Regulatory Maps, Gene Networks, and High Throughput Functional Validation

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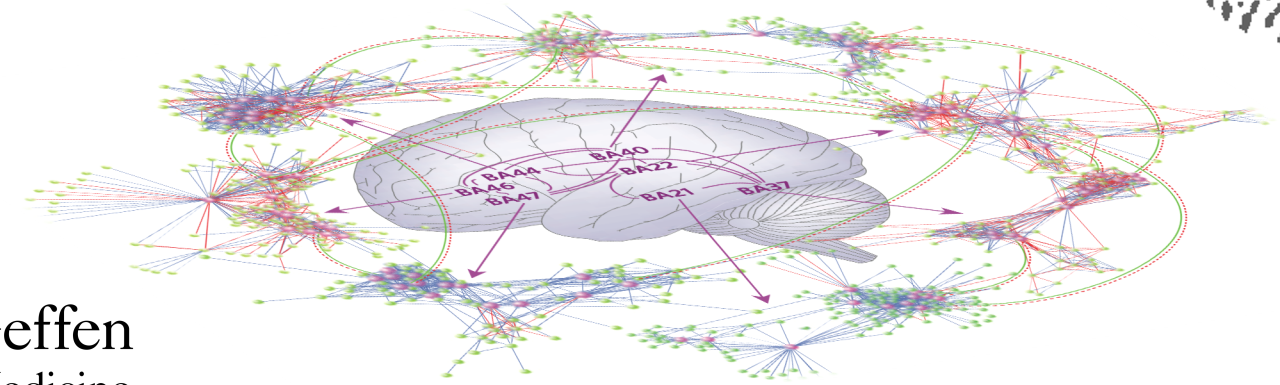
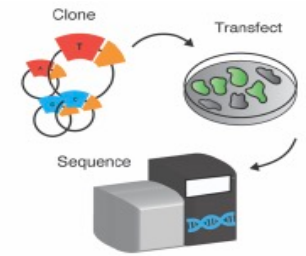


David Geffen School of Medicine

The UCLA Integrative Center for NEUROGENETICS

Three major challenges facing genetic studies of disease

- Which variants are causal?

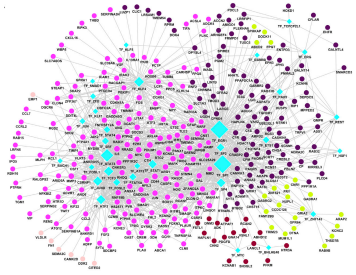


Massively Parallel Reporter Assays (MPRA), CRISPR screens…

- What gene (s) do they regulate?

Chromatin conformation/eQTL….

