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High-fat diet generally exacerbates, but is sometimes protective against, cognitive dysfunction in female AD mice depending on genetic background

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Abstract

Background: Alzheimer's disease (AD) is highly complex, with individual genetic and environmental factors mediating disease risk and progression. There are also significant sex differences in aging and AD risk, and several common comorbidities (e.g. metabolic dysfunction) further adding challenges to understanding disease mechanisms and targeting potential treatment strategies.

Method: We recently developed a population of genetically diverse mice carrying the 5XFAD transgene (AD-BXDs; Neuner, et al. 2019). Because they model human genetic heterogeneity, AD-BXDs are ideally suited to investigate translationally-relevant genetic, environmental, and sex factors contributing to AD. Here, we used AD-BXDs to determine how genetics, diet, and sex interact to modify cognitive and metabolic symptoms of AD. We fed either normal chow diet, or 45% high-fat diet (HFD) starting at ~2.5mo of age, to 39 strains of AD-BXDs and nontransgenic littermates. We measured various metabolic and cognitive traits across their lifespan.

Result: There was extensive variation across the AD-BXD population in metabolic and cognitive response to aging, diet, and the 5XFAD transgene. In general, female mice were more susceptible to AD-related cognitive decline and metabolic dysfunction compared to males, and response to HFD differed by sex and AD genotype across phenotype domains. Female strains that were able to maintain body weight on HFD were less susceptible to AD-related cognitive decline, suggesting that HFD may be protective in some individual females. We identified a locus on Chr. 18 associated with susceptibility to diet-sensitized AD-risk that was specific to female mice, indicating that genetic control of response to HFD in AD is also distinct in females vs males.

Conclusion: Our results suggest that AD risk and progression depends on an interaction between sex, genetic background, and response to diet. We observed that females are more susceptible to AD- related cognitive decline and metabolic dysfunction when fed either chow or HFD, and we identified a novel genetic locus contributing to increased vulnerability to AD- and HFD-related cognitive decline in females. Future analyses aim to identify genetic and molecular targets that contribute to AD pathogenesis sensitized by sex and HFD that may be exploited to delay, prevent or treat AD.