Integrative genomics in human psychiatric and neurologic disorders for novel therapeutics

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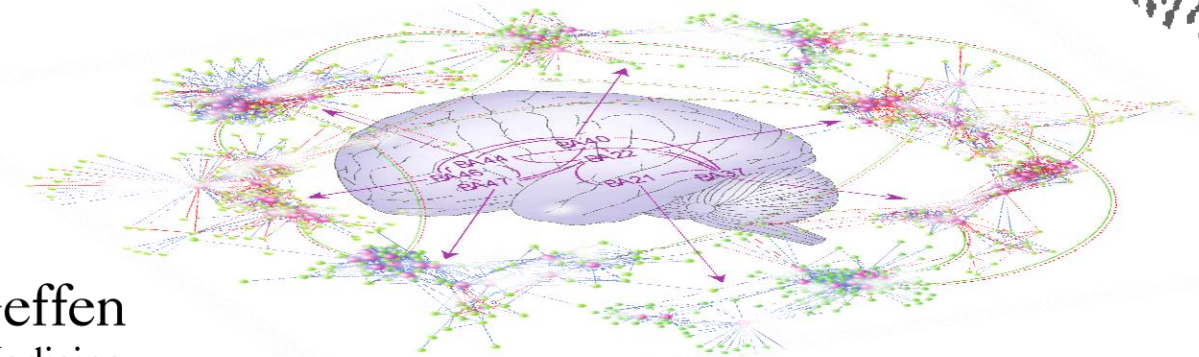
First Annual MGH Conference on Precision Psychiatry

October 1, 2021



David Geffen School of Medicine

The UCLA Integrative Center for NEUROGENETICS

Acknowledgements

Neuropsychiatric Disease

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- – Hyejung Won*
- – Luis De La Torre Ubieta*
- – Gokul Ramaswami
- – Rebecca Walker
- – Damion Pouliadakis
- Vivek Swarup*
- Chris Hartl
- Grant T Belgard
- Elizabeth Ruzzo
- Jenni Lowe

Tau/Dementia Networks:

- Vivek Swarup, PhD
- Jessica Rexach, MD PhD
- Timothy Chang, MD PhD
- Flora Hinz, PhD
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- John Trojanowski, Upenn
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- International FTD-Genomics Consortium (IFGC) for FTD GWAS data

Neural Repair

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Steve Horvath
Clifford J. Woolf (HMS)

- Takao Omura, Michael Costigan

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CIRM CALIFORNIA STEM CELL AGENCY

SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

AGRE Autism Genetic Resource Exchange — A SCIENCE PROGRAM OF AUTISM SPEAKS

NEW YORK GENOME CENTER

The PsychENCODE project

The PsychENCODE Consortium*, Schahram Akbarian, Chunyu Liu, James A Knowles, Flora M Vaccarino, Peggy J Farnham, Gregory E Crawford, Andrew E Jaffe, Dalila Pinto, Stella Dracheva, Daniel H Geschwind, Jonathan Mill, Angus C Nairn, Alexej Abyzov, Sirisha Pochareddy, Shyam Prabhakar, Sherman Weissman, Patrick F Sullivan, Matthew W State, Zhiping Weng, Mette A Peters, Kevin P White, Mark B Gerstein, Geetha Senthil, Thomas Lehner, Pamela Sklar & Nenad Sestan

LARRY L. HILLBLOM FOUNDATION
Advancing Medical Knowledge

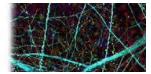
NIH National Institute on Aging

Tau Consortium

Brain Tissue: UCSF, Upenn, Emory, UCLA

The UCLA Integrative Center for NEUROGENETICS

Geschwind Lab



Conflict of Interest

Dr. Geschwind has received research funding or consulting fees from Ovid Therapeutics, Axial Bio-therapeutics, Roche, Acurastem, Takeda and Falcon Computing.

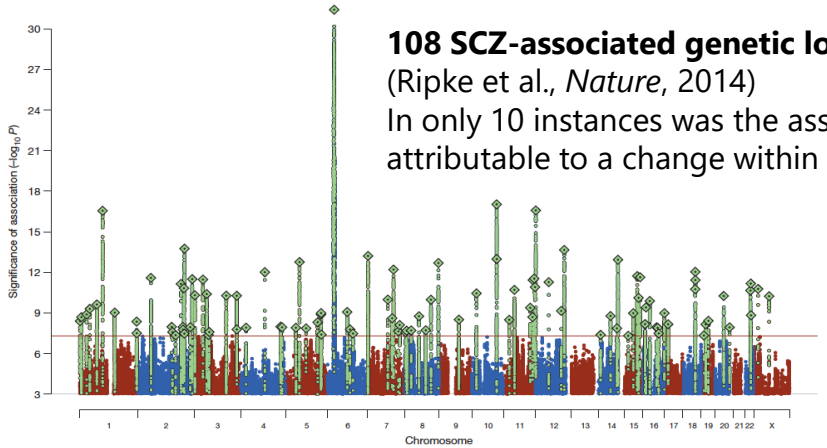
Outline

- Introduce the Challenge
  - Identify functional variants and target genes

  --Grapple with genetic heterogeneity
- Use gene networks to systematically explore nervous system function and disease:
  - Define a molecular pathology of a psychiatric disease in brain and understand how disease risk genes converge on specific biological processes (cells, circuits, pathways).
  - Understand the fidelity of model systems and inform disease modeling.
- Use gene networks as a tool for drug screening

