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

Ravi S. Pandey1, K. Kotredes2, K. Borkowski3, D. Garceau4, A. Haber1, S. Mahmoudiandehkordi1, A. Shantaraman5, A. D. Duong6, N. Seyfried5, R. Kaddurah-Daouk1, M. Sasner2, G. R. Howell1, A. Oblak1, B. T. Lamb6, G. W. Carter1,2 for the MODEL-AD Consortium and the Alzheimer Disease Metabolomics Consortium

1The Jackson Lab. for Genomic Medicine, Farmington, CT; 2The Jackson Lab., Bar Harbor, ME; University of California, Davis, CA; 3Duke University School of Medicine, Durham, NC; 4Emory University School of Medicine, Atlanta, GA; 5Stark Neurosciences Res. Inst., Indianapolis, IN

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 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-omics omics in a cohort of mouse models expressing humanized Aβ and two genetic risk factors (APOE4 and Trem2+R49R) at multiple ages for both sexes. Data from metabolomics, proteomics, transcriptomics, and genomics were analyzed at single-omic level as well as integrated in an unbiased fashion; considering interaction between modalities using multi-omics factor analysis (MOFA). We also systematically aligned multimodal mouse data to relevant human studies cohort. Results: Multi-omics integrations identified major components of heterogeneity explaining the variance within the cohort and differentially associated with sex, age, 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 AD human. We also observed weak correlation between changes in RNA expression in mouse models compared to controls, similar to recent report 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 areas of variance 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 mRNAs profiling alone provide an incomplete picture of molecular mechanism of AD. In this study, we highlighted that assembling multi-omics measurements reveal interrelated pathological alterations in AD and the ability to identify biomarkers combinations that may inform clinical practice.

References

Methodology/analytical workflow

Humanage AD genes enriched in Aβ
Integrative strong risk variants meta-omics
Environmental risk Diet and Sex

Overview of multi-modal data and integrative analysis

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

Factor 5 Captures age-related heterogeneity

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

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.

Acknowledgements
The IJU/JAX/PITT MODEL-AD Center was established with funding from The National Institute on Aging, grant U54 AG045345-01.