AN INTEGRATIVE MULTI-OMIS APPROACH REVEALS MOLECULAR SIGNATURES ASSOCIATED WITH AGE AND HIGH-FAT DIET IN MOUSE MODELS OF ALZHEIMER'S DISEASE

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

Abstract

Objective: Alzheimer's disease (AD) is a complex, multifactorial pathology with high heterogeneity in biological alterations. Our understanding of cellular and molecular mechanisms from disease risk variants to various phenotypes is still limited. Therefore, it is required to integrate the information from multiple data modalities for thorough exploration of endophenotype networks, biological interactions related to disease and thus accelerate our understanding of heterogeneity in Alzheimer's disease. **Methods:** In this study, we performed multi-level omics in a cohort of mouse models expressing humanized Abeta and two genetic risk factors (APOE4 and Trem2*R47H) at multiple ages for both sexes. Data from multiple omics platforms (transcriptomics, proteomics, and metabolomics) were analyzed at single-omic level as well as integrated in an unbiased fashion, considering interaction between modalities using multi-omics factor analysis (MOFA)[1]. We also systematically aligned multimodal mouse data to relevant human studies cohort. **Results:** Multi-omics integration identified major components of heterogeneity explaining the variance within the cohort and differentially associated with age, sex, and high fat diet. Enrichment analysis of genes and protein associated with these components were significantly enriched for multiple AD-related processes. Specifically, components associated with age and diet related heterogeneity exhibited overrepresentation of immune response and metabolic processes as well as increased levels of long-chain acylcarnitine's and reduced levels of spermidine in aged and high-fat diet fed AD mouse models, similar to human AD[2]. In addition, we observed weak correspondence between change in protein and RNA expression in mouse models compared to controls, similar to recent results[3] from the ROSMAP cohort, which reported weak correlation between protein and RNA expression. We also identified a negative correlation for the change in RNA expression between male and female mice. **Conclusions**: We identified axes of variation within a cohort of LOAD mouse models using integrative multi-omics approach. Our analysis revealed multiple interaction between distinct multi-omics molecular signatures associated with Alzheimer's disease. We determined that mRNA profiling alone provides an incomplete picture of molecular mechanism of AD. In this study, we highlighted that assembling multi-omics measurements reveal interrelated pathway alterations in AD and the ability to identify biomarkers combinations that may inform clinical practice.