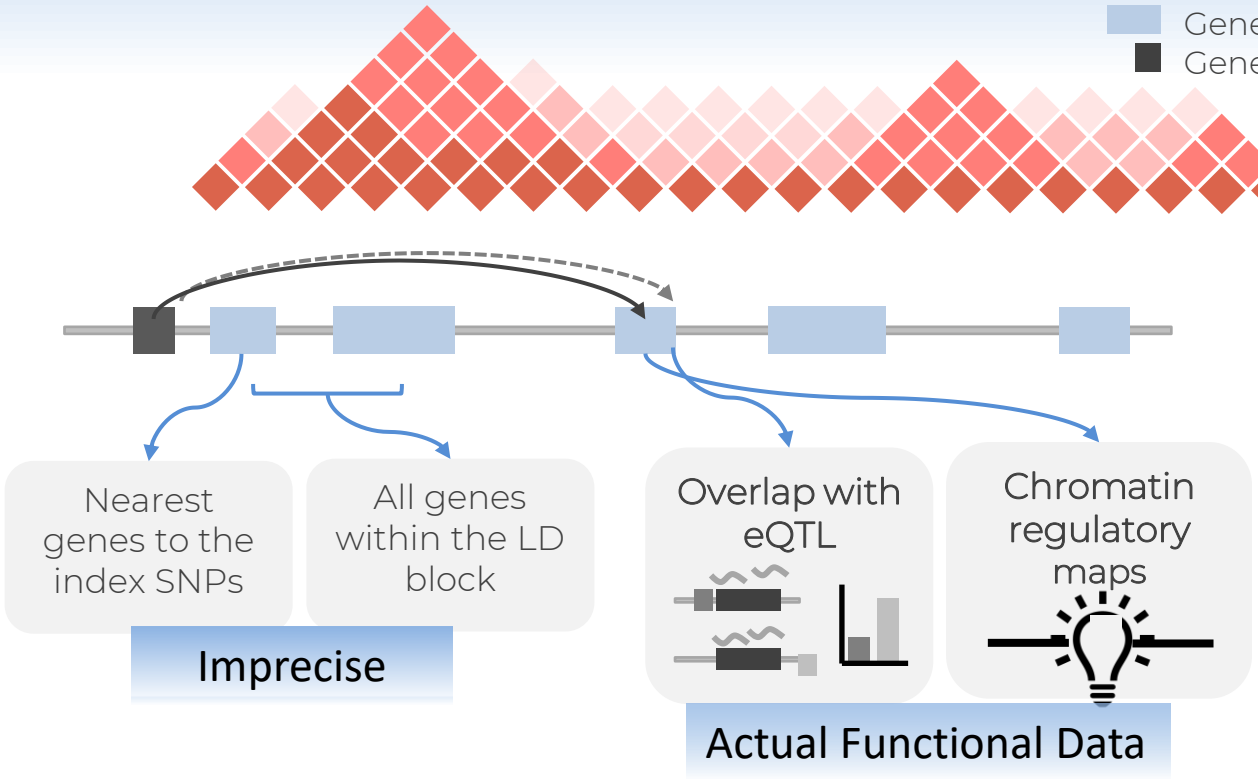
Understand How Genes Act to Cause Disease: Schizophrenia

- Most GWAS SNPs lie in non-coding genomic regions whose function is not known, but thought to regulate other genes (e.g. enhancers).
- Usually, SNPs or enhancers are just assigned to the closest gene, but there is little evidence to support this practice.



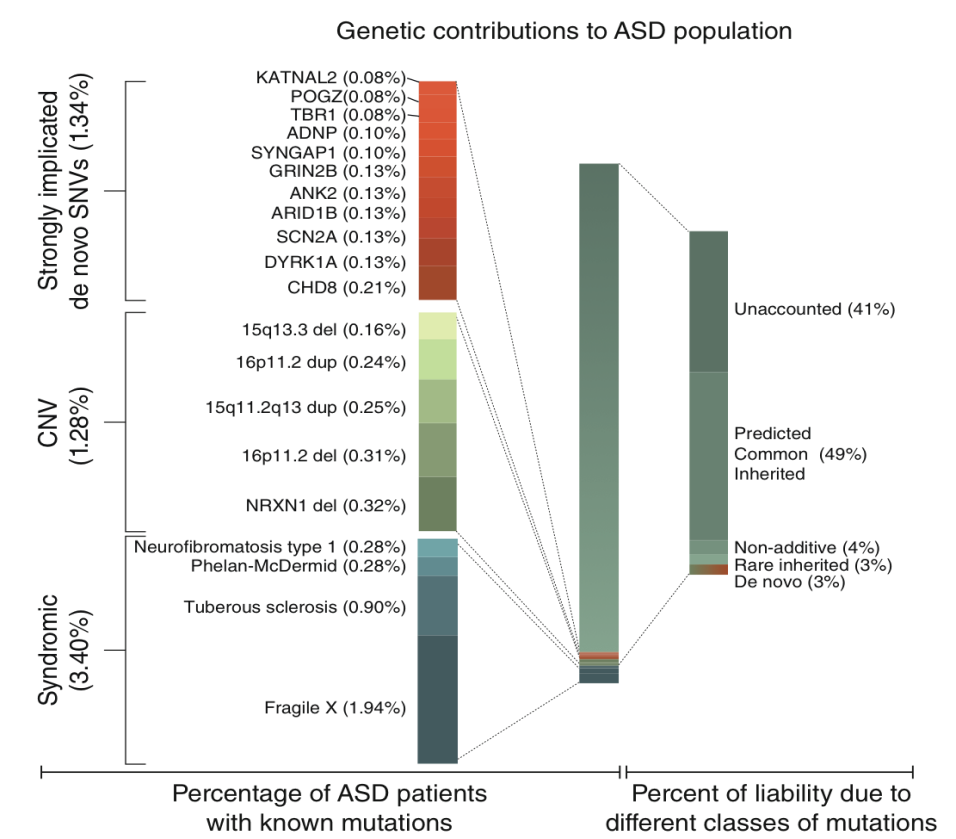
108 SCZ-associated genetic loci
(Ripke et al., *Nature*, 2014)
In only 10 instances was the association signal attributable to a change within a known gene

