Meta-analysis of hundreds of seizure-related traits reveals putative modifiers of epilepsy resilience and susceptibility

The Jackson Laboratory

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Mouse Phenome Database
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BRAINS: A CRASH COURSE

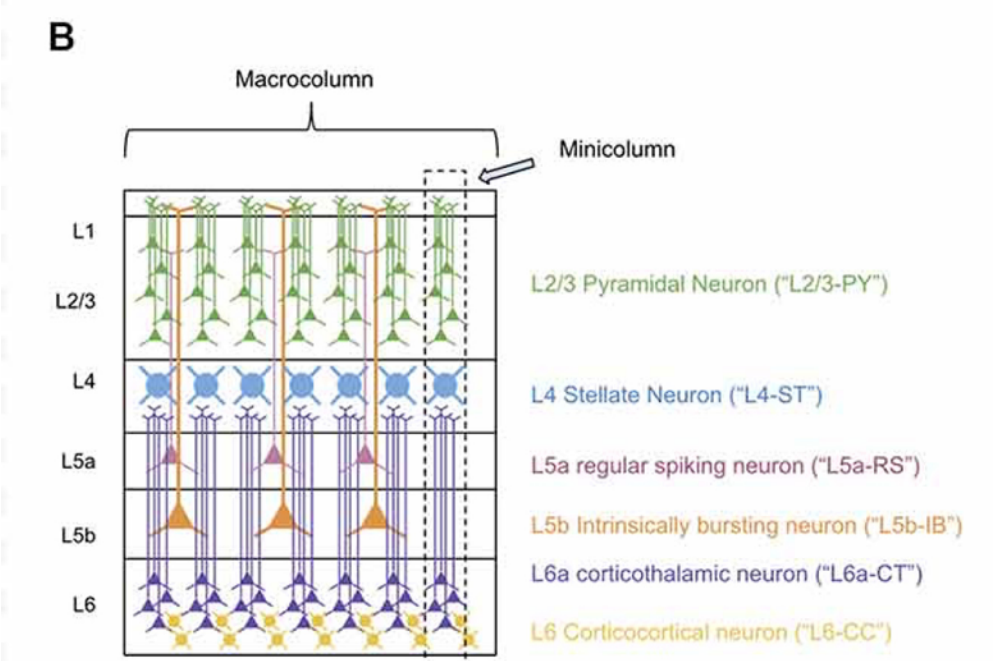
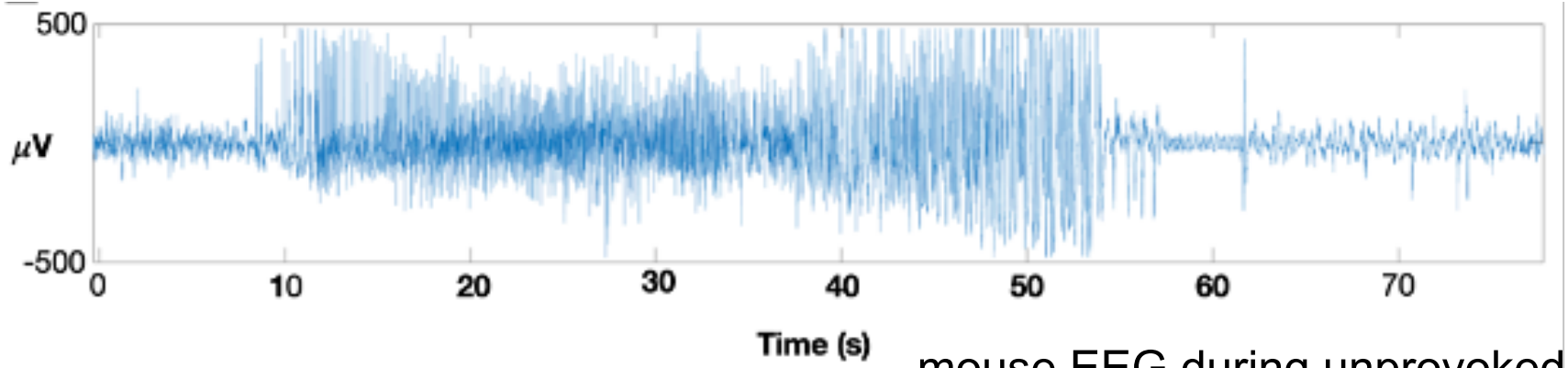


Figure 2.B) Visualization of morphology and laminar distribution of the main types of excitatory neurons within the neocortical microcircuit. From:
An Attempt at a Unified Theory of the Neocortical Microcircuit in Sensory Cortex
Original: https://www.frontiersin.org/articles/10.3389/fncir.2020.00040

- **Excitatory** and **inhibitory** neurons form microcircuits that are **coupled** to produce a whole brain
- **Synchrony** occurs when many microcircuits entrain to oscillate in the same phase
- Synchrony supports major brain functions
  - Sleep-wake transitions
  - Attention
  - Information gating

SEIZURES ARE PATHOLOGICAL HYPERSYNCHRONY



mouse EEG during unprovoked seizure

- Cause loss of consciousness and/or control of motor function
- Brains are complicated => Many kinds of seizures
- Combination of **neuron autonomous** and **network** factors

