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Understanding comorbid metabolic dysfunctions in Alzheimer's disease using the AD-BXDs

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Abstract

Background: Alzheimer's disease (AD) is a neurogenerative disease characterized by cognitive deficits. Cognitive decline in AD is often accompanied and preceded by non-cognitive comorbidities, including metabolic dysfunctions such as weight loss. Therefore, understanding how comorbid metabolic dysfunctions contribute to AD disease progression can provide useful insights into early disease risk detection and intervention.

Method: We investigated how genetics, diet, and sex interact to modify metabolic symptoms of AD using 39 mouse strains from the AD-BXD panel (Neuner et al., 2019, *Neuron*) at 4, 6 and 14 months of age. Mice were fed normal chow diet, or 45% high-fat diet (HFD) starting at ~2.5 months of age. We monitored food/water intake as well as the activity of mice over a period of five days, and measured metabolic phenotypes via indirect calorimetry, nuclear magnetic resonance, and glucose tolerance test. Plasma samples were collected and assayed for lipid panel, cytokines, and metabolism-related hormones to investigate molecular changes in the periphery. Heritability of metabolic traits were calculated, and heritable traits were mapped using GEMMA with appropriate covariates (Zhou and Stephens, 2012, *Nature Genetics*) to identify associated genetic variants.

Result: We observed a wide range of variations across the AD-BXD population in metabolic and cognitive responses to aging and diet. Overall, the presence of the 5XFAD transgene reduced lean and fat mass across the population. Aging exacerbated the loss of lean mass due to the 5XFAD transgene but does not have such interactive effect on percent fat mass. Genetic background significantly modifies the effect of the transgene on multiple phenotypes including body weight, sleep, and glucose tolerance. Responses to a HFD also differed by sex and AD genotype and are substantially modulated by gene-by-environment interactions across phenotypic domains. Both cognitive and metabolic phenotypes have moderate to high heritability, allowing us to identify genetic loci associated with these traits.

Conclusion: Our data characterizing metabolic and cognitive phenotypes from the genetically diverse AD-BXDs are important resources to study the role and origin of comorbidities in AD. Future studies on mechanism of the observed metabolic disruptions may lead to discovery of therapeutic targets to delay, prevent, or treat AD.