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



- 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…

ASD: Many forms of genetic variation and modes of inheritance



De La Torre Ubieta et al. *Nat Med* 2016

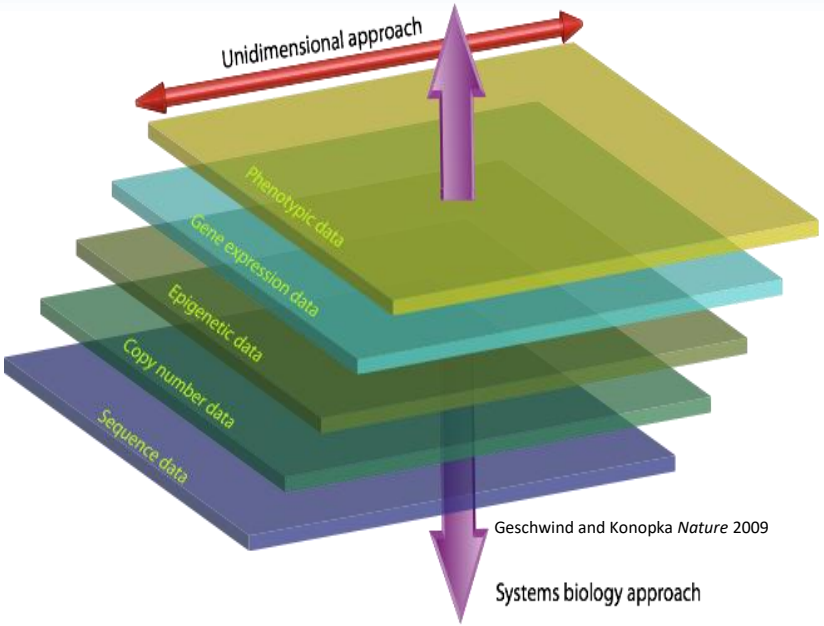
- Many Genes (1000+?)
- None account for >1% of cases
- Highly additive effects
- Strong pleiotropy

We now need to translate these data to the individual

- The genetic data are at the population level.
- We still need to know what comprises disease risk in the individual.
  - What if any mix of pathways is critical?
  - Are their distinct subgroups of disease?
- Whole genome sequencing in large populations will likely be necessary.

Challenges to genetics paradigm in complex disorders

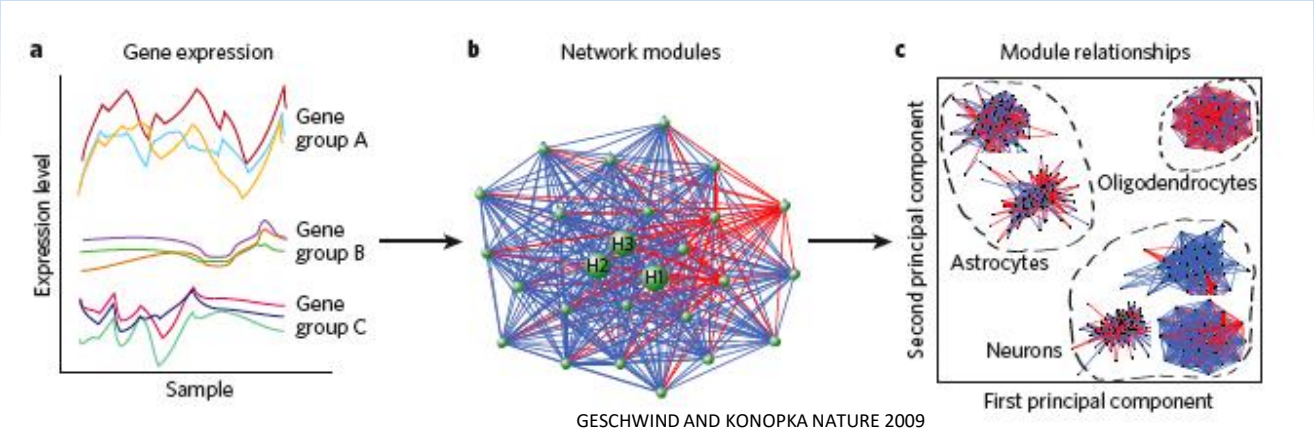
- There is extreme genetic heterogeneity at the population and individual levels.
- Genes don't act in isolation, they are components of biological signaling pathways, and in the brain, complex neural networks.
- Integrative, systems biology approaches are necessary to identify these networks and translate genetic findings into biological mechanism (s).
- Will we have to develop a specific treatment for each disorder, or *will there be convergence* in specific biological pathways, developmental stages/processes or circuitry?



Geschwind and Konopka *Nature* 2009

Weighted Gene Co-expression Network Analysis

(WGCNA; Zhang and Horvath 2005)



GESCHWIND AND KONOPKA NATURE 2009

Network structure is robust and reproducible (it is real: Oldham et al. *Nat Neurosci* 2008; Miller et al. P*NAS* 2010;Voineagu et al. *Nature* 2011; Parikshak et al. *Cell* 2013; Miller et al. *Nature* 2014; Hartl et al. *Nat Neuro* 2021).

A gene's network position is biologically meaningful

We can identify groups of co-expressed genes called modules that correspond to key elements of biological function (Oldham et al. 2008; Winden et al. *Mol Sys Bio* 2009; Voineagu et al. *Nature* 2011).

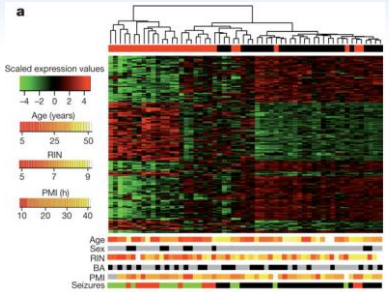
And within modules, we can identify the most central, "hub" genes (Horvath et al. 2006; Oldham et al. 2008, Winden et al. 2009; Wexler et al. *Sci Signaling* 2012; Chandran et al. *Neuron* 2016).

This structure serves as a basis for identification of biological meaningful insights

- Comparative network analysis – modules (Gandal et al. *Science* 2018a and 2018b; Walker *Cell* 2019)
- Comparative network analysis - gene connectivity (Hartl et al. *Nat Neurosci.* 2021)
- Guilt by association—functional annotation (Winden et al. 2009; Hartl et al. 2021)

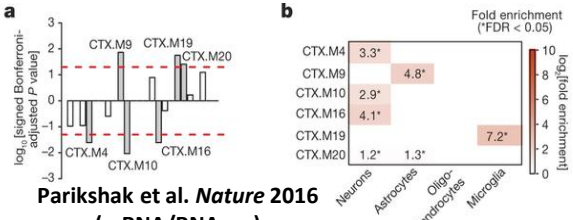
Despite extensive genetic heterogeneity there is a convergent pattern of pathology in post mortem brain from subjects who had ASD

- Two thirds of cases show up-regulation of microglia and astrocyte genes.
- There is parallel down-regulation of neuronal genes involved in vesicle transport and synaptic signaling.
- A “major locus” form of ASD, (dup)15q11-13 shares this pattern.
- Causal genes affect the neuronal component predominantly.
- Cortex Wide (Haney et al. BioRxiv 2020)