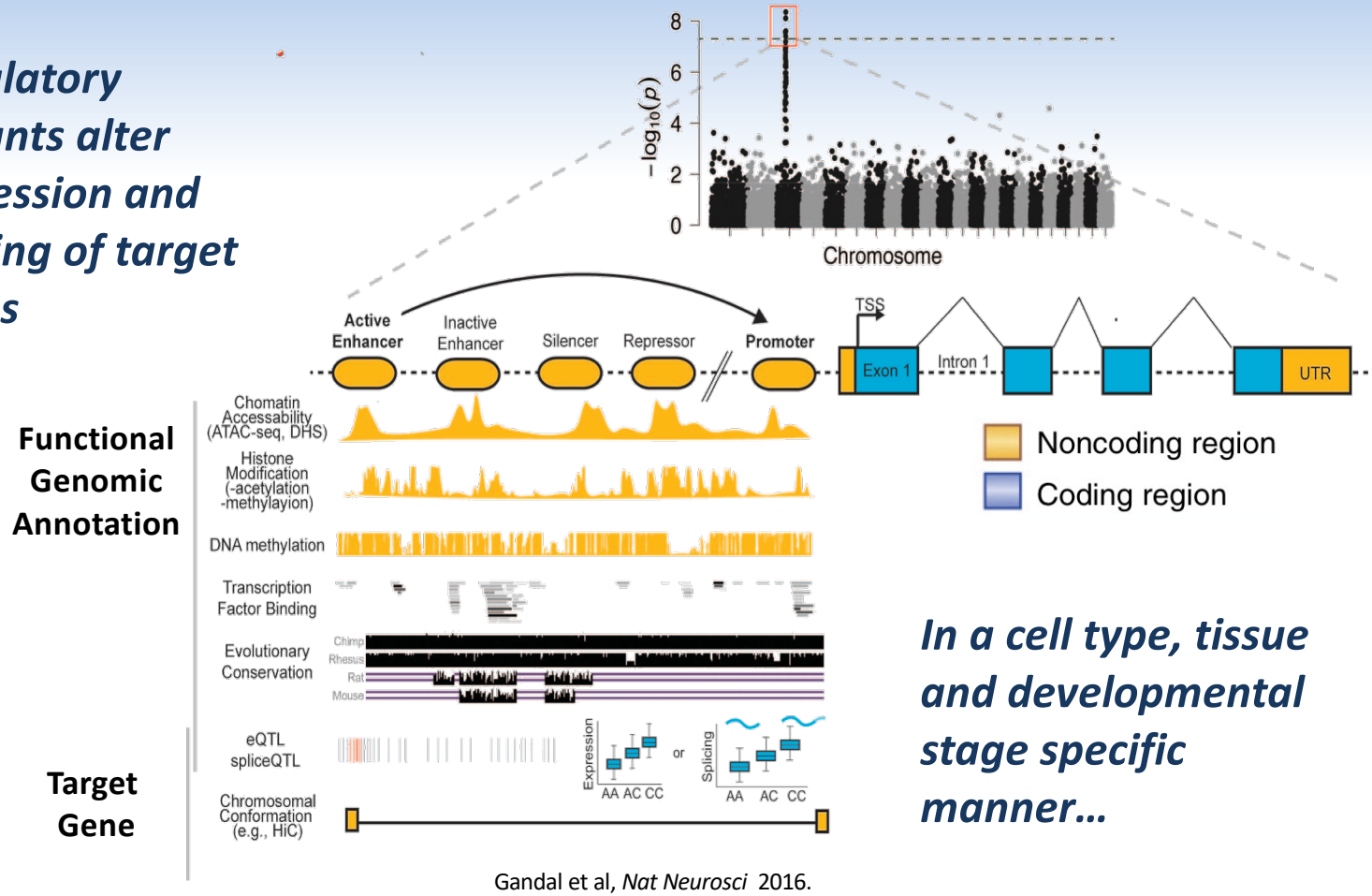
- What is the functional/neurobiological consequence?



Gene Networks

Identifying causal variants and their targets

Regulatory variants alter expression and splicing of target genes

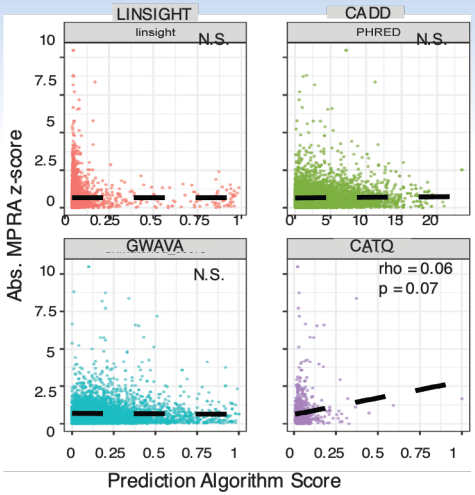


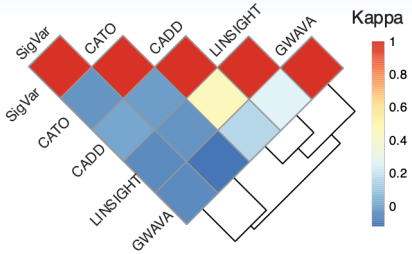
In a cell type, tissue and developmental stage specific manner…

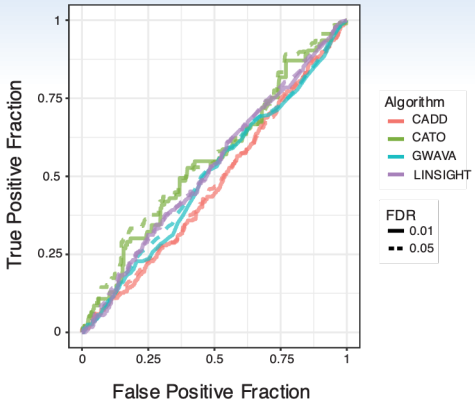
Gandal et al, *Nat Neurosci* 2016.

