NOVEL APOE4.TREM2*R47H MOUSE MODEL: BUILDING A BETTER TOOL FOR LATE-ONSET ALZHEIMER’S DISEASE

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ABSTRACT

Alzheimer’s disease (AD) is a debilitating neurodegenerative disorder. More than 46 million people are affected worldwide, with no effective treatment currently available. Of this AD population, those suffering from late-onset Alzheimer’s Disease (LOAD) represent the largest subset of dementia patients. Unfortunately, current animal models do not fully recapitulate LOAD, thus are not ideal for therapy development. To address this, the Model Organism Development and Evaluation for Late-onset AD consortium (MODEL-AD) has created a novel LOAD mouse carrying two common risk alleles, human APOE4, and the R47H allele of Trem2. Characterization of this model at young and advanced ages will reveal more appropriate disease mechanisms useful in the treatment of LOAD. This model will also serve as a backbone strain for the further addition of risk alleles identified from human LOAD patients to more properly represent the heterogeneity of the disease and better align phenotypes in the mouse to outcomes observed in the human patient population.

METHODS

Humanized APOE4 and the Trem2'R47H mutation, two prominent genetic risk factors for LOAD, were inserted into the genome of C57BL/6J mice to create the B6.APOE4.Trem2'R47H (B6J.hAT) model. Cohorts of B6J.hAT mice were established at JAX and IU and aged to 2, 6, 12, and 22 months prior to behavioral testing. At the JAX campus, in vivo behavioral and wellness assays measured activity (open field), frailty, grip strength, coordination (rotarod), and cognitive ability (spontaneous alternation). Repeated constrictively at Indiana University (IU) facilities were all behavior and physical phenotype. Additionally, in vivo MRI and PET studies using [18F]FDG and [84Cu]FlrPET were completed at IU. Post-mortem analyses at both sites included blood chemistry, brain immunohistochemistry, transcriptomics, and proteomics. Analyses of subsequent RNA sequencing data in combination with behavioral and molecular phenotypes has yielded additional insight into the transcriptional differences influencing animal health.

RESULTS

Over 24 months, B6J.hAT mice displayed progressively increasing frailty index scores, a measure of aging and vulnerability, and decreased survival. Similarly, decreases over time were observed in coordination (rotarod) and locomotion (open field) assays, however working memory (spontaneous alternation) remained intact. B6J.hAT and B6J.APOE4 mice showed decreased levels of total cholesterol, LDL, and HDL at multiple time points compared to control mice - an effect of human APOE alleles reported previously. PET data showed changes in glucose uptake over time in B6J.hAT mice, but MRI showed no gross abnormalities of the brain. RNA sequencing revealed age- and sex-related changes in B6J.hAT brain samples compared to controls. Differentially expressed genes were present in pathways central to AD pathogenesis, including metabolism, immunity, and mRNP processing. These expression changes appear to be most prominent in mice expressing Trem2'R47H. We also observed a novel splicing event in Trem due the R47H mutation. Decreased survival of B6J.hAT mice at 24 months was greater in females than males. PET data showed changes in glucose uptake over time in B6J.hAT mice, but MRI showed no gross abnormalities of the brain. RNA sequencing revealed age- and sex-related changes in B6J.hAT brain samples compared to controls. Differentially expressed genes were present in pathways central to AD pathogenesis, including metabolism, immunity, and mRNP processing. These expression changes appear to be most prominent in mice expressing Trem2'R47H. We also observed a novel splicing event in Trem due the R47H mutation.

Table 1. Differentially expressed genes across strains. RNAseq analysis of brains from 4-, 6-, and 14-month-old APOE4, Trem2'R47H, and APOE4.Trem2 mouse models. PET/MRI images were co-registered to Paxinos-Franklin atlas and 27 brain regions were extracted. Representative autoradiography and MRI images, with regional heatmaps shown.

CONCLUSIONS

The MODEL-AD consortium has established a new mouse strain to study the effects of two strong risk factors for LOAD. Characterization of this model is ongoing and will serve as a backbone strain for the further addition of LOAD risk alleles to more closely align phenotypes in the mouse to outcomes observed in human AD (see poster IP2-133, "Initial Characterization of Novel Mouse Models of Late Onset Alzheimer’s Disease Based on Human Genetic Associations." South Hall GH, July 15th, 2019). APOE-ε allele mice showed expected aberrant cholesterol levels. Age-dependent increases in frailty across all strains, however no significant differences in working memory. Phenotypic changes in both brain perfusion and metabolism by 8 months. Decreased survival of B6J.hAT mice at 24 months. In vivo imaging, transcriptomic, histological, and biochemical analysis continues on all time points for additional insight into the transcriptional differences influencing animal health.

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
- Alzheimer’s Drug Project: https://www.adp.org
- Alzheimer’s Association: https://www.alz.org
- Alzheimer’s Disease Cooperative Study: https://www.adcs.org
- Alzheimer’s Research Trust: https://www.artz.org
- Alzheimer’s Association Alzheimer’s Network: https://www.alz.org/alznet

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