THE EPILEPSIES

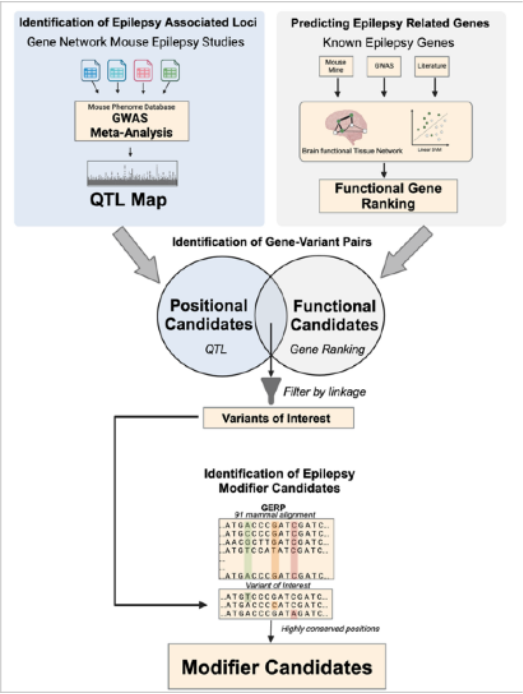
- Family of syndromes characterized by **unprovoked seizures**
- Common and rare forms
- Genetic and acquired forms (~1000 genes implicated)

Epidemiology

- 1 in 26 Americans will develop epilepsy
- 1 in 150 American children are diagnosed
- 3.4 M worldwide prevalence
- 150k / year incidence

https://www.cureepilepsy.org/understanding-epilepsy/epilepsy-basics/what-is-epilepsy/

SYSTEMS ANALYSIS OF SEIZURE MODIFIER GENETICS

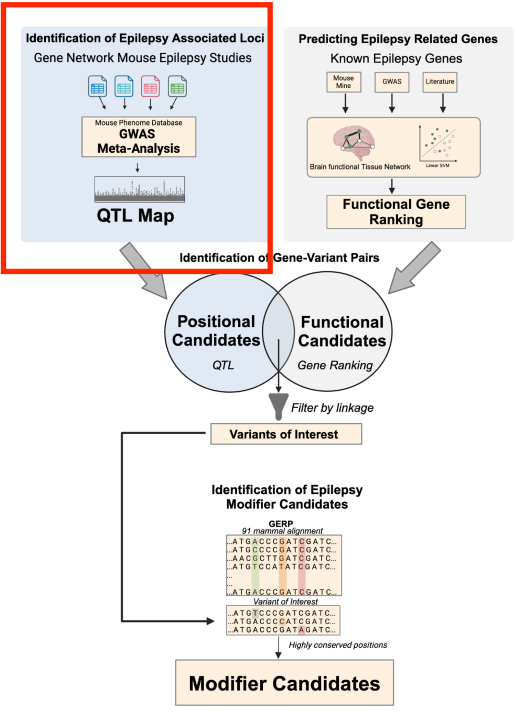


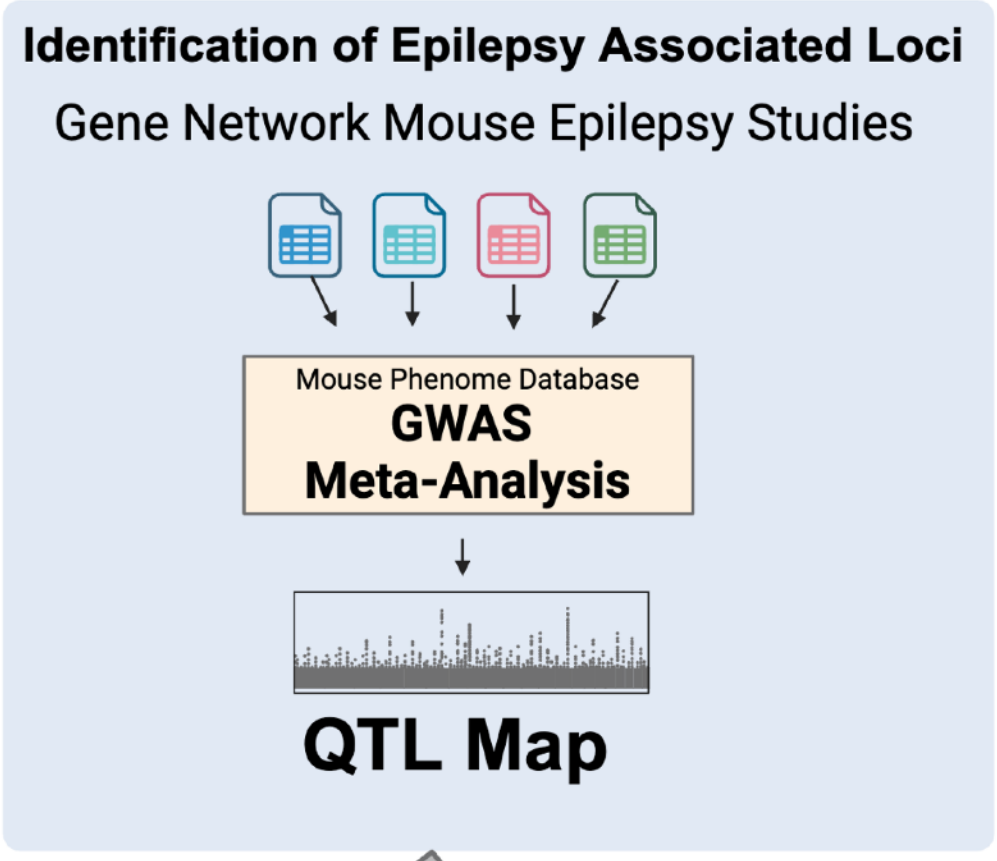
Goal: Identify modifier genes in mice that are predicted to act in human seizure gene networks

Rationale: Drug targets with (human) genetic support are 2.6x more likely to succeed in trials

