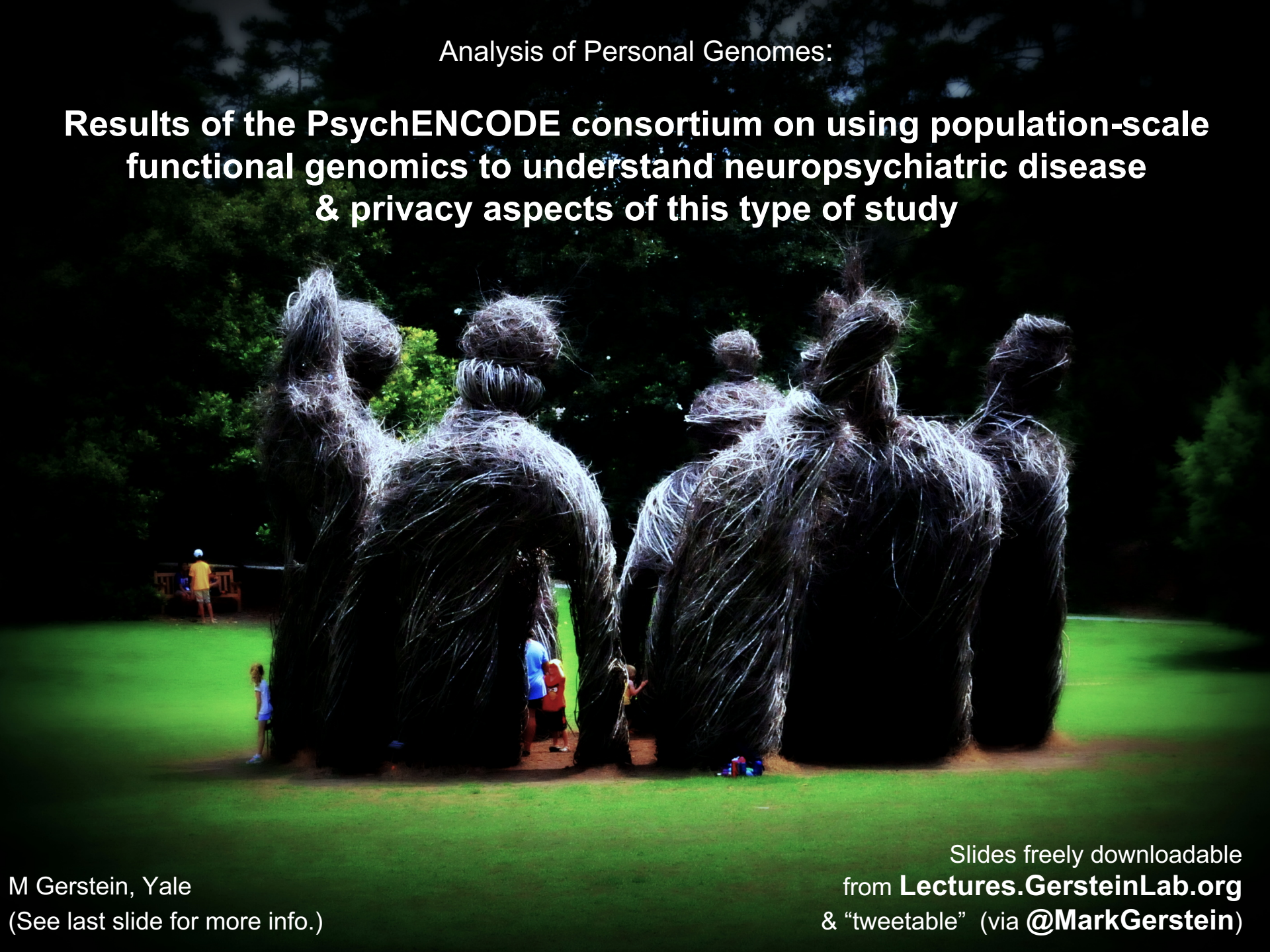
Analysis of Personal Genomes:

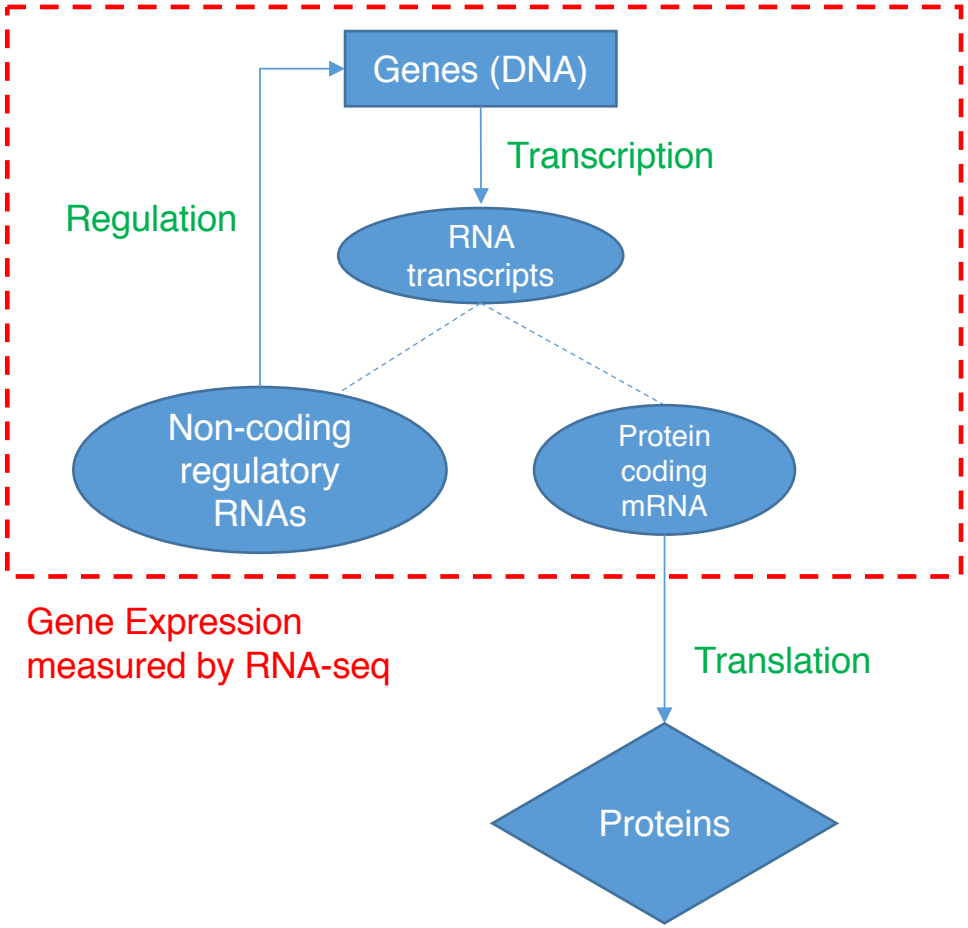
Results of the PsychENCODE consortium on using population-scale functional genomics to understand neuropsychiatric disease & privacy aspects of this type of study



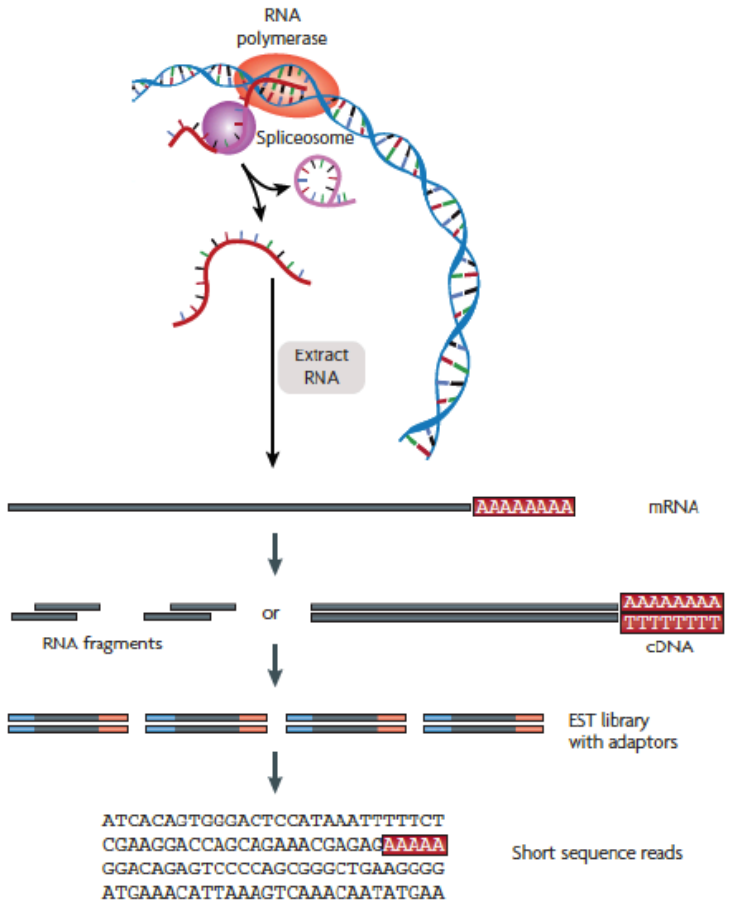
M Gerstein, Yale
(See last slide for more info.)

Slides freely downloadable
from **Lectures.GersteinLab.org**
& "tweetable" (via **@MarkGerstein**)

Transcriptome = Gene Activity of All Genes in the Genome, usually quantified by RNA-seq



Gene Expression measured by RNA-seq



[*NATURE 459: 927; NAT. REV. GEN. 10: 57*]

Expression of genes is quantified by transcription:
RNA-Seq measures mRNA transcript amounts

RNA-Seq Overview

Successive steps of Data Reduction

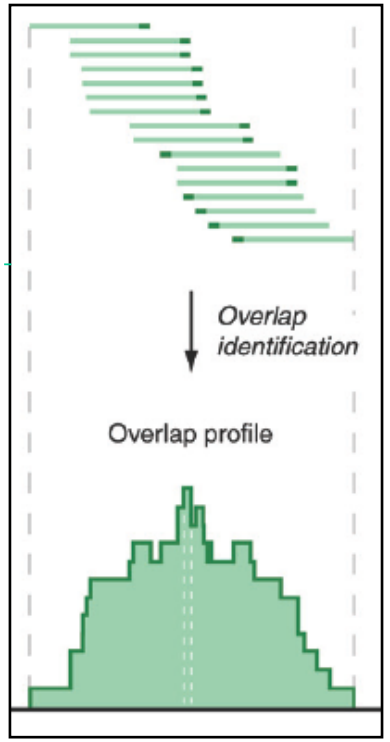
Fastq sequence files
~5-10 GB

```
ATACAAGCAAGTATAAGTTCGTATGCCGTCTT
GGAGGCTGGAGTTGGGGACGTATGCGGCATAG
TACCGATCGAGTCGACTGTAAACGTAGGCATA
ATTCTGACTGGTGTCATGCTGATGTACTTAAA
```

Index-building + Alignment to reference genome

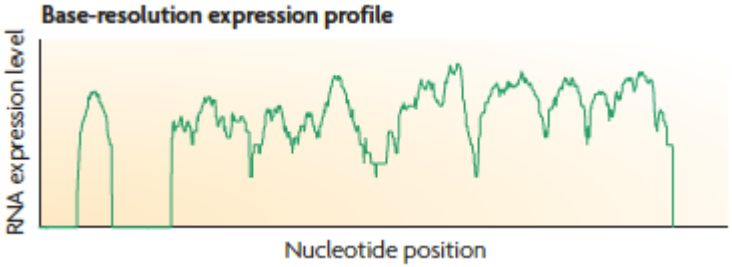
BAM files
~1-2-fold reduction

Conversion to signal track by overlapping reads



Reads => Signal

BigWig files
~25-fold reduction



Quantitative information from RNA-seq signal:
average signals at exon level (RPKMs)

Mapping to genes

Gene/Transcript expression matrix
~20-fold reduction

[*NAT. REV.* 10: 57; *PLOS CB* 4:e1000158; *PNAS* 4:107: 5254]

Activity Patterns

- RNA Seq. gives rise to activity patterns of genes & regions in the genome

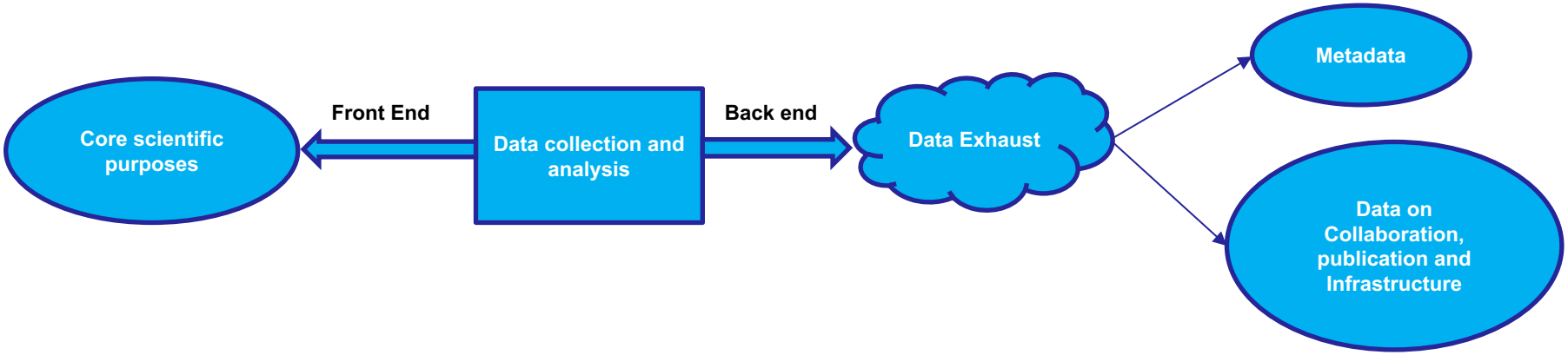
Some Core Science Qs Addressed by RNA-seq

- Gene activity as a function of:
  - **Developmental** stage: basic patterns of co-active genes across development
  - **Cell-type** & Tissue: relationship to specialized functions
  - **Evolutionary** relationships: behavior preserved across a wide range of organisms; patterns in model organisms in relation to those in humans
  - **Individual**, across the human population
  - **Disease** phenotypes: disruption of patterns in disease

- Some overarching Qs:
  Are there core patterns of gene activity ?
  How do they vary across individual ?
  Are they disrupted by disease?

Studying large-scale transcriptome data also produces

Data Exhaust



- Data Exhaust = Exploitable byproducts of big data collection and analysis
- Creative use of Data is key to Data Science !

