Genetic diversity differentially regulates molecular mechanisms of brain aging under normal and pathological conditions

Aslı Uyar, Kristen D’Onos, Kelly J Keezer, for the MODEL-AD Consortium
Indiana University, Indianapolis, IN; The Jackson Laboratory, Bar Harbor, Maine 04609; University of Pittsburgh, Pittsburgh, PA; Sage Bionetworks, Seattle, WA

BACKGROUND
- Genetically diverse mouse strains have varying life-spans and varying brain-aging hallmarks under normal conditions.
- Alzheimer’s Disease (AD) mouse models on diverse genomic backgrounds also show heterogeneity in AD-relevant neuropathological and molecular phenotypes.
- In our previous studies, we generated mouse models carrying mutant APP and PS1 alleles (APPPS1/2) on eight diverse mouse strains, and observed significant strain-specific differences in amyloid deposition, vascular phenotypes, neurodegeneration and transcriptomic signatures.
- Among those, wild-derived strains WSB/Ei (WSB) and PWKPhj (PWK) gained further attention in AD research.

In this study, we aim to identify strain specific transcriptomic signatures associated with the deviation from normal brain aging trajectories in presence of amyloid pathogenesis.

METHODS
- Wild-derived strains were originally generated via a backcross strategy, and all PWK/APP-P51 and WSB/APP-P51 used in this study were congeneric.
- Cohorts of male and female PWK/APP-P51 and WSB/APP-P51 mice and wild-type (WT) controls were aged to 4- and 14-months, and brain hemispheres were processed for RNA-Seq transcriptomics and neuropathological assessment.

Study design

<table>
<thead>
<tr>
<th>WSB</th>
<th>WT and APP-P51</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKW</td>
<td>4mo</td>
</tr>
<tr>
<td>PKW</td>
<td>14mo</td>
</tr>
</tbody>
</table>

Approximate human life phase equivalence of mouse ages 4- and 14-months is 24- and 47-years old, respectively.

In both strains:
- 14-month-old wild-type mice were compared to 4-month-old wild-type controls to assess brain aging under normal conditions, and
- 14-month-old APP-P51 mice were compared to 4-month-old wild-type group to assess aging in presence of amyloid pathology (n=12).

Differentially expressed genes were identified and gene set enrichment analysis were performed to determine gene modules and biological pathways associated with brain aging in health and disease.

CONCLUSIONS
- This study suggests that molecular mechanisms of brain aging under normal conditions is modulated by genetic background, and is associated with the response to amyloid pathogenesis.
- Our findings suggest a potential link between aging-associated inflammatory state in wild-type WSB mice and elevated neuronal damage in amyloid pathogenesis, and between preservation of cellular communication in the brain of aged PWK mice and neuronal resilience.

FURTHER INFORMATION
- MODEL-AD: model-ad.org
- AD Knowledge portal: adknowledgeportal.org
- AD Data Explorer: model-adexplorer.org

ACKNOWLEDGEMENT
MODEL-AD was established with funding from The National Institute on Aging (U54 AG056345)