References

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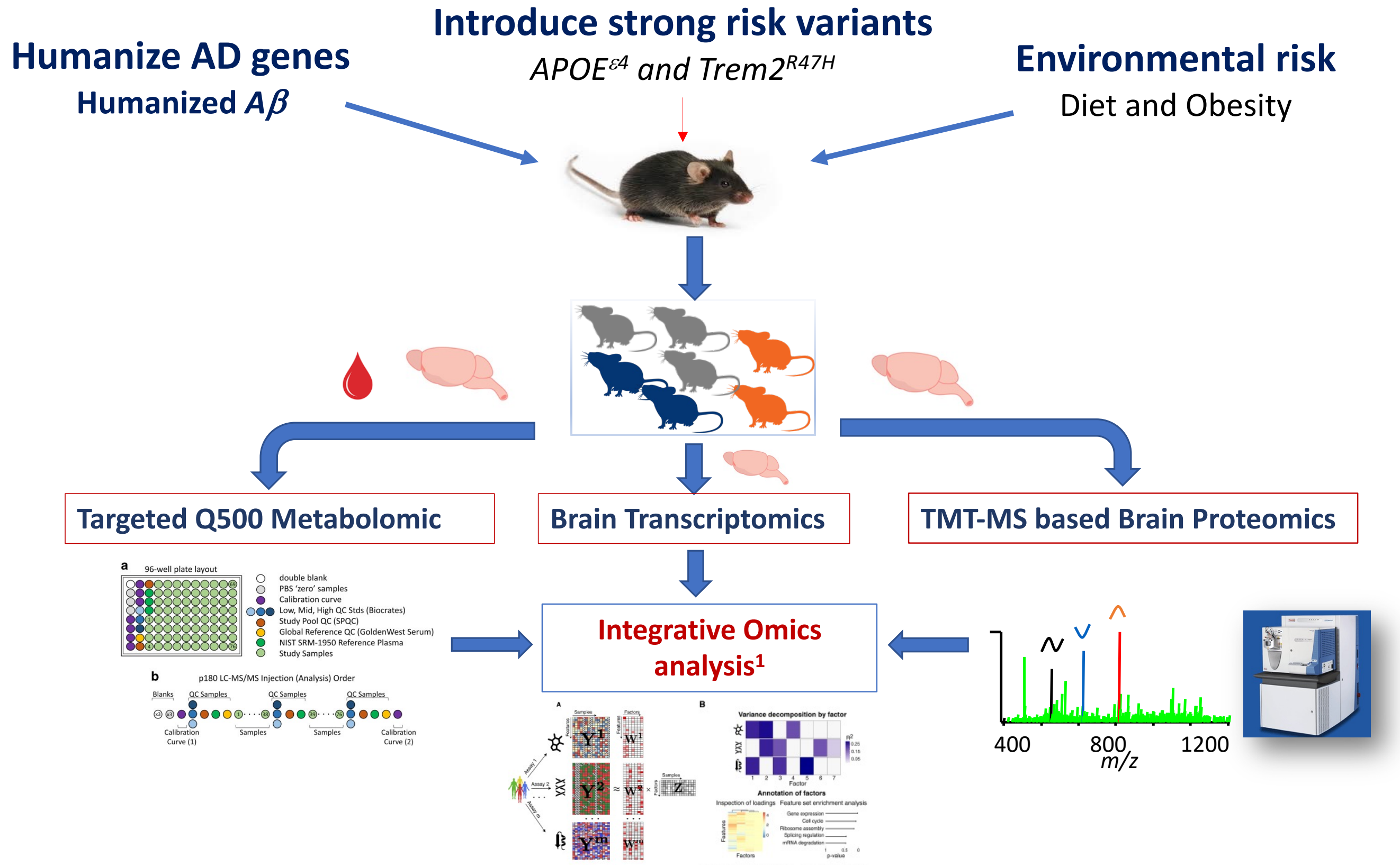
Methodology/analytical workflow



