

MODEL-AD

Bioinformatics and Data Management Core

Greg Carter (Head) The Jackson Laboratory

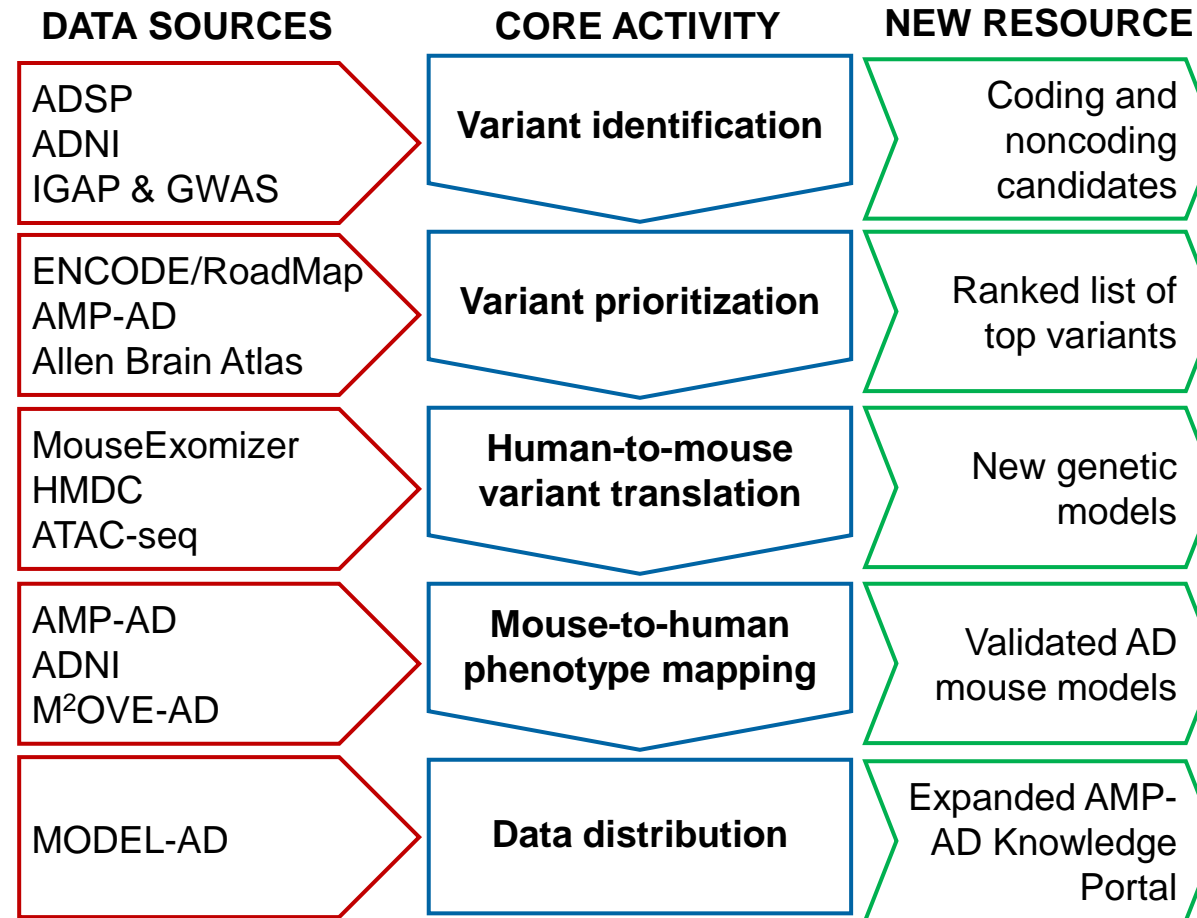
Ali Mortazavi (Head) University of California, Irvine

Lara Mangravite (Co-Head) Sage Bionetworks

Andrew Saykin (Co-Head) Indiana University



Bioinformatics Overview

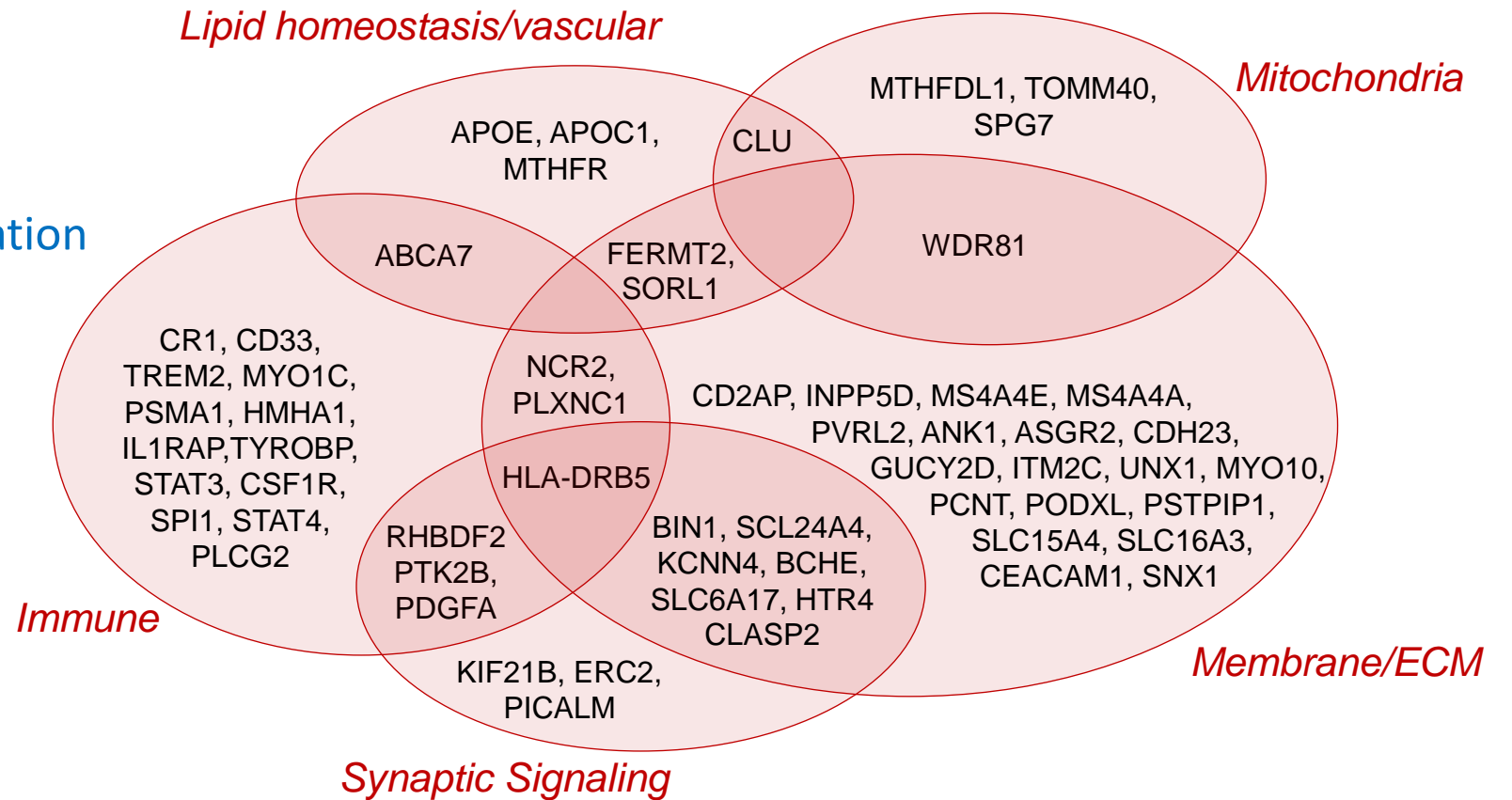


Variant Prioritization

Systematic assessment of LOAD loci

- Significance in multiple studies
- Predicted effect on function
- Human-mouse sequence conservation
- Differential expression in AD
- Noncoding variant effects

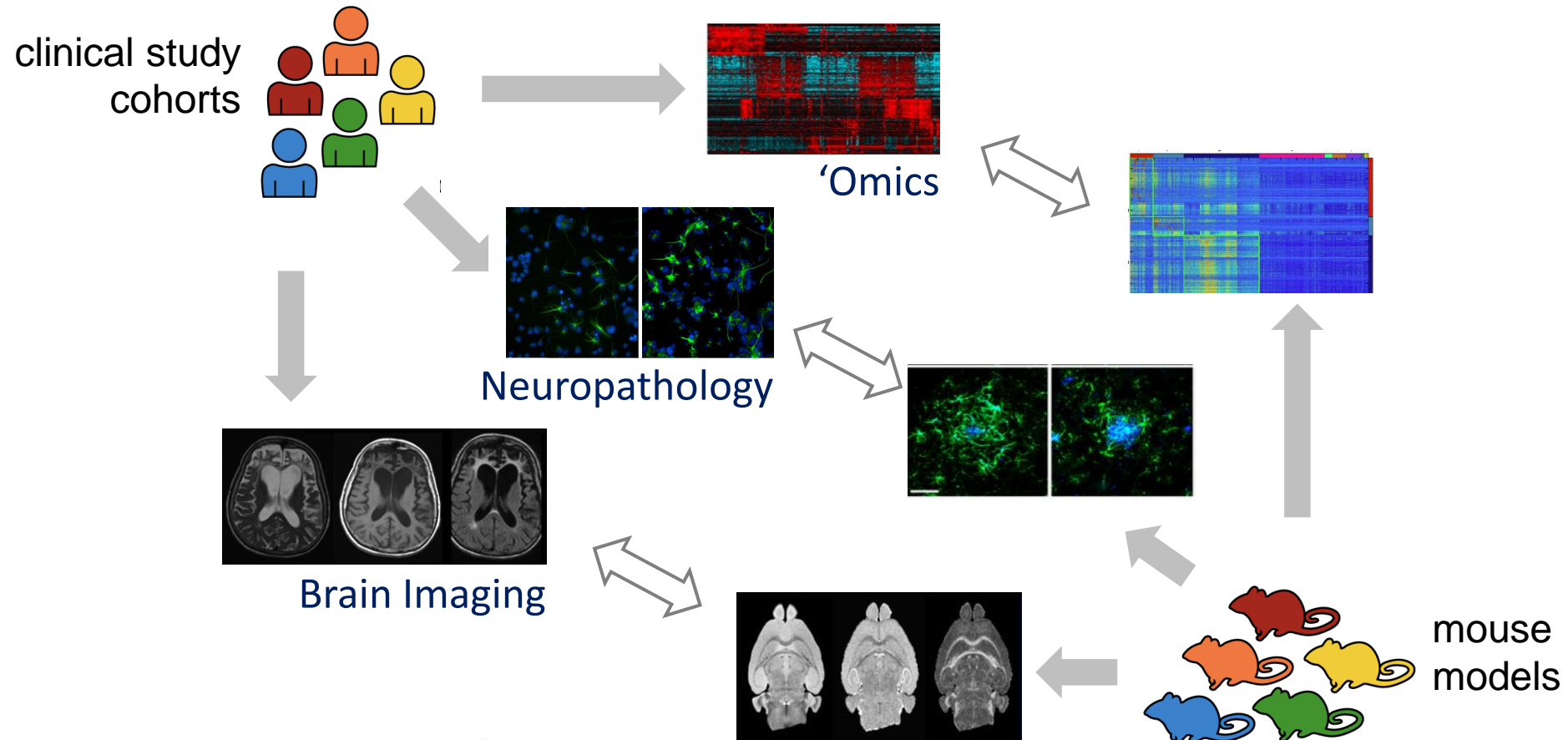
➤ Ali Mortazavi, UCI BDMC






Variant Summary Metrics

Gene	significant association	SNP/gene replication	pathogenic	conserved	differential expression in AD	AD biology
<i>EXO5</i>	✓	✓	✗	✓	↓	?
<i>CLASP2</i>	✓	✓	✓	✓	↓	✓ Reelin Signaling
<i>MS4A6E</i>	✓	✓	✗	✗	?	?
<i>SORL1</i>	✓	✓	✓	✓	↓	✓ Retromer Trafficking
<i>PLCG2</i>	✓	✗	✓	✓	↑	?
<i>MAPT</i>	✓	✓	✗	✗	✗	✓ Tau pathology
<i>MTMR4</i>	✓	✓	✓	✓	↓	✓ TGF-beta signaling
<i>SHC2</i>	✓	✗	✓	✗	✗	?

