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

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MODEL-AD
Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease

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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 (APP^{swe},$PS1^{de9}$) 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/Eij (WSB) and PWK/Phj (PWK) gained further attention in AD research.
- Compared to the *APP/PS1* model on standard C57BL/6J (B6) mice:
  - WSB.*APP/PS1* was associated with elevated neuronal and vascular impairments;
  - PWK.*APP/PS1* was shown to be resilient to neurodegeneration in presence of amyloid deposition.

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/PS1* and WSB.*APP/PS1* used in this study were congenic.
- Cohorts of male and female PWK.*APP/PS1* and WSB.*APP/PS1* 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

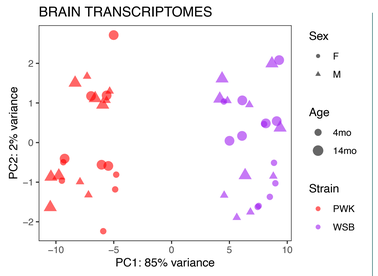
Approximate human life phase equivalence of mouse ages 4- and 14-months is 24- and 47-years old, respectively.

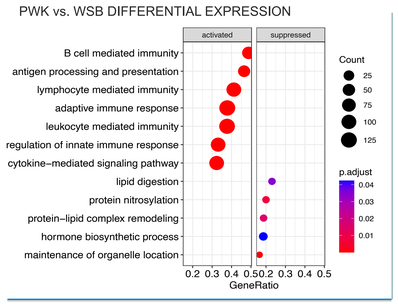
In both strains:

- 14-months-old wild-type mice were compared to 4-months-old wild-type controls to assess brain aging under normal conditions, and
- 14-months-old *APP/PS1* mice were compared to 4-months-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.

Gene expression signatures in the brain of wild type PWK and WSB mice



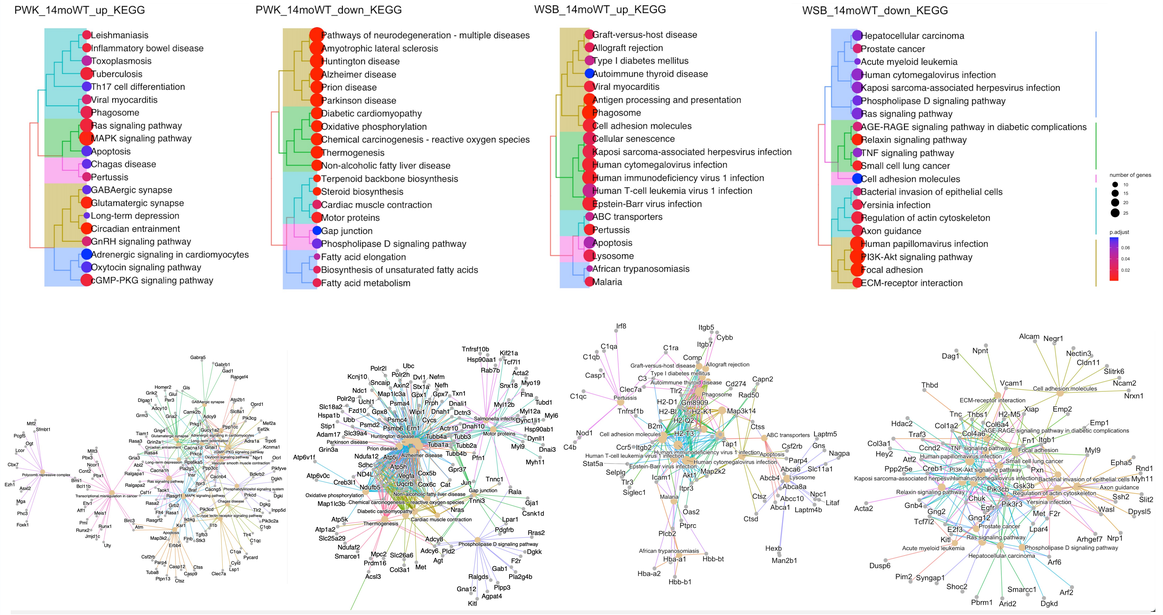


- PCA shows strong separation of RNA-Seq transcriptomic profiles by strain background with 85% variance represented in PC1.
- Differential expression (DE) analysis identified
  - 1829 up-regulated and
  - 1973 down-regulated genes

  in WT PWK mice compared to WT WSB mice (*padj < 0.001 & log2FC > 0.5*).
- GSEA showed strong up-regulation of innate and adaptive immune system pathways in PWK.

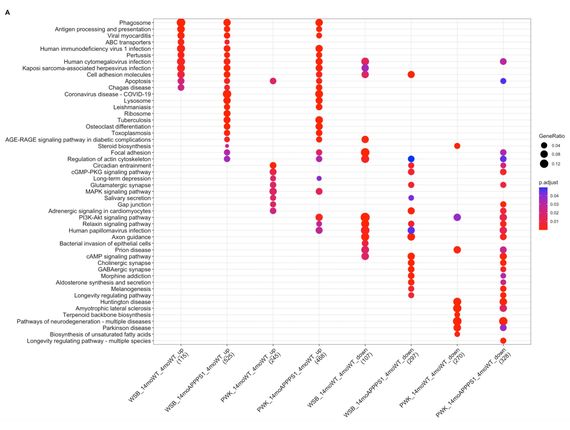
Strain specific gene expression changes associated with brain aging

14-months-old WT vs. 4-months-old WT

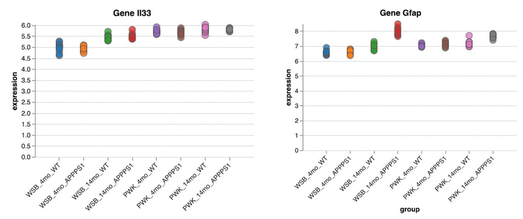


- Wild-type aging signatures were mainly strain-specific with a strong up-regulation of immune response in WSB, and up-regulation of metabolic and signaling pathways in PWK.
- Varying levels of amyloid plaques deposition was observed in the brain of both WSB.APP/PS1 and PWK.APP/PS1 mice.
- In presence of amyloid, consistent up-regulation of microglia genes and an elevated immune response was observed.
- Down-regulated genes were enriched in synaptic function in WSB, and in pathways of neurodegeneration in PWK.

Age related and amyloid response related pathways



Gene expression levels



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: modeladexplorer.org

ACKNOWLEDGEMENT

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