Humanize AD genes
Humanized $A\beta$

Introduce strong risk variants
APOE$^{\varepsilon4}$ and Trem2^{R47H}

Environmental risk
Diet and Obesity

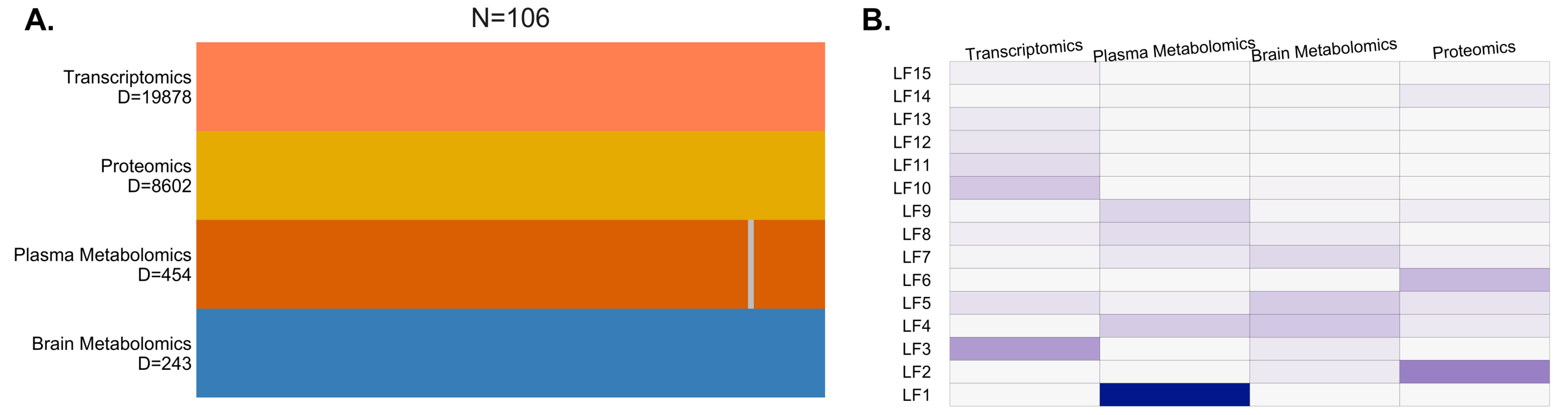
Targeted Q500 Metabolomic

Brain Transcriptomics

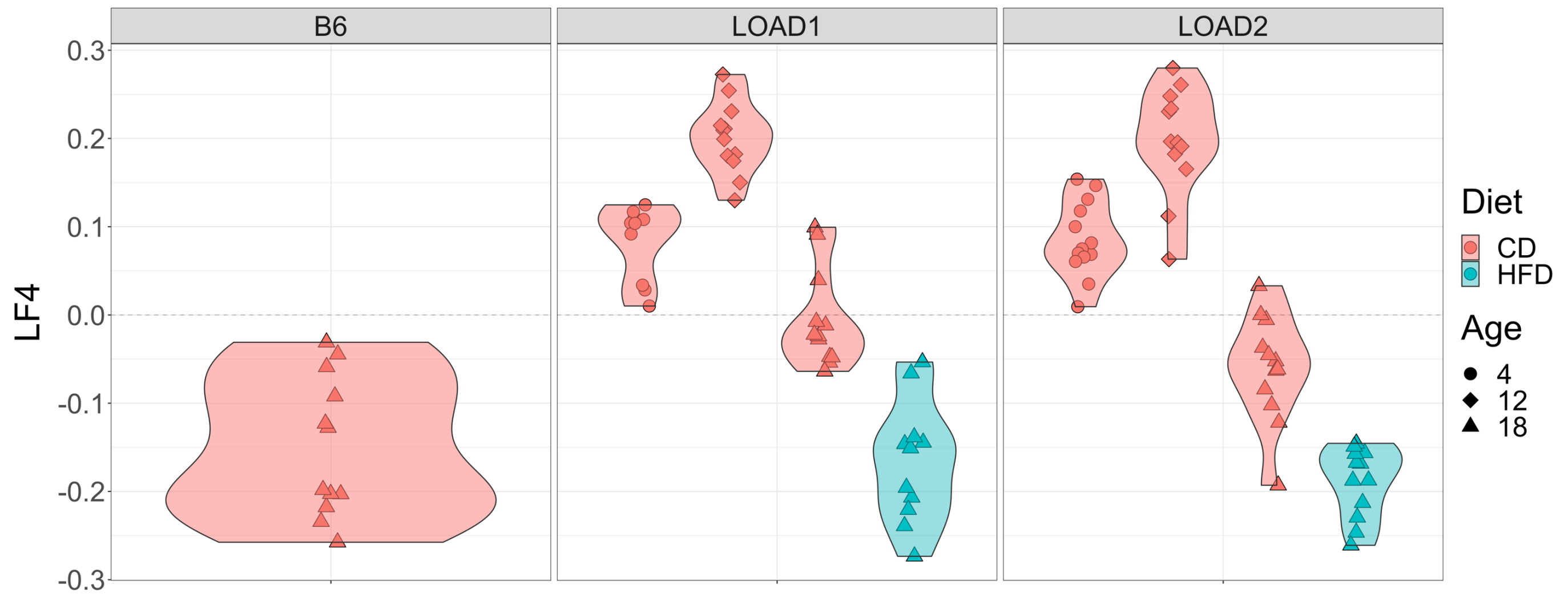
TMT-MS based Brain Proteomics

Integrative Omics analysis[1]