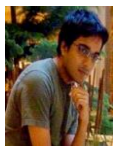


Irina Voineagu PhD

Voineagu et al. *Nature* 2011 (mRNA/microarray)



Parikshak et al. *Nature* 2016 (mRNA/RNAseq)



Neel Parikshak,

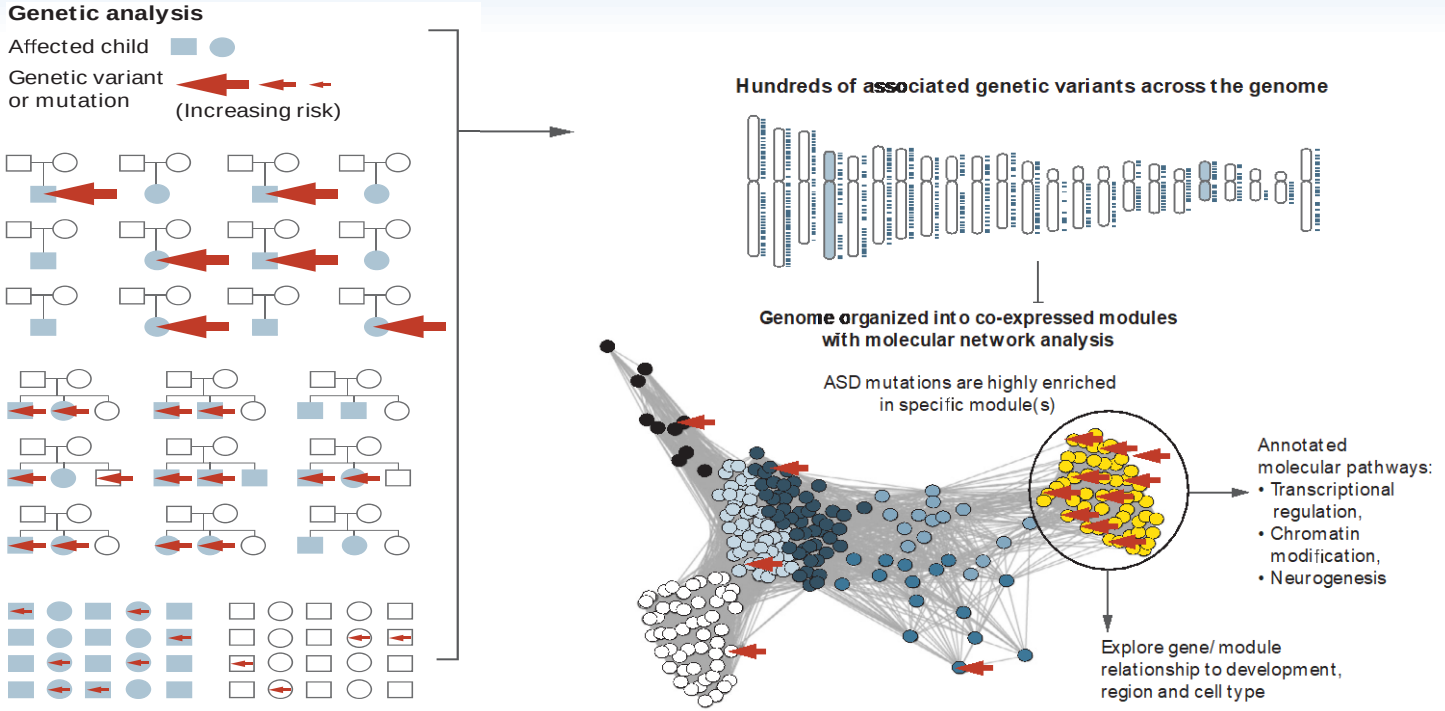
Vivek Swarup,

Grant Belgard,

Gandal et al. 2018

- Massively refined transcriptional networks in ASD and extend comparisons to other disorders (SCZ and BD)..
- Isoforms show larger disease and cell type specificity than gene level analysis!
- ASD, BD and SCZ impact distinct pathways and cell type vulnerability.

Do ASD Risk Genes Converge on Any Developmental Time Point or Biological Process?



Parikshak et al. *Cell* 2013; Parikshak et al. *Nat Rev Genet* 2015; Geschwind and Flint *Science* 2015

ASD risk genes map onto specific pathways and developmental networks

Timing:

ASD genes from multiple sources converge on prenatal neuro-developmental processes.

Regulation:

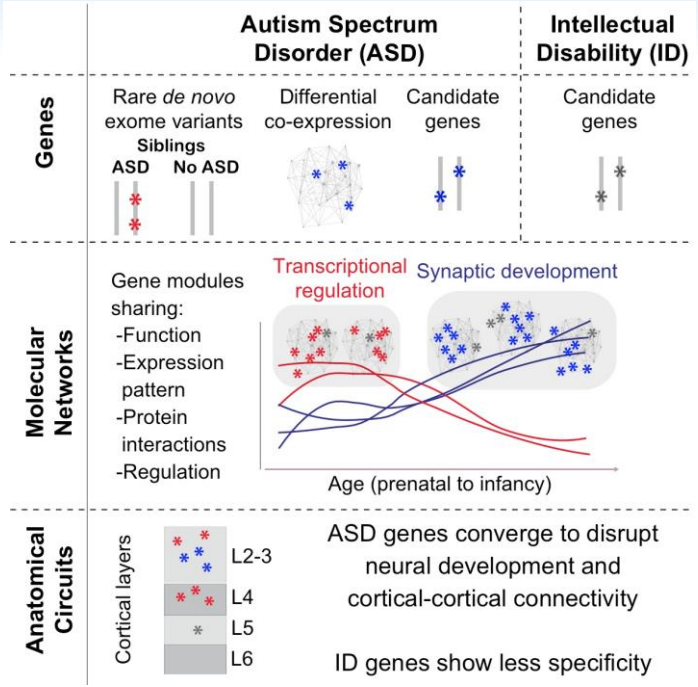
Transcriptional and translational co-regulation link ASD genes at multiple levels.

Cell types/circuits:

Multiple ASD risk gene modules are enriched in cortical glutamatergic projection neurons.

