Novel mouse models of late-onset Alzheimer’s disease based on GWAS

Michael Sasner\(^2\) on behalf of the IU/JAX MODEL-AD consortium\(^{1,3}\)

\(^{1}\)Stark Neuroscience Research Institute, Indianapolis, Indianapolis, Indiana, USA; \(^2\)The Jackson Laboratory, Bar Harbor, Maine USA; \(^3\)Sage Bionetworks, Seattle, Washington, USA

Abstract
The Alzheimer’s Disease (AD) patient population consists almost entirely (~98%) of the late-onset form of AD (LOAD). However, most mouse models currently used to develop therapies for AD are based on familial AD (fAD) mutations due to the lack of appropriate mouse models for LOAD. The goal of the IU/JAX MODEL-AD consortium was to develop mouse models for LOAD leveraging genetic information from GWAS. The consortium focused on developing mouse models with LOAD-like pathologies, and performed an in-depth characterization of more than 100 mouse models. A central focus was on developing LOAD mouse models using the APOE4/Trem2*R47H mutation in the mouse genome, which was previously identified by GWAS using data from the ADNI and ADSP projects. These variants were then engineered into the APOE4/Trem2 model to increase the risk of developing LOAD-like phenotypes. We have created models including SNPs corresponding to risk variants in AD and PLGC2, and knockouts of mouse APOE3, ABCA7, and Ceacam1. We have developed LOAD models by altering the three amino acids that differ between human LOAD patient populations. We used CRISPR to target the first coding exon. A founder with a deletion of 387bp was selected. We used CRISPR to engineer this mutation into the homologous region of the mouse gene to humanize this variant, as common human SNP to a mouse KO, resembling rare human LOF variants.

Modeling Strategy
Existing animal models (e.g., APP/PS1, APOE4/PSEN1; these model only a small percentage of the patient population. We used CRISPR to target the first coding exon. A founder with a deletion of 387bp was selected. We used CRISPR to engineer this mutation into the homologous region of the mouse gene to humanize this variant, as common human SNP to a mouse KO, resembling rare human LOF variants.

Both rare and common ABCA7 variants are associated with AD
The first large GWAS of LOAD identified a genetic variant in the PLECS2 gene associated with amyloid accumulation in the ADNI cohort. The PLECS2 locus has been previously associated with AD risk (Chen et al., Nature Genetics 2017). PLGC2 is a protein interacting network containing AD risk genes and is highly expressed in microglia. Analysis of ADSP whole-exome data revealed a novel PLGC2 risk variant rs17490044, which is highly conserved across species and predicted to be deleterious by Polyphen and SIFT.

A rare PLGC2 missense variant is associated with AD in the ADSP cohort
Two rare variants in PLGC2 have previously been associated with AD risk (Chen et al., Nature Genetics 2017). PLGC2 is a protein interacting network containing AD risk genes and is highly expressed in microglia. Analysis of ADSP whole-exome data revealed a novel PLGC2 risk variant rs17490044, which is highly conserved across species and predicted to be deleterious by Polyphen and SIFT.

Phenotyping of new models
These models are underlining a primary phenotyping screen as homologues for all three disease models (APOE4 and Trem2/R47H). A more robust model battery will be developed to assess mouse models of AD based on human APOE4 and APOE4/Trem2/R47H mice. These models may be used to identify new therapeutic targets for AD and to develop new pheno-screens to put clinical models of AD into a deep phenotyping pipeline, in order to test the hypotheses that these models are emerging therapies for AD.

Further information
- MODEL-AD: www.model-ad.org
- Amy-AD Program: http://www.synap.org/amyad
- JAX AD models: https://www.jax.org/alzheimers
- AZFAM research models: http://www.azfarm.org/research-models

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