Cross-Species Phenotype Alignment

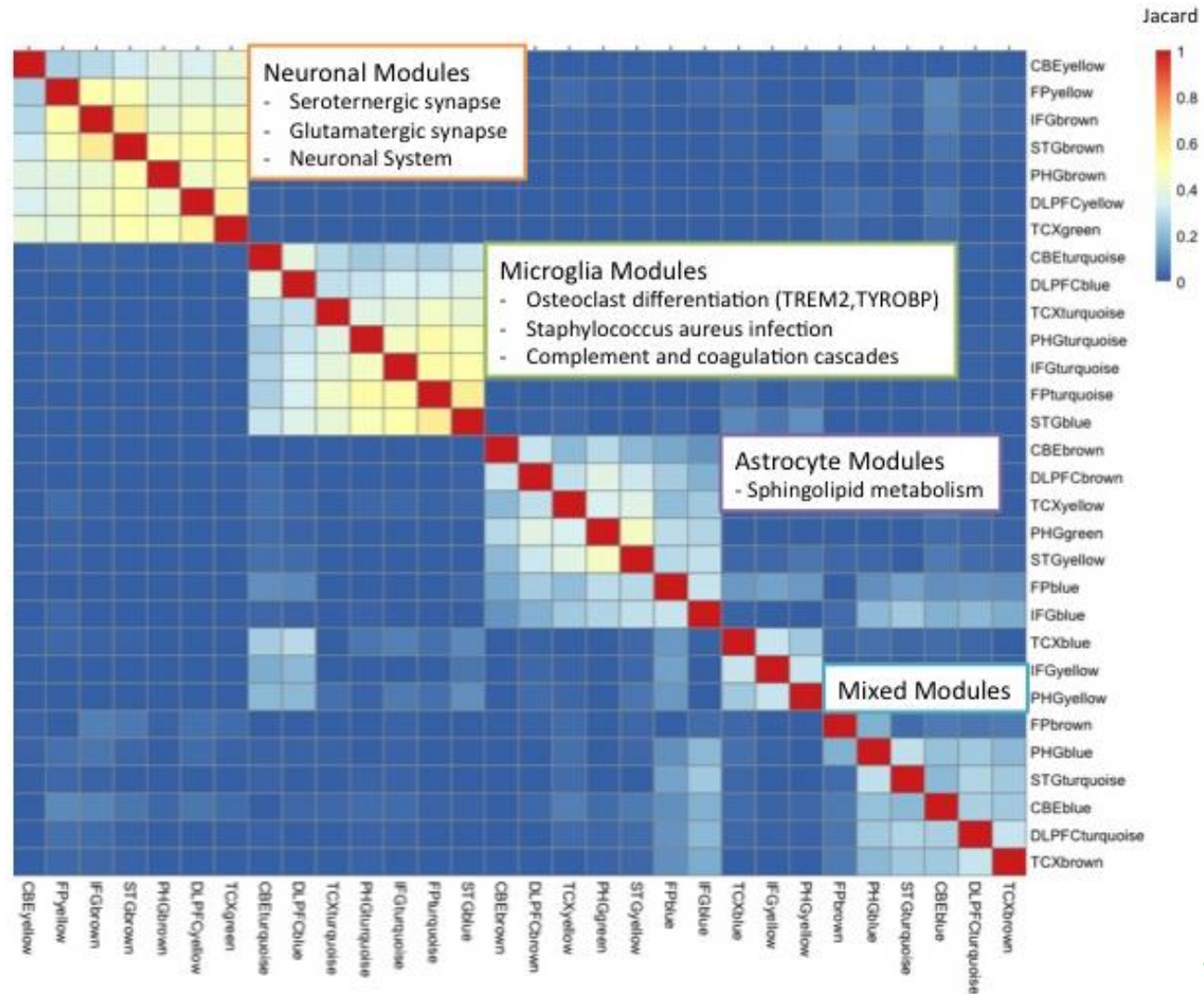


Human Genomics of AD via AMP-AD

Study	N	Brain Regions
ROS/MAP	700	 dorsolateral prefrontal cortex
Mt Sinai Brain Bank	300	 frontal pole superior temporal gyrus parahippocampal gyrus inferior frontal gyrus
Mayo Clinic	270	 cerebellum temporal cortex

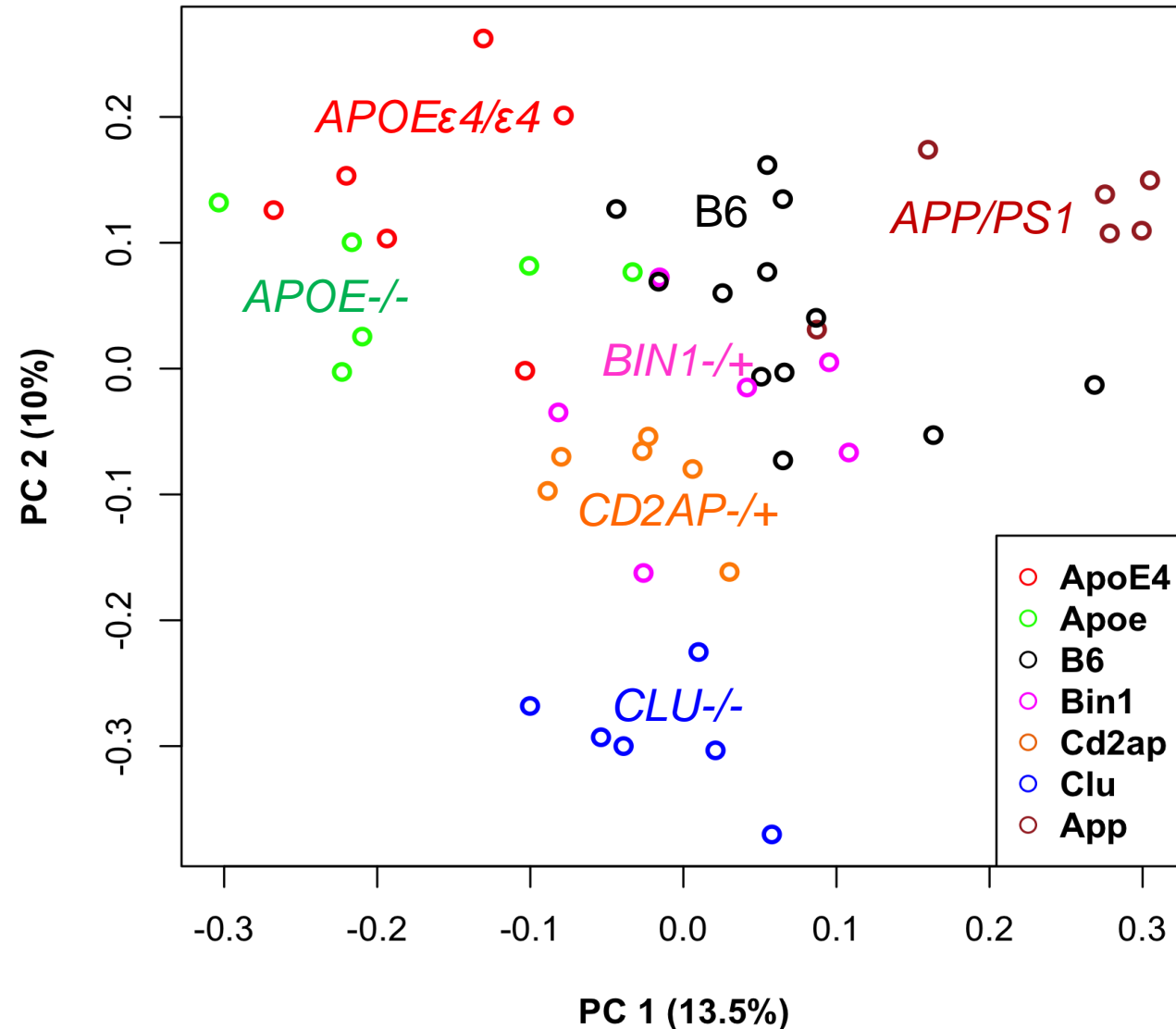
AMP-AD Knowledge Portal

AMP-AD Gene Modules

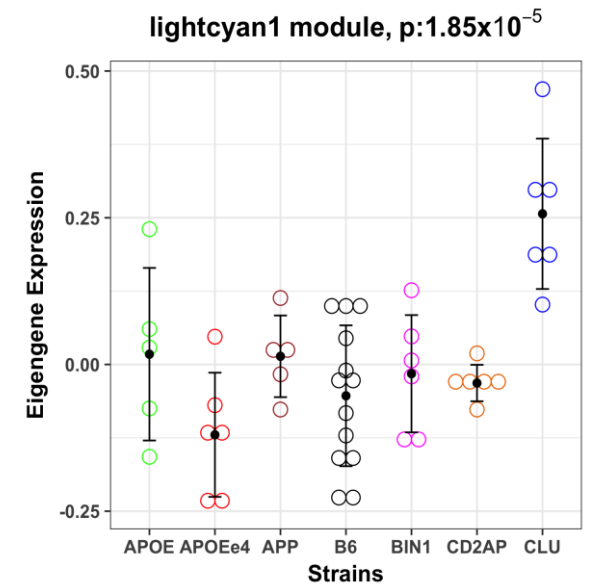
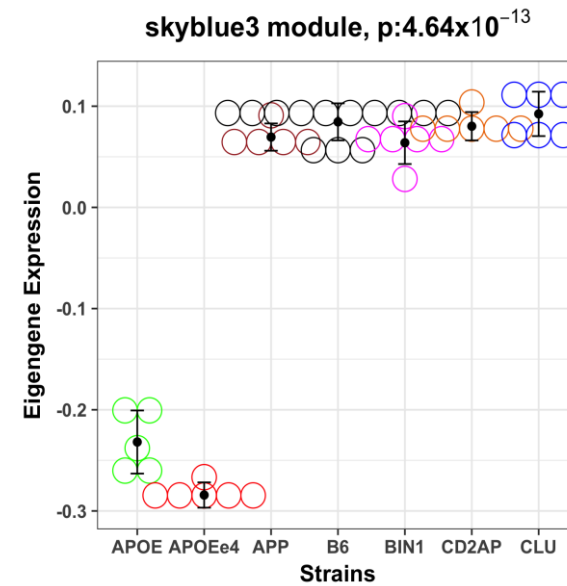
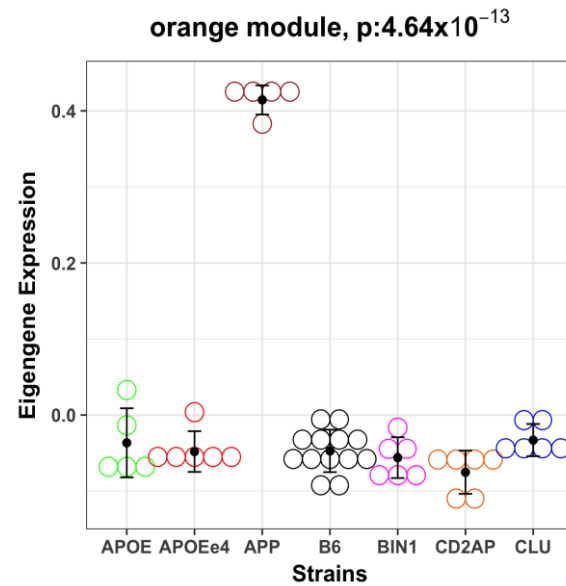
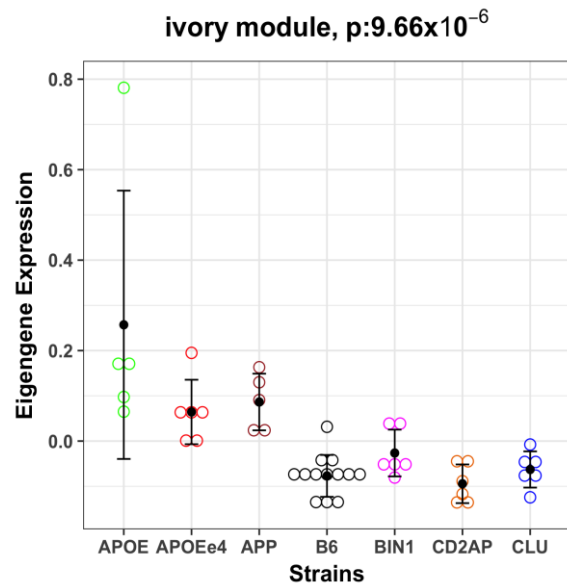