Minikel, *et al.*, *Nature*, 2024

SYSTEMS ANALYSIS OF SEIZURE MODIFIER GENETICS



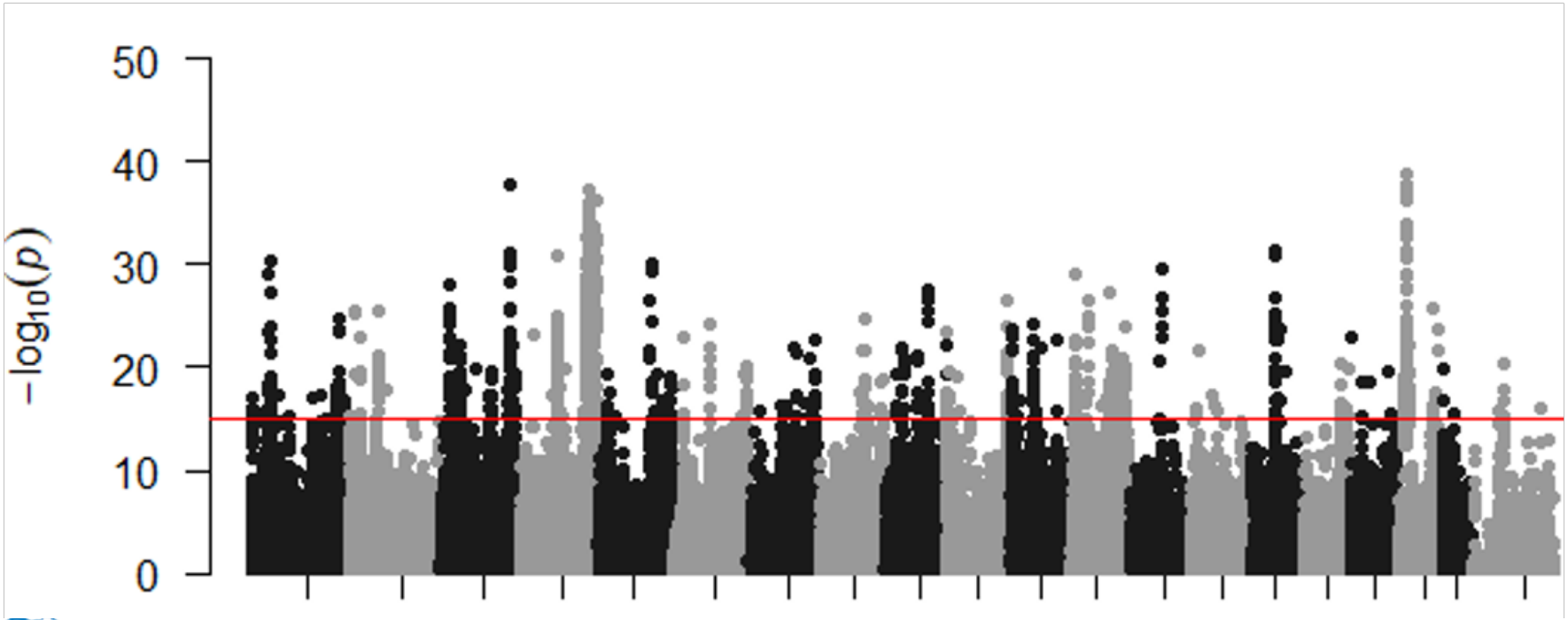


EXTENSIVE LEGACY DATA ON GENE NETWORK

Population	Measured Phenotype	Induction Method
AXBXA	•Latency to seizures •Threshold dosage	•Toxins •Visual stimulation
BXD	•Generalized seizure threshold (GST) •Myoclonic jerk threshold (MJT) •Audiogenic seizure severity •Kindling	•Toxins (flurothyl, Pentylenetetrazol) •Drug withdrawal •Audio stimuli •Changing Pressure
MDP	•GST •MJT	•Toxins (flurothyl) •Shock

