Distinct mouse models correspond to distinct AD molecular subtypes

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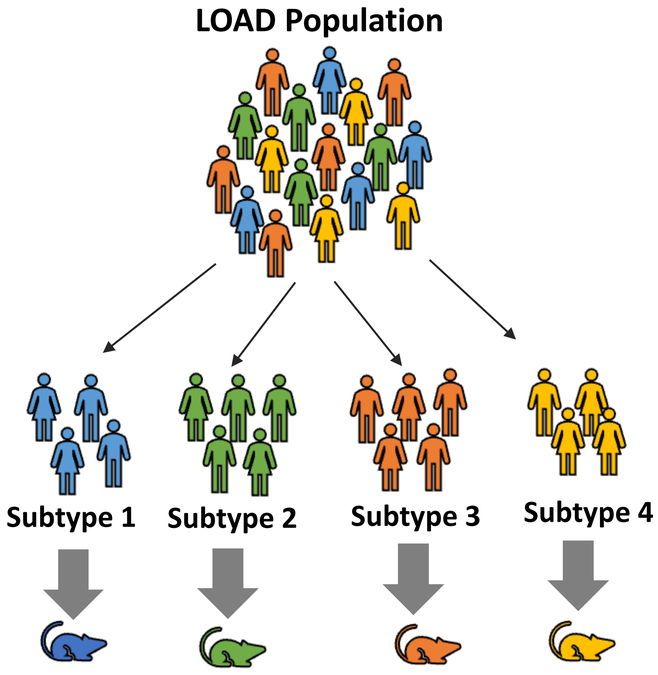
MODEL-AD

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

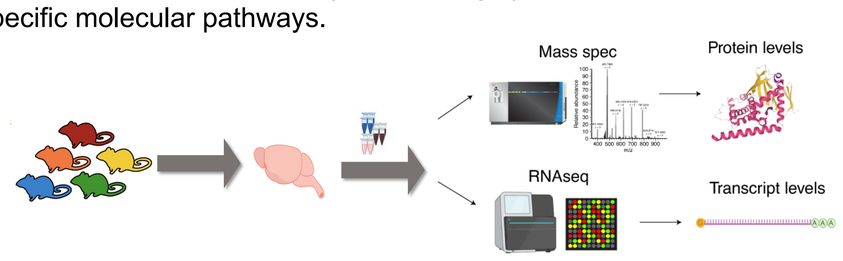
OBJECTIVE

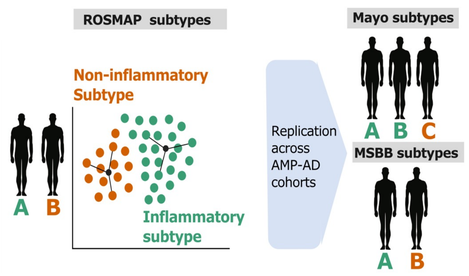
Alzheimer's disease (AD) is a complex, multifactorial pathology with high heterogeneity in biological alterations. Our understanding of cellular and molecular mechanisms from disease risk variants to various phenotypes is still limited. Mouse models of AD serve as indispensable platforms for comprehensively characterizing AD pathology, disease progression, biological mechanisms, and cognitive performance. However, selection of the right model in preclinical research and translation of findings to clinical populations are intricate processes that require identification of pathophysiological resemblance between model organisms and humans. Many existing clinical trials that showed promising efficacy in one particular mouse model later do not align with human trial results, assuming that study participants had consisted of a heterogeneous group of participants across many AD subtypes and individual animal models may only recapitulate features of a subgroup of human cases. To improve interspecies translation, it is necessary to comprehensively compare molecular signatures in AD mouse models with subgroup of human AD cases with distinct molecular signatures.



METHODOLOGY

We performed transcriptomic and proteomics analysis on whole brain samples from mouse models carrying LOAD risk variants. To assess the human disease relevance of LOAD risk variants in mice, we determined the extent to which changes due to genetic perturbations in mice matched those observed in human AD subtypes and disease stages of AD in the ROS/MAP, Mayo, and Mount Sinai Brain Bank (MSBB) cohorts. Gene sets in within these disease subtypes are highly co-expressed and represent specific molecular pathways.