Specificity:

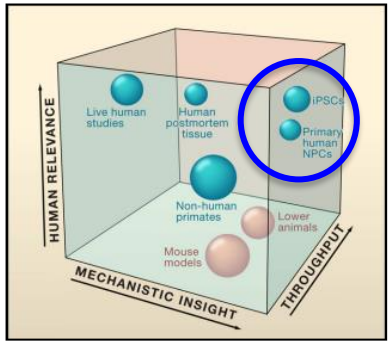
These patterns highlight features that distinguish ASD from ID.



Parikshak et al. *Cell* 2013
Ruzzo et al. *Cell* 2019

We have good *in vitro* tools for modeling the effects of mutations in the proper cell context

- Gene networks inform the validity of in vitro models



Functional cortical neurons and astrocytes from human pluripotent stem cells in 3D culture

Anca M Paşca[1,13], Steven A Sloan[2,13], Laura E Clarke[2], Yuan Tian[3–5], Christopher D Makinson[6], Nina Huber[7], Chul Hoon Kim[8,9], Jin-Young Park[7], Nancy A O'Rourke[10], Khoa D Nguyen[11], Stephen J Smith[10,12], John R Huguenard[6], Daniel H Geschwind[3–5], Ben A Barres[2] & Sergiu P Paşca[7]

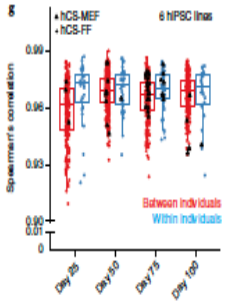
NATURE METHODS | VOL.12 NO.7 | JULY 2015

- *How well do these human model systems recapitulate human neural development and function?*
- *We can use the in vivo gene networks that we have identified to determine this.*

nature methods
BRIEF COMMUNICATION
https://doi.org/10.1038/s41592-018-0255-0

Reliability of human cortical organoid generation

Se-Jin Yoon[1], Lubayna S. Elahi[1], Anca M. Paşca[2], Rebecca M. Marton[1], Aaron Gordon[3], Omer Revah[1], Yuki Miura[1], Elisabeth M. Walczak[4], Gwendolyn M. Holdgate[4], H. Christina Fan[4], John R. Huguenard[5], Daniel H. Geschwind[3,6] and Sergiu P. Paşca[1,7]*

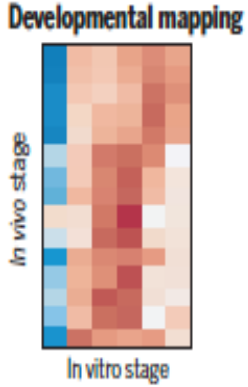


RESEARCH ARTICLE SUMMARY

NEUROGENETICS

Chromatin accessibility dynamics in a model of human forebrain development

Alexandro E. Trevino*, Nasa Sinnott-Armstrong*, Jimena Andersen*, Se-Jin Yoon, Nina Huber, Jonathan K. Pritchard, Howard Y. Chang, William J. Greenleaf†, Sergiu P. Paşca†



3-D cultures model prenatal and postnatal development

nature neuroscience
ARTICLES
https://doi.org/10.1038/s41593-021-00802-y
Check for updates
2021

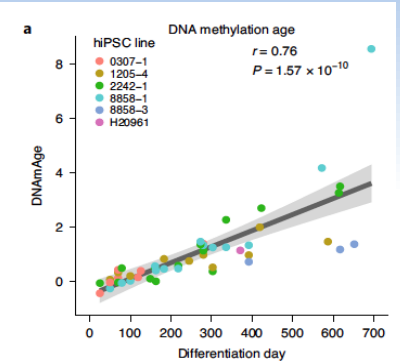
Long-term maturation of human cortical organoids matches key early postnatal transitions

Aaron Gordon[1], Se-Jin Yoon[2,3], Stephen S. Tran[4,5], Christopher D. Makinson[6], Jin Young Park[2,3], Jimena Andersen[2,3], Alfredo M. Valencia[2,3], Steve Horvath[7,8], Xinshu Xiao[5,9,10], John R. Huguenard[6], Sergiu P. Pașca[2,3] ✉ and Daniel H. Geschwind[1,8,11,12] ✉

- Transcription
- Methylation/Epigenetic Clock
- RNA editing
- Physiological Switches

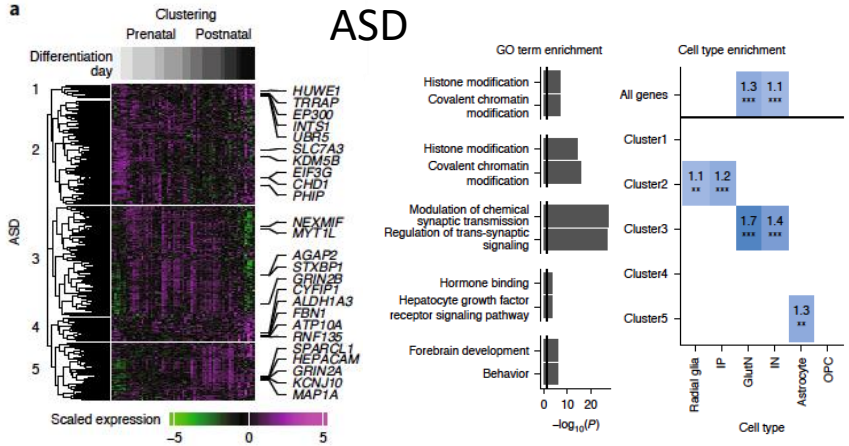
Browser: Gene **E**xpression in **C**ortical **O**rganoids

http://solo.bmap.ucla.edu/shiny/GECO/

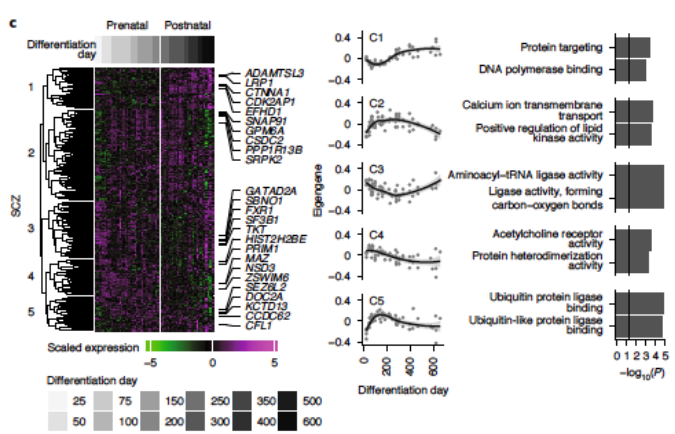


Risk Genes fall into distinct expression trajectories and biology pathways

ASD



SCZ



CAN WE TARGET A NETWORK?