- 127 phenotype measures in total

META-ANALYSIS REVEALS MANY PUTATIVE MODIFIERS

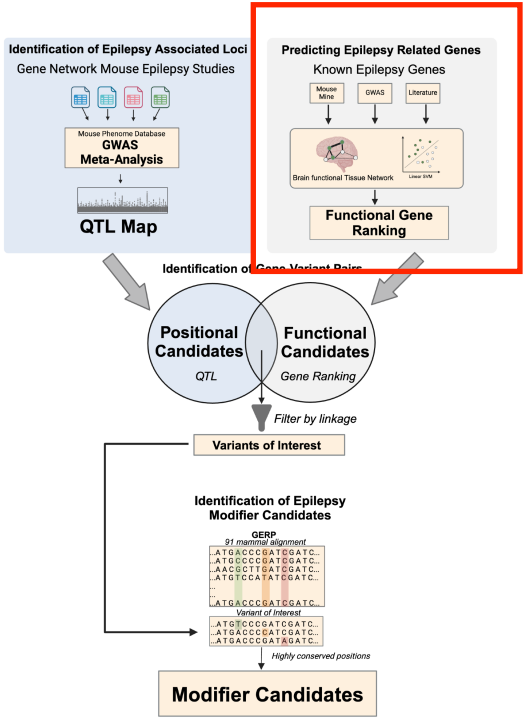


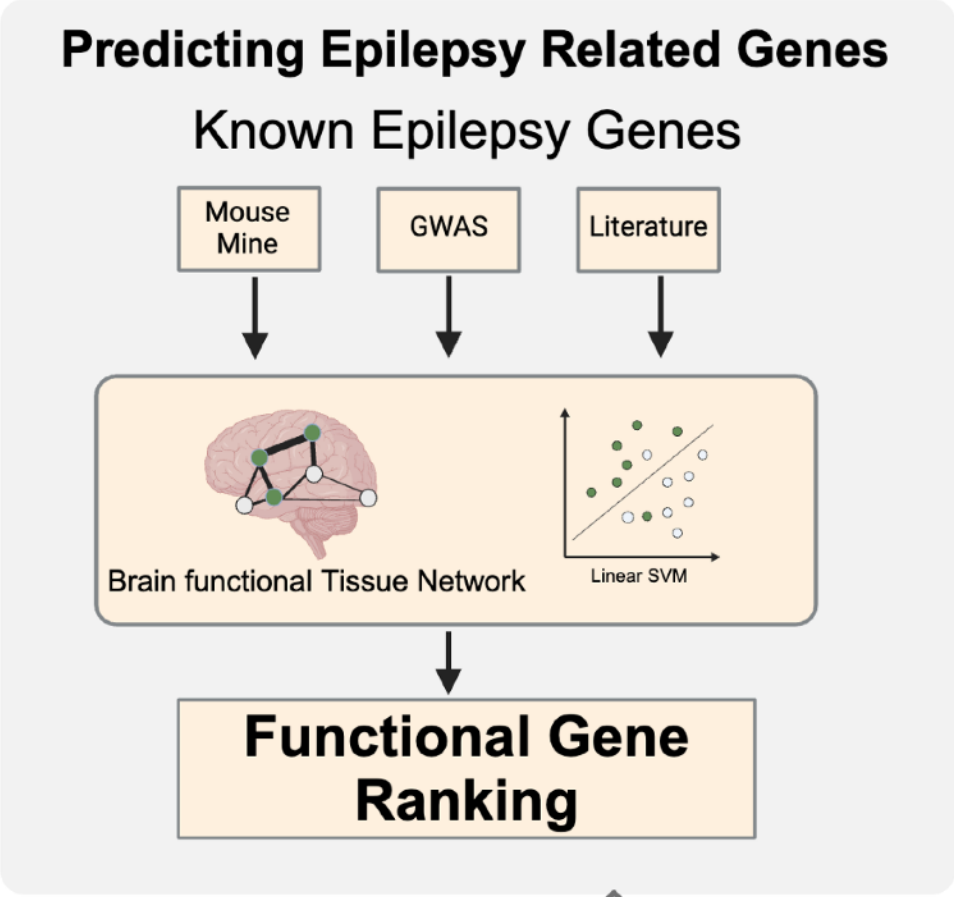
Mouse Phenome Database
at The Jackson Laboratory

