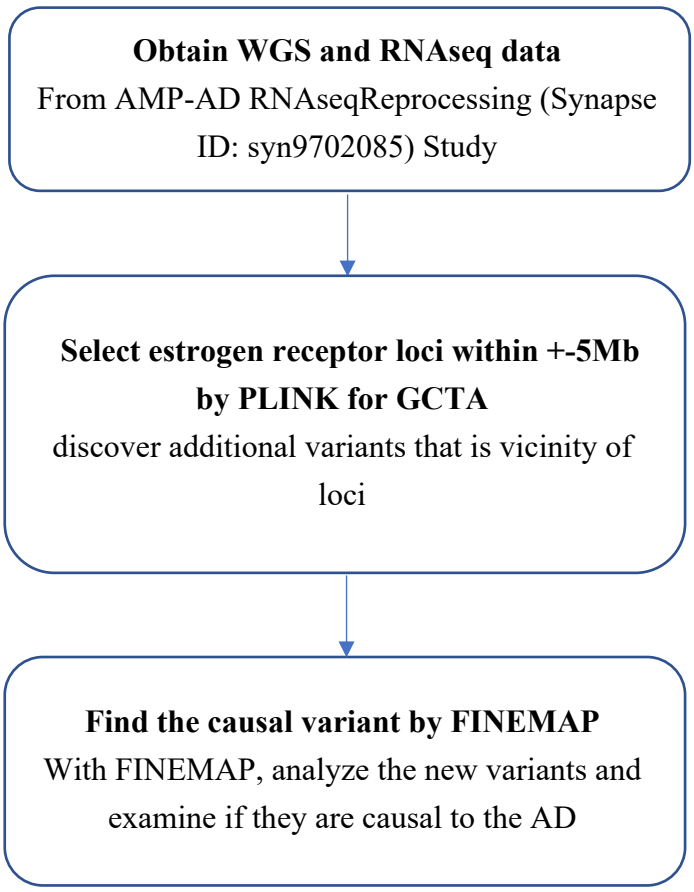

fig 1. The flowchart of examining causal variants of LOAD

Reference:

1. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med*. 2016;8(6):595-608. doi:10.15252/emmm.201606210

2. Roque CG, Phatnani H, Hengst U. The broken Alzheimer's disease genome. *Cell Genomics*. 2024;4(5). doi:10.1016/j.xgen.2024.100555

3. Genin E, Hannequin D, Wallon D, et al. APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol Psychiatry*. 2011;16(9):903-907. doi:10.1038/mp.2011.52

4. Dato S, De Rango F, Crocco P, et al. Sex- and APOE-specific genetic risk factors for late-onset Alzheimer's disease: Evidence from gene–gene interaction of longevity-related loci. *Aging Cell*. 2023;22(9):e13938. doi:10.1111/acel.13938

5. Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet*. 2022;54(4):412-436. doi:10.1038/s41588-022-01024-z

6. Schwartzentruber J, Cooper S, Liu JZ, et al. *Nat Genet*. 2021;53(3):392-402. doi:10.1038/s41588-020-00776-w

7. Purcell S, Neale B, Todd-Brown K, et al. PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. *Am J Hum Genet*. 2007;81(3):559-575. doi:10.1086/519795

8. Schwartzentruber J, Cooper S, Liu JZ, et al. Genome-wide meta-analysis, fine-mapping and integrative prioritization implicate new Alzheimer's disease risk genes. *Nat Genet*. 2021;53(3):392-402. doi:10.1038/s41588-020-00776-w

9. Lopez-Lee C, Torres ERS, Carling G, Gan L. Mechanisms of sex differences in Alzheimer's disease. *Neuron*. 2024;112(8):1208-1221. doi:10.1016/j.neuron.2024.01.024

10. Du H, Mizokami A, Ni J, et al. Role of Testosterone Signaling in Microglia: A Potential Role for Sex-Related Differences in Alzheimer's Disease. *Adv Sci*. n/a(n/a):2413375. doi:10.1002/advs.202413375

11. Wu D, Bi X, Chow KHM. Identification of female-enriched and disease-associated microglia (FDAMic) contributes to sexual dimorphism in late-onset Alzheimer's disease. *J Neuroinflammation*. 2024;21(1):1. doi:10.1186/s12974-023-02987-4