Ben Logsdon
Sage Bionetworks

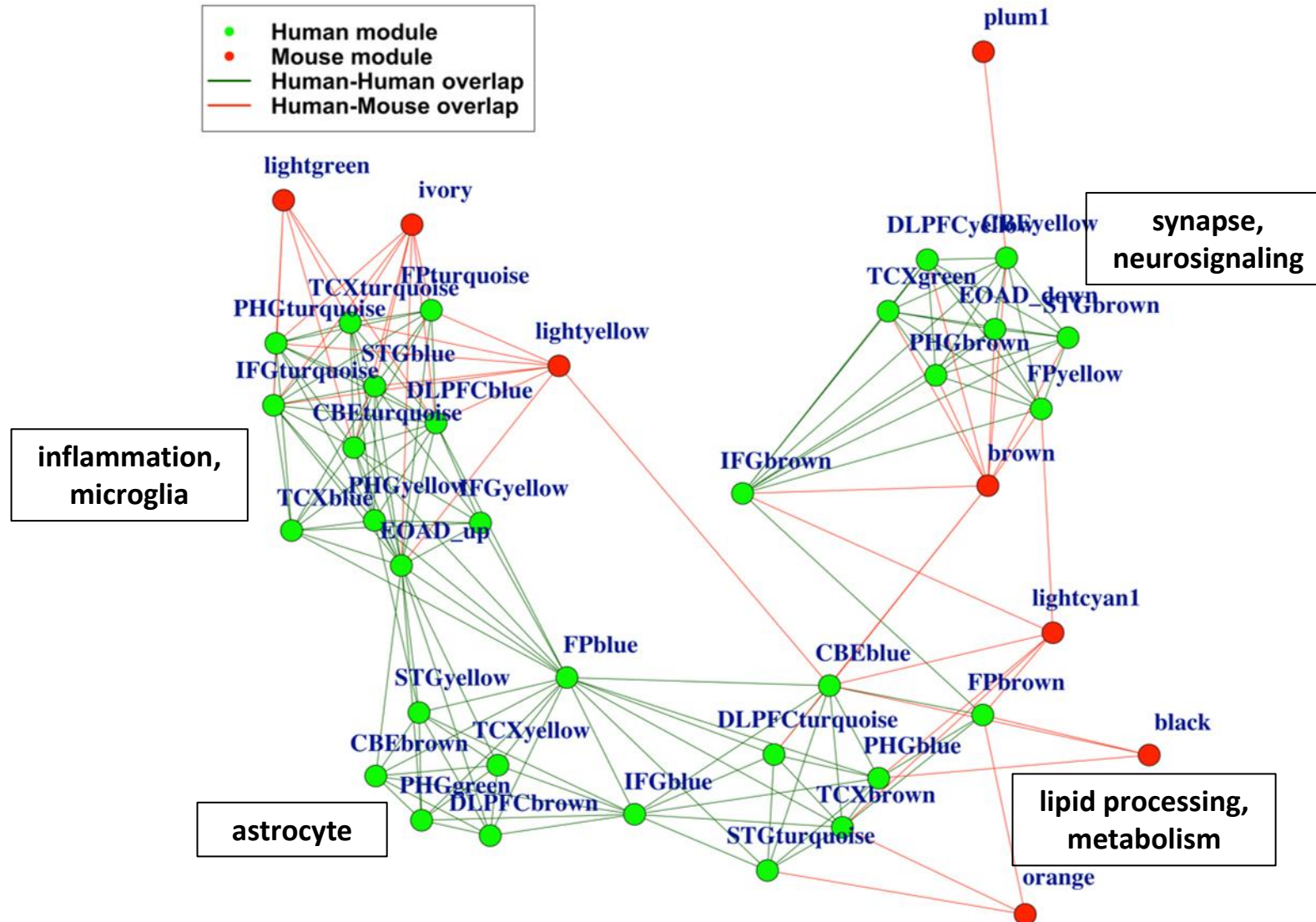
Mouse Model Transcriptomes



Mouse Gene Modules via WGCNA

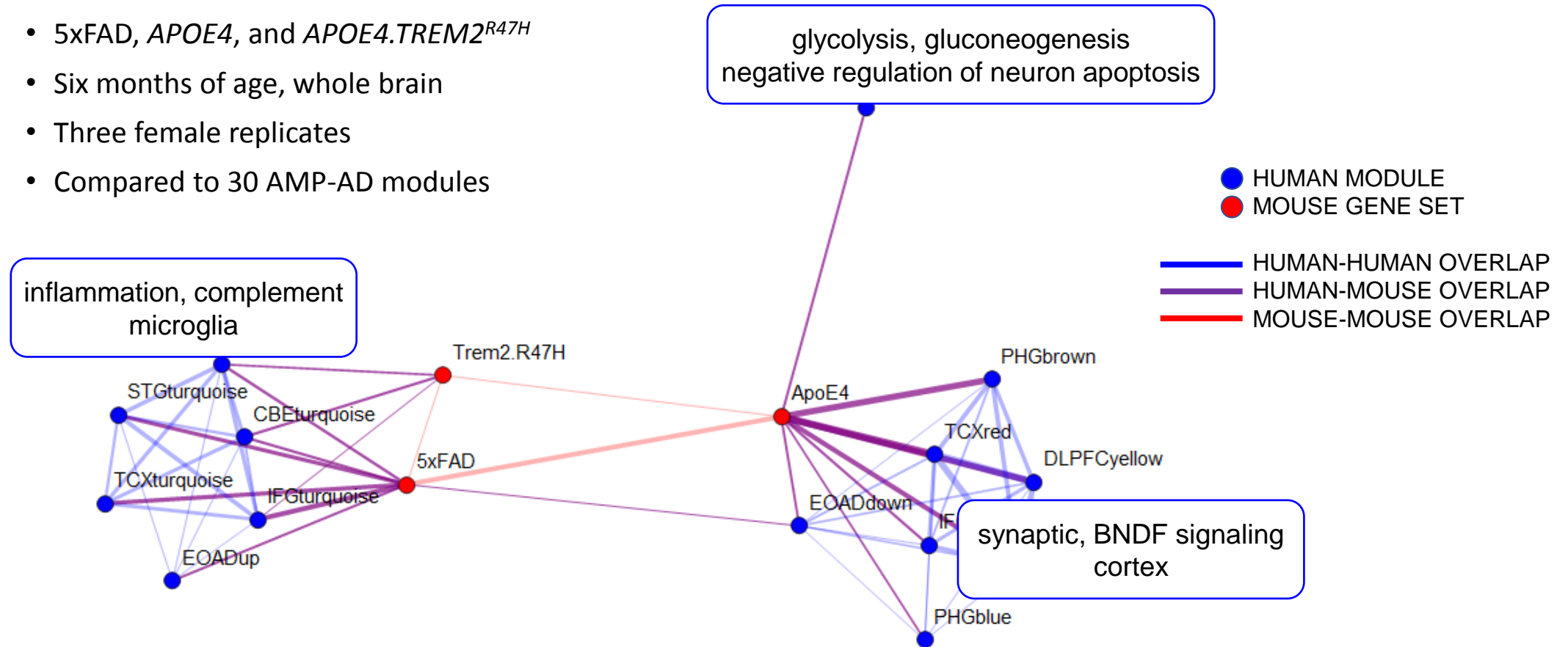


Human-Mouse Transcriptome Alignments



nanoString Neuropath Analysis

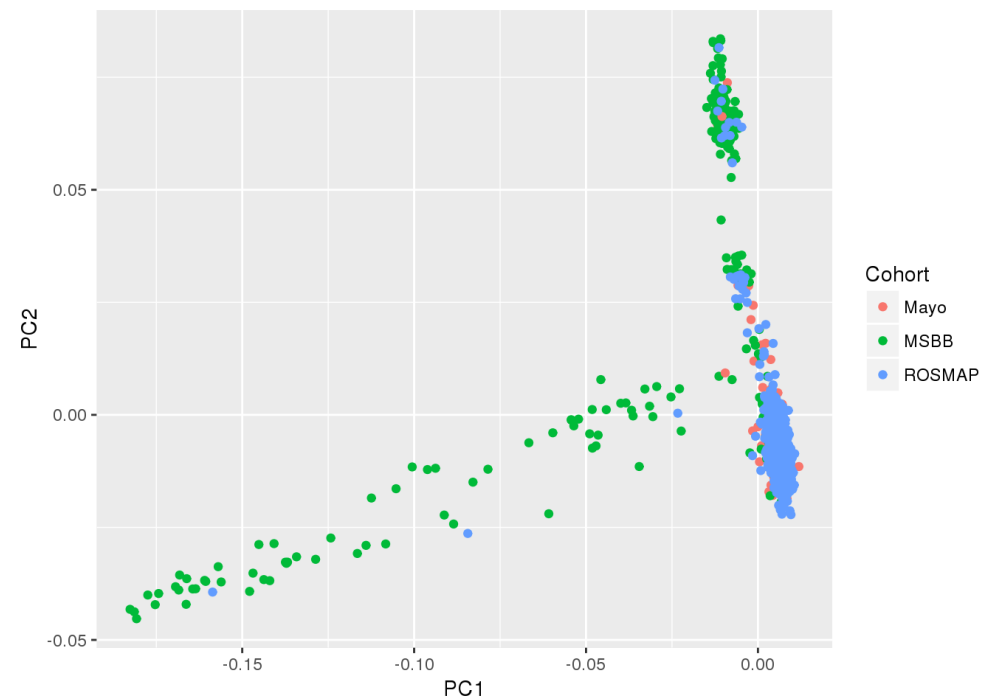
- 5xFAD, *APOE4*, and *APOE4.TREM2^{R47H}*
- Six months of age, whole brain
- Three female replicates
- Compared to 30 AMP-AD modules



Integrating AMP-AD WGS Data

Imported 1800+ whole genomes from AMP-AD Knowledge Portal

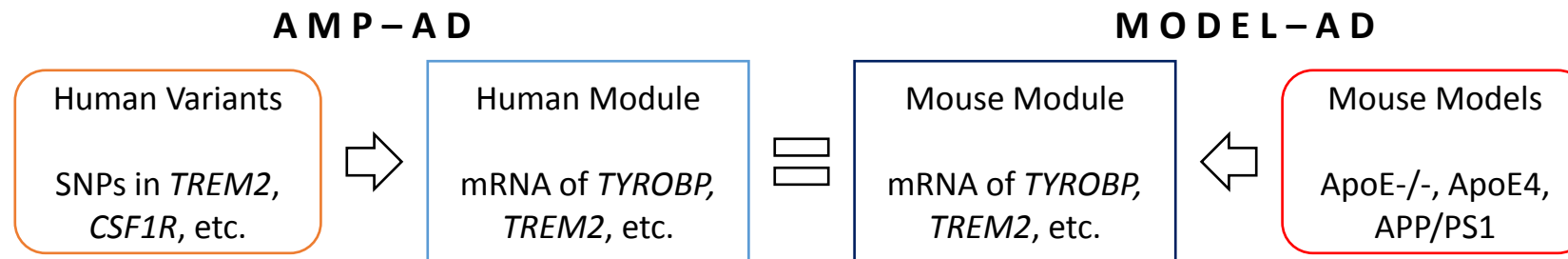
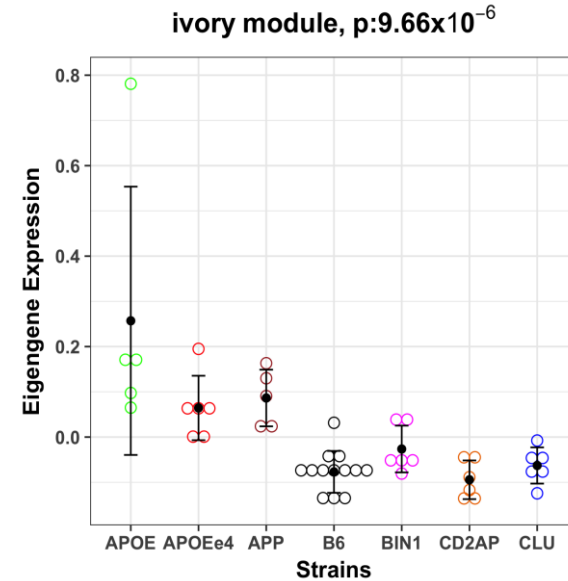
- QC checks for quality scores, sample duplication, etc
- LD pruning, MAF filtering
- PCA for population structure
- Comparison to 1000 Genomes to validate populations