[PHOTO: RELAXNEWS; from http://www.lapresse.ca]

Results of the PsychENCODE consortium on using population-scale functional genomics to understand neuropsychiatric disease & privacy aspects of this type of study

- *[Core]* **PsychENCODE:** Population-level analysis of functional genomics data related to mental illness
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  - Introduction to Genomic Privacy
    - The dilemma: The genome as fundamental, inherited info that's very private v. need for large-scale mining for med. research
    - 2-sided nature of functional genomics data presents particularly tricky privacy issues
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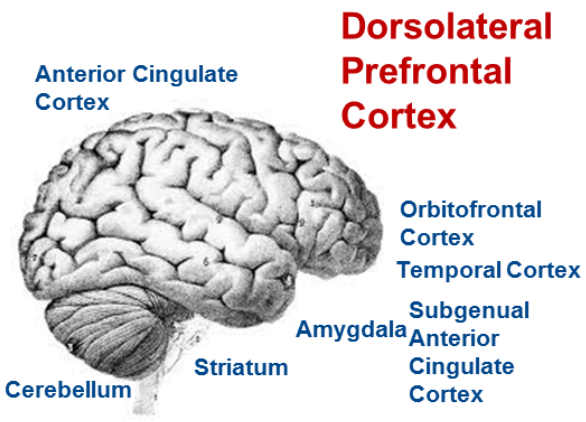
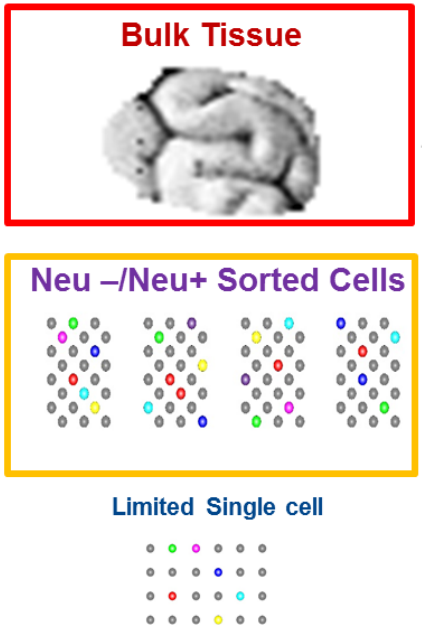
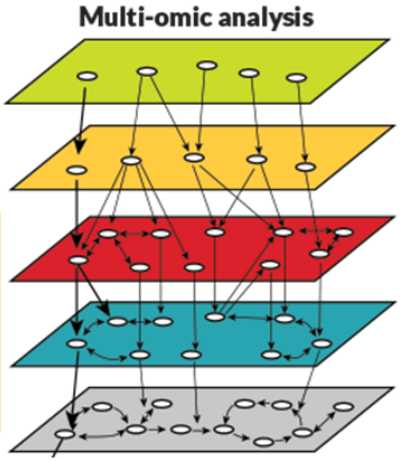
Sample Sources: >2,500 brains

Cross-disorder: ASD, SCZ, BP, Neurodevelopmental, Neurotypical







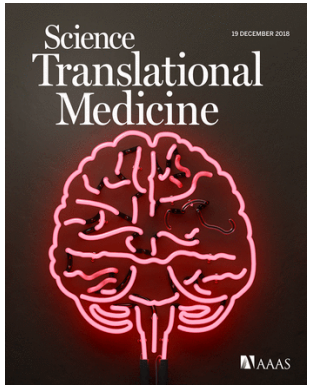
Genome:
WGS, genotype

Epigenome:
ChIP-seq, ATAC-seq, HiC, ERRBS, Array Methylation, NOMeSeq

Transcriptome:
RNA-seq, lncRNAseq,

Proteome:
MWP, LC-MS/MS

Data Coordination/Analysis Center - Uniformly processed data across disorders and developmental time periods!



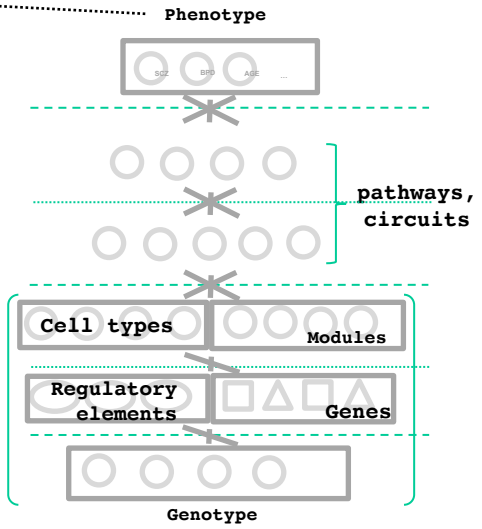
PsychENCODE '18 rollout in Science

11 papers in total.
Major material in the 3 capstones:

Wang et al. ('18), Li et al. ('18), Gandal et al. ('18)

A core issue addressed by PsychENCODE: Using functional genomics to reveal molecular mechanisms between genotype and phenotype in brain disorders

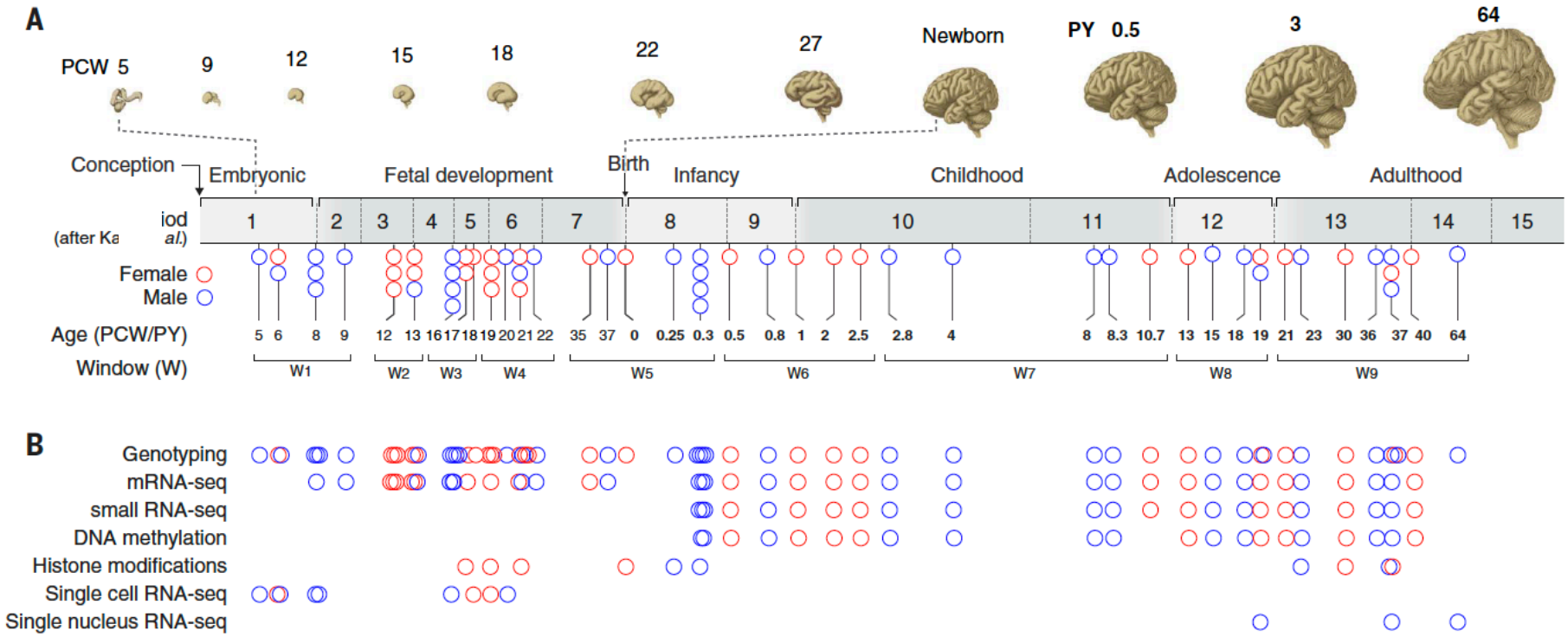
Disease	Heritability*	Molecular **Mechanisms**
Schizophrenia	**81%**	**(C4A)**
Bipolar disorder	70%	-
Alzheimer's disease	58 - 79%	Apolipoprotein E (APOE), Tau
Hypertension	30%	Renin–angiotensin–aldosterone
Heart disease	34-53%	Atherosclerosis, VCAM-1
Stroke	32%	Reactive oxygen species (ROS), Ischemia
Type-2 diabetes	26%	Insulin resistance
Breast Cancer	25-56%	BRCA, PTEN



*https://www.snpedia.com/index.php/Heritability

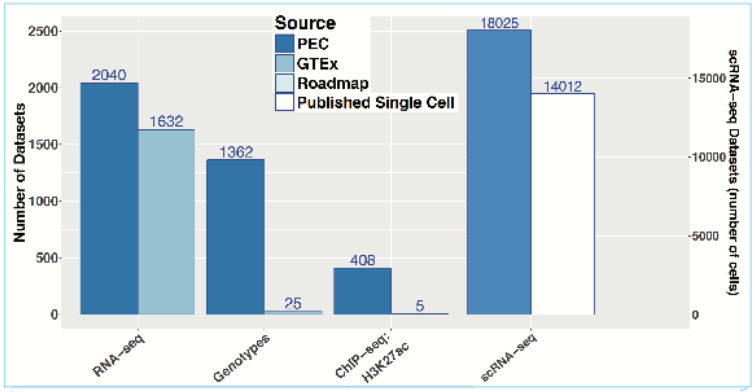
Many psychiatric conditions are highly heritable
Schizophrenia: up to 80%
But we don't understand basic molecular mechanisms underpinning this association
(in contrast to many other diseases such as cancer & heart disease)
Moreover, current models substantially underestimate heritability using genetic data
Schizophrenia : ~25%
Thus, interested in developing predictive models of psychiatric traits which:
Use observations at intermediate (molecular levels) levels to inform latent structure
Use the predictive features of these "molecular endo phenotypes" to begin to suggest actors involved in mechanism

Developmental Capstone Data Set

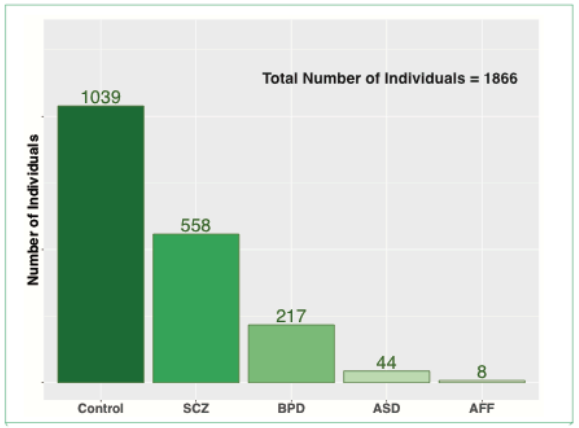


- 60 Individuals in total
- Ages from 5 PCW to 64 yrs.
- 16 brain regions for > 9 PCW

[Li et al. (‘18) Science]