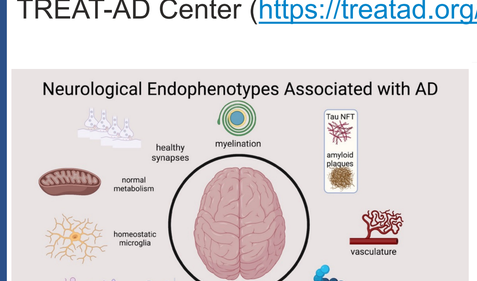


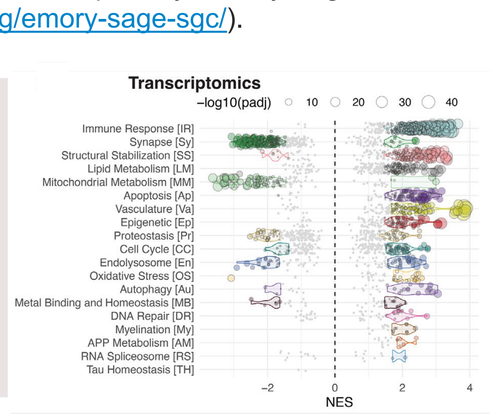
Molecular AD subtypes in ROS/MAP, Mayo, and MSBB cohort identified by Milind et al. [1]

Metrics	Subtype A	Subtype B		Subtype C	
		B1	B2	C1	C2
Compared to the Blalock signatures of AD	Atypical	Intermediate		typical	
Ab- and tau-related pathways	microtubule associated protein tau (*MAPT*)–activity predominant			Ab activity predominant	
neuronal activity	vulnerable to synaptic excitation			vulnerable to synaptic depression	
immune system activities	Downregulated		upregulated	up-regulated	

Molecular AD subtypes in the PHG brain region from the MSBB cohort identified by Neff et al. [2].

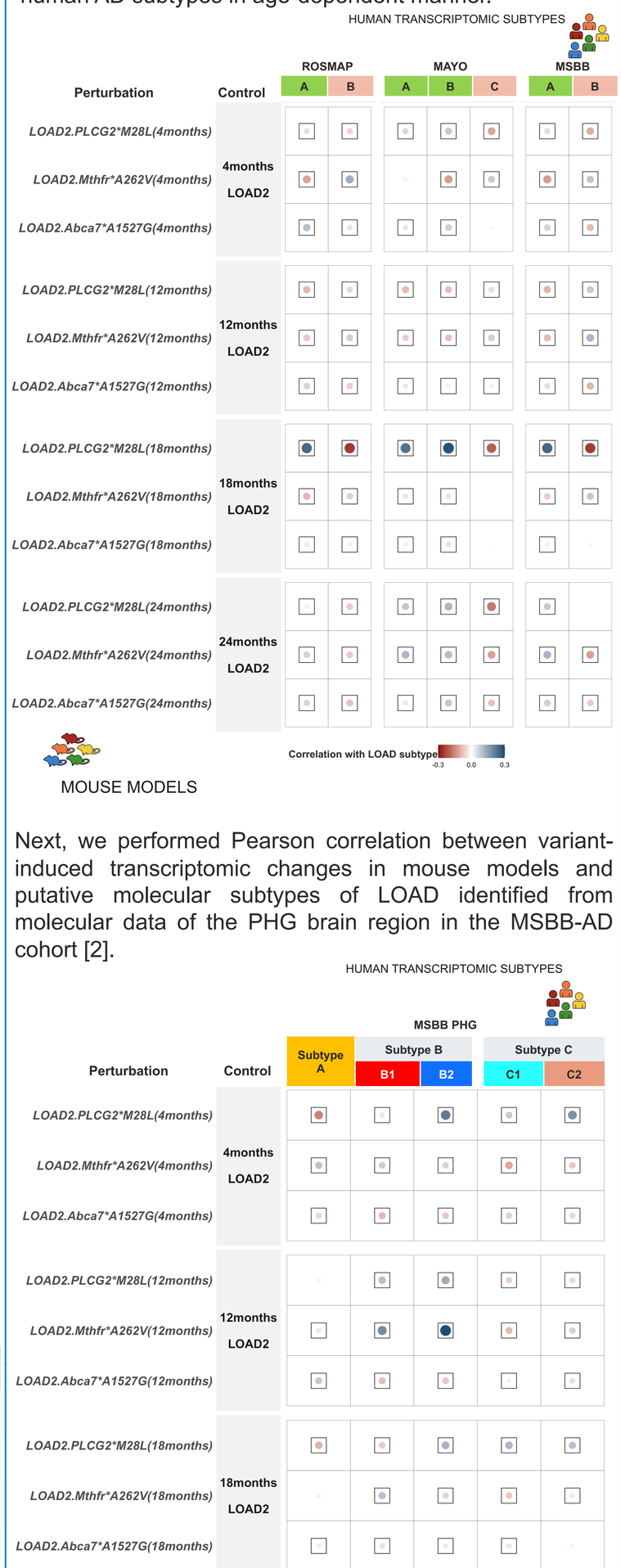
Next, we also annotated transcriptomic changes in AD subtypes with 19 distinct AD biological domains [3] developed by Emory/Sage/SGC/JAX TREAT-AD Center (https://treatad.org/emory-sage-sgc/).