Matching transcriptional profiles from gene networks to find drugs

ConnectivityMap

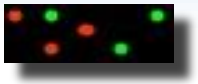
Lamb et al., Science 2006.

Broad Connectivity Map:
7,000 expression profiles in cells after treatment with 1309 “FDA-approved” compounds*.

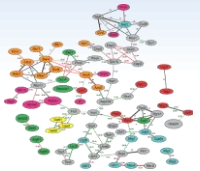
Pattern Matching

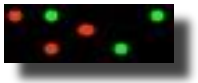
Gene Expression in Disease Models or Patient Tissue:
Measure expression profiles

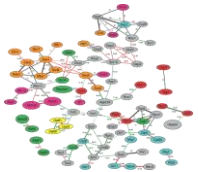
Identify Drugs that Reverse Pattern:
Test the Drugs in Model Systems



Gene expression classifier







(e.g. Chandran et al. *Neuron* 2016)

*now > 1M profiles in many cell types

Use Core Transcriptional Programs to Identify Drugs:

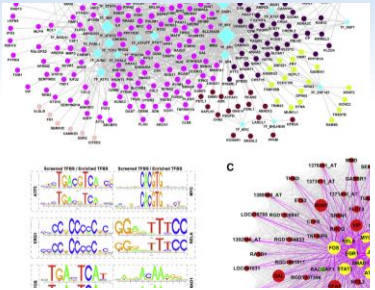
- **That promote regeneration in the CNS:**

Neuron
Article
Neuron 89, 2016

CellPress

A Systems-Level Analysis of the Peripheral Nerve Intrinsic Axonal Growth Program

Vijayendran Chandran,[1] Giovanni Coppola,[1,8] Homaira Nawabi,[2] Takao Omura,[2] Revital Versano,[1] Eric A. Huebner,[2] Alice Zhang,[3] Michael Costigan,[2] Ajay Yekkirala,[2] Lee Barrett,[2] Armin Blesch,[4,9] Izhak Michaelevski,[5,10] Jeremy Davis-Turak,[1,11] Fuying Gao,[6] Peter Langfelder,[6,7] Steve Horvath,[6,7] Zhigang He,[2] Larry Benowitz,[2] Mike Fainzilber,[5] Mark Tuszynski,[4] Clifford J. Woolf,[2] and Daniel H. Geschwind[1,6,*]

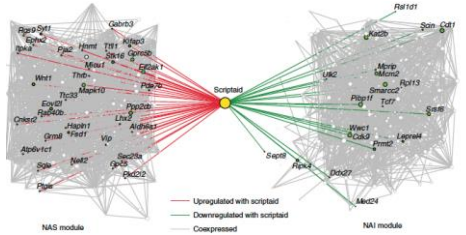


- **That inhibit neurodegeneration:**

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-018-0223-3

Identification of evolutionarily conserved gene networks mediating neurodegenerative dementia

Vivek Swarup[1,11], Flora I. Hinz[1,11], Jessica E. Rexach[1], Ken-ichi Noguchi[2], Hiroyoshi Toyoshiba[2], Akira Oda[2], Keisuke Hirai[2], Arjun Sarkar[1], Nicholas T. Seyfried[3,4], Chialin Cheng[5], Stephen J. Haggarty[5], International Frontotemporal Dementia Genomics Consortium[6], Murray Grossman[7], Vivianna M. Van Deerlin[8], John Q. Trojanowski[8], James J. Lah[4], Allan I. Levey[4], Shinichi Kondou[2] and Daniel H. Geschwind[1,9,10]*

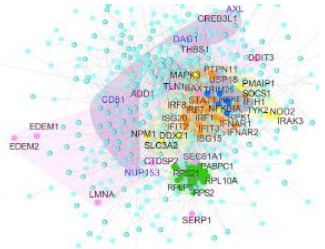


- **That modify neuroinflammation:**

Article
Cell Reports

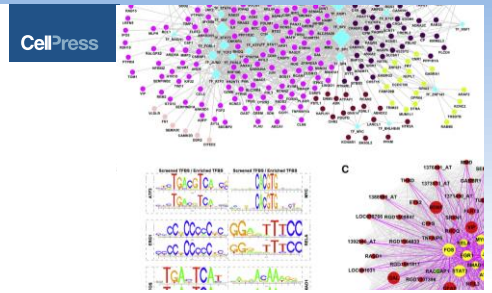
Tau Pathology Drives Dementia Risk-Associated Gene Networks toward Chronic Inflammatory States and Immunosuppression

Rexach et al. Cell Reports 33, 108398, November 17, 2020



In each case, we have a clear phenotypic readout for validation

Neuron
Article *Neuron* 89, 2016



A Systems-Level Analysis of the Peripheral Nerve Intrinsic Axonal Growth Program

Vijayendran Chandran,[1] Giovanni Coppola,[1,8] Homaira Nawabi,[2] Takao Omura,[2] Revital Versano,[1] Eric A. Huebner,[2] Alice Zhang,[3] Michael Costigan,[2] Ajay Yekkirala,[2] Lee Barrett,[2] Armin Blesch,[4,9] Izhak Michaelevski,[5,10] Jeremy Davis-Turak,[1,11] Fuying Gao,[8] Peter Langfelder,[6,7] Steve Horvath,[6,7] Zhigang He,[2] Larry Benowitz,[2] Mike Fainzilber,[5] Mark Tuszynski,[4] Clifford J. Woolf,[2] and Daniel H. Geschwind[1,6,*]

