A Novel Systems Biology Approach to Evaluate Mouse Models of Late Onset Alzheimer's Disease: nCounter Mouse AD Panel

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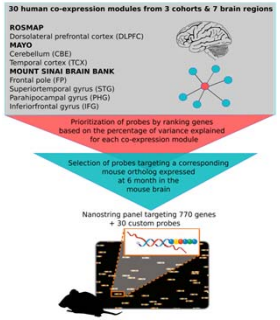
MODEL-AD
Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease

ABSTRACT

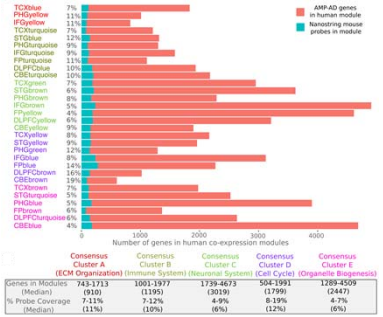
Background: Late-onset Alzheimer disease (LOAD) is the most common cause of dementia worldwide. Despite recent efforts, there is a lack of predictive animals models that can be used to study the progressive neurodegenerative disorder. This is partly due to the cross-species gap presenting a major challenge for translating molecular data between human and mouse.
Method: Here, we developed a novel systems biology approach to align human post mortem brain transcriptome data with key mouse transcripts to evaluate novel LOAD disease mouse models in a highly reproducible manner. A total of 30 harmonized co-expression modules derived from 2,114 human samples across seven brain regions and three research studies was used to create a molecular catalog of LOAD associated processes. A novel NanoString gene expression panel composed of 770 mouse gene probes was designed to rapidly and effectively correlate mouse samples with key human disease processes and pathways. Comprehensive comparison with full transcriptome data from same-sample RNA-seq was performed to assess platform specific effects.
Results: Analysis of two LOAD mouse models, APOE4 and Trem2*R47H (137 samples) at different ages (2-14 months) showed an overlap with distinct human co-expression modules linked to specific disease associated pathways, including immune related and DNA-repair pathways. Cross-platform comparison between the novel nCounter Mouse AD panel with RNA-seq data shows a robust and strong correlation between mouse gene expression changes independent of platform related effects.
Conclusion: Taken together, we show that the novel Mouse AD expression panel offers a rapid, cost-effective and highly reproducible approach to assess disease relevance of novel LOAD mouse models.

NanoString nCounter MOUSE AD PANEL



OVERVIEW nCounter PANEL

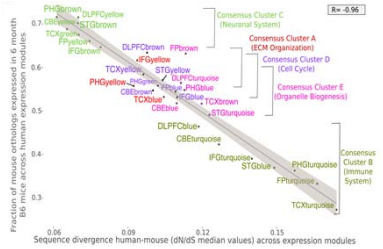
- Coverage of 770 selected mouse NanoString probes for 30 human co-expression modules
- Size and number of human co-expression modules differs across brain regions and cohorts resulting in a varying degree of probe coverage for each co-expression module



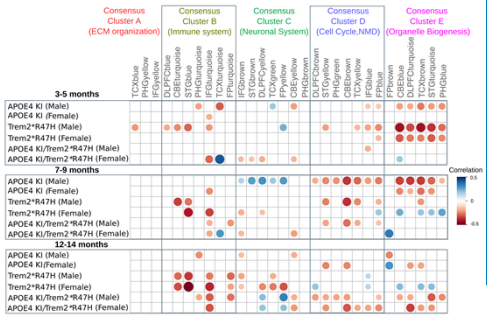
	Consensus Cluster A (ECM Organization)	Consensus Cluster B (Immune System)	Consensus Cluster C (Neuronal System)	Consensus Cluster D (Cell Cycle)	Consensus Cluster E (Organelle Biogenesis)
Genes in Modules (Median)	743-1713 (910)	1001-1977 (1195)	1739-4673 (3019)	504-1991 (1799)	1289-4509 (2447)
% Probe Coverage (Median)	7-11% (11%)	7-12% (10%)	4-9% (6%)	8-19% (12%)	4-7% (6%)

HUMAN TO MOUSE COMPARISON

- Human-mouse sequence divergence (median dN/dS values) is inversely correlated with the fraction of genes expressed in 6months B6 mouse brains for human co-expression modules

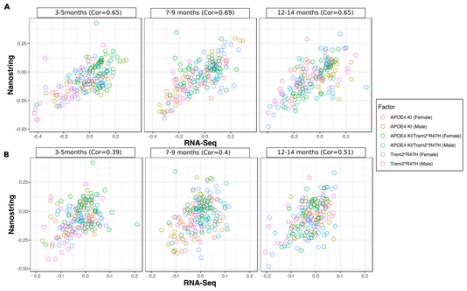


- Circles correspond to significant (p<0.05) positive and negative correlations with human co-expression modules for three mouse models carrying two LOAD associated risk variants. See also **Poster P2-131** on the APOE4.TREM2*R47H model.
- Human co-expression modules are ordered into Consensus Clusters describing major sources of AD-related alterations



PLATFORM COMPARISON

- (A) Correlation between the RNA-Seq and NanoString platforms were high across all age groups
- (B) Alignment of human and mouse modules based on the expression of all genes within each modules showed a weaker range of correlations when compared to transcripts covered by the 770 NanoString probes



CONCLUSIONS

- Novel nCounter Mouse AD panel offers a rapid, cost-effective and highly reproducible approach to assess disease relevance of potential LOAD mouse models .

. For further information, please see

- MODEL AD: www.modelad.org
- AMP-AD Knowledge portal: www.ampadportal.org
- Jax AD models: https://www.jax.org/alzheimers
- AlzForum research models: http://www.alzforum.org/research-models

Acknowledgements

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