Human-Mouse Neuroimmune Similarity

Ivory mouse module

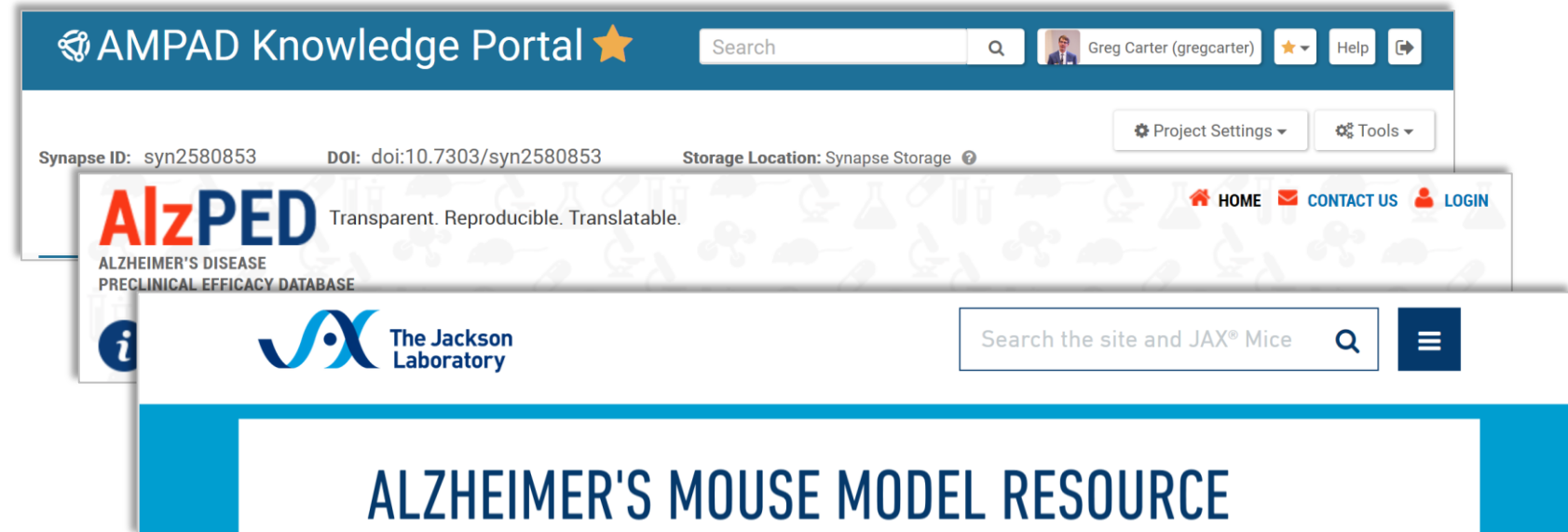
- Upregulated in ApoE^{-/-}, ApoE4, APP/PS1 mice
- Overlap with human immune modules from AMP-AD ($p = 10^{-29}$)
- Contains *TYROBP*, *TREM2*, *C1QA*, *CSF1R*



Data Dissemination

Data sharing online

- Mouse genetic information: variant(s), strain background
- Mouse phenotype data: RNA-seq, imaging, etc.
- Preclinical data: standards, protocols, results
- Preclinical results searchable on AlzPED



The image shows a screenshot of the AMPAD Knowledge Portal interface. The top navigation bar includes the AMPAD logo, a search bar, a user profile for Greg Carter (gregcarter), and links for Help and Project Settings. Below the navigation bar, the Synapse ID (syn2580853) and DOI (doi:10.7303/syn2580853) are displayed, along with the Storage Location (Synapse Storage). The main content area features the AlzPED logo and the text "Transparent. Reproducible. Translatable." with links for HOME, CONTACT US, and LOGIN. The AlzPED logo is followed by "ALZHEIMER'S DISEASE PRECLINICAL EFFICACY DATABASE". Below this, the The Jackson Laboratory logo is visible, along with a search bar for the site and JAX® Mice. The bottom section of the screenshot displays the text "ALZHEIMER'S MOUSE MODEL RESOURCE" in a large, bold font.

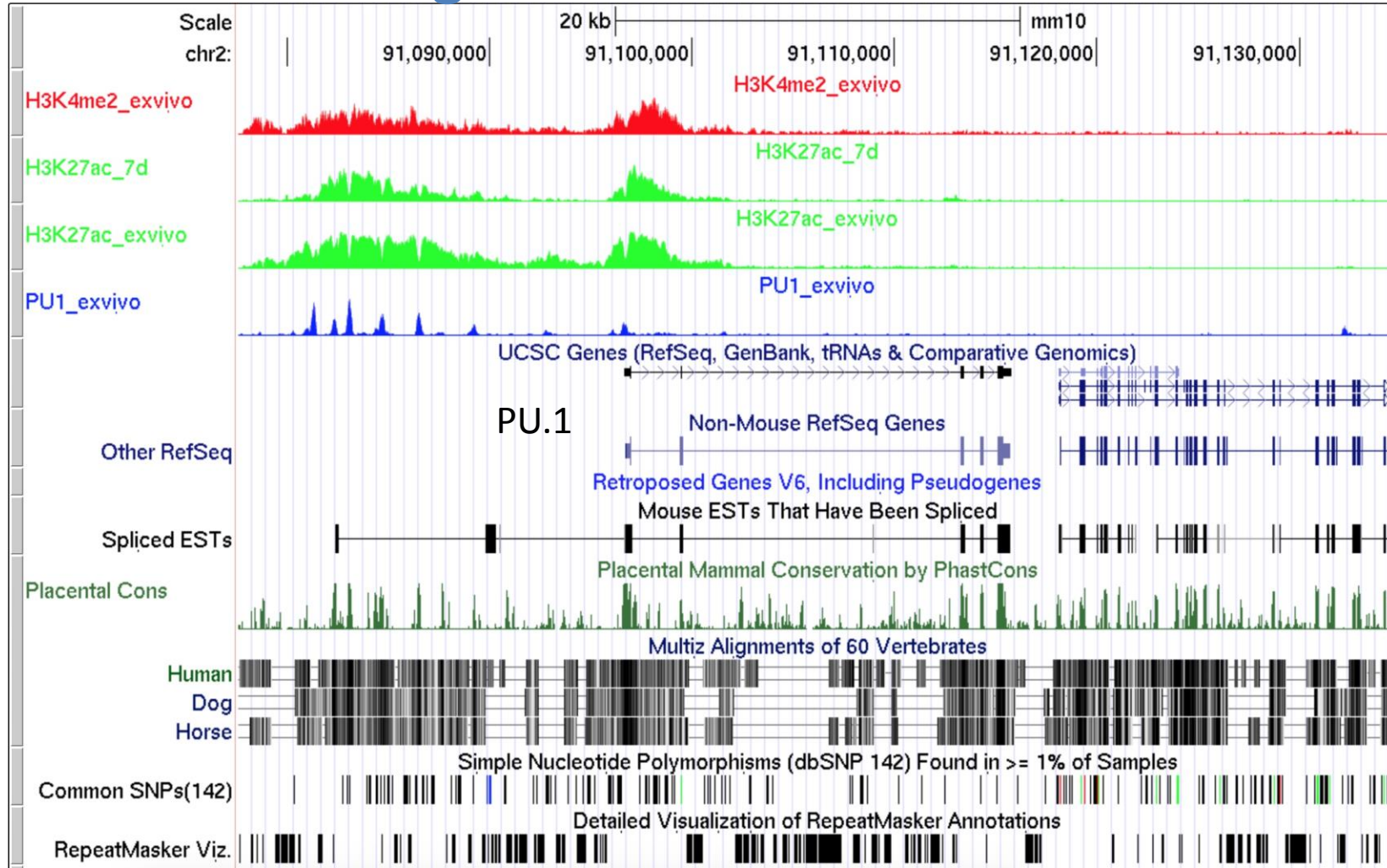
UCI BDMC Activities

1. Support variant identification and prioritization
 - Focus on non-coding variants
 - Coordinate with IU/Jax/SAGE
2. Reanalyze publicly available data to support variant prioritization in mouse
3. Analyze UCI RNA-seq data produced by center
4. Submit RNA-seq results to Synapse

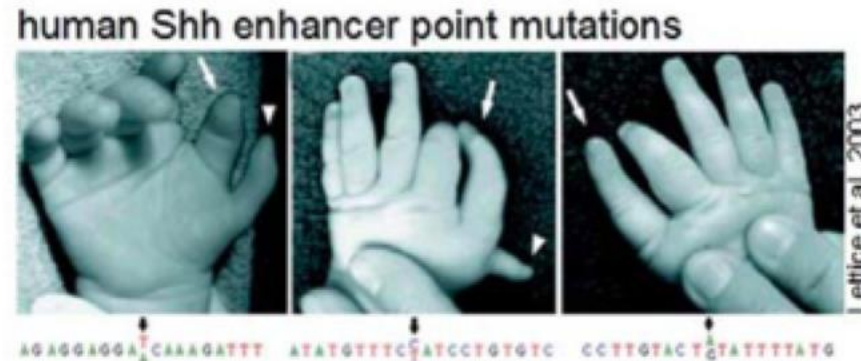
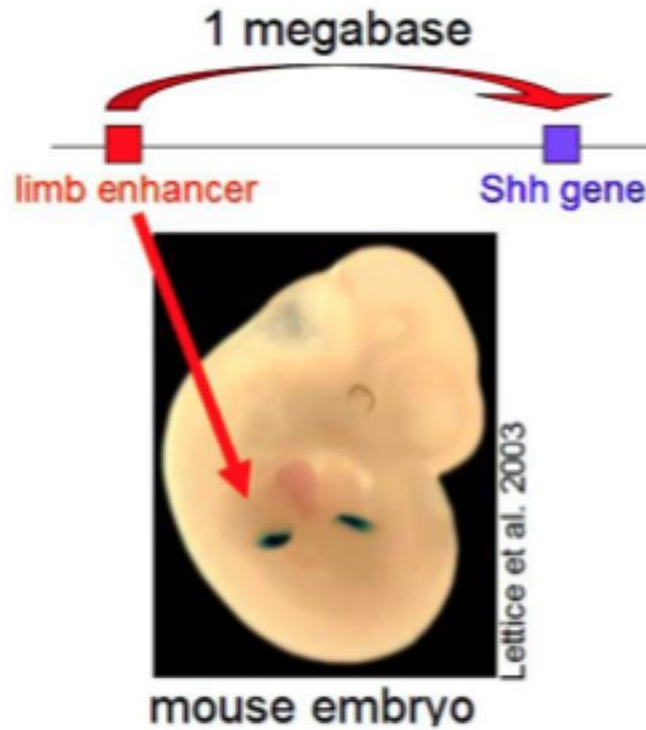
Focus on #2 and #3 today