- We identify a transcriptional program observed after PNS, but not CNS injury in rodents **(integrating dozens of data sets)**
- This program links known signaling pathways via a core set of transcription factors **(conserved at PPI level in humans)**
- We experimentally and bio-informatically validate several network predictions **(identify and validate putative drivers)**
- We use the core transcriptional profile to identify a drug that promotes regeneration **(combine pharmacology and genetic screens)**

Giovanni Coppola

VJ Chandran

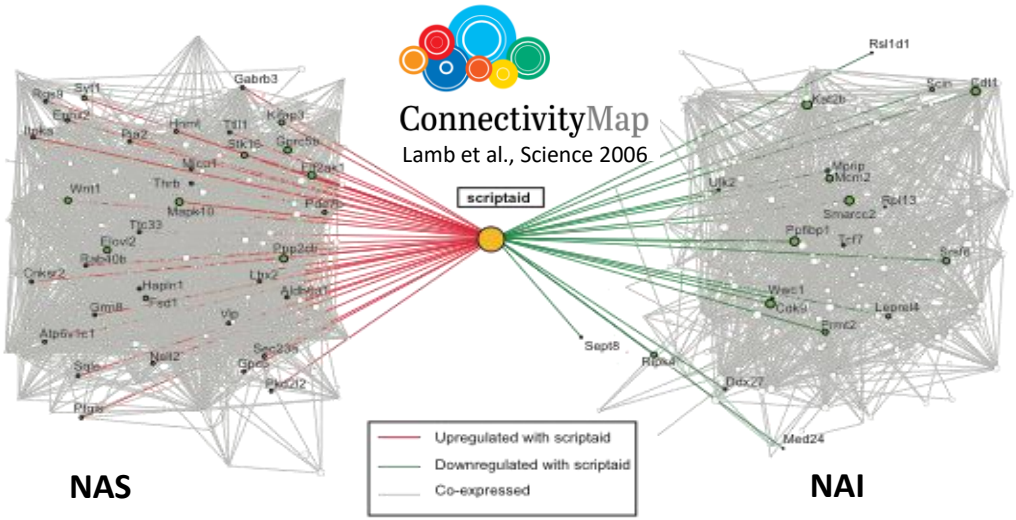
Use neurodegeneration-associated modules to screen CMAP

(Hypothesis: reversal of these robustly associated patterns should ameliorate cell death)

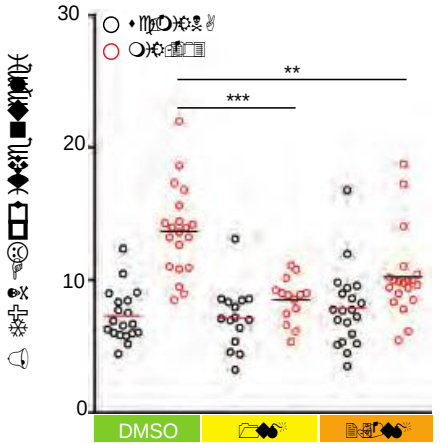
nature medicine ARTICLES
https://doi.org/10.1038/s41591-018-0223-3

Identification of evolutionarily conserved gene networks mediating neurodegenerative dementia

Vivek Swarup[1,11], Flora I. Hinz[1,11], Jessica E. Rexach[1], Ken-ichi Noguchi[2], Hiroyoshi Toyoshiba[2], Akira Oda[2], Keisuke Hirai[2], Arjun Sarkar[1], Nicholas T. Seyfried[3,4], Chialin Cheng[5], Stephen J. Haggarty[5], International Frontotemporal Dementia Genomics Consortium[6], Murray Grossman[7], Vivianna M. Van Deerlin[8], John Q. Trojanowski[8], James J. Lah[4], Allan I. Levey[4], Shinichi Kondou[2] and Daniel H. Geschwind[1,9,10]*



- Identify drugs with opposing gene network changes
- 4/6 HDAC inhibitors identified in top hits (permutation, $p < 10^{-5}$)
- Do they inhibit cell death?



Scriptaid

Swarup et al. *Nat Med* 2019

Article

Tau Pathology Drives Dementia Risk-Associated Gene Networks toward Chronic Inflammatory States and Immunosuppression

Cell Reports

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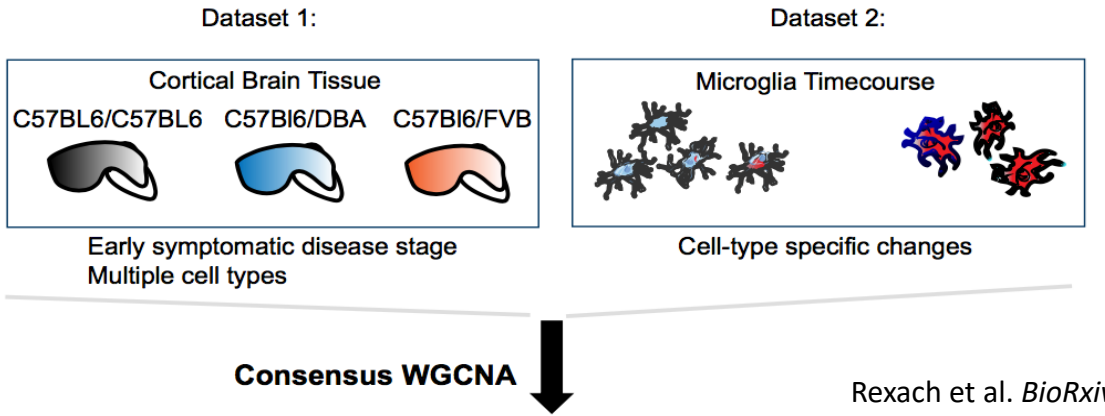
Opportunity:
Neurodegeneration involves sequential neuropathological stages involving multiple cell types

Problem:
Microglial molecular changes are confounded at the ***tissue-level*** changes in cell-type abundance and marker gene regulation

Solution: Integrating microglia specific time course data with bulk tissue to delineate microglial transitions phased with tissue-level pathological stages.