- 118 distinct loci at p < 1e-15

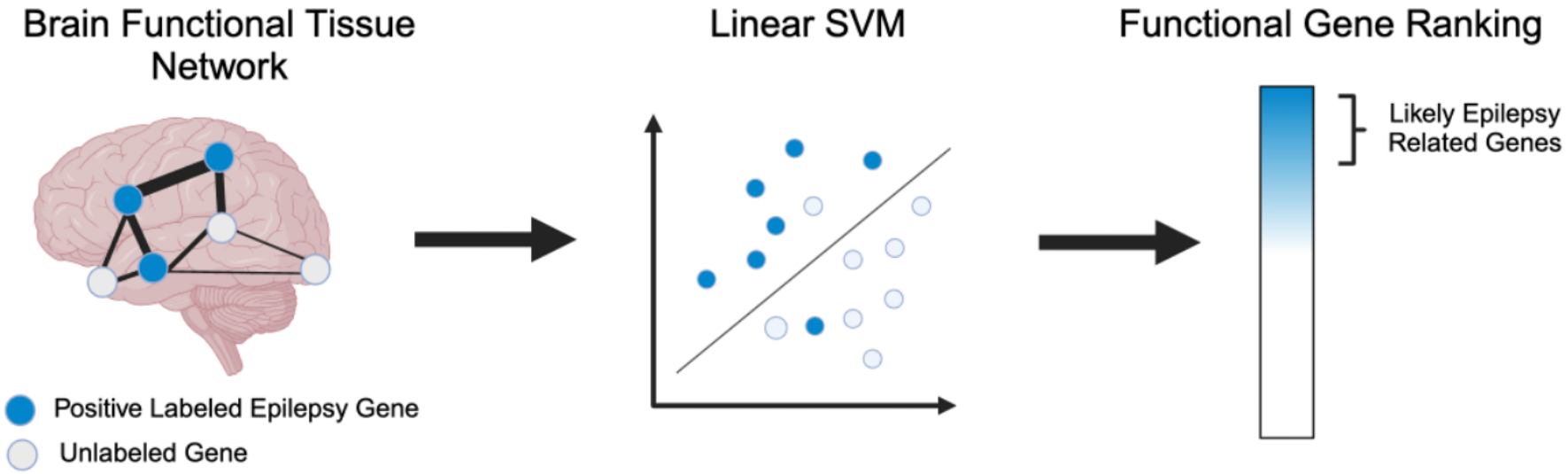
- METASOFT meta-analysis

SYSTEMS ANALYSIS OF SEIZURE MODIFIER GENETICS





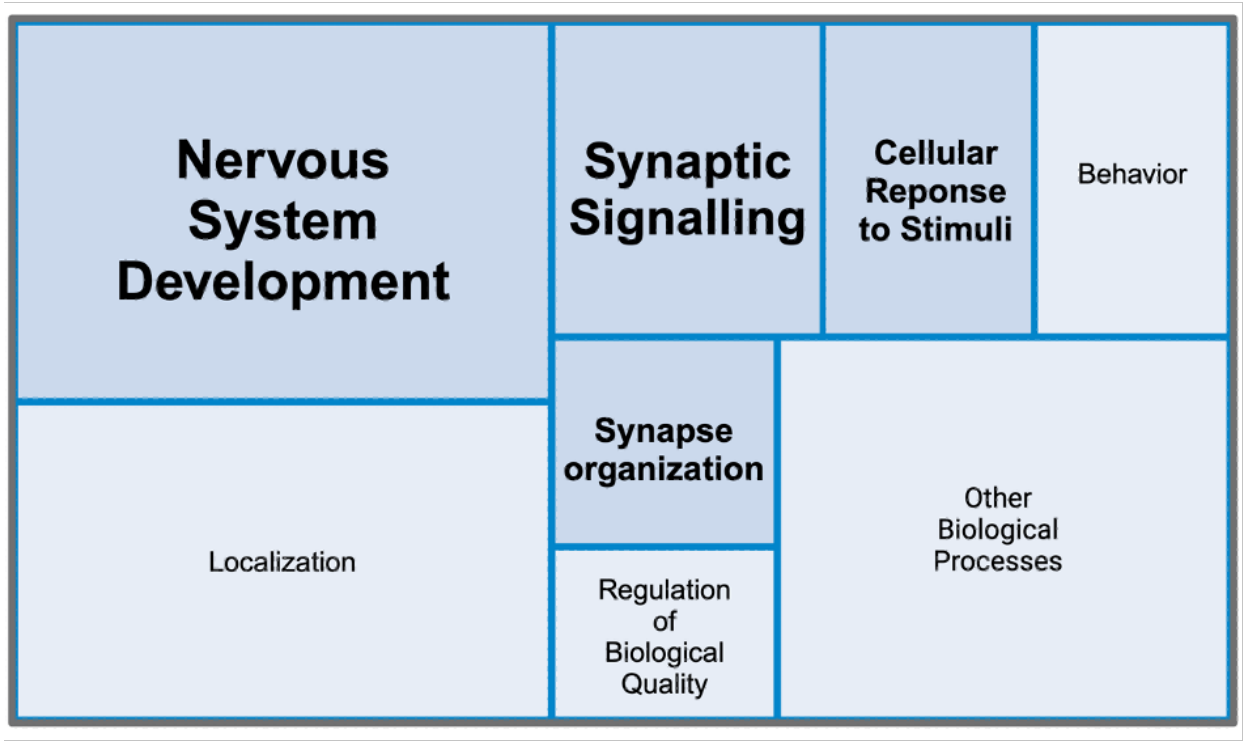
NETWORK-BASED RANKINGS FOR IMPORTANCE TO EPILEPSY