Using publicly available chromatin marks in mouse to guide element selection

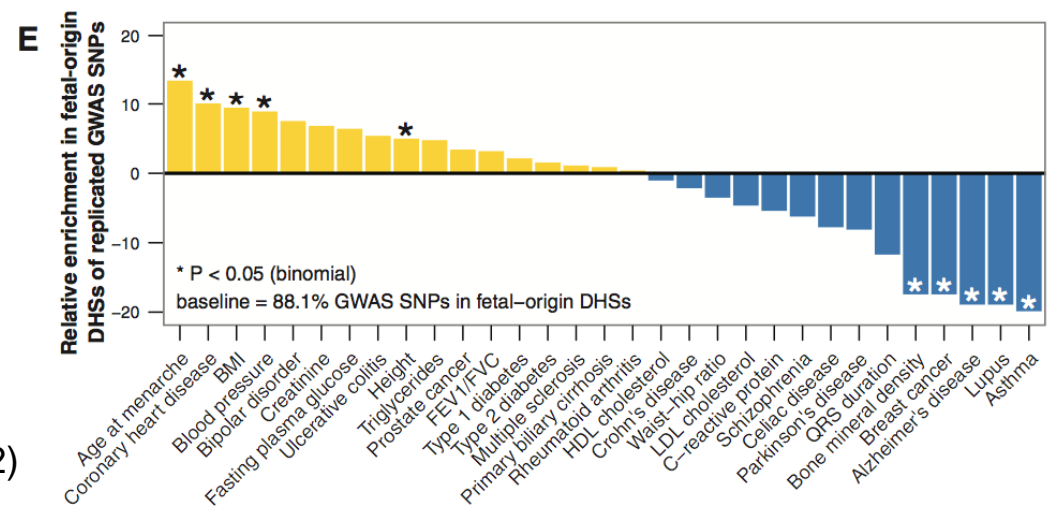
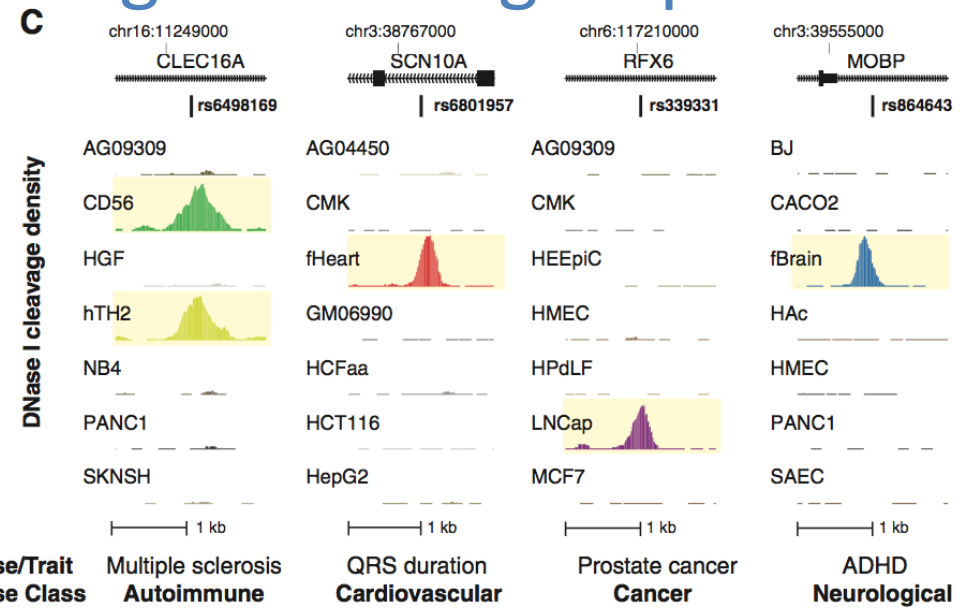
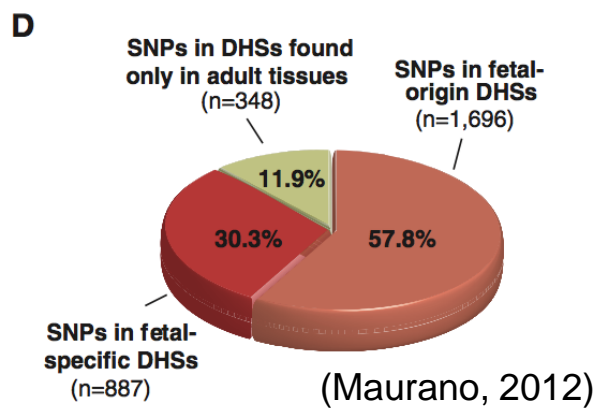
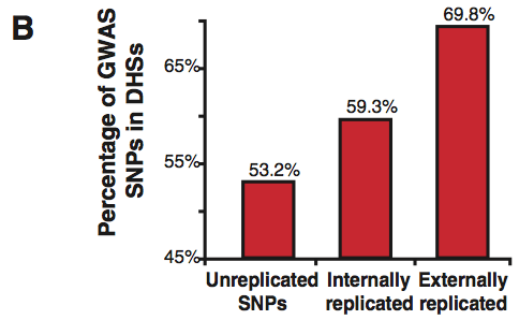
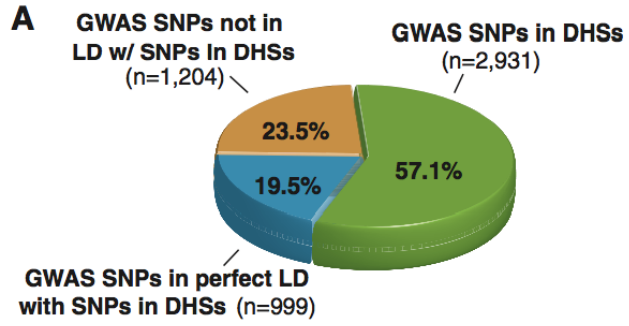


Enhancers controlling gene expression can be very far from their gene



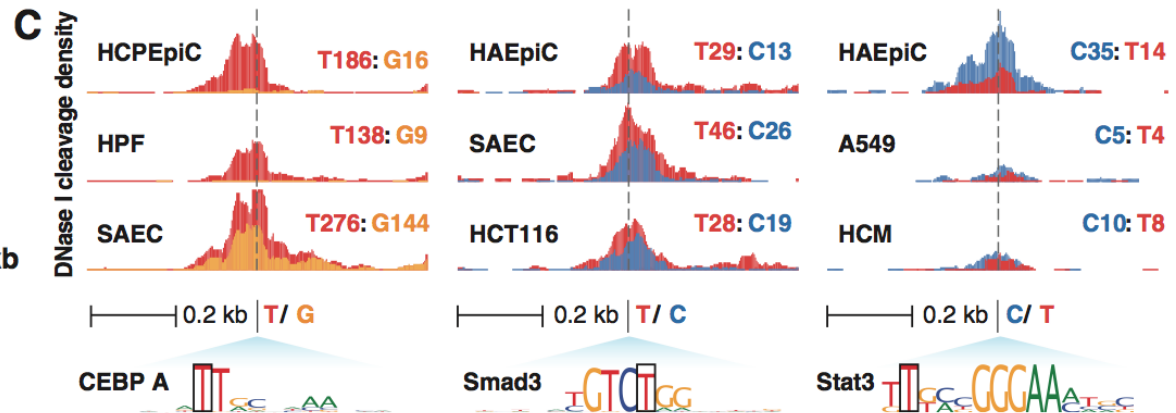
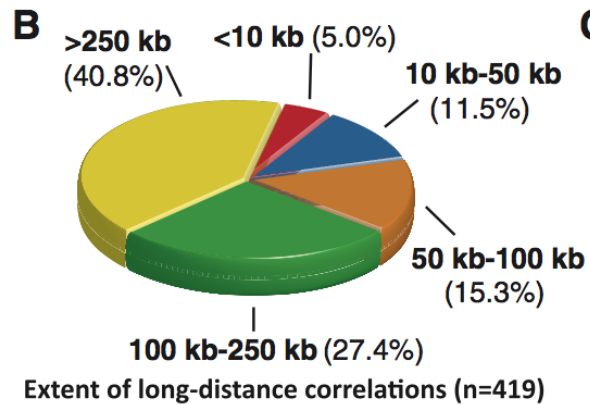
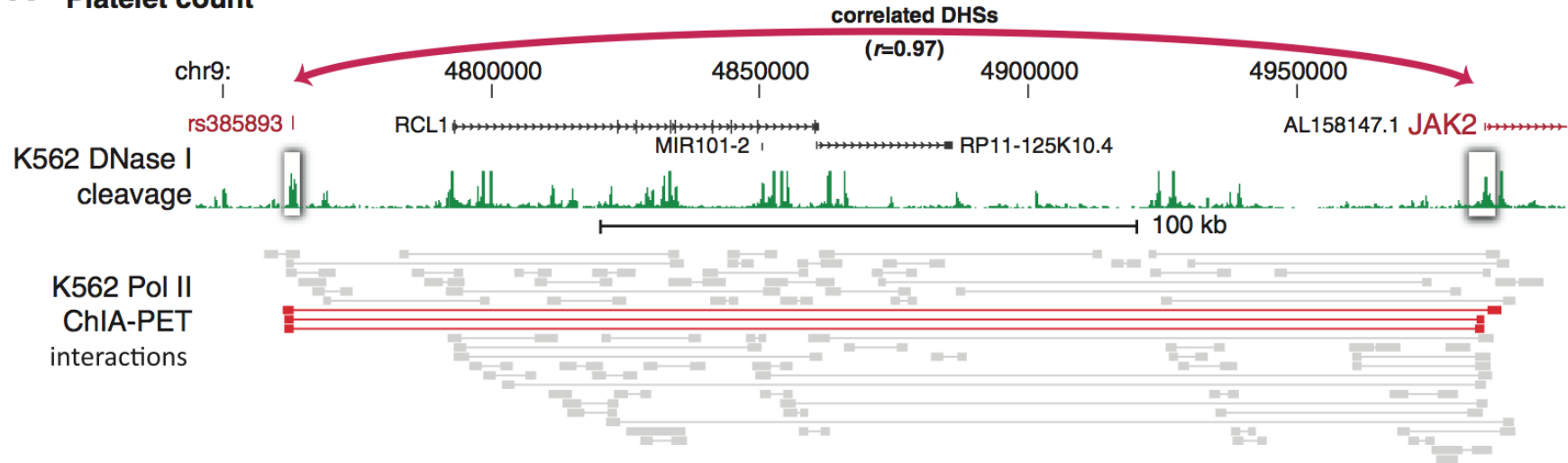
To complicate matters, the Sonic Hedgehog limb enhancer is in the intron of another gene that it does not regulate

Majority of GWAS SNPs map to open chromatin elements outside of gene coding sequences



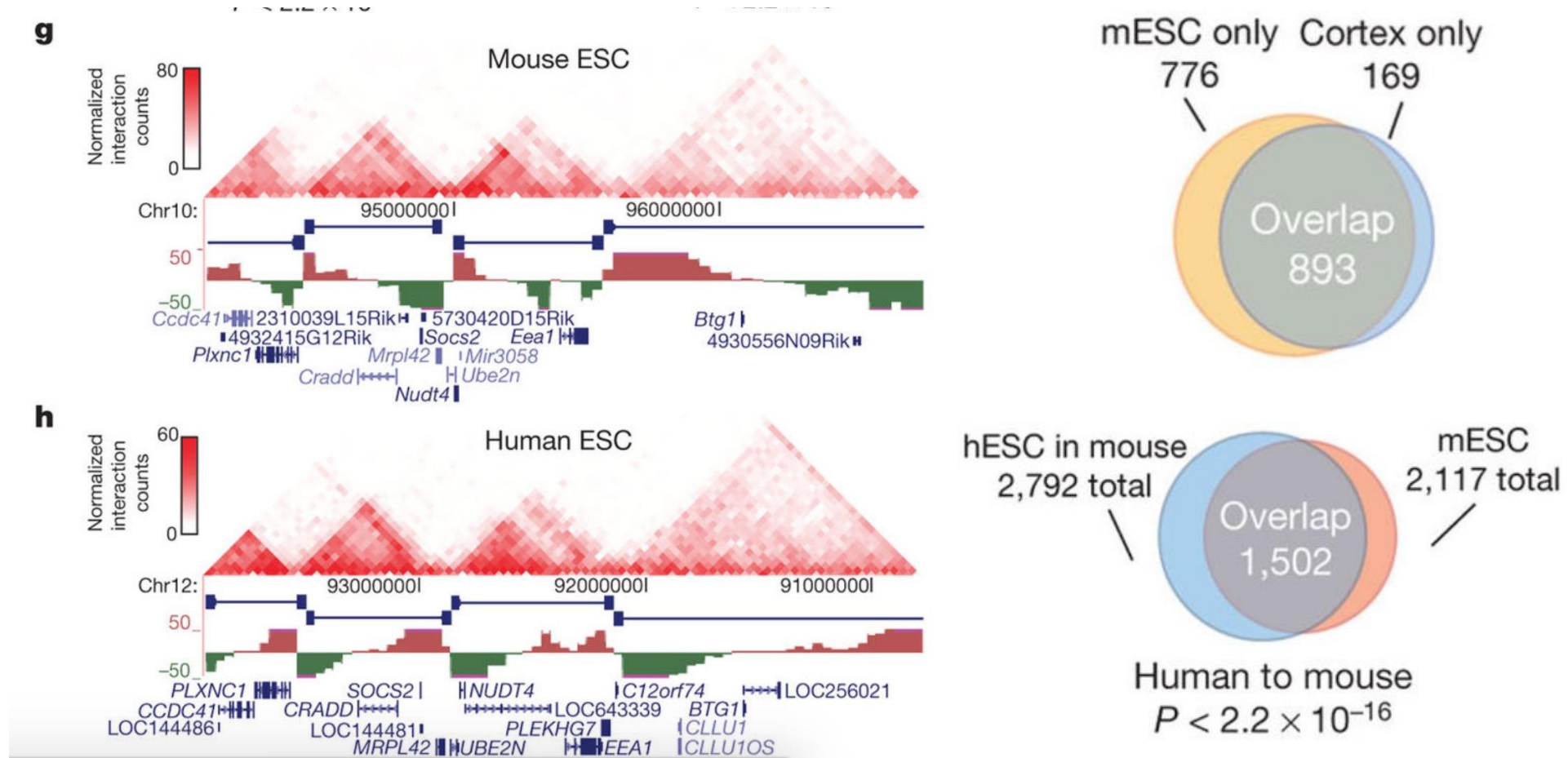
Distal GWAS SNPs mapping to cognate promoters