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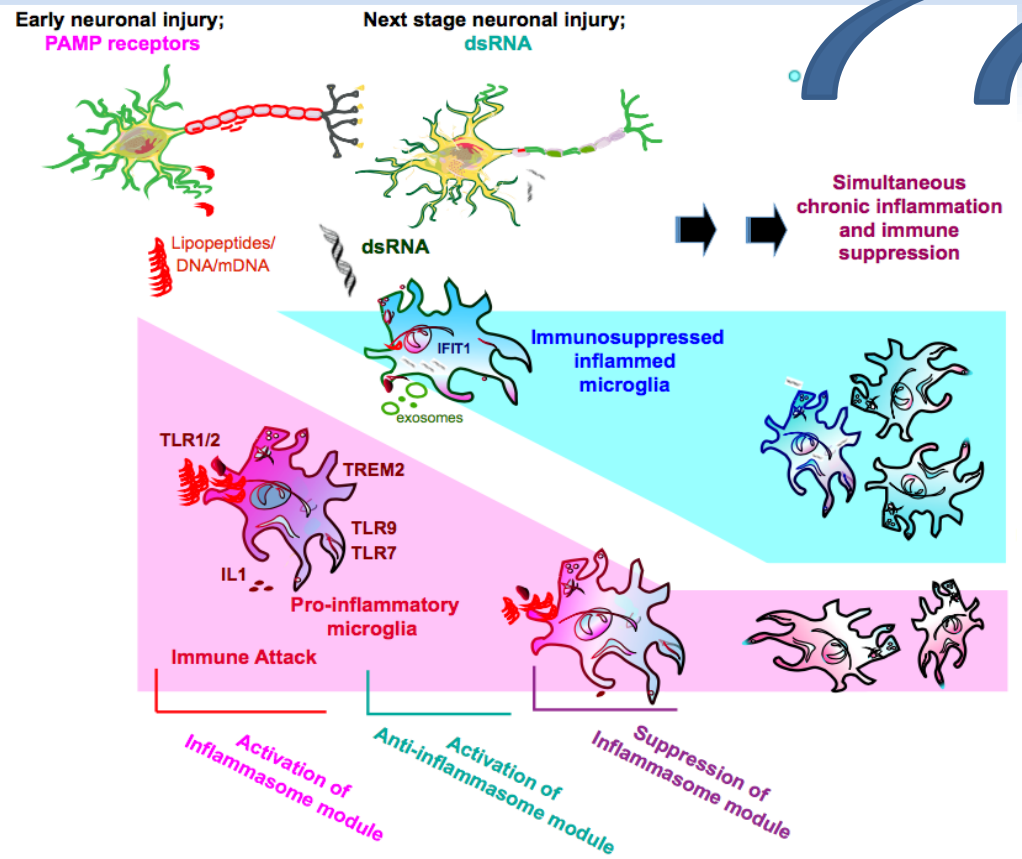
Early microglia activity includes both immune activators and suppressors that we can distinguish and chemically reprogram

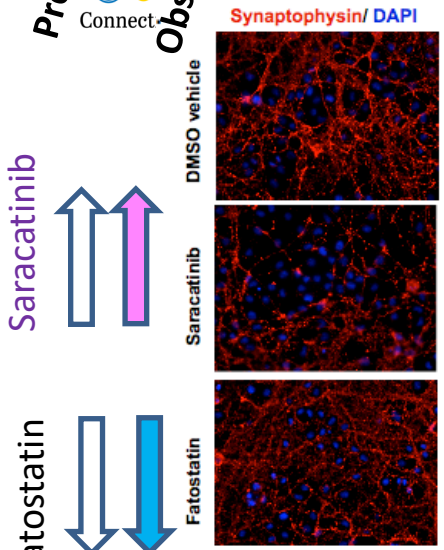


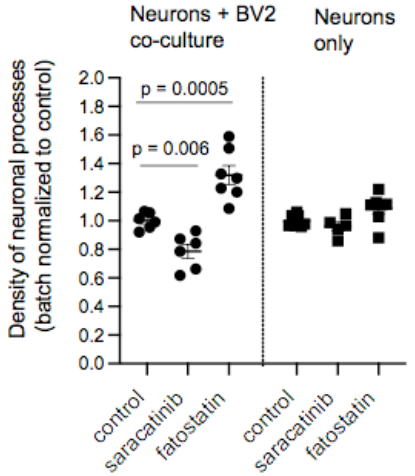
chemical reprogramming

Predicted Observed

Connect

microglia-mediated synapse clearance





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

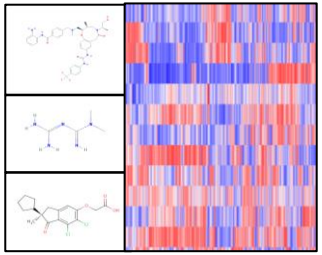
Identify **Drugs** that induce network gene expression patterns

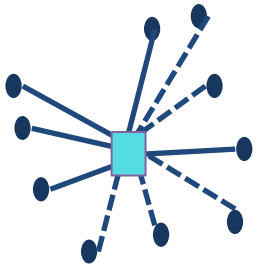
Validate drug engagement of disease biology or biomarker

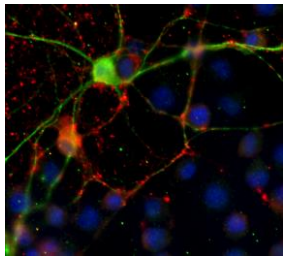
Map validated drugs back to network genes

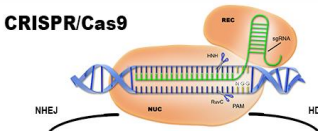
Functionally confirm genes as drug effectors

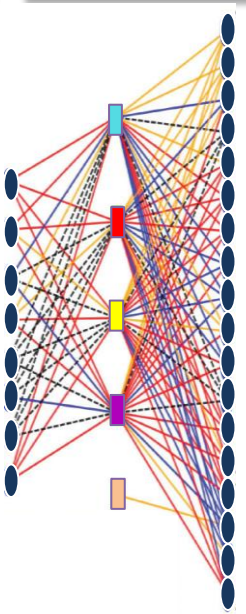
Rebuild the original network from validated drug-target gene maps











Conclusions

- We are on the threshold of identifying hundreds of causal genetic factors for most neuropsychiatric disorders.
- The next challenge is to understand their function.
- Network approaches provide an unbiased systems level framework for integrating genomic data.
- Integrative genomics and network analysis provides an “unbiased” genome-wide guide for mechanistic and therapeutic studies in model systems, biomarkers, and drug screening.