Which Variants are Causal?:

Predictive algorithms perform poorly





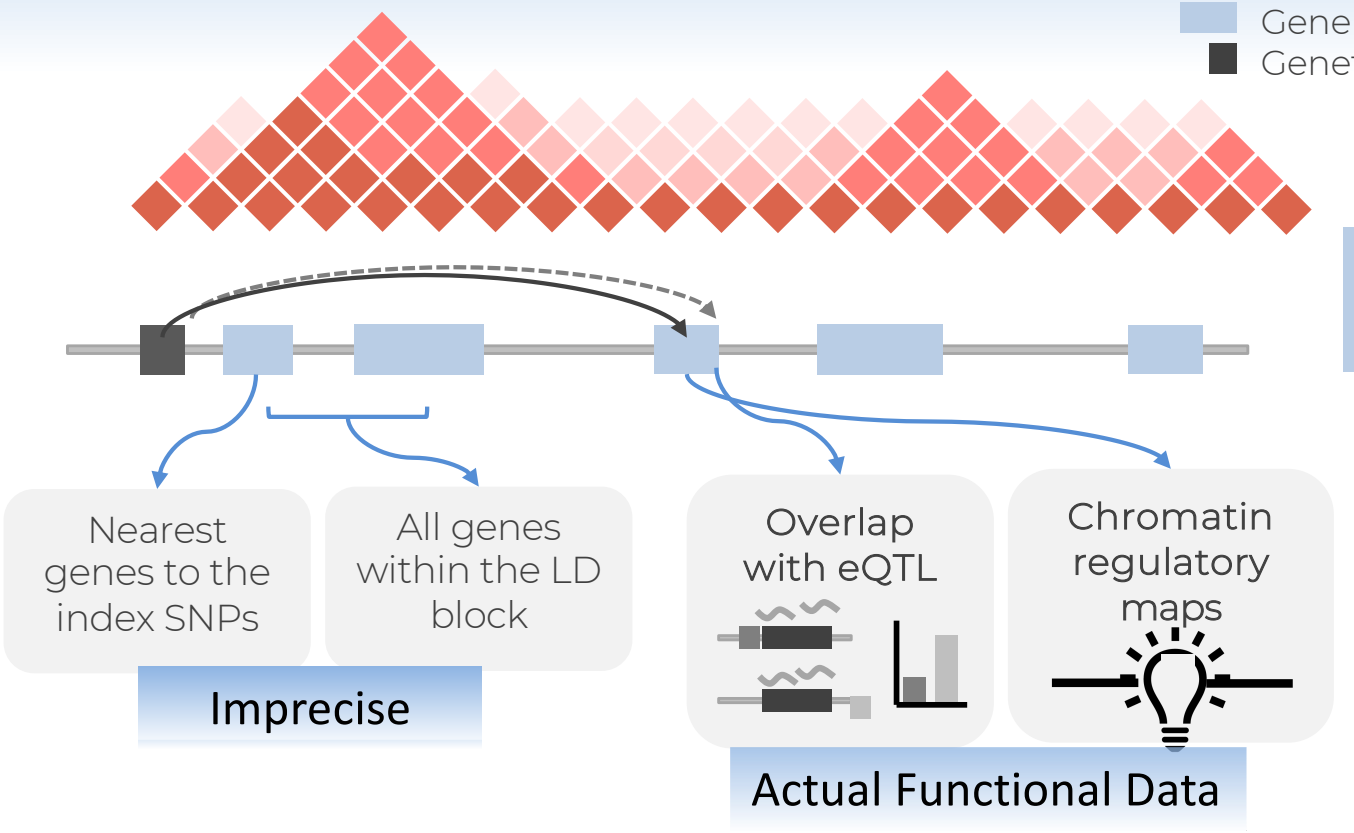


Massively Parallel Reporter Assays: high-throughput experimental testing of regulatory effects of thousands of variants in parallel.

- 20 dementia risk loci, >5000-10,000 variants
- 320 variants are functional
- Validate with CRISPR and add pooled CRISPR screening…..