Jntm

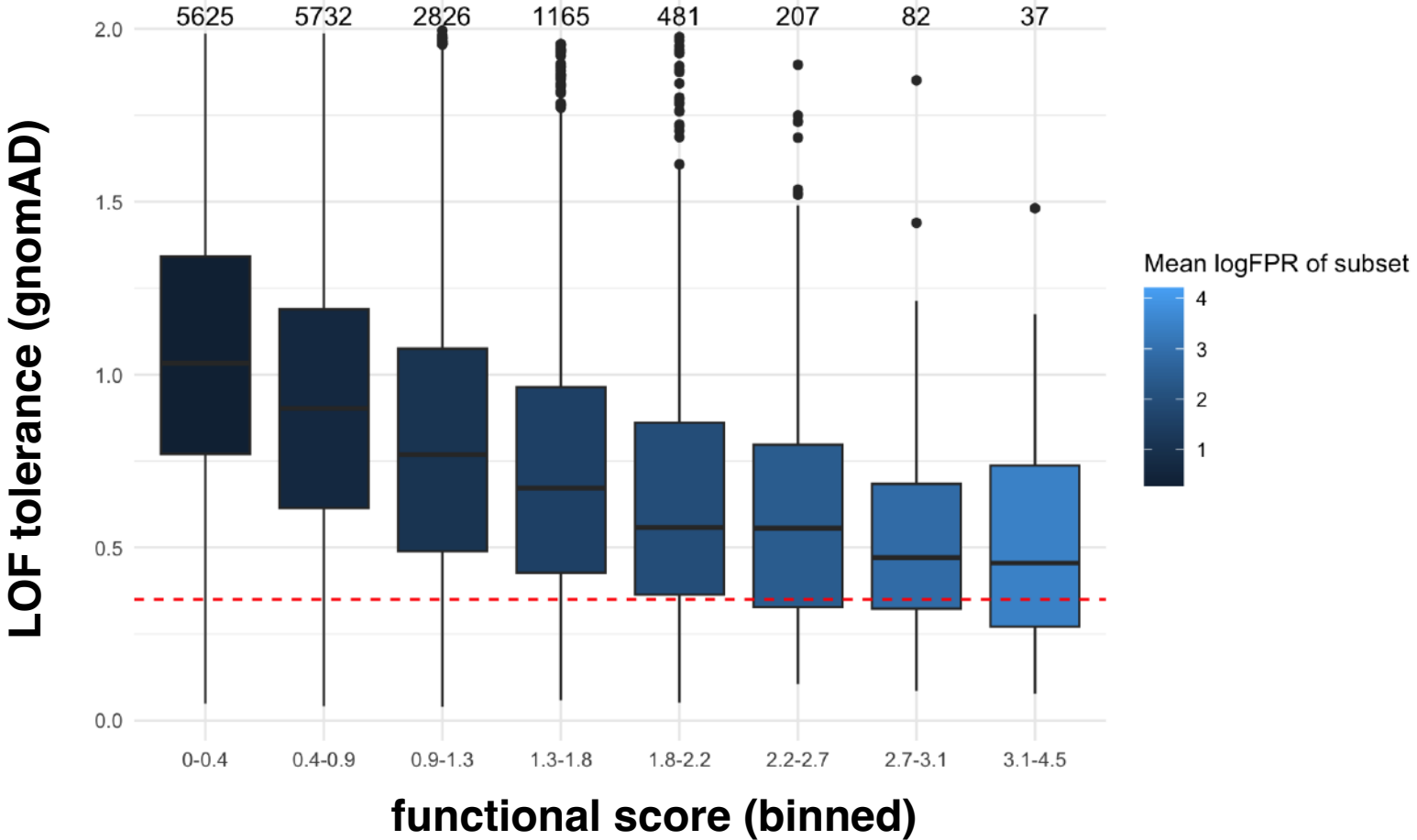
humanbase

CNS DEVELOPMENT AND SYNAPTIC FUNCTION ARE ENRICHED IN EPILEPSY INTERACTOME

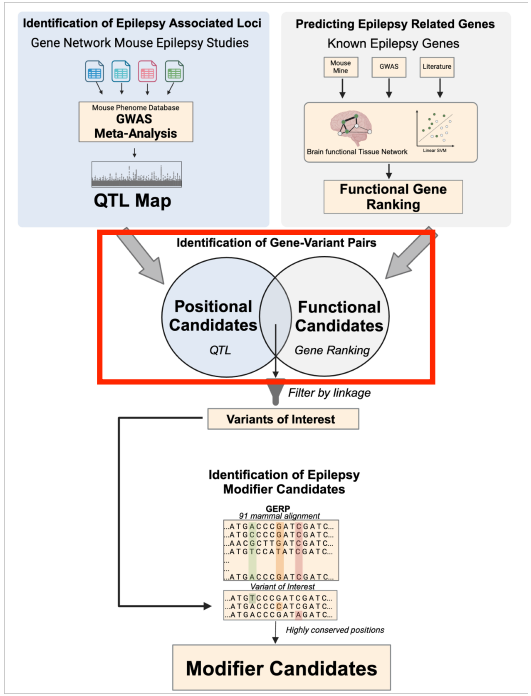


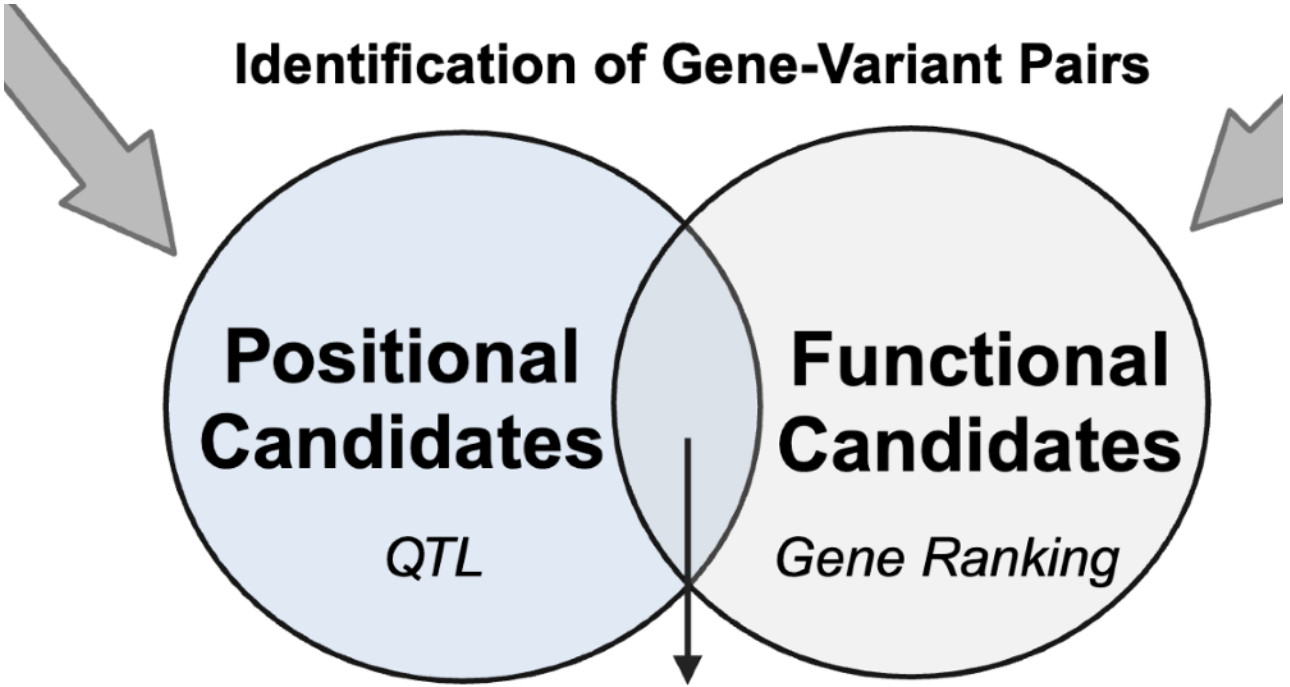
- REVIGO treemap of enriched processed

FUNCTIONAL SCORE CORRELATES WITH LOF TOLERANCE

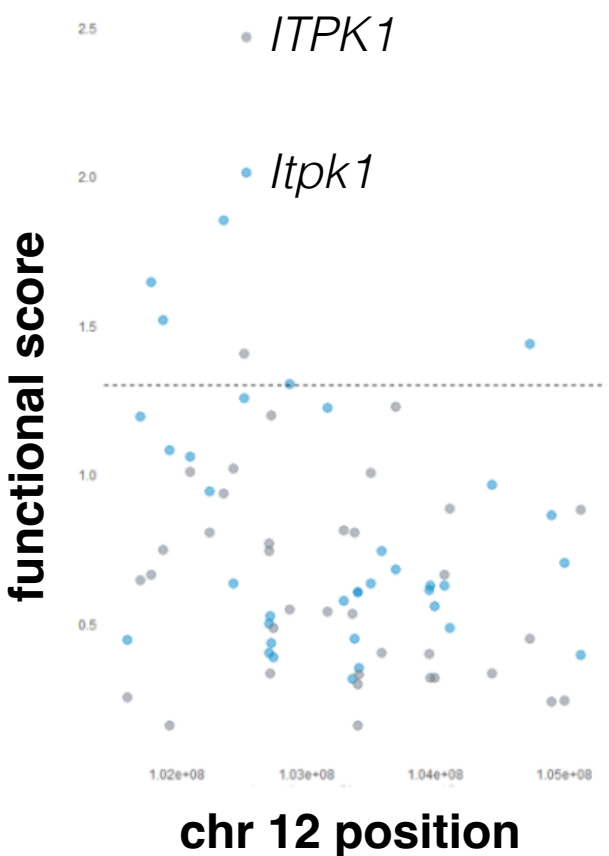


FILTERING TO HIGH-QUALITY CANDIDATE GENES

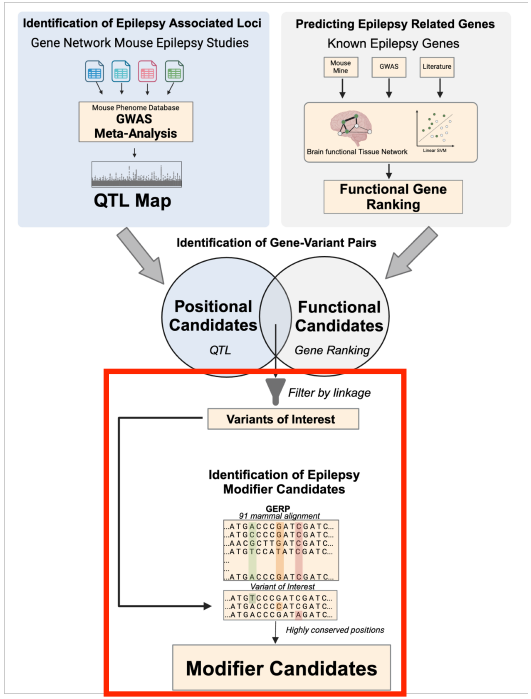


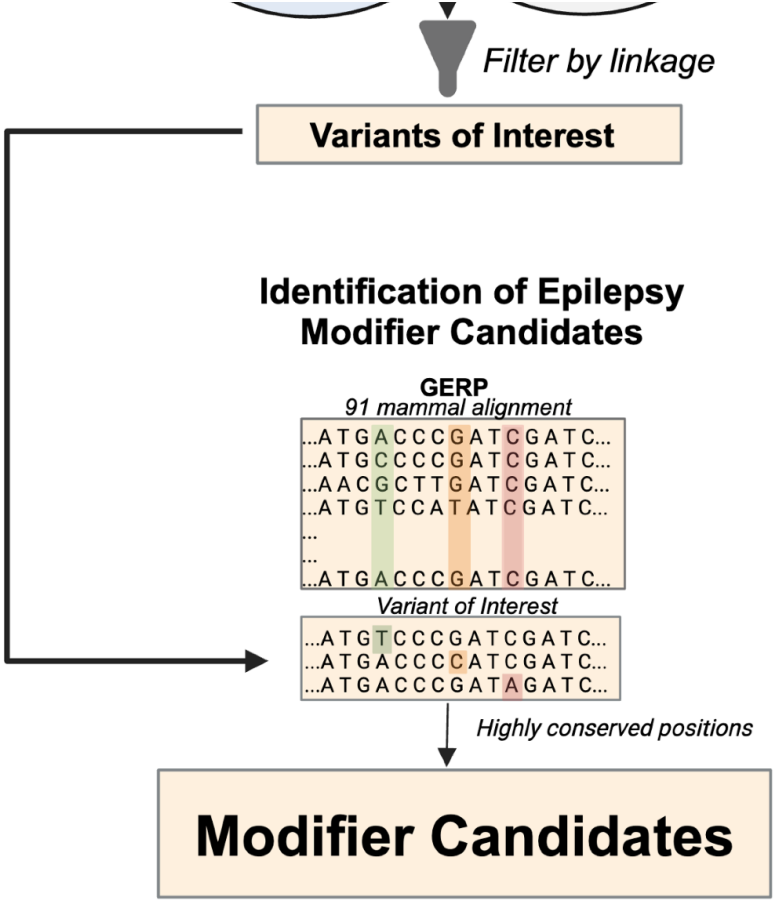


EXAMPLE LOCUS WITH STRONG FUNCTIONAL CANDIDATE



FILTERING TO HIGH-QUALITY CANDIDATE VARIANTS





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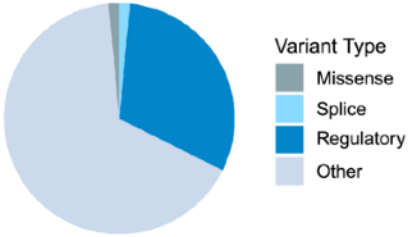