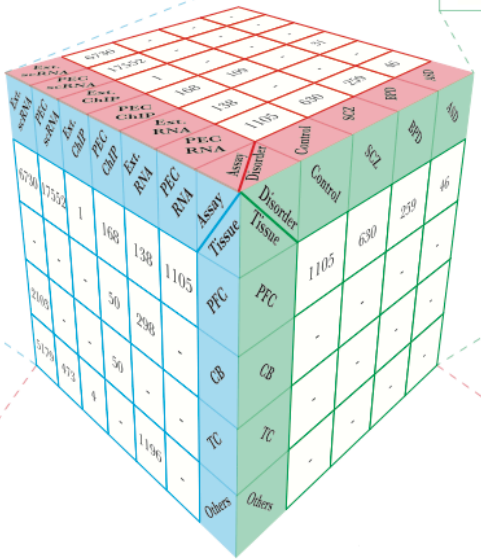


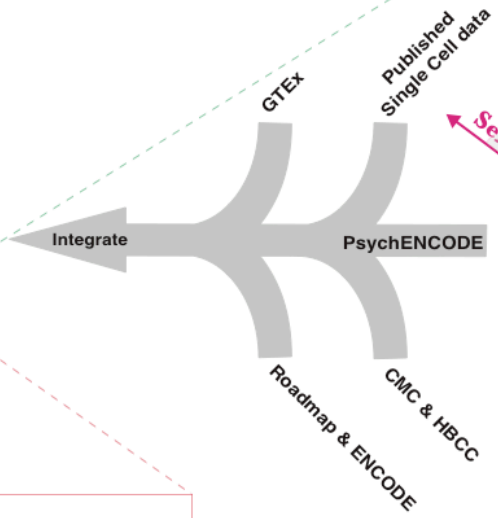
Assay

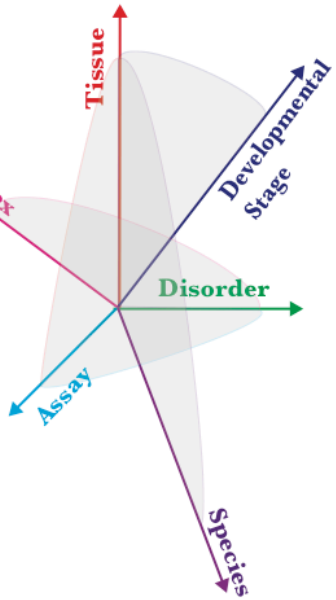


Disorder

1866
Individuals
~3.7K bulk RNA-seq
~32K single-cells

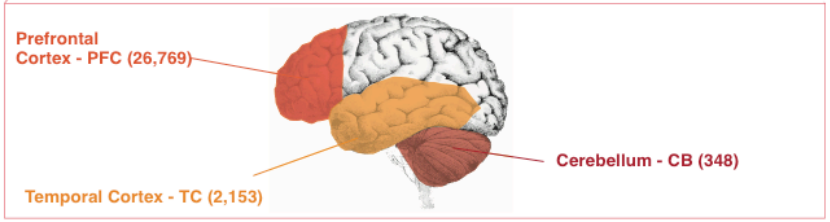




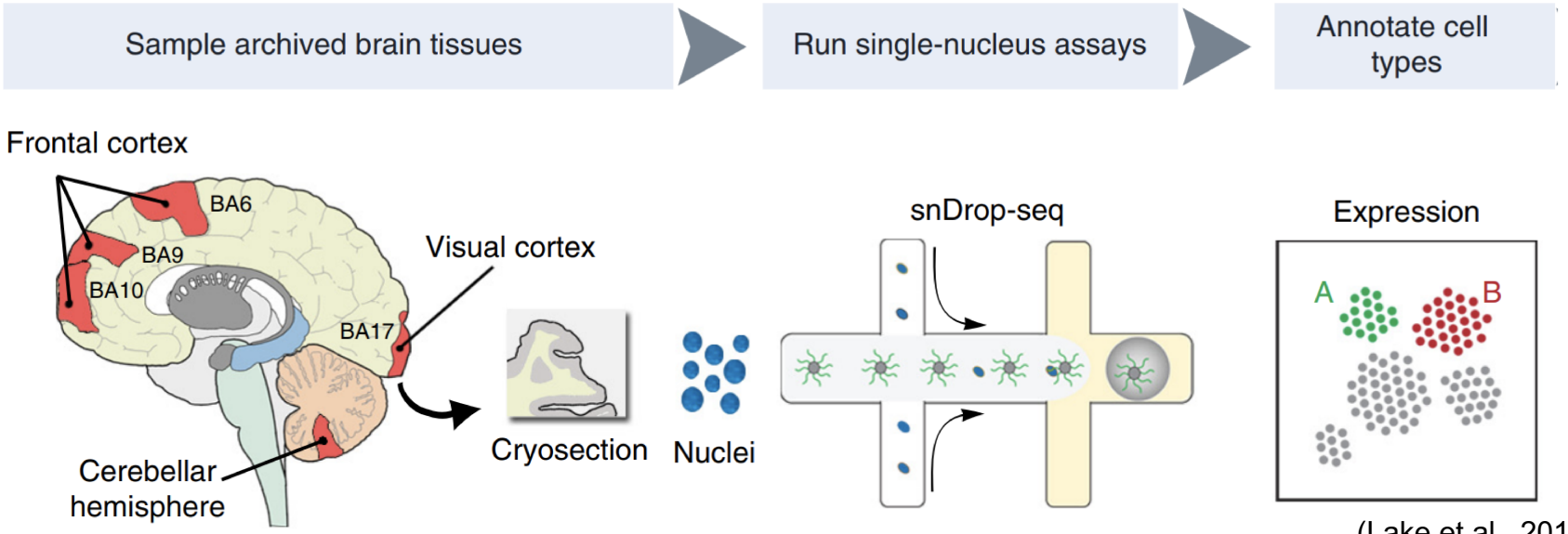


Collecting functional genomic datasets for the adult brain

from PsychENCODE, other large consortia & single cell studies

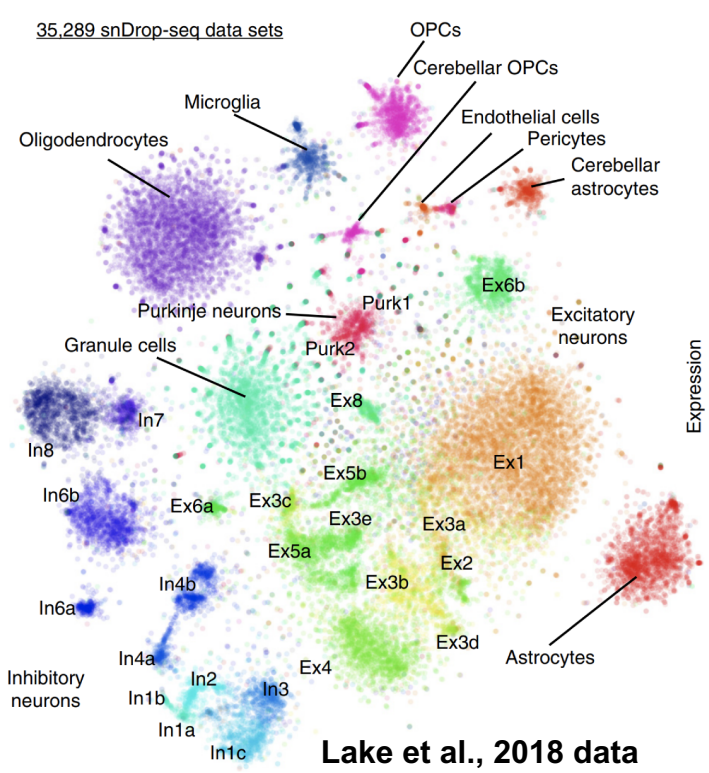


[Wang et al. (‘18) Science]

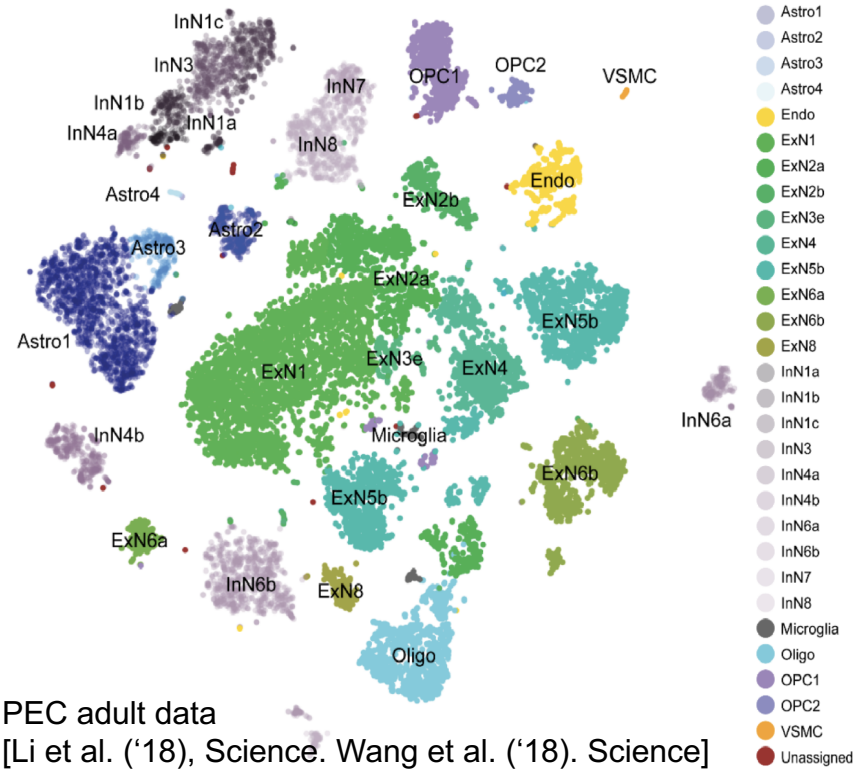


(Lake et al., 2018)

Merging & Clust-ering Single Cell Data Sets



Lake et al., 2018 data



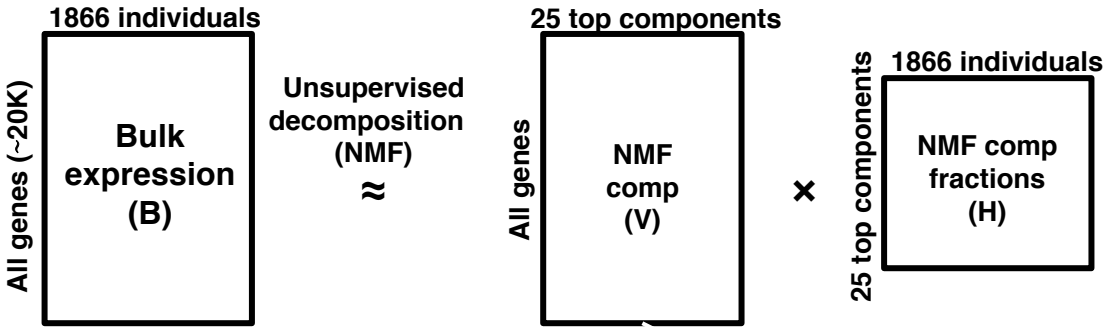
PEC adult data
[Li et al. ('18), Science. Wang et al. ('18). Science]

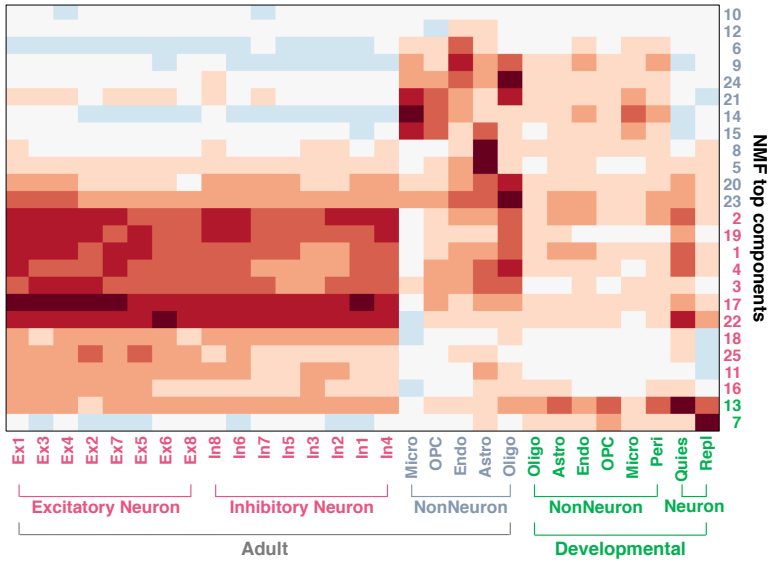
Single-cell deconvolution Step 1:

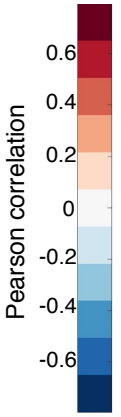
Unsupervised learning to determine relevant cell types

Single cell signatures, from:

- ~14K cells
  (Lake et al.,'16 & '18)
- ~400 cells
  (Darmanis et al., PNAS, '15)
- ~18K cells (PsychENCODE)





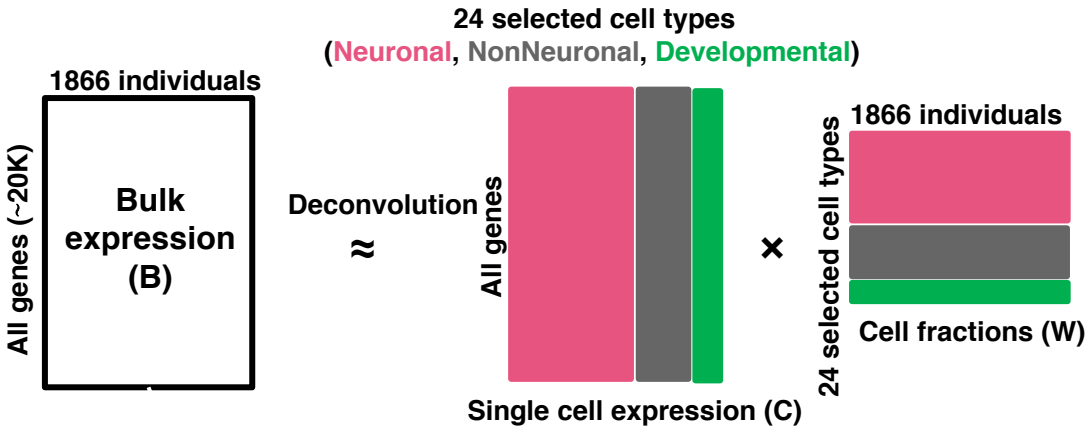


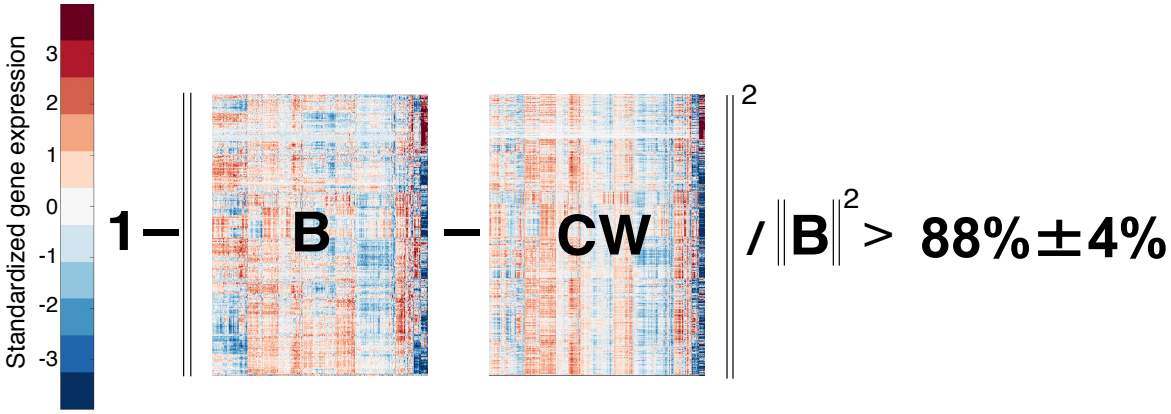
[Wang et al. ('18) Science]

Single-cell deconvolution

Step 2:

Supervised learning to estimate cell fractions

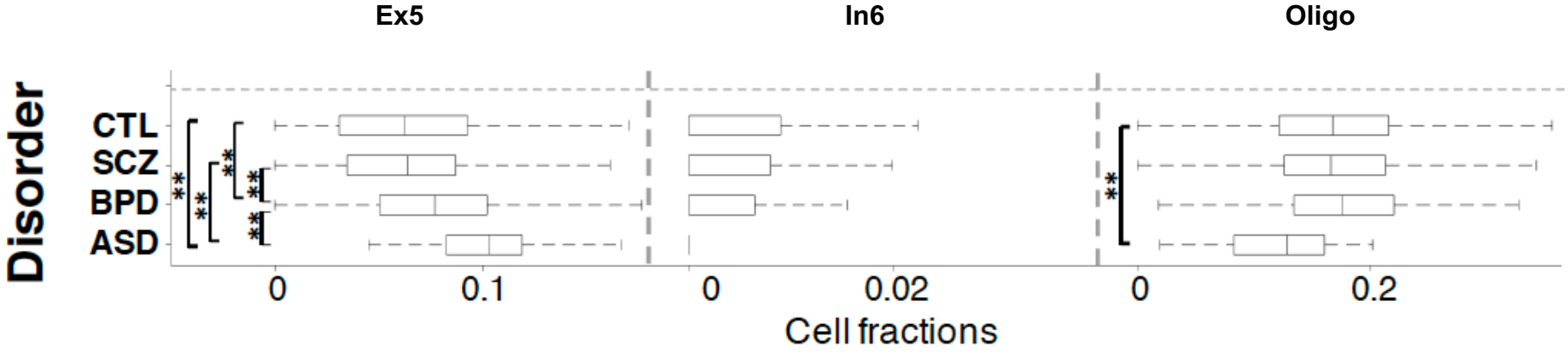




Individual and cross-population reconstruction accuracy via deconvolution

[Wang et al. ('18) Science]

Different neuronal & glial cell fractions across disorders

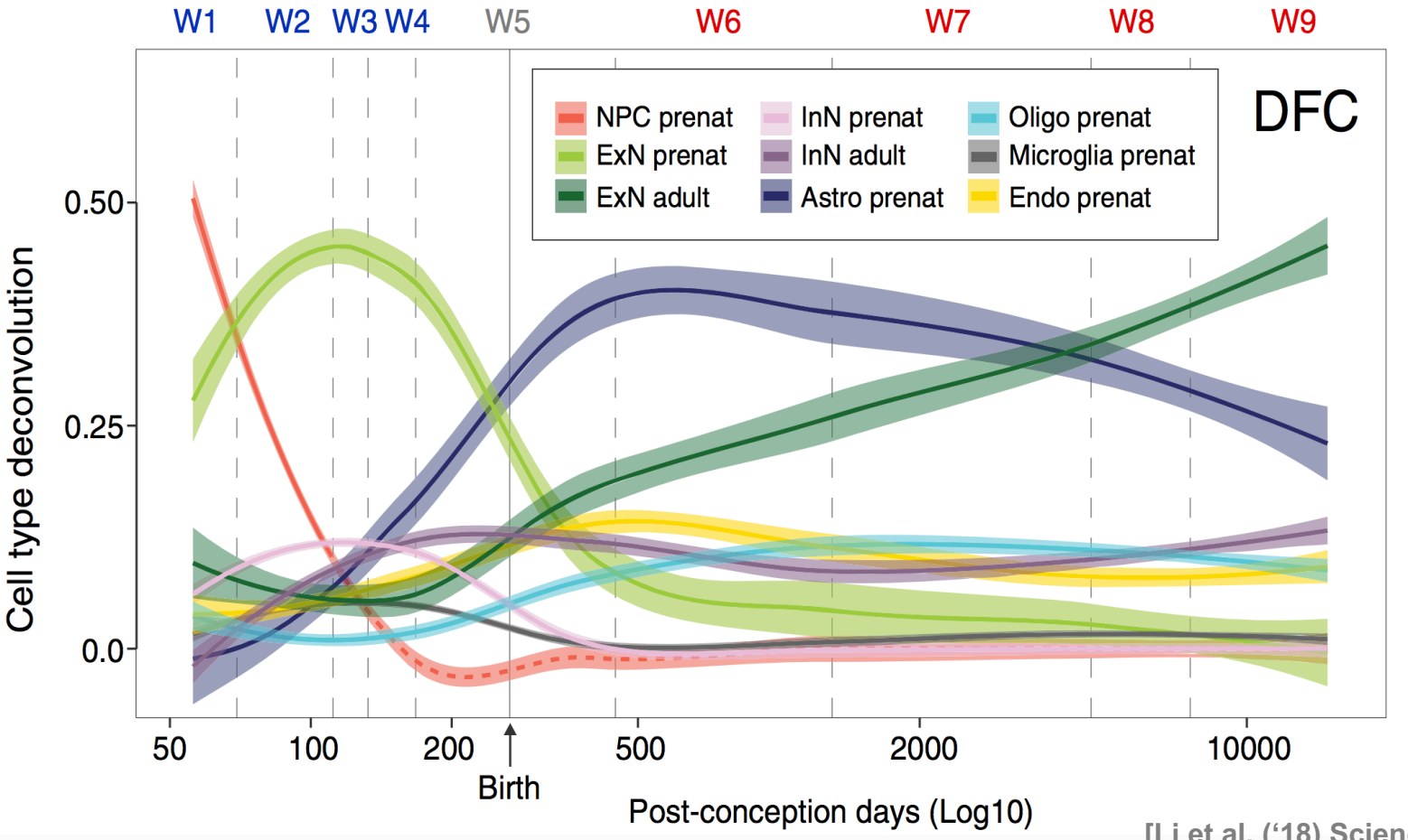


Excitatory to Inhibitory imbalance at neuronal subtype level for ASD*

*** Rubenstein et al., Model of autism: increased ratio of excitation/inhibition in key neural systems, Genes Brain Behav. 2003**