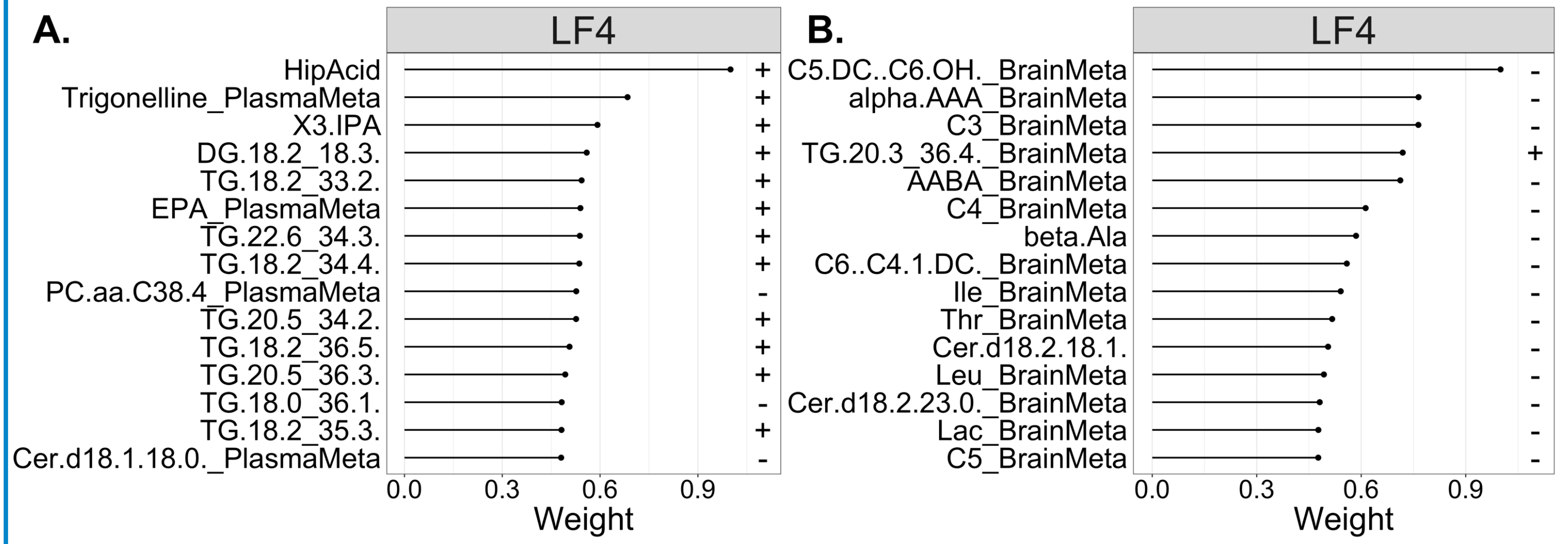
Overview of multi-modal data and integrative analysis