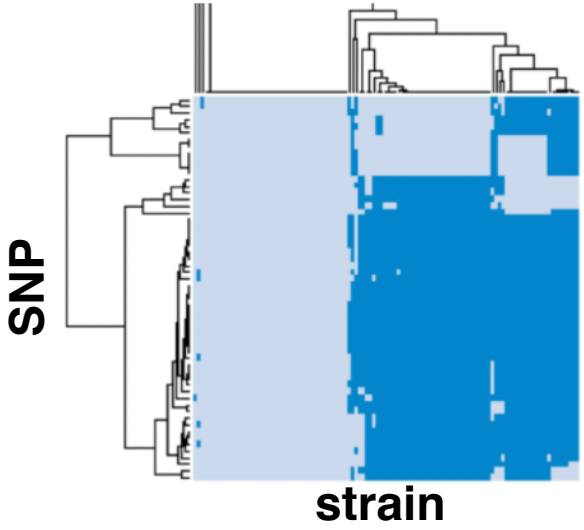
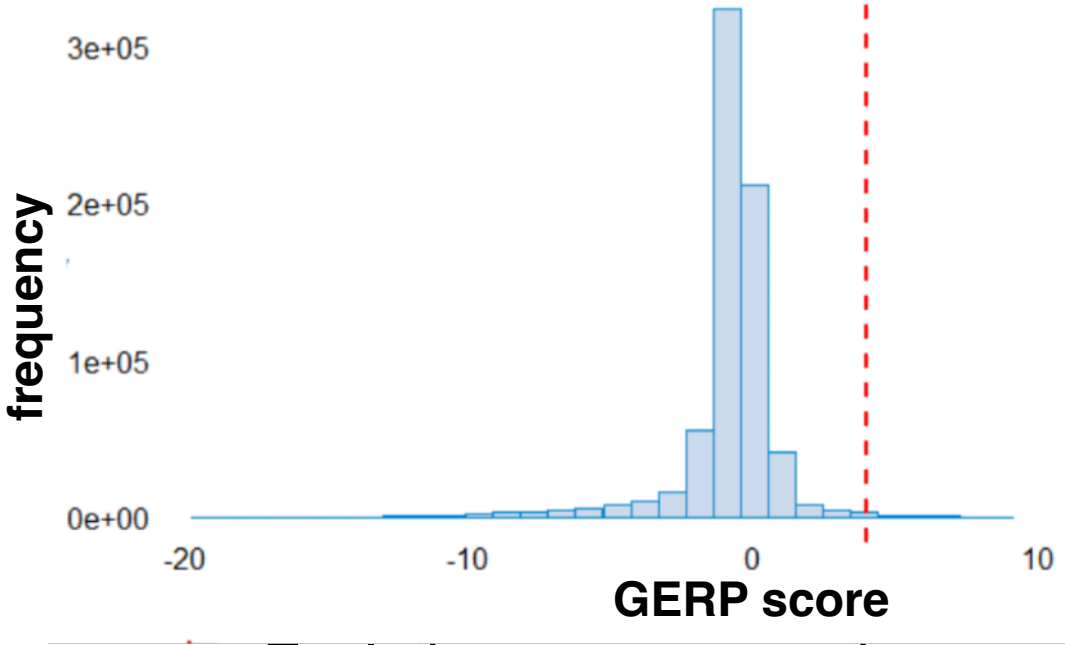






- Example locus on chr 1
- Evolutionary conservation

CANDIDATE MODIFIERS PREDICTED TO DISRUPT TF BINDING SITES

Gene	Predicted Impact of Lower Expression
Igsf21	Inhibited GABAergic synapse differentiation and growth.
Cadps2	Decreased number parvalbumin-positive GABAergic interneurons
Dtna	Inhibited localization of GABA receptors
Itpk1	Modified activity-related response and altered synaptic plasticity
Tenm4	Inhibited neurite outgrowth and differentiation

CONCLUSIONS

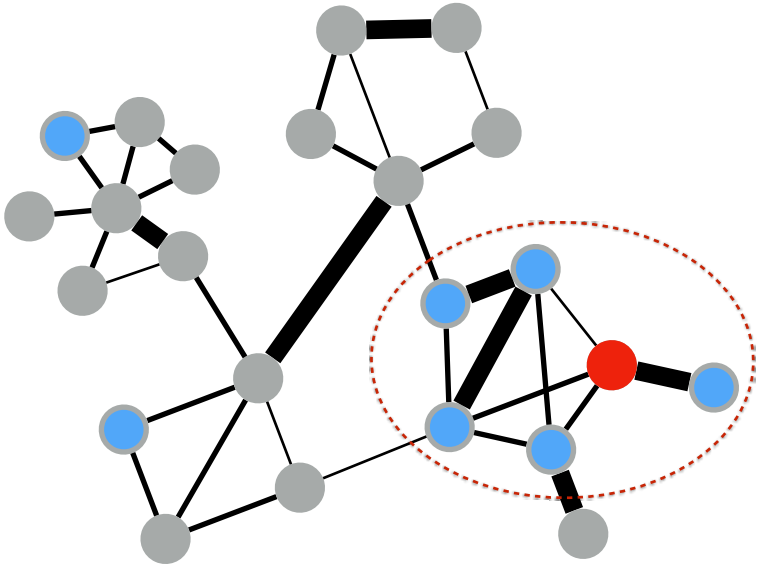
- Shared genetic networks of epilepsy between artificial mouse models and human disease
- Downstream bioinformatics for potential drugs and high-quality targets

PHILOSOPHICAL MUSINGS

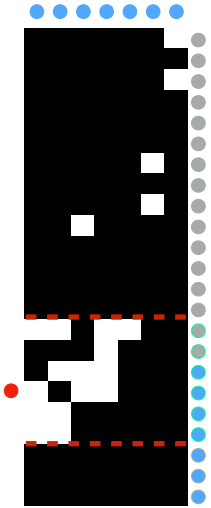
- Networks can reveal the convergence between human and mice
- Network analyses cope will false positives (can loosen stringent mapping criteria)
- Meta-analysis in “biobank scale” data reveals lots of loci

THANKS!

Interactome



Feature matrix



- Propagate annotation of **disease gene** to other genes in the genome

$$class(g) = \text{sign}\left(w_0 + \sum_{p \in P} A_{gp} w_p\right)$$