[Wang et al. ('18) Science]

Different neuronal & glial cell fractions across ages



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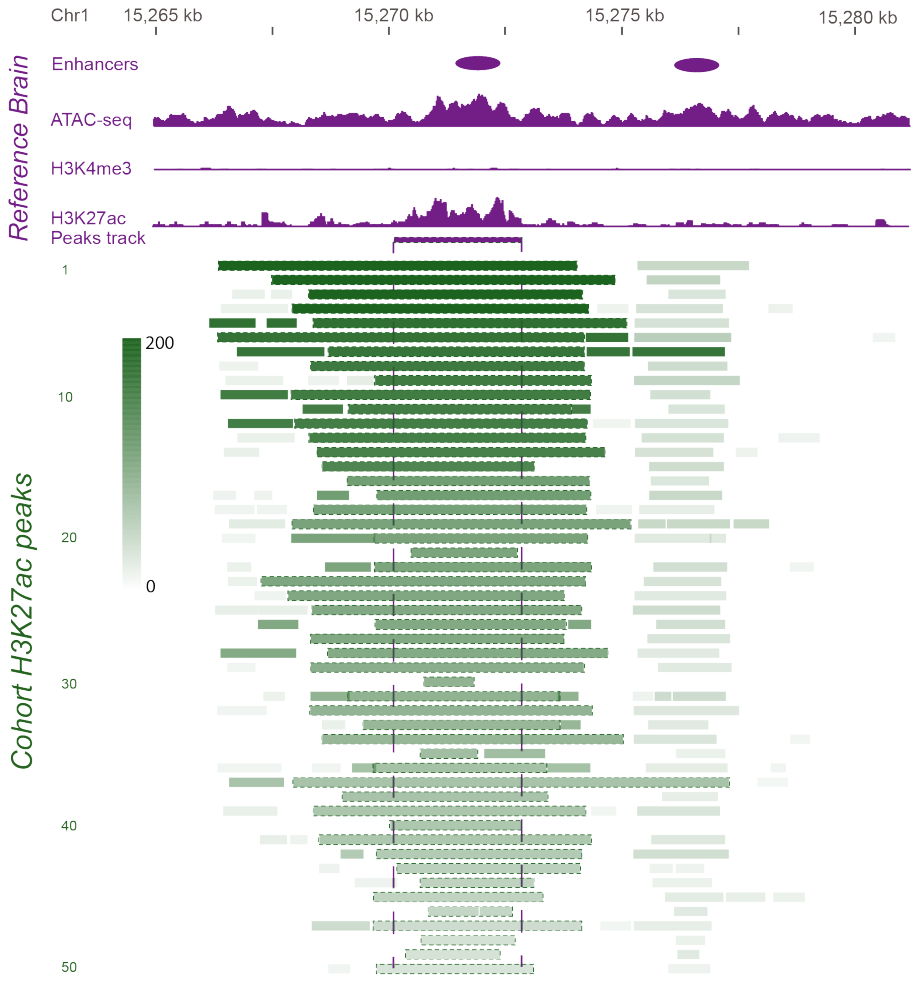
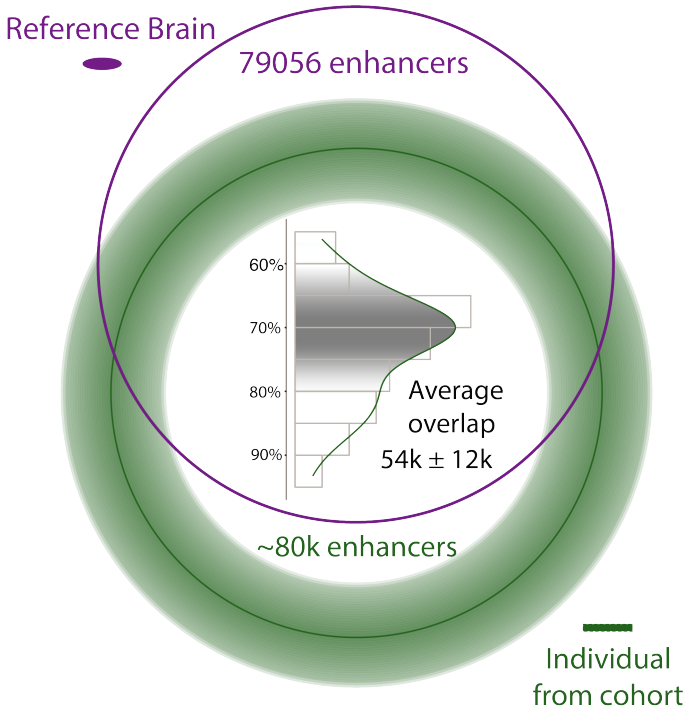
Developing a Reference Set of ~79K PFC Enhancers & Studying Their Population Variation

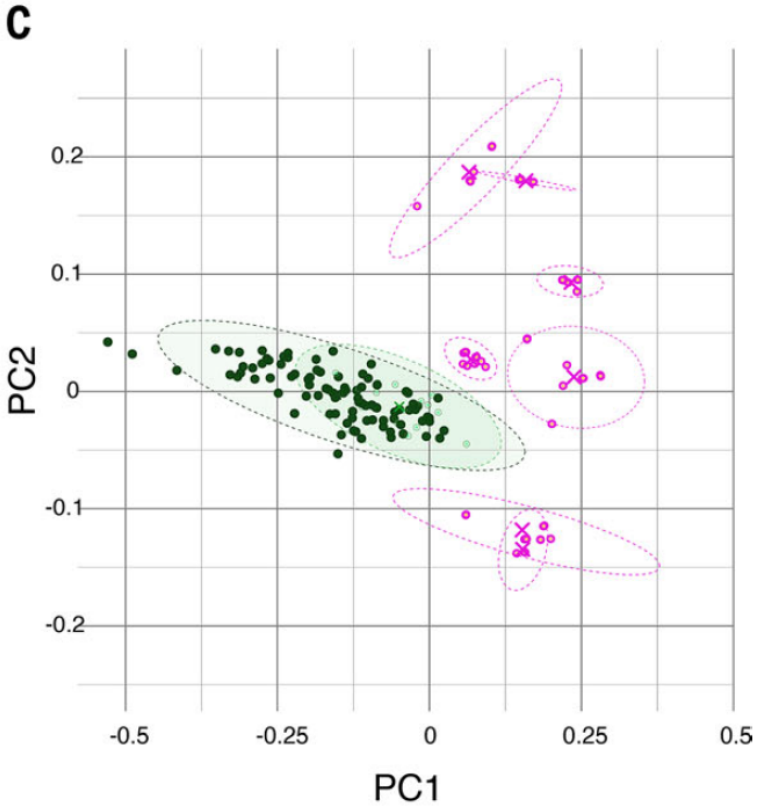




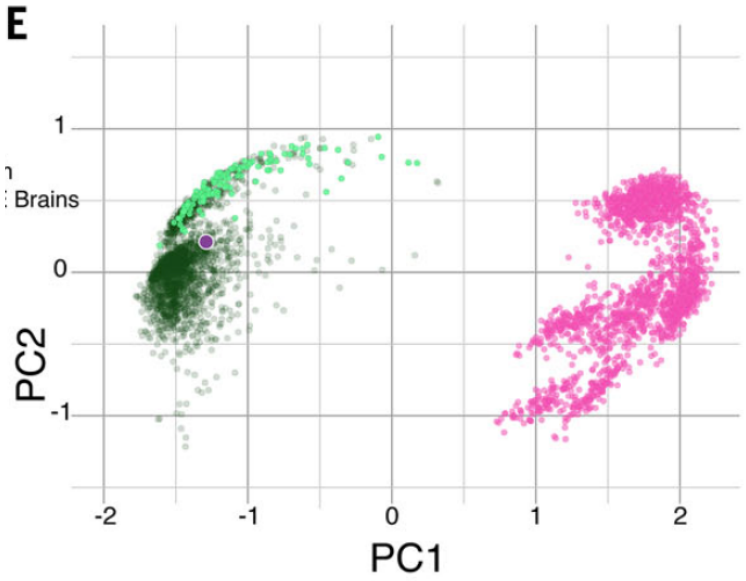
[Wang et al. ('18) Science]

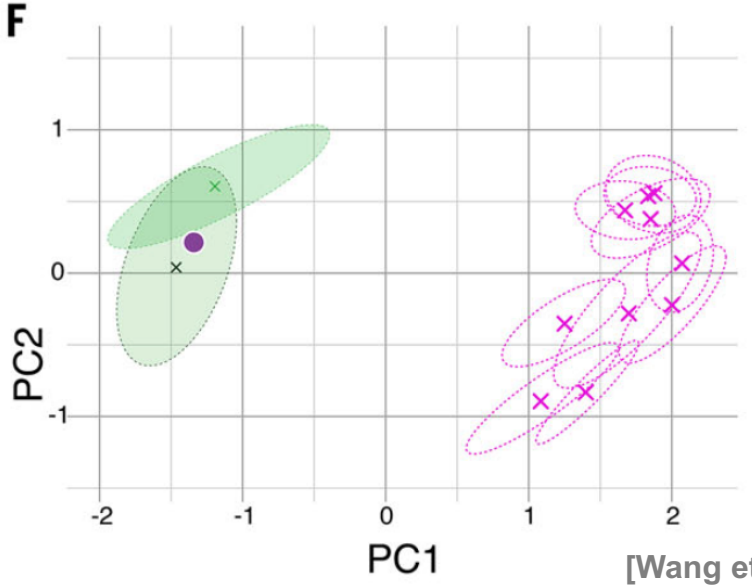
Consistently Comparing Variation in Chromatin & Expression

Placing the Brain in context of all other Body Tissues



Chromatin





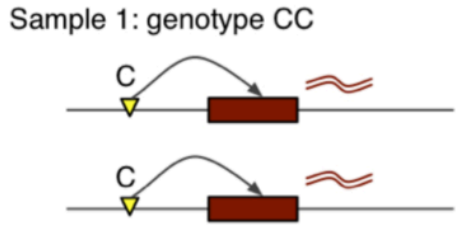
Expression

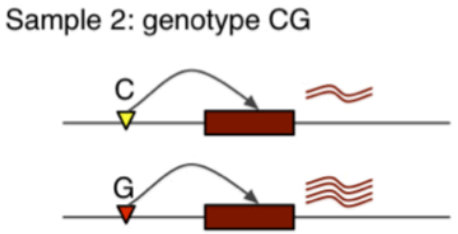
[Wang et al. ('18) Science]

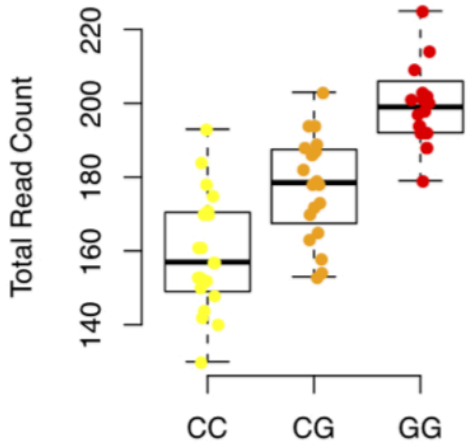
Chromatin variation in the population

Quantitaive Trait Loci (QTL) associated with variations

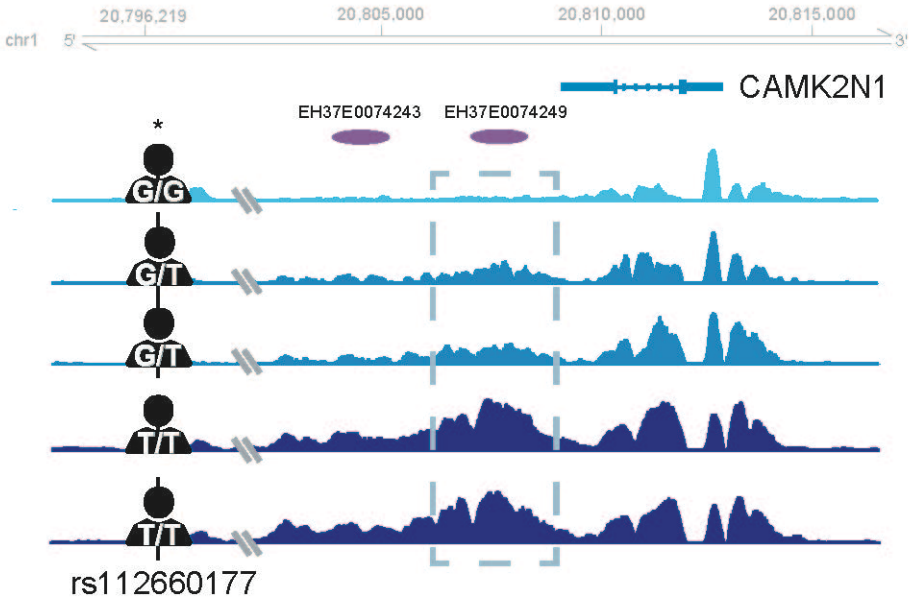
Gene expression (eQTL)







Chromatin (cQTL)

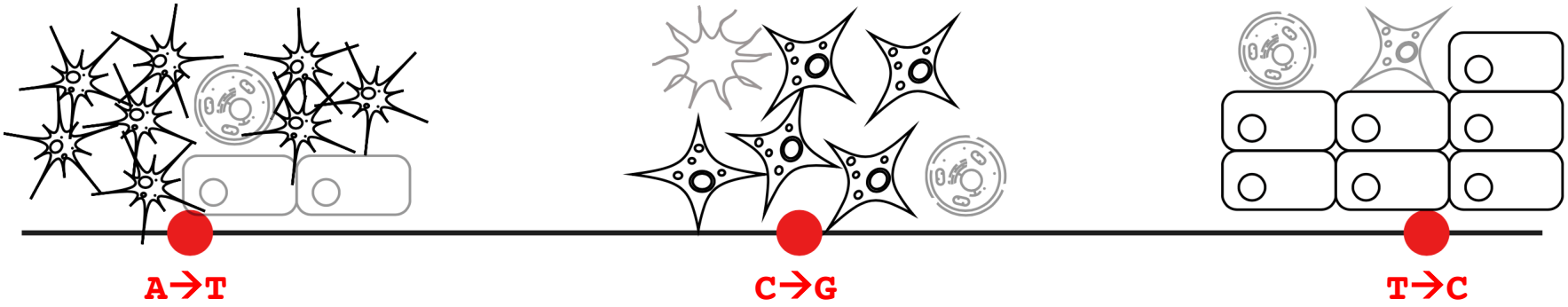


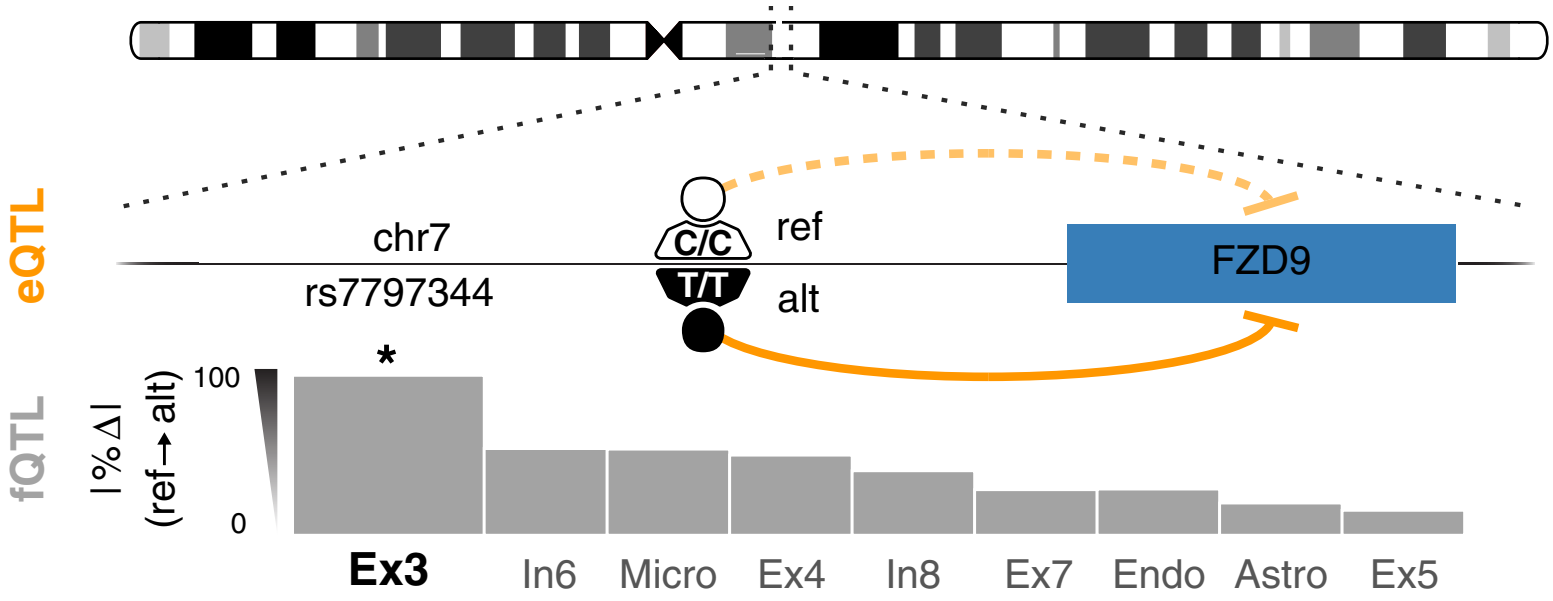
	Number of intermediate phenotype	SNPs
eQTL	32,944 eGenes	1,341,182
cQTL*	8,484 Enhancers	7,983

[Wang et al. ('18) Science]

Sun, Wei, and Yijuan Hu. "eQTL mapping using RNA-seq data." Statistics in biosciences 5.1 (2013): 198-219.

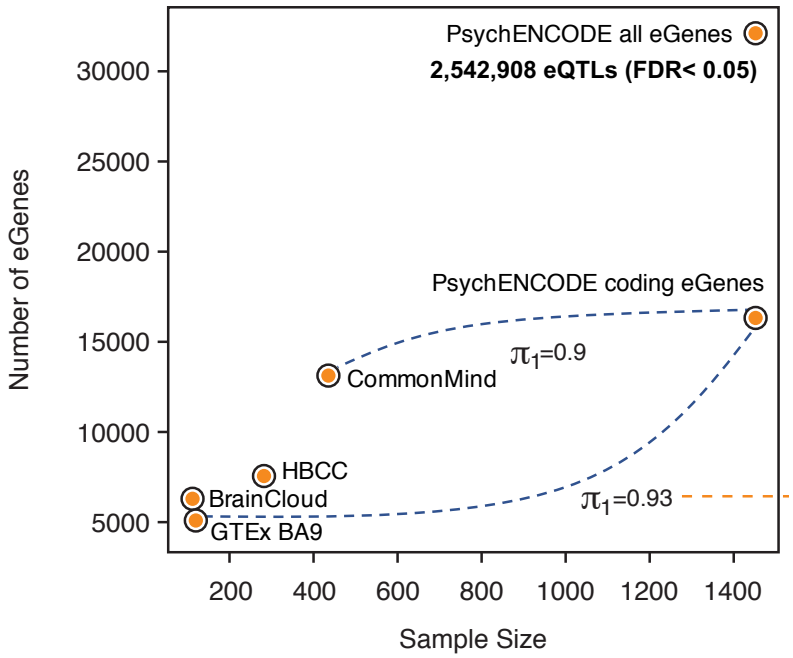
Cell fraction QTLs (fQTLs)

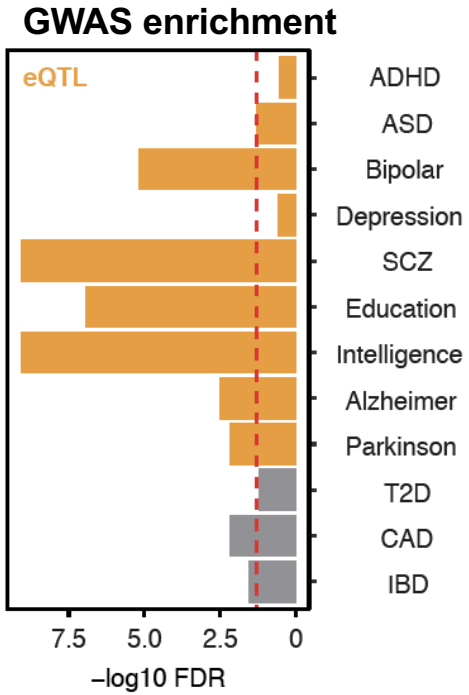




[Wang et al. ('18) Science]

Larger Brain eQTL sets than previous studies

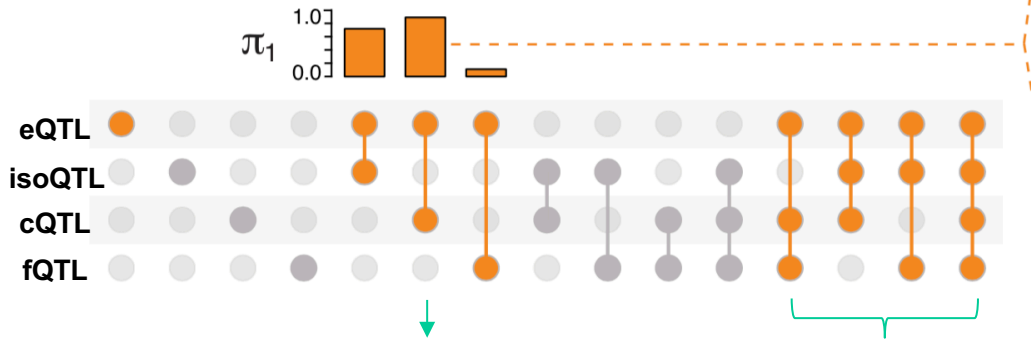




[Wang et al. ('18) Science]

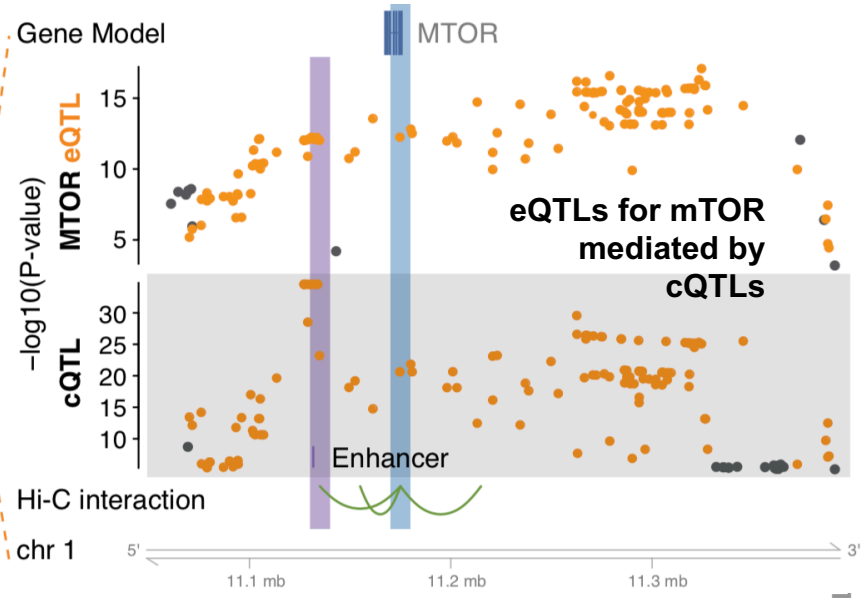
multi-QTLs from overlapping different types of QTLs: cQTL, fQTL, eQTL & isoQTL

	Numbers of QTLs	eGenes Enhancers Cell types	SNPs
eQTL	2,542,908	32,944	1,341,182
isoQTL	2,628,259	19,790	1,052,939
cQTL*	8,464	8,484	7,983
fQTL	4,199	9	1,672



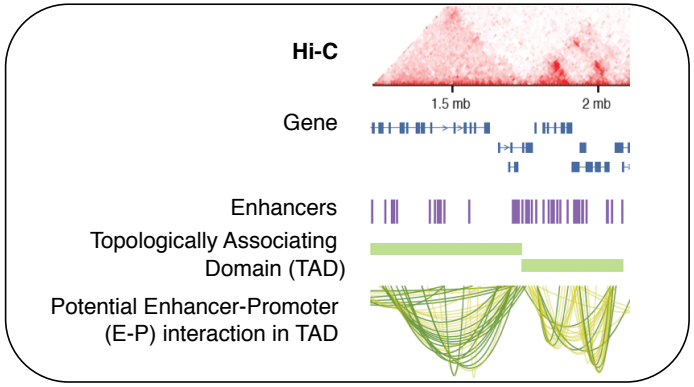
eQTLs and cQTLs significantly overlap

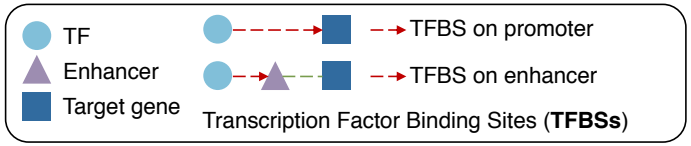
1391 SNPs (multi-QTLs) in at least three types among eQTLs, isoQTLs, cQTLs, fQTLs

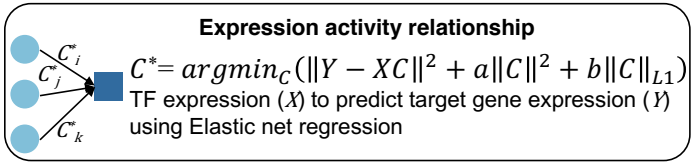


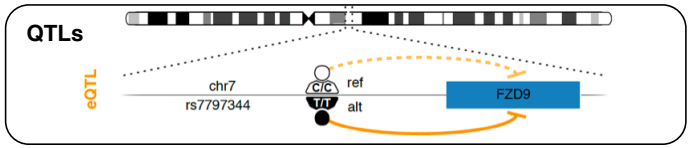
[Wang et al. ('18) Science]

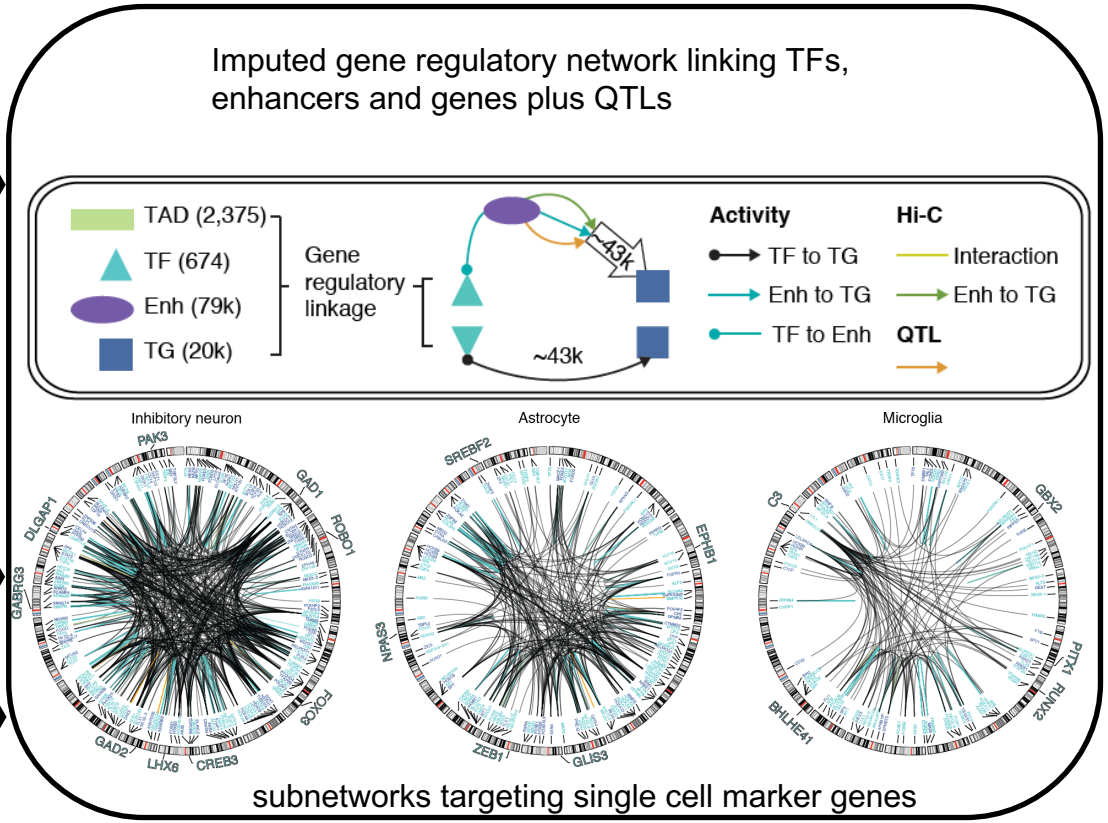
Gene regulatory network inference from Hi-C, QTLs & Activity Correlations





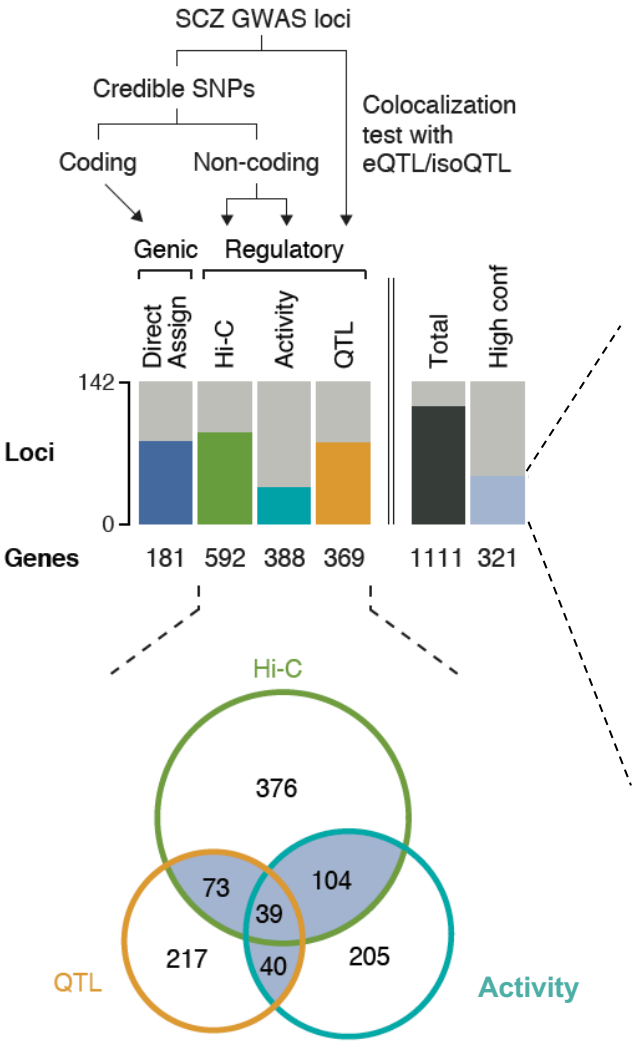


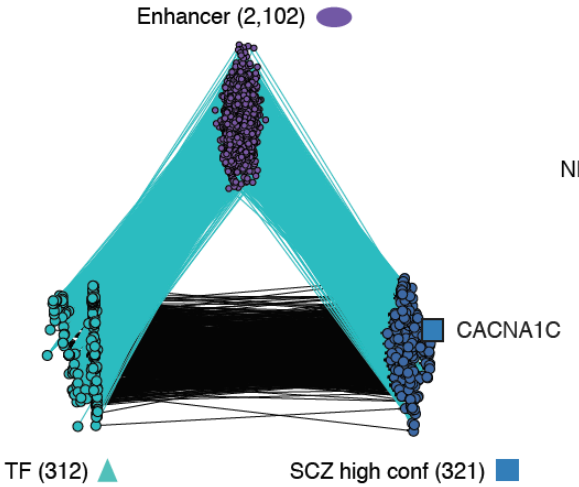


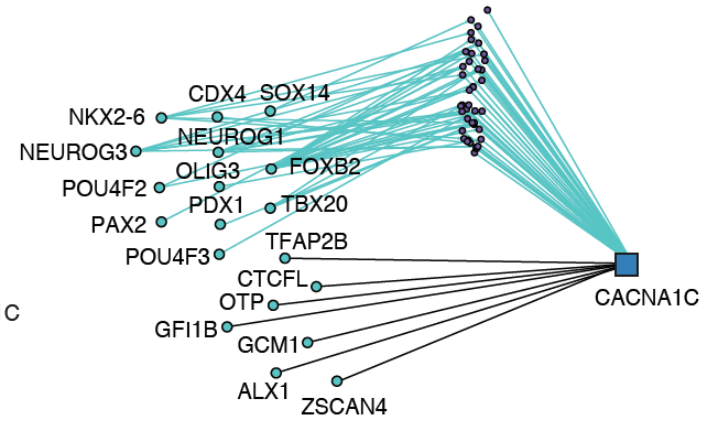


[Wang et al. (‘18) Science]

Linking GWAS SNPs to disease genes using the regulatory network



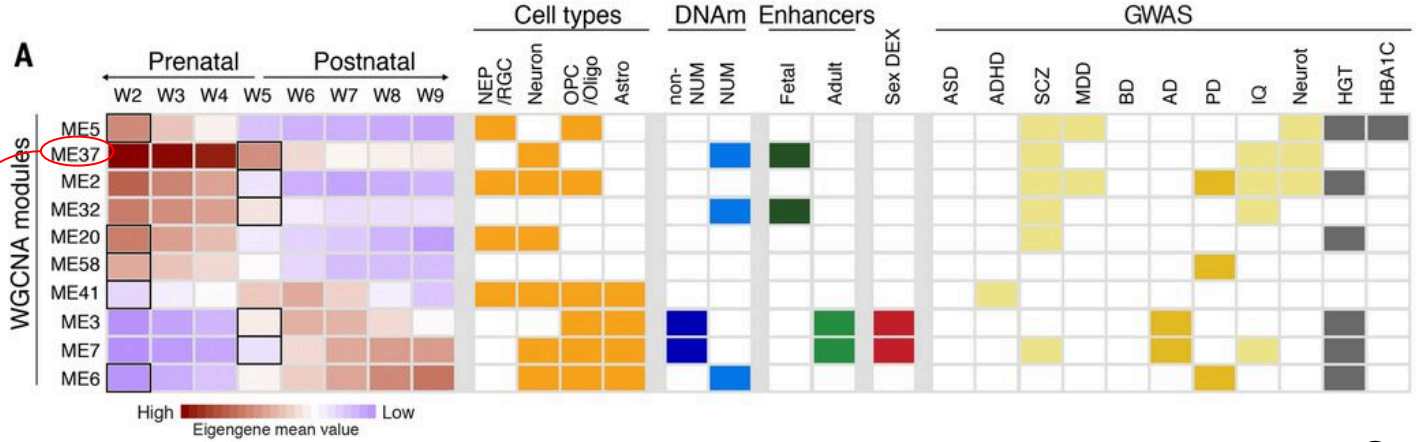


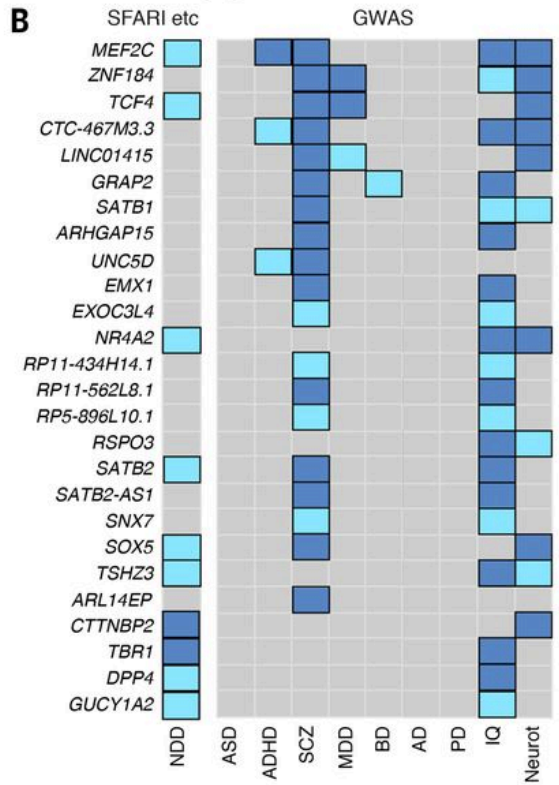


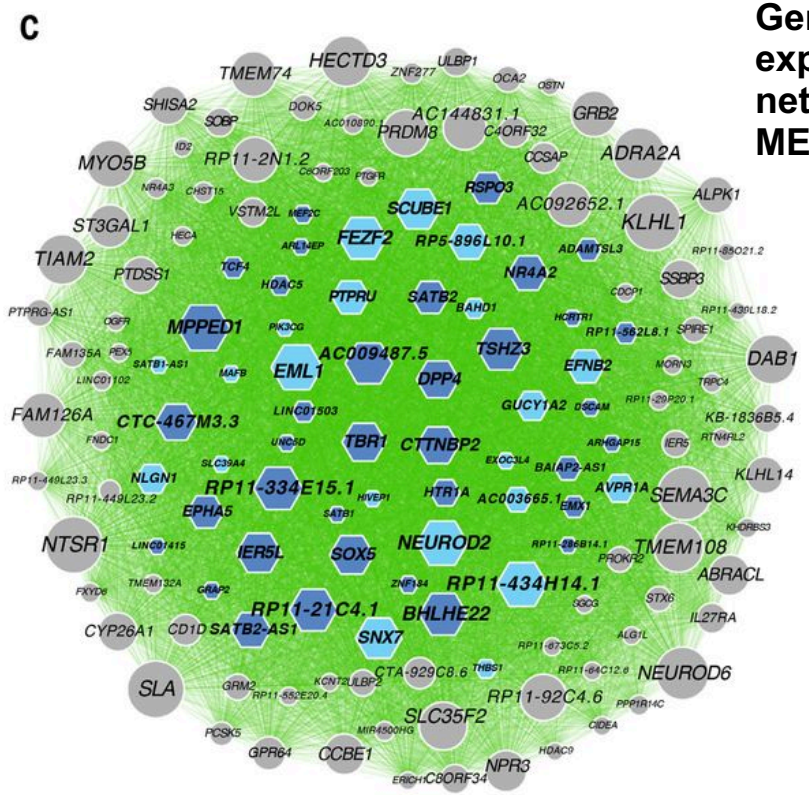
321
high-confident SCZ genes

[Wang et al. ('18) Science]

Convergence of risk for brain disorders (SCZ) on discrete co-expression modules (often prenatally expressed) and cell types.







Gene co-expression network for ME37

Disorders genes (ADHD, SCZ, MDD, BD)

Mingfeng Li et al. Science 2018;362:eaat7615

Results of the PsychENCODE consortium on using population-scale functional genomics to understand neuropsychiatric disease & privacy aspects of this type of study

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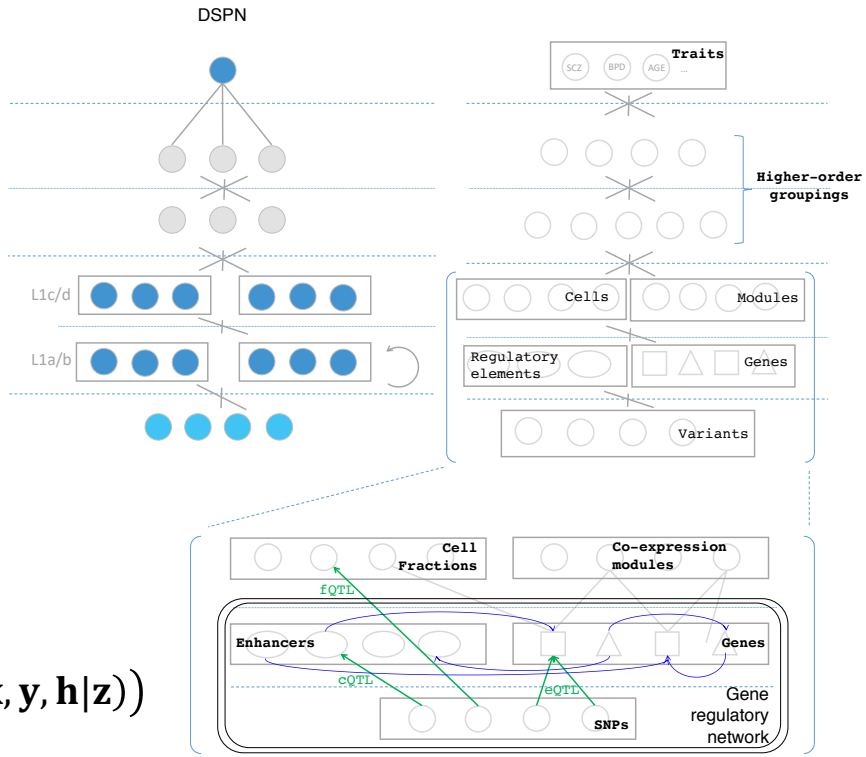
Deep Structured Phenotype Network (DSPN)

Gene regulatory network builds skeleton



Boltzmann machine

y: phenotypes

h: hidden units (e.g., circuits)

x: intermediate phenotypes (e.g., genes, enhancers)

z: genotypes (e.g., SNPs)

W: weights (e.g., regulatory network)

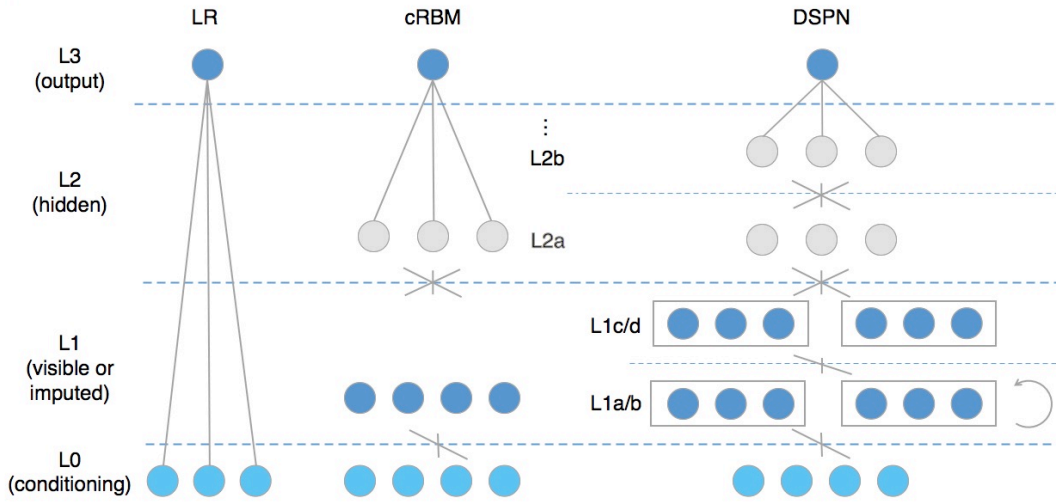
Energy model:

$$p(\mathbf{x}, \mathbf{y}, \mathbf{h}|\mathbf{z}) \propto \exp\left(-E(\mathbf{x}, \mathbf{y}, \mathbf{h}|\mathbf{z})\right)$$

$$E(\mathbf{x}, \mathbf{y}, \mathbf{h}|\mathbf{z}) = -\mathbf{z}^{\mathrm{T}}\mathbf{W}_1\mathbf{x} - \mathbf{x}^{\mathrm{T}}\mathbf{W}_2\mathbf{x} - \mathbf{x}^{\mathrm{T}}\mathbf{W}_3\mathbf{h} - \mathbf{h}^{\mathrm{T}}\mathbf{W}_4\mathbf{h} - \mathbf{h}^{\mathrm{T}}\mathbf{W}_5\mathbf{y} - \boldsymbol{Bias}$$

[Wang et al. ('18) Science]

DSPN improves brain disease prediction by adding deep layers



Method	LR-genotype	LR-transcriptome	cRBM	DSPN-imputation	DSPN-full
Schizophrenia	**54.6%**	63.0%	70.0%	59.0%	**73.6%**
Bipolar Disorder	**56.7%**	63.3%	71.1%	67.2%	**76.7%**
Autism Spectrum Disorder	**50.0%**	51.7%	67.2%	62.5%	**68.3%**

X 6.0

Accuracy = chance to correctly predict disease/health

[Wang et al. ('18) Science]

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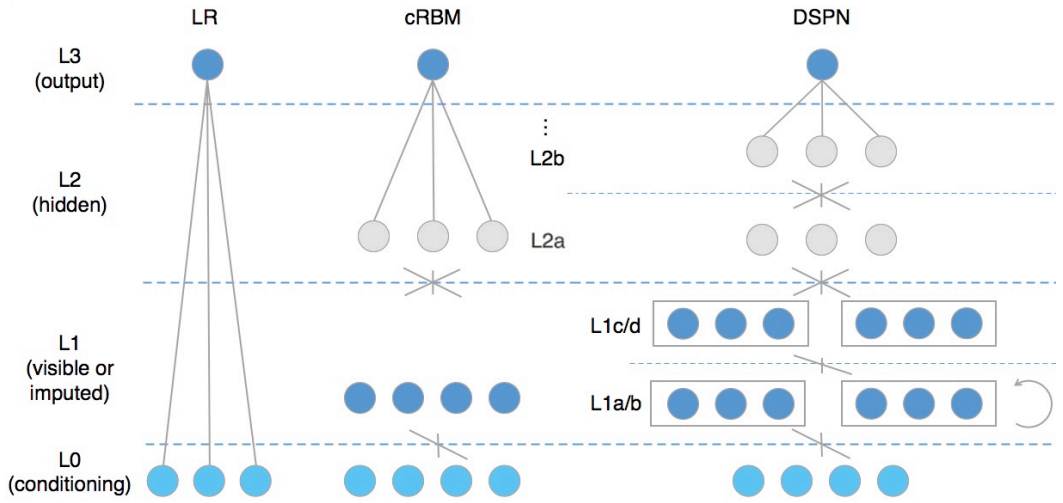

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X 2.5

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[Wang et al. ('18) Science]

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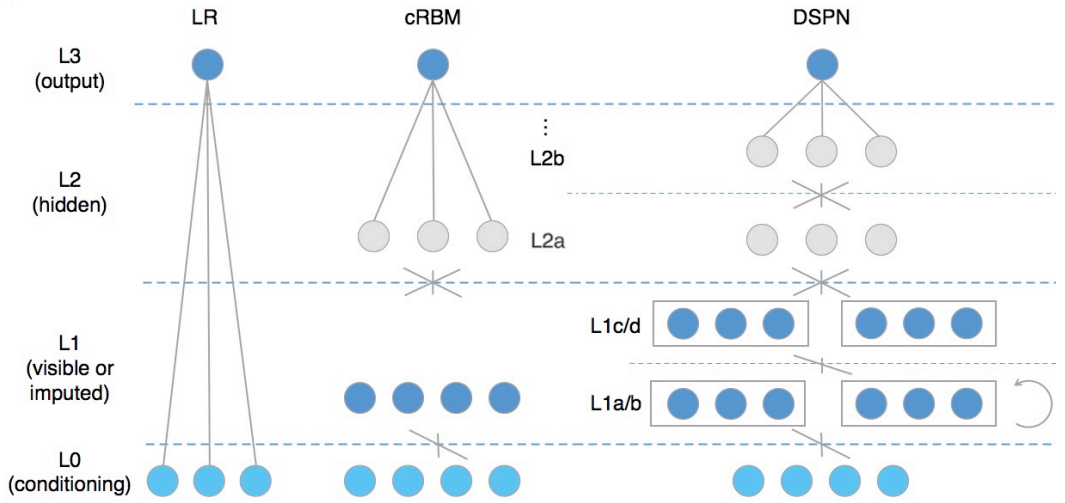

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X 3.1

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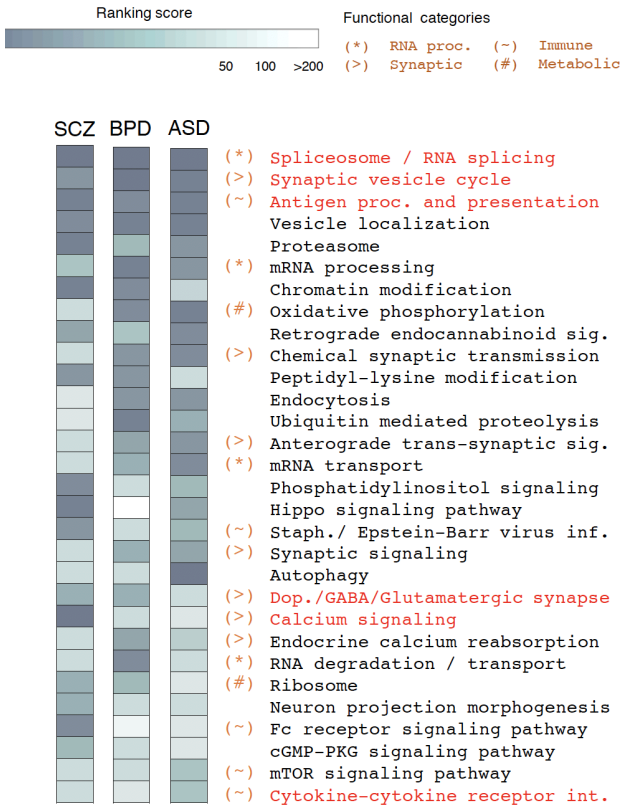
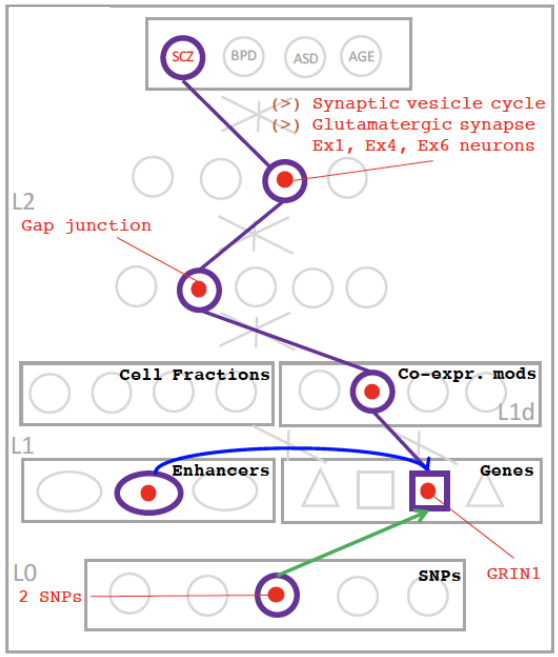
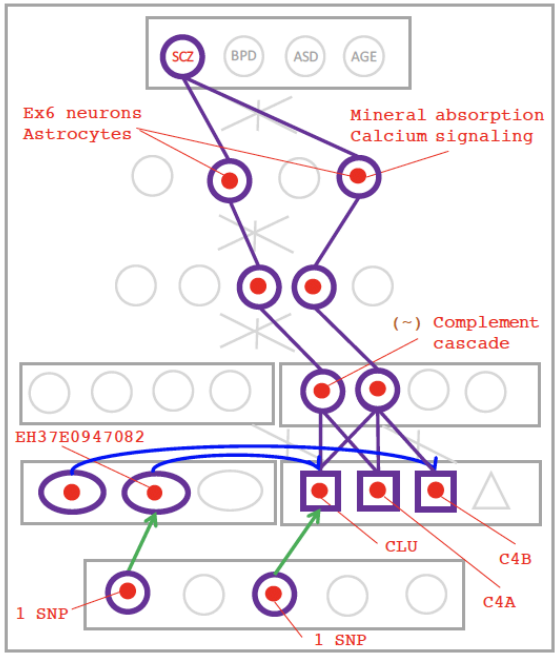
[Wang et al. ('18) Science]

DSPN discovers molecular pathways from genotype to phenotype







[Wang et al. ('18) Science]

Thoughts on Missing Heritability, Polygenic Risk Scores & Our Model

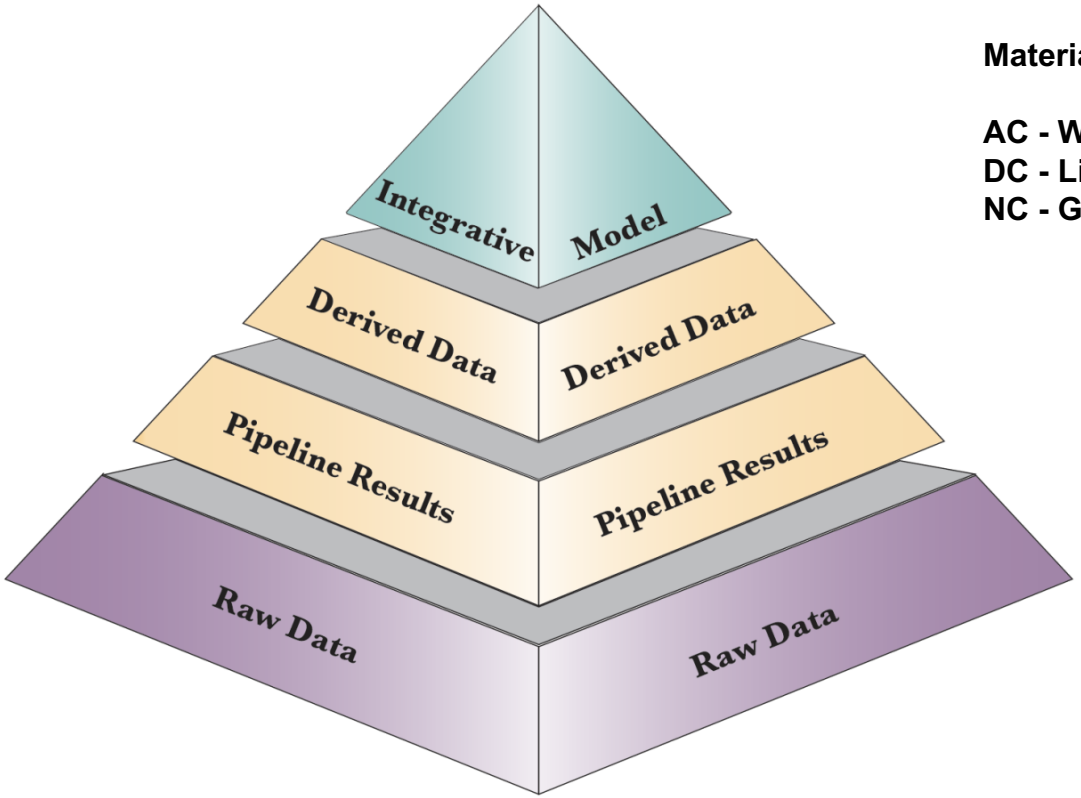
- Many psychiatric conditions are highly heritable
  - Schizophrenia: up to 80% (family studies)
- Psychiatric traits appear to be highly polygenic
  - PRSs typically use an additive model to predict genetic risk; space of possible epistatic models is vast and requires huge sample sizes for unique identification
- However, Common SNPs only explain ~25% heritability
- Possible explanations:
  - Significant (additive) contribution of rare SNPs
  - Important roles for epistasis and gene-environment interactions

- We circumvent this problem:
  - Use observations at intermediate levels (molecular endophenotypes) to inform latent structure
  - Use a deep-learning framework for optimization; proven capacity to learn complex predictors which generalize
- Epistatic interactions in our model are implicit: develop model interpretation methods to suggest actors involved in mechanism

[Wang et al. (‘18) Science]

Review of the Phase 1 PsychENCODE capstone resource:

Layers of distributed information



Material in the 3 capstones:

AC - Wang et al. ('18)
DC - Li et al. ('18)
NC - Gandal et al. ('18)

Resource.psychencode.org
Development.psychencode.org

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2-sided nature of functional genomics data: Analysis can be very General/Public or Individual/Private

- **General quantifications** related to overall aspects of a condition – ie gene activity as a function of:
  - Developmental stage, Evolutionary relationships, Cell-type, Disease

- **Above are not tied to an individual's genotype. However, data is derived from individuals & tagged with their genotypes**

- (Note, a few calculations aim to use explicitly genotype to derive general relations related to sequence variation & gene expression - eg allelic activity)

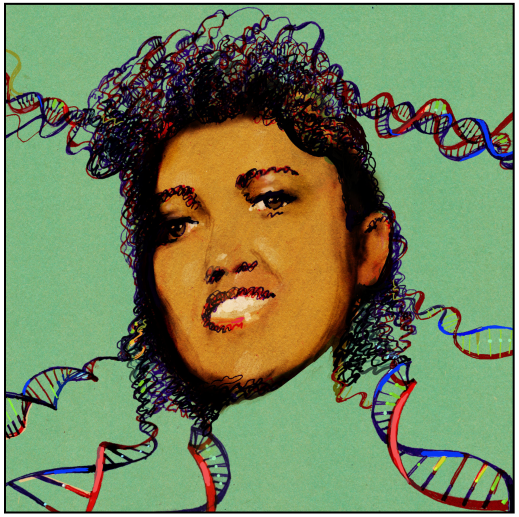
Genomics has similar "Big Data" Dilemma in the Rest of Society

- Sharing & "peer-production" is central to success of many new ventures, with the same risks as in genomics
  - **EG web search**: Large-scale mining essential
- We confront privacy risks every day we access the internet

[Seringhaus & Gerstein ('09), *Hart. Courant* (Jun 5); Greenbaum & Gerstein ('11), *NY Times* (6 Oct)]

Tricky Privacy Considerations in Personal Genomics

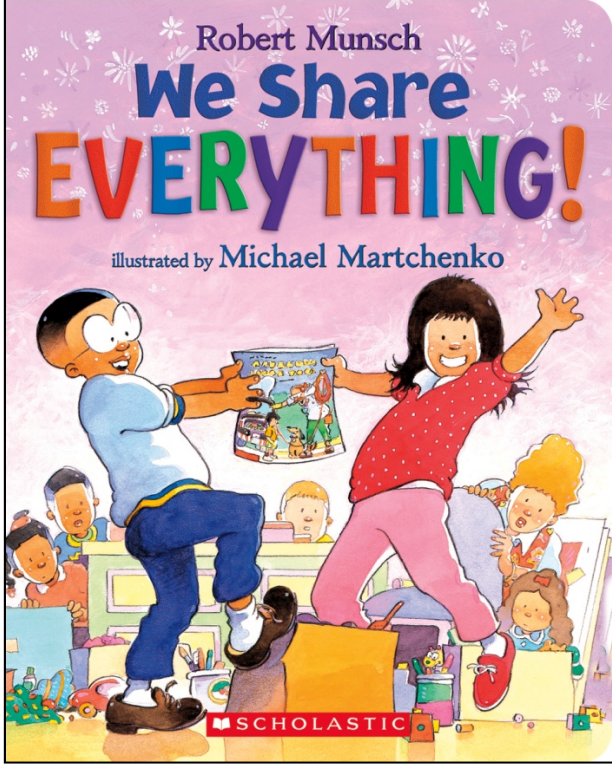
- **Genetic Exceptionalism :** The Genome is very fundamental data, potentially very revealing about one's identity & characteristics
- **Personal Genomic info. essentially meaningless currently but will it be in 20 yrs? 50 yrs?**
  - Genomic sequence very revealing about one's children. Is true consent possible?
  - Once put on the web it can't be taken back
- **Culture Clash:** Genomics historically has been a proponent of "open data" but not clear personal genomics fits this.
  - Clinical Medline has a very different culture.
- **Ethically challenged** history of genetics
  - Ownership of the data & what consent means (Hela)
    - Could your genetic data give rise to a product line?



[D Greenbaum & M Gerstein ('08). Am J. Bioethics; D Greenbaum & M Gerstein, Hartford Courant, 10 Jul. '08 ; SF Chronicle, 2 Nov. '08; Greenbaum et al. *PLOS CB* ('11) ; Greenbaum & Gerstein ('13), The Scientist; Photo from NY Times]

The Other Side of the Coin: Why we should share

- Sharing helps **speed research**
  - Large-scale mining of this information is important for medical research
  - Privacy is cumbersome, particularly for big data
- Sharing is important for **reproducible research**
- Sharing is useful for **education**
  - More fun to study a known person's genome
    - Eg Zimmer's Game of Genomes in STAT



[Yale Law Roundtable ('10). Comp. in Sci. & Eng. 12:8; D Greenbaum & M Gerstein ('09). Am. J. Bioethics; D Greenbaum & M Gerstein ('10). SF Chronicle, May 2, Page E-4; Greenbaum et al. *PLOS CB* ('11)]

[Economist, 15 Aug '15]

The Dilemma

- The individual (harmed?) v the collective (benefits)
  - But do sick patients care about their privacy?
- How to balance risks v rewards - Quantification
  - What is acceptable risk?
    Can we quantify leakage?
    - Ex: photos of eye color
  - Cost Benefit Analysis

Current Social & Technical Solutions

- **Closed Data** Approach
  - Consents
  - "Protected" distribution via dbGAP
  - Local computes on secure computer
- Issues with Closed Data
  - Non-uniformity of consents & paperwork
    - Different international norms, leading to confusion
  - Encryption & computer security creates burdensome requirements on data sharing & large scale analysis
  - Many schemes get "hacked"

- **Open Data**
  - Genomic "test pilots" (ala PGP)?
    - Sports stars & celebrities?
  - Some public data & data donation is helpful but is this a realistic solution for an unbiased sample of ~1M

[Greenbuam et al ('04), Nat. Biotech; Greenbaum & Gerstein ('13), The Scientist]

Strawman Hybrid Social & Tech Proposed Solution?

- Fundamentally, researchers have to keep genetic secrets.
  - **Need for an (international) legal framework**
  - Genetic Licensure & training for individuals (similar to medical license, drivers license)
- Technology to make things easier
  - Cloud computing & enclaves (eg solution of Genomics England)
- Technological barriers shouldn't create a social incentive for “hacking”

- **Quantifying Leakage & allowing a small amounts of it**
- **Careful separation & coupling of private & public data**
  - **Lightweight, freely accessible secondary datasets coupled to underlying variants**
  - Selection of stub & "test pilot" datasets for benchmarking
  - Develop programs on public stubs on your laptop, then move the program to the cloud for private production run

[D Greenbaum, M Gerstein (‘11). Am J Bioeth 11:39. Greenbaum & Gerstein, The Scientist ('13)]

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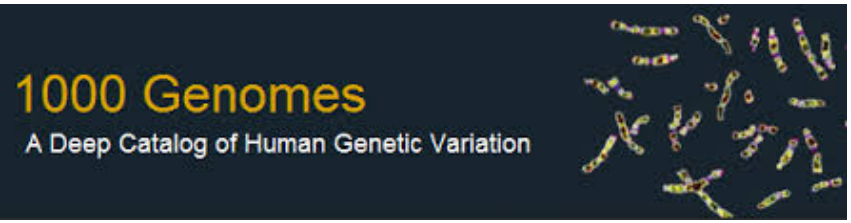
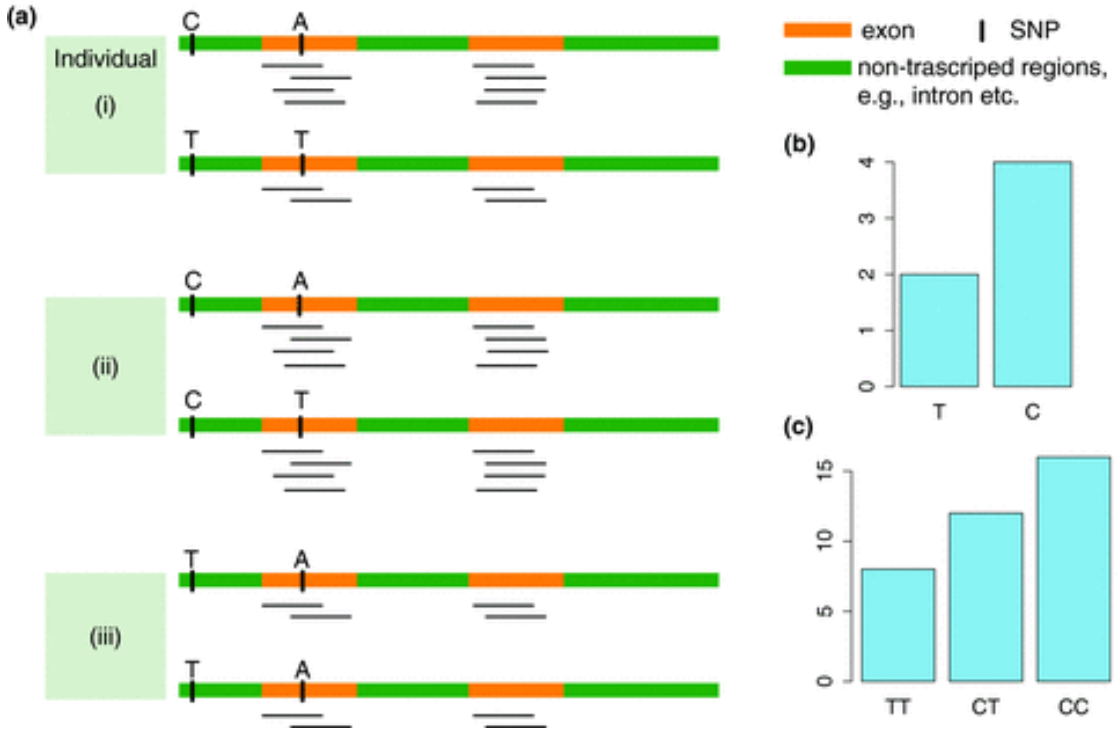
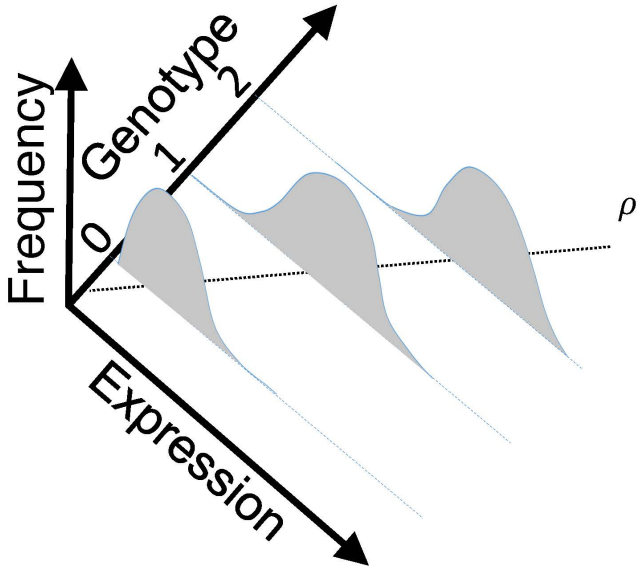
Representative Functional Genomics, Genotype, eQTL Datasets

- Genotypes are available from the 1000 Genomes Project
- mRNA sequencing for 462 individuals from gEUVADIS and ENCODE
  - Publicly available quantification for protein coding genes
- Functional genomics data (ChIP-Seq, RNA-Seq, Hi-C) available from ENCODE
- Approximately 3,000 cis-eQTL (FDR<0.05)





[*Biometrics 68(1) 1–11*]

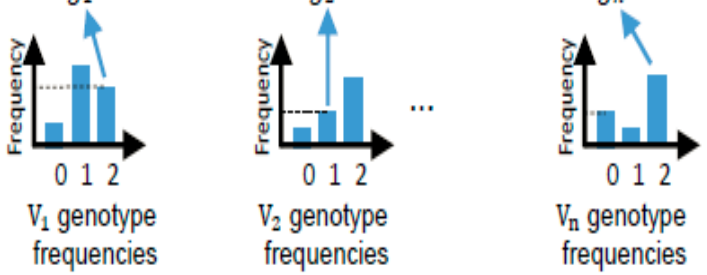


eQTL Mapping Using RNA-Seq Data

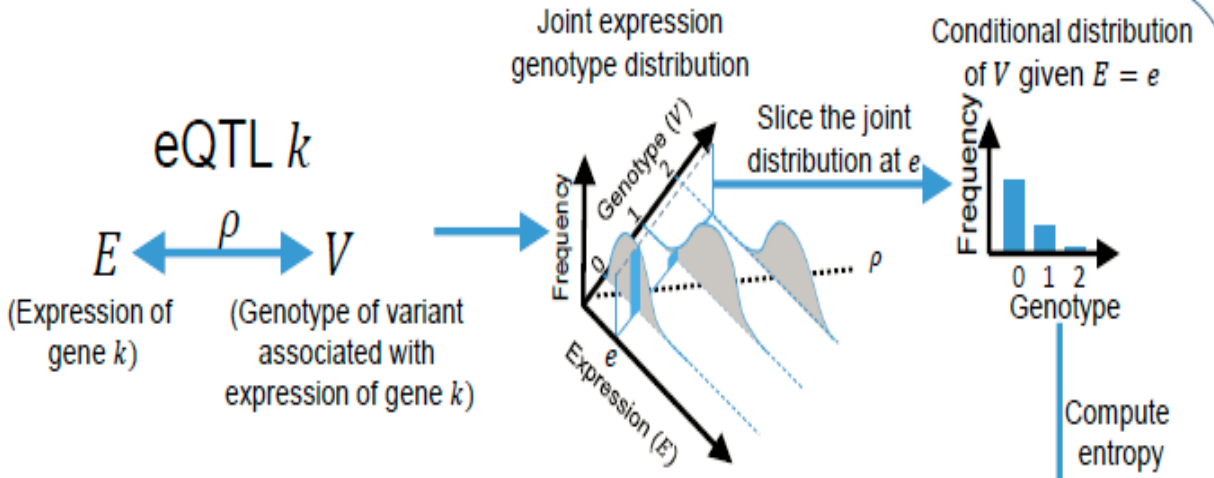
- eQTLs are genomic loci that contribute to variation in mRNA expression levels
- eQTLs provide insights on transcription regulation, and the molecular basis of phenotypic outcomes
- eQTL mapping can be done with RNA-Seq data

Information Content and Predictability

$$ICI\left(\begin{array}{l}\text{Individual has variant}\\ \text{genotypes } g_1, g_2, \ldots, g_n\\ \text{for variants } V_1, V_1, \ldots, V_n\end{array}\right) = \log\left(\frac{1}{\text{Frequency of } V_1 \text{ genotype } g_1 = 2}\right) + \log\left(\frac{1}{\text{Frequency of } V_2 \text{ genotype } g_2 = 1}\right) + \ldots + \log\left(\frac{1}{\text{Frequency of } V_n \text{ genotype } g_n = 2}\right)$$



- Naive measure of information (no LD, distant correlations, pop. struc., &c)
- Higher frequency: Lower ICI
- Additive for multiple variants

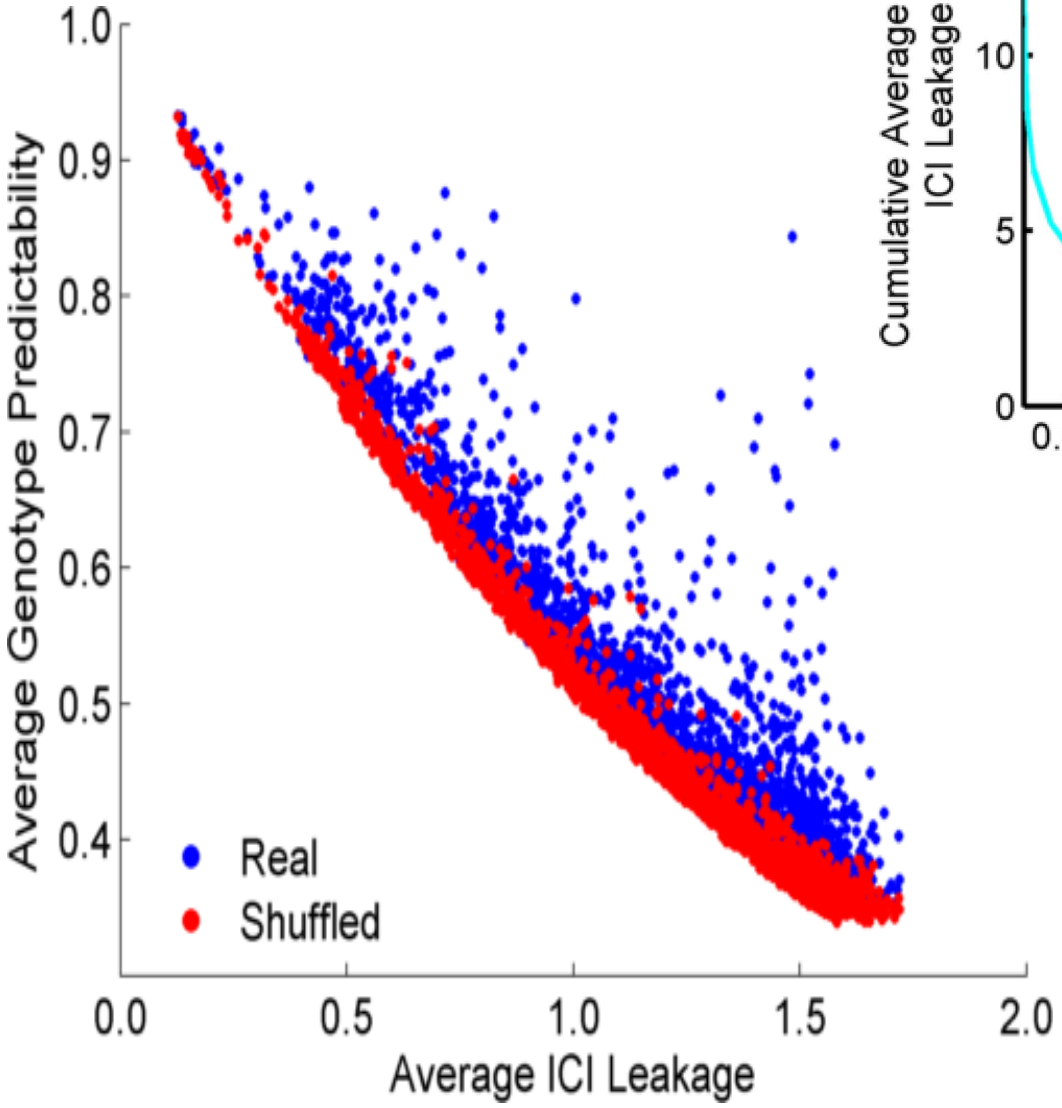


