Stratification of Alzheimer's patients using post-mortem co-expression data reveals novel genetic modifiers mediating inflammatory aging

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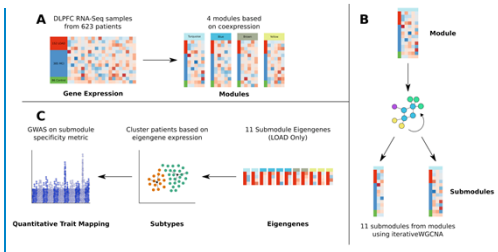
MODEL-AD
Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease

ABSTRACT

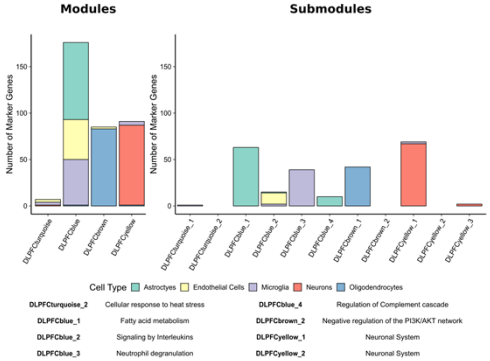
Background: The genetic and clinical heterogeneity of late-onset Alzheimer's disease (LOAD) poses a major challenge for targeted therapies and the identification of novel disease associated variants. Case-control approaches in LOAD are often limited to examine a specific outcome in a group of heterogenous patients with different clinical characteristics.
Method: Here, we developed a novel approach to stratify LOAD patients based on molecular profiles. By integrating post-mortem brain transcriptome data from 2,114 human samples, a novel quantitative, composite phenotype was developed that can better account for the differences in genetic architecture underlying LOAD. Co-expression data from the AMP-AD consortium across seven brain regions and three research studies (ROS/MAP, Mount Sinai, Mayo Clinic) was used to group patients into different molecular subtypes based on gene co-expression profiles. Singular value decomposition and iterative WGCNA analysis dimensionally reduced the data to isolate gene sets that are highly co-expressed among LOAD subtypes representing specific molecular pathways. Single variant association testing was performed using AMP-AD whole genome-sequencing data for the novel composite phenotype in order to identify genetic loci that contribute to disease heterogeneity.
Results: Three distinct LOAD subtypes were identified for each study cohort (ROS/MAP, Mount Sinai, Mayo Clinic). Differential expression analysis revealed an up-regulation of immune related pathways (KEGG: cytokine-cytokine interaction, complement activation) across subtypes. Single variant association analysis identified a genome-wide significant variant in TMEM106B (p-value< 10xE-07, rs1990620[G]) in the ROS/MAP cohort that confers protection from the inflammatory LOAD subtype. TMEM106B has been previously identified as an important modifier of cognitive aging in patients with frontotemporal dementia.

METHODS



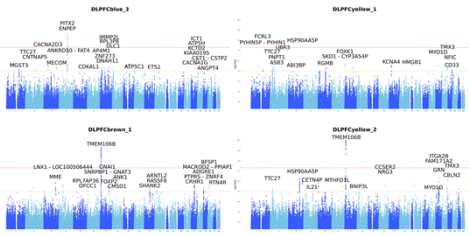
SUBMODULES ARE CELL-TYPE SPECIFIC

- Dividing ROSMAP AMP-AD modules into submodules reveals cell-type specific submodules
- AMP-AD submodules are associated with specific disease associated processes and pathways

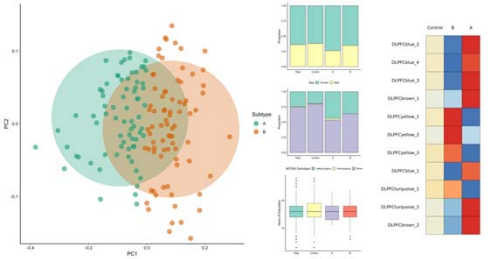


GENETIC FACTORS AFFECT SUBMODULE EXPRESSION

- Single variant association revealed known and novel loci contributing to submodule co-expression signatures
- TMEM106B is associated with myelination submodule DLPFCbrown_1 & neuronal submodule DLPFCyellow_2

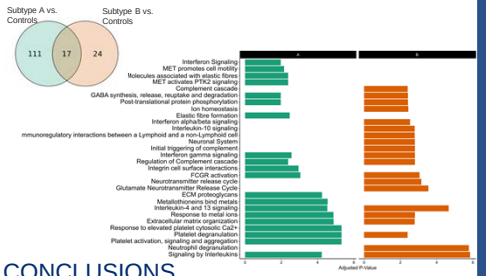


- Clustering patients based on submodule eigengene expression in the ROSMAP cohort revealed two distinct subtypes
- Subtypes are not significantly enriched for sex, APOE status or other LOAD related endophenotypes



SUBTYPES ANALYSIS REVEALS INFLAMMATORY SIGNATURE

- Subtype A showed a strong inflammatory signature when compared to controls and subtype B
- Functional enrichment points to microglia associated pathways driving inflammatory response across subtypes



CONCLUSIONS

- Novel approach, which dimensionally reduces heterogenous post-mortem RNA-Seq data, can be used to stratify patients into distinct molecular subtypes
- Single-variant association revealed specific candidate genes (*TMEM106B, CSMD1*) implicated in immune function

For further information, please see

- MODEL AD: www.modelad.org
- AMP-AD Knowledge portal: www.ampadportal.org
- Jax AD models: https://www.jax.org/alzheimers
- AlzForum research models: http://www.alzforum.org/research-models

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