Yonatan Cooper et al. 2021
BioRxiv:
doi.org/10.1101/2021.06.14.448395

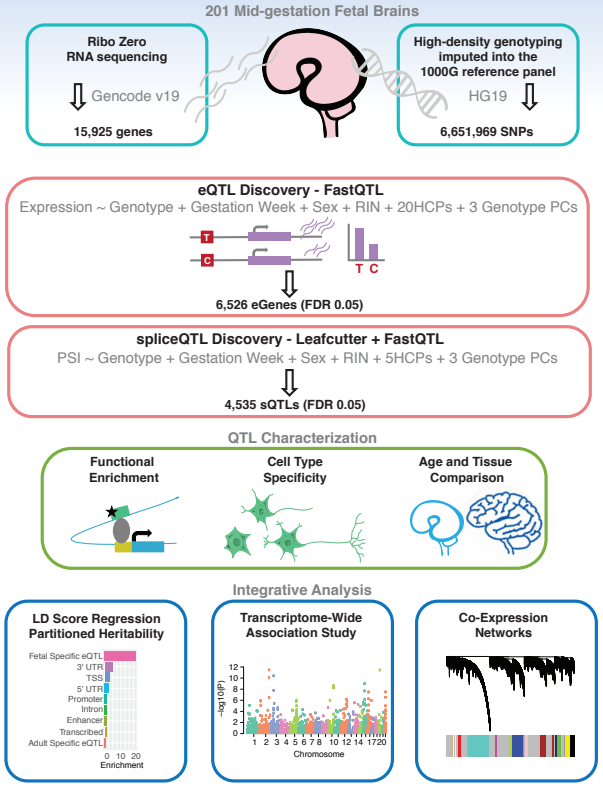
How do we infer target genes for GWAS/Regulatory Variants?



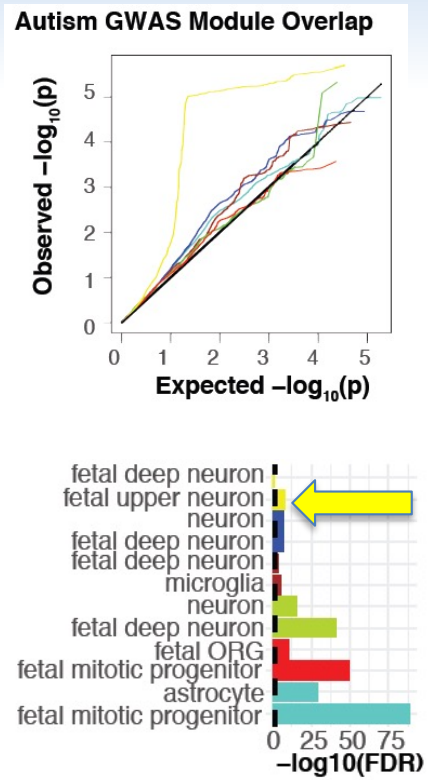
Build Tissue Relevant Regulatory Maps

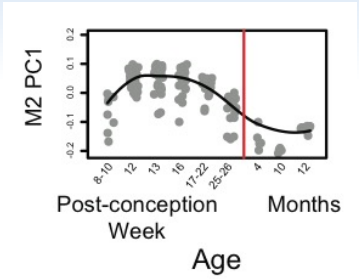
- Won et al. *Nature* (538) 2016
- De La Torre Ubieta et al. *Cell* 2018
- Walker et al. *Cell* 2019
- Cooper et al. *BioRxiv* 2021
- PsychENCODE…

Genetic enrichment in human developmental eQTL



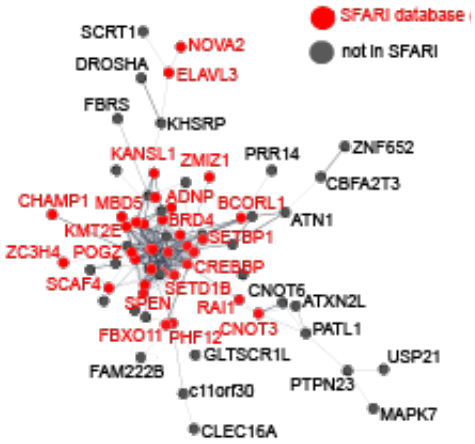
Walker et al. *Cell* 2019





Significant Overlap with Genes impacted by RARE variants: Module M2 from Parikshak et al. *Cell* 2013 **(p = 9.8e-63; OR = 7.3)**