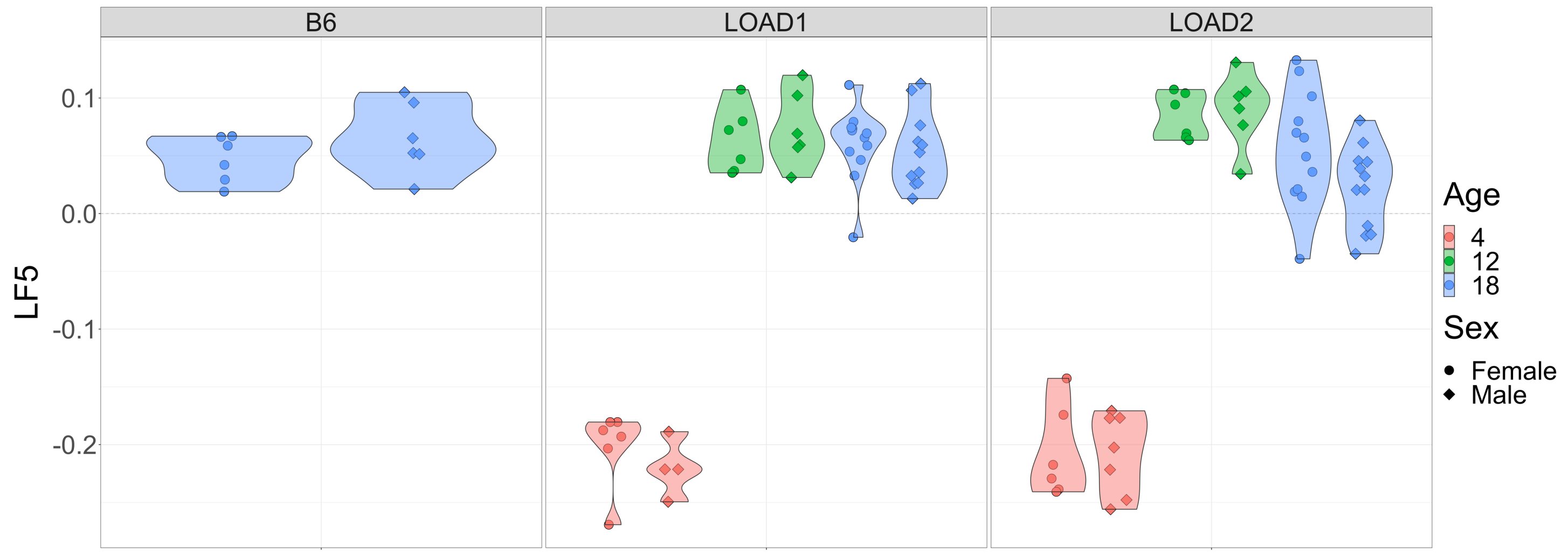
Factor 4 captures diet-related heterogeneity and describes the brain and plasma metabolome

