Characterizing the APOE4/Trem2R47H Mouse Model for Late Onset Alzheimer’s Disease

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ABSTRACT

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder. More than 45 million people are affected annually, with no effective treatment currently available. Research into fully understanding the disease has been fuelled by animal models with familial AD (FAD) mutations, which accounts for 2% of the AD population. While these models have proved fruitful in understanding some of the baseline endophenotypes of AD, they have not been adequate to develop therapies or fully elucidate the biological processes leading to AD. One component of this lack of effective therapeutic is due to the inability to fully reproduce the AD phenotypes in these animals.

Here, the MODEL-AD consortium presents a new mouse model for Late Onset Alzheimer’s disease (LOAD). We have developed a model carrying the two highest genetic risk factors for LOAD, the most common and strongest risk factor, APOE4, and the R47H allele of Trem2. To characterize this model, we have looked at three time points to understand the aging phenotype of these APOE4/Trem2R47H mice. At these three time points, mice were exposed to a battery of behavioral assays, analysis of continuous activity monitoring, frailty assessment, motor function, diet, strength, spontaneous alternation, rotod, delayed spatial novelty, and episodic memory. One consistent finding was a decrease in body weight in male APOE4/Trem2R47H mice at both time points. As such, mice were examined for hallmark signs of AD, such as beta-amyloid plaques and neurofilibrillary tangles, as well as levels of neuroinflammation, vascular remodeling, and neurodegeneration.

The development of this new model will enable us to gain a deeper understanding into the two of the genetic factors contributing to LOAD. Our goal is that the new models will be used to better understand the pathogenesis of AD as well as determining if new therapies or actions can be taken to impede the onset of AD. For more information see the AD Curriculum.

Deep phenotyping testing paradigm and histological analysis

Further Information

- MODEL-AD: www.model-ad.org
- AMP-AD Knowledge Portal: http://www.amp.org/ampad
- JAX AD model: https://www.jax.org/strain/alzheimer
- AlzForum research models: http://www.alzforum.org/research-models/ALZ

Background

Behavioral Characterization

- C57BL/IJ
- APOE4
- Trem2
- APOE4/Trem2

- 2 months
- 12 months

Locomotor Activity: At 12 months, mice appeared to have age-related dependent reductions in total distance traveled in the open field (60x90 cm2). Nsk yum release revealed a significant effect of genotype or sex. Motor Coordination: There was no age-related dependent reduction in motor performance in the rotarod. The effects of Trem2 and APOE4 were maintained balance on the rotarod. Inflammatory factors: One consistent finding was in APOE4/Trem2R47H mice, which was an increase in motor impairment was attenuated by Trem2 males of satee and female mice of a sex effect. Frailty Index & Core Body Strength: There was a significant reduction in body temperature with age. However, in females more was observed. Trem2 males and females were APOE4/Trem2R47H mice at 12 months of age did not show the expected age-related increase in frailty measures or reduction in body temperature relative to APOE4/Trem2 alone.

Non-essential Fatty Acids

- Male
- Female

Histological imaging and analysis methods

- Hematoxylin & Eosin
- GFAP
- Iba1
- DAPI
- AT8
- H&E

Conclusion

A comprehensive characterization revealed the expected age-dependent alterations across phenotypes with no effect of genotype up to 12 months of age which would be anticipated in a model of LOAD. Further testing at 18mo of age is in progress. While there are no gross statistical differences between regions at all, around 20% in PET and Autoradiographic analysis continues for additional time points. In vivo imaging, testosterone, histological, and biochemical analysis continues on all time points.

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