33 SFARI (1/2/Syn) genes out of 146 genes (OR =10.7; p <.0001)

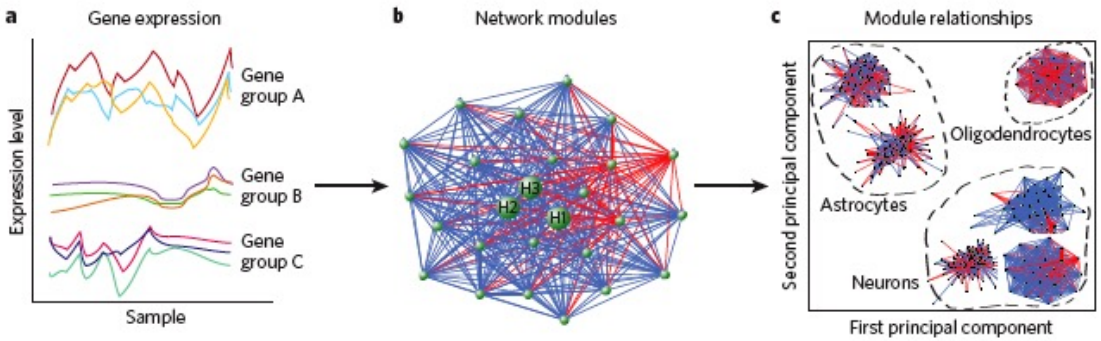


UNLABELED SFARI HUB GENES:

TRRAP	EP400
SRCAP	SETD2
KDM6B	SETD1A
SMARCA4	MED12
TET3	HCFC1
HUWE1	KMT2A
EP300	KMT2C

Katie Eyring PhD

Gene Network Analysis Provides an Organizing Framework



GESCHWIND AND KONOPKA NATURE 2009

Network structure is robust and reproducible. Oldham et al. *Nat Neurosci* 2008; Miller et al. *Nature* 2014; Gandal et al. *Science* 2018; Hartl et al. *Nat Neuro* 2021).

A gene's network position is biologically meaningful. (Horvath et al. 2006; Oldham et al. 2008, Winden et al. 2009; Wexler et al. *Sci Signaling* 2012; Chandran et al. *Neuron* 2016).

Network structure serves as a basis for biological meaningful insights. Parikshak et al. *Nature 2016;* Gandal et al. *Science* 2018a and 2018b; Walker *Cell* 2019; Swarup et al. *Nat Med* 2019, Hartl et al. *Nat Neurosci.* 2021)

- Define the molecular pathology of psychiatric disorders (ASD)

  (Voineagu et al. *Nature* 2011*,* Parikshak et al. *Nature* 2016*)*
- Serves as a quantitative phenotype for cross disorder comparisons

  (Gandal et al. *Science* 2018a,b)
- Basis for genetic enrichment analyses

  (e.g. Swarup et al. *Nat Med 2019, Cell Reports* 2020; Gandal et al. *Science 2018;* Walker et al. *Cell* 2019)
- Permits assessment of reliability and relevance of in vitro models (IPSC –organoids)

  (Stein et al. *Neuron* 2015; Yoon et al. *Nat Methods 2019;* Khan et al. *Nat Med* 2020, Gordon et al. *Nat Neurosci* 2021)

Reverse engineering of disease networks from large-scale gene perturbation data

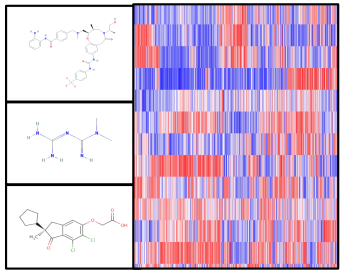
Identify **Drugs/Driver genes** that induce network gene expression patterns

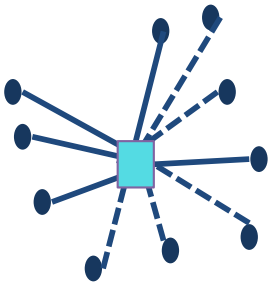
Validate engagement of disease biology or biomarker

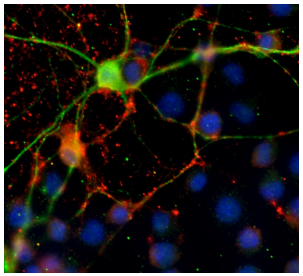
Map validated drugs/genes back to network genes

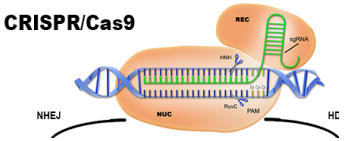
Functionally confirm genes as drug effectors

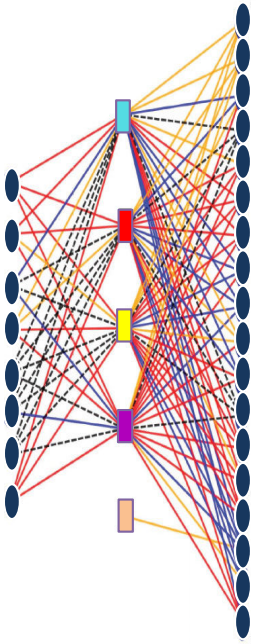
Rebuild the original network from validated drug-target gene maps











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