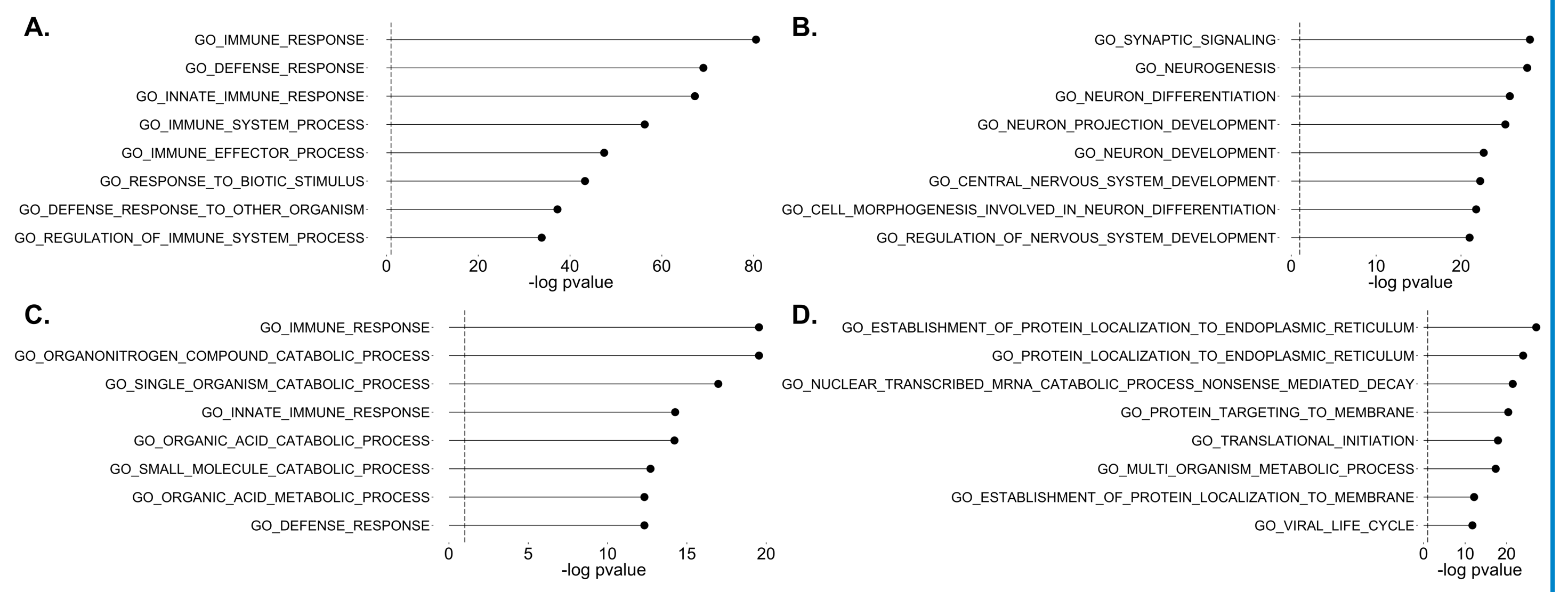


Top metabolites associated with factor 4 in plasma (A) and brain (B). Negative sign indicates increased levels and positive sign indicates decreased levels in high-fat diet (HFD) fed mice