A Platelet count



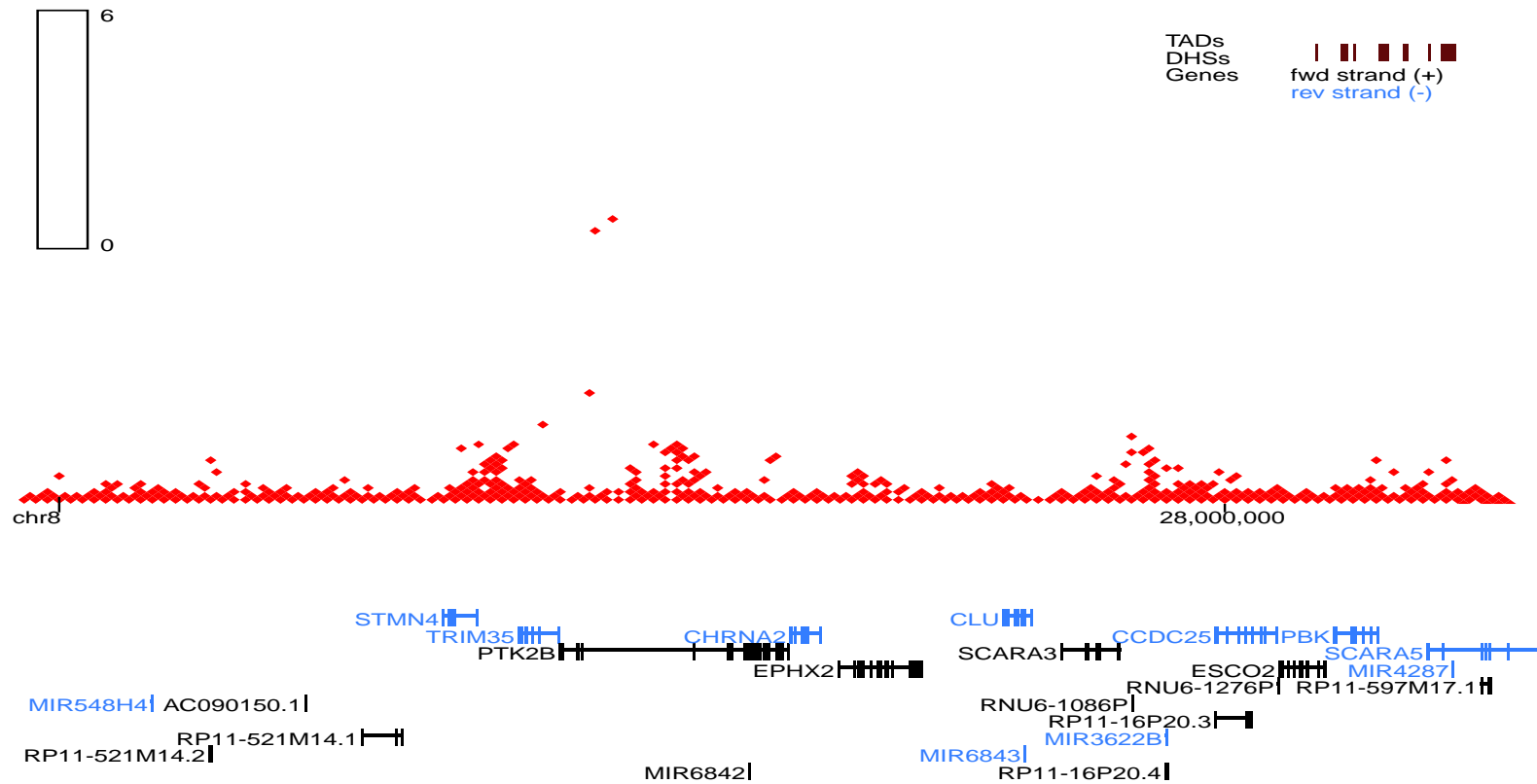
(Maurano, 2012)

Topologically associated domains defined by HiC identify interacting regions

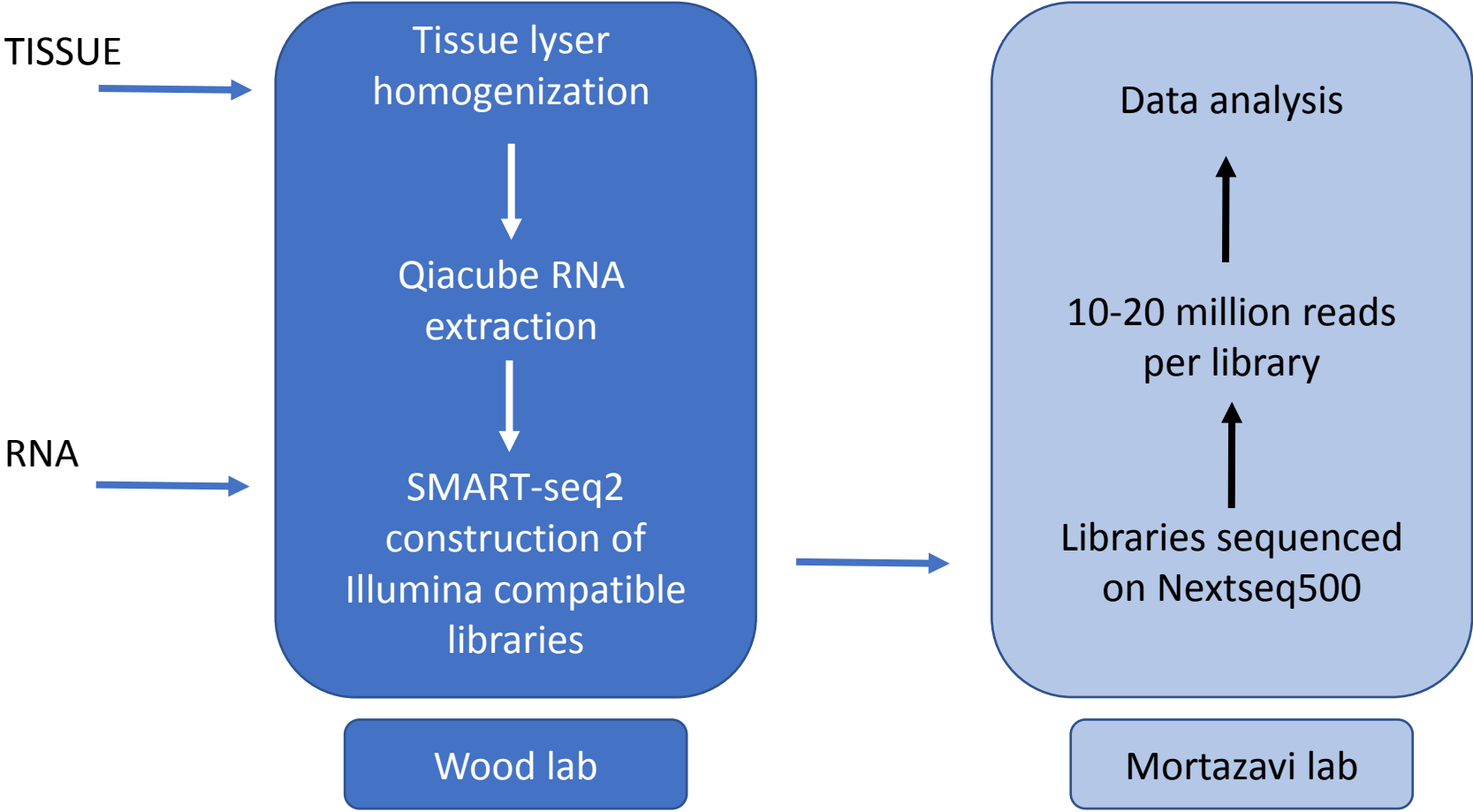


From Dixon, 2013

Some of the GWAS hits are on the same TAD – do they interact ?



RNA SEQUENCING PIPELINE

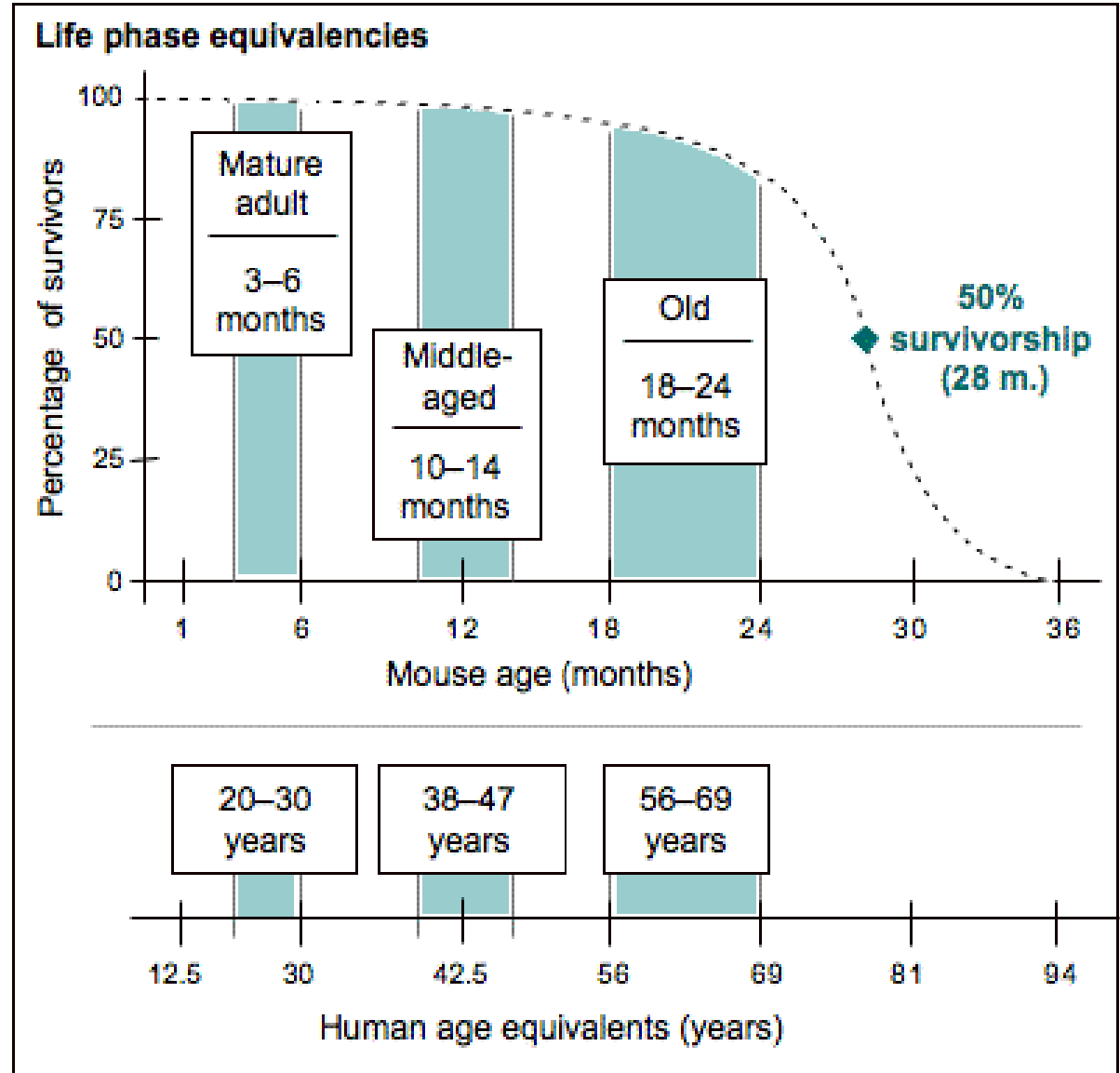


Mouse versus human ages

- 2 month old BL6 mouse would correspond to a teenager
- 8 month old BL6 mouse would correspond to a 35 year old human
- 22 month old BL6 mouse would correspond to a 65 year old human

- RNA-seq data in young mice → early disruption and biomarkers

- RNA-seq data in older mice → better match to to LOAD ?