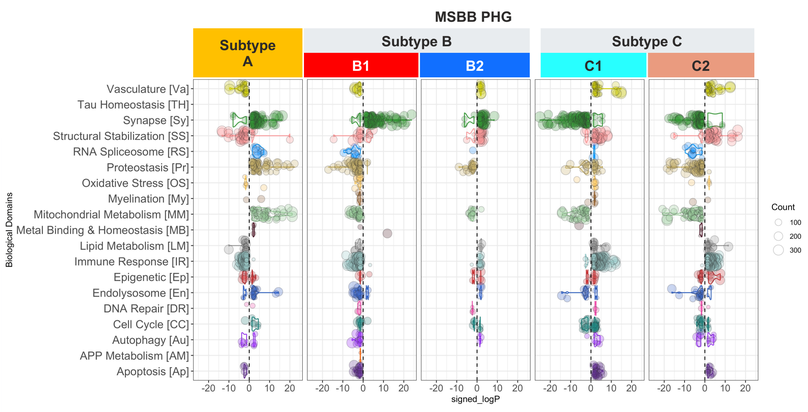
RESULTS

We first performed Pearson correlation between variant-induced transcriptomic changes in mouse models and molecular subtypes of LOAD subtypes identified for all three AD study cohorts (ROS/MAP, Mayo, and MSBB) [1] and identified that distinct mouse models match to distinct human AD subtypes in age-dependent manner.

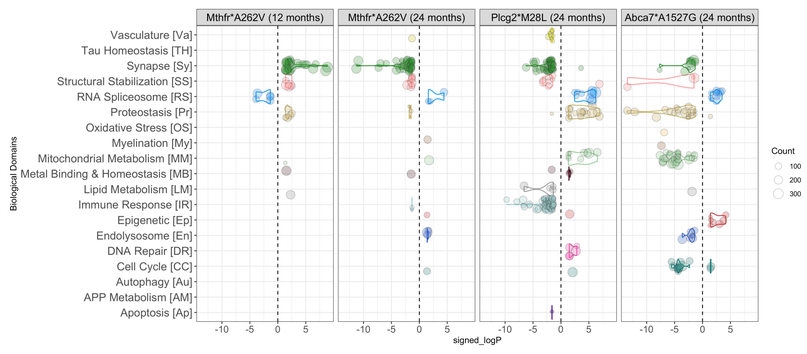


Next, we performed Pearson correlation between variant-induced transcriptomic changes in mouse models and putative molecular subtypes of LOAD identified from molecular data of the PHG brain region in the MSBB-AD cohort [2].

Next, we annotated transcriptomic changes in these molecular subtypes of LOAD identified from molecular data of the PHG brain region in the MSBB-AD cohort with 19 distinct AD biological domains [3]. We observed distinct perturbation in AD associated biological processes in distinct AD subtypes.



We also annotated transcriptomic changes in selected mouse models that showed strong significant positive correlations with molecular subtype B and C with AD biological domains [3].



SUMMARY

- In this study, we highlighted that mouse model of AD may match to a particular subset of human AD subtypes but not all subtypes simultaneously, and that risk for these subtypes may be influenced by distinct AD genetic factors.
- Mouse models with the human AD risk variant *Mthfr*A262V* demonstrated a strong association with non-inflammatory AD subtypes at a young age and exhibited transcriptomic changes similar to inflammatory AD subtypes at an older age.
- Annotation of AD subtypes with biological domains identified distinct changes in multiple AD associated pathways across AD subtypes.
- Additional work toward validating and better understanding the role of each subtype key regulator in its matching mouse model will provide great value and have a great impact on future studies of AD.

REFERENCES

1. Milind N, Preuss C, et al. Transcriptomic stratification of late-onset Alzheimer's cases reveals novel genetic modifiers of disease pathology. PLoS Genet. 2020 Jun 3;16(6):e1008775. doi: 10.1371/journal.pgen.1008775. PMID: 32492070.
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3. Cary GA, Wiley JC, et al. Genetic and multi-omic risk assessment of Alzheimer's disease implicates core associated biological domains. Alzheimers Dement (N Y). 2024 Apr 22;10(2):e12461. doi: 10.1002/trc2.12461. PMID: 38650747.

FURTHER INFORMATION

- MODEL AD: www.modelad.org
- AD Knowledge portal: https://adknowledgeportal.synapse.org/
- AD Data Explorer: https://modeladexplorer.org
- AlzForum research model: http://www.alzforum.org/research-models

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