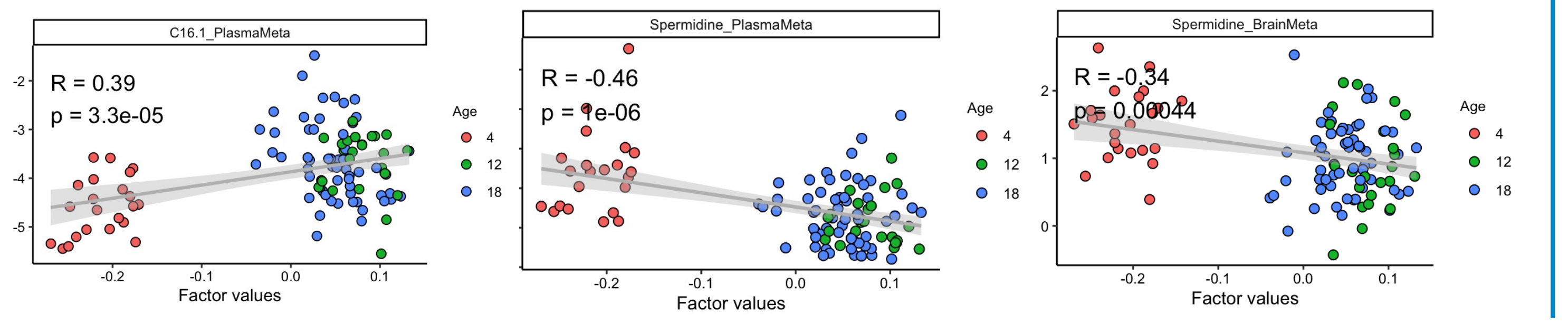


Factor 5 Captures age-related heterogeneity



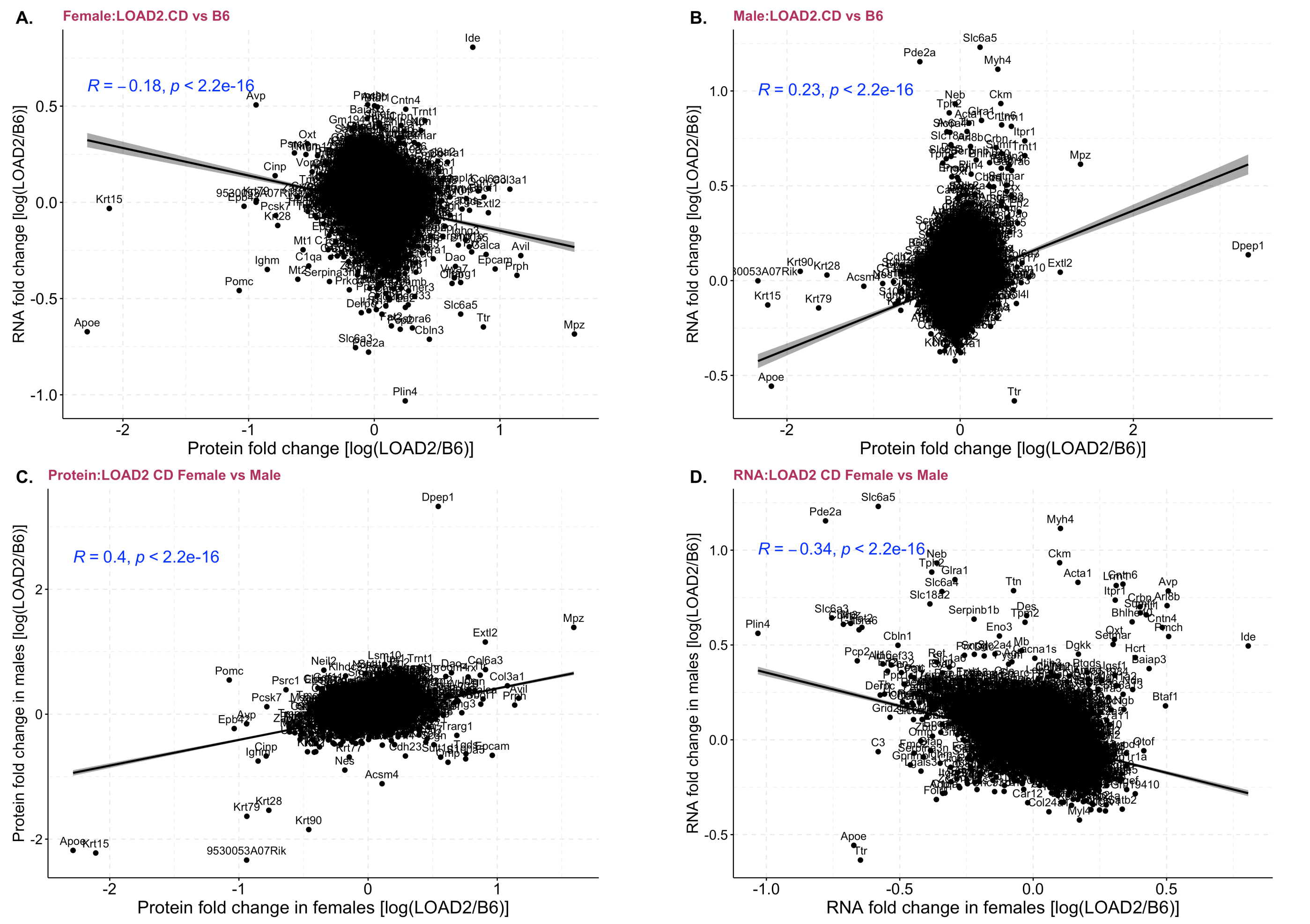


Enriched biological processes in genes with increased (A), decreased expression (B); and in proteins with increased (C), and decreased expression (D) in aged mice.



Increased levels of long-chain acylcarnitine's and reduced levels of spermidine in aged mice

Male and female mice exhibit similar proteomic changes but dissimilar transcriptomic changes



(A) Positive correlations between protein and mRNA changes in male, (B) Anti-correlation in females. (C) Protein changes in LOAD2 mice are generally the same in females and males. (D) RNA changes in LOAD2 mice do *not* match in males and females. CD refers to control diet.

Conclusions

- Integrative multi-omics analyses identified multiple dimensions of heterogeneity that together comprehensively explained the variance within the cohort and were associated with age, sex and high-fat diet.
- Factors associated with age and diet were overrepresented in immune response and metabolic processes as well as increased levels of long-chain acylcarnitine's and reduced levels of spermidine in aged and high-fat diet fed AD mouse models, similar to human AD.
- Proteomics and transcriptomics profiling capture different aspects of aging in the brain. We observed a negative correlation between protein and mRNA changes in female mice, similar to human AD cases.

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