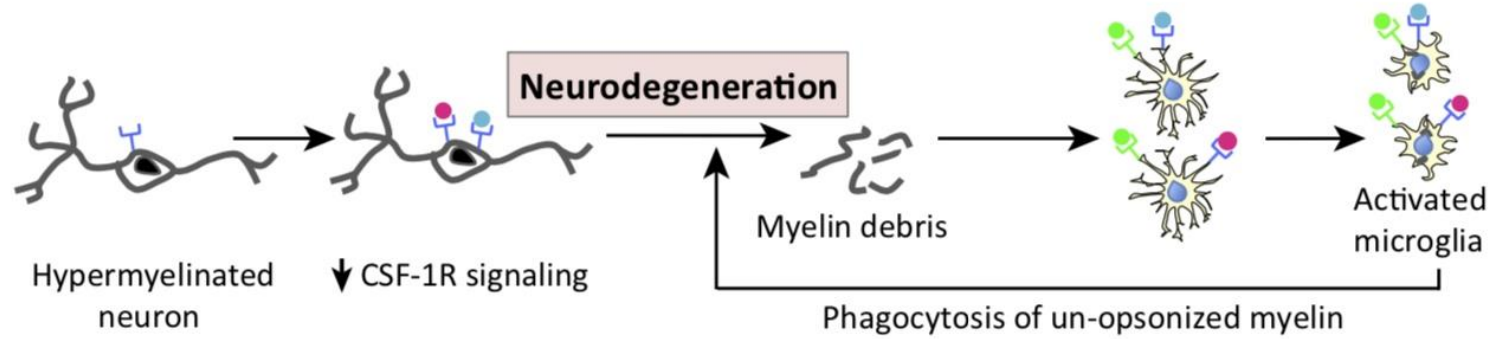


CSF1R – an AMP-AD target

Csf1r^{+/-}: rapid degeneration coupled with inflammation

CSF1R^{+/-} het mice have:

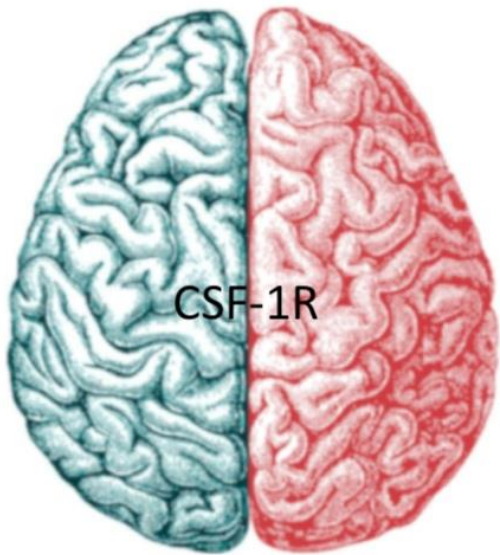
- Impaired memory
- Normal brain size
- Impaired myelination
- Increased microglia



(B)

Positive role

- Survival and quiescence of microglia
- Differentiation of neurons and glial cells
- Neuronal survival
- Improved neurogenesis; clearance of myelin debris and remyelination (GCL)

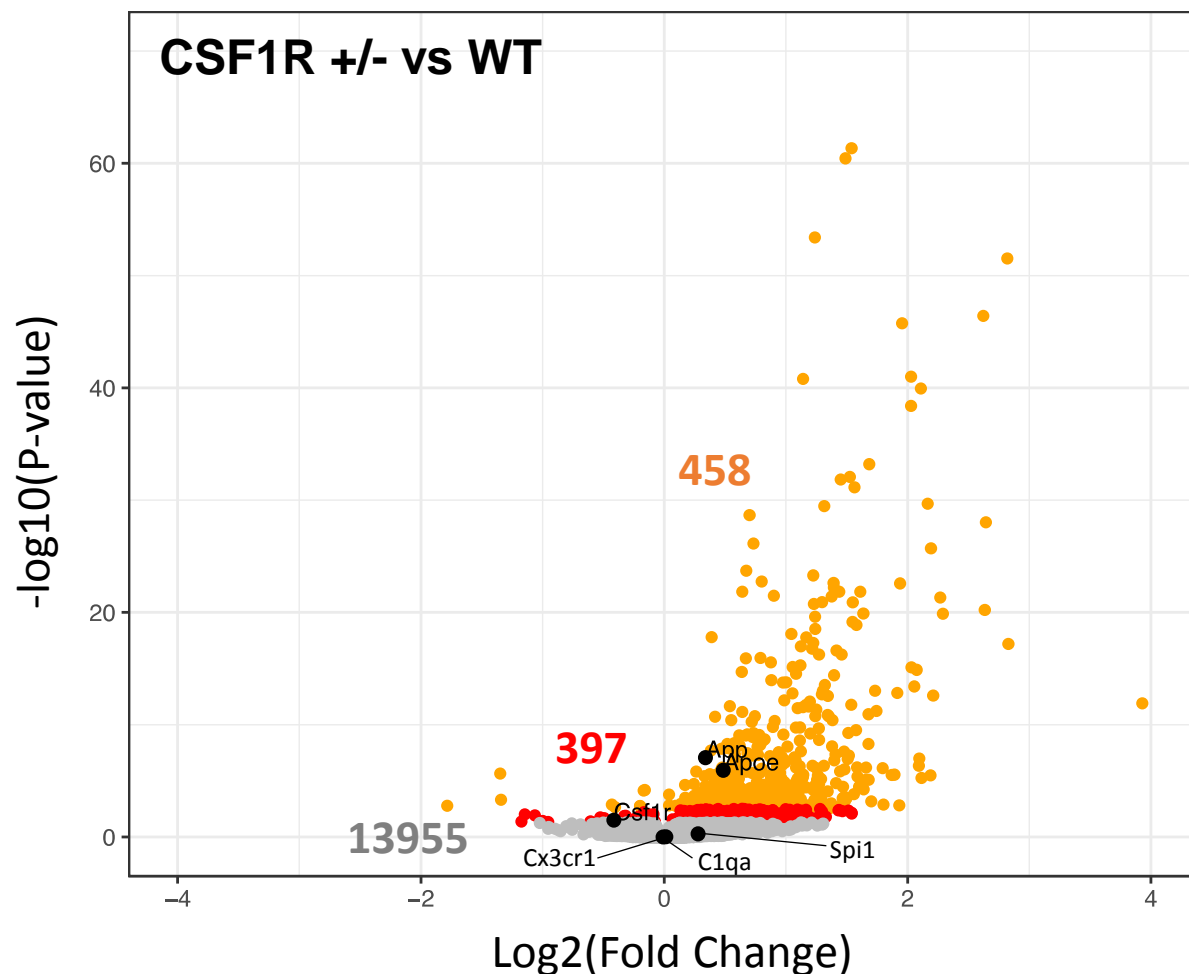


Negative role

- Expansion of demyelinating MΦ and microglia; schwann cell dedifferentiation (CMT1X)
- Increased myeloid cells and autoimmune responses (EAE)
- Glioma progression

(Chitu, 2016)

Differential Expression Analysis



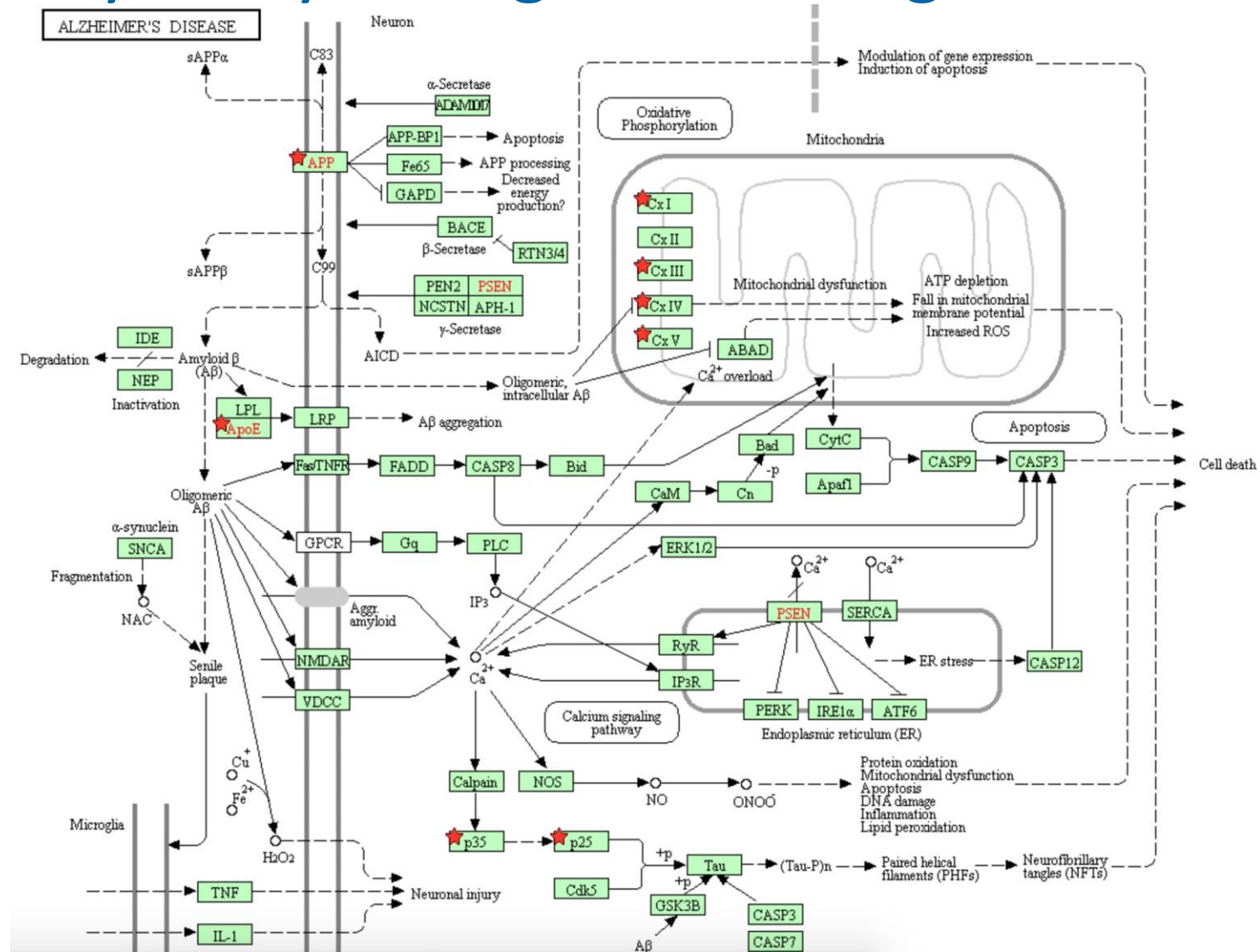
Frontal Cortex RNA, 8 months old
6 WT vs 6 CSF1R hets

APP and APOE are significantly
higher in the CSF1R +/- mice

- P ≤ 0.05, FDR ≤ 0.1
- P ≤ 0.05, FDR > 0.1
- P > 0.05, FDR > 0.1

Pathway analysis flags AD among others

David
P-value 1.9E-3
FDR 7.5E-2



Humanizing A β as a platform to introduce GWAS variants



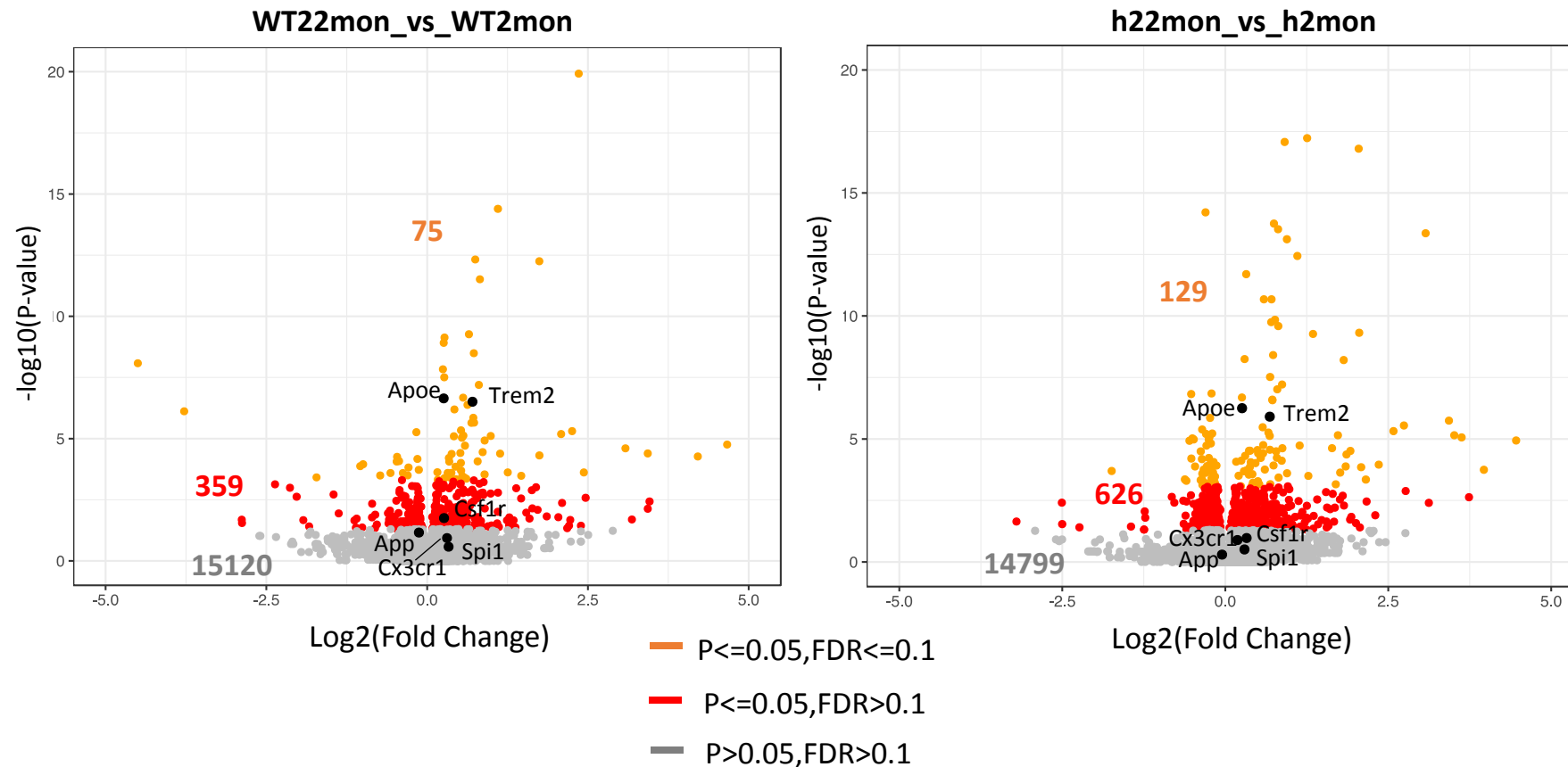
Alzheimer's Association International Conference (AAIC)
O #23414

01-01 Development of New Models and Analysis Methods:
Novel Model Systems to Study Dementia, *Sunday, July 22, 2018:*
8:00 AM - 9:30 AM, *McCormick Place, Room - 184*

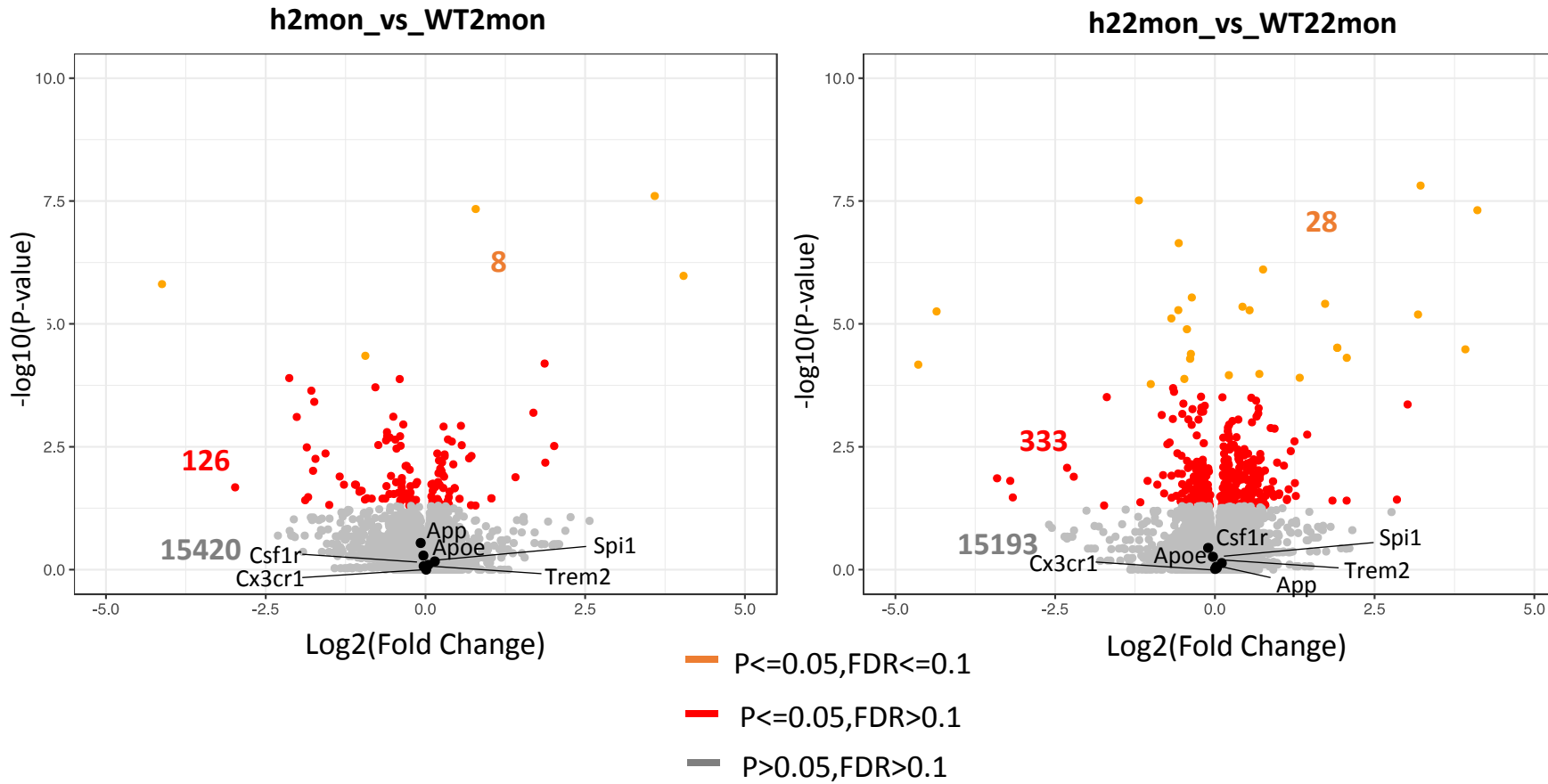
01-01-04 Ha β -KI: A Knock-in Mouse Model for Sporadic Alzheimer's Disease

Differential expression analysis of hAβKI vs WT by age

2 genotypes x 2 time-points x 2 sexes x 2 replicates = 32 mice

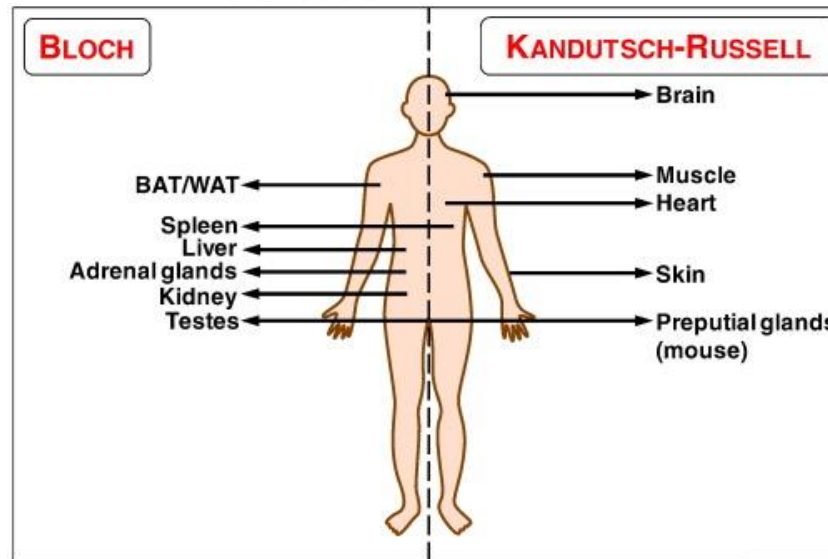
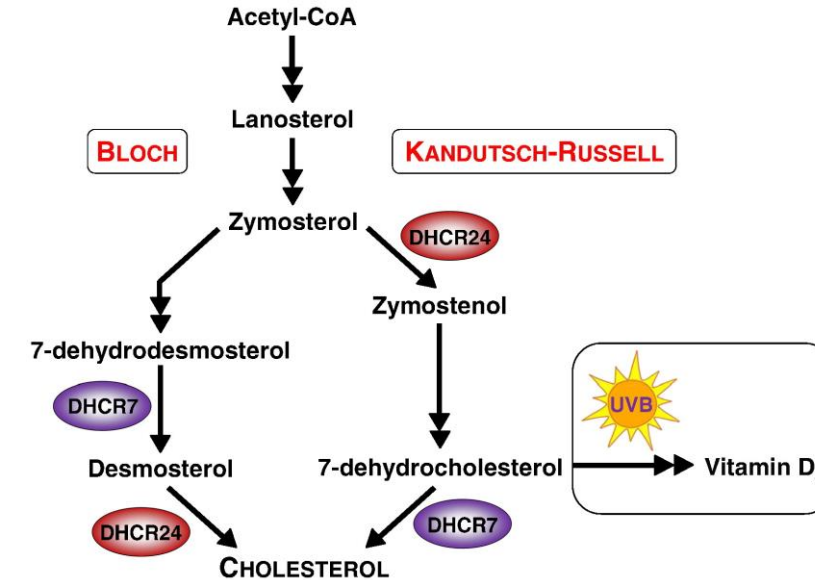
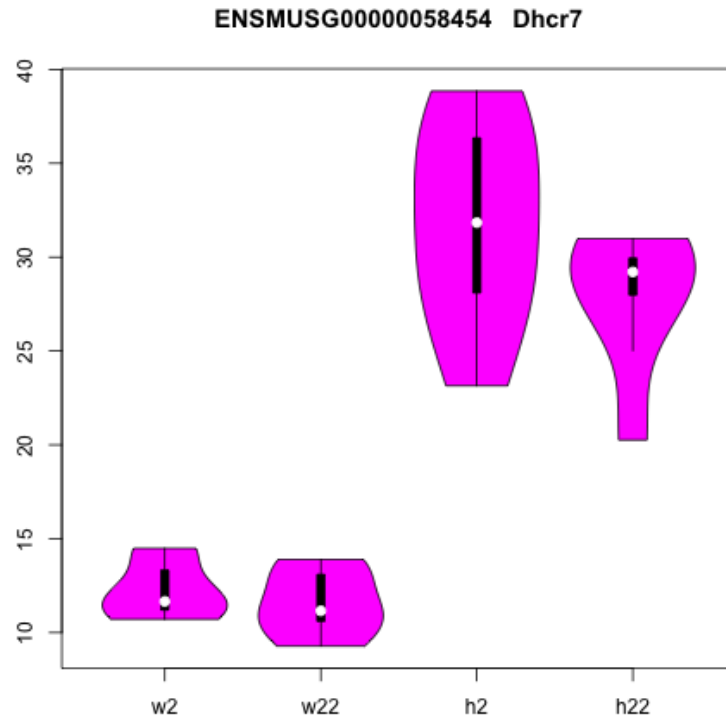


Differential expression analysis of hAβKI vs WT by genotype



Talk by David Baglietto-Vargas

DHCR7 is more highly expressed in hAbKI



- Last enzymatic step in cholesterol synthesis in the adult brain
- What is the cell type overexpressing Dhcr7 ?

From Prabhu, 2016

Upcoming UCI BDMC Activities

1. Support variant identification and prioritization
 - Focus on non-coding variants
 - Coordinate with IU/Jax/SAGE
2. Reanalyze publicly available data to support variant prioritization in mouse
3. Analyze UCI RNA-seq data produced by center
4. Submit RNA-seq results to Synapse
5. Analyze single-cell RNA-seq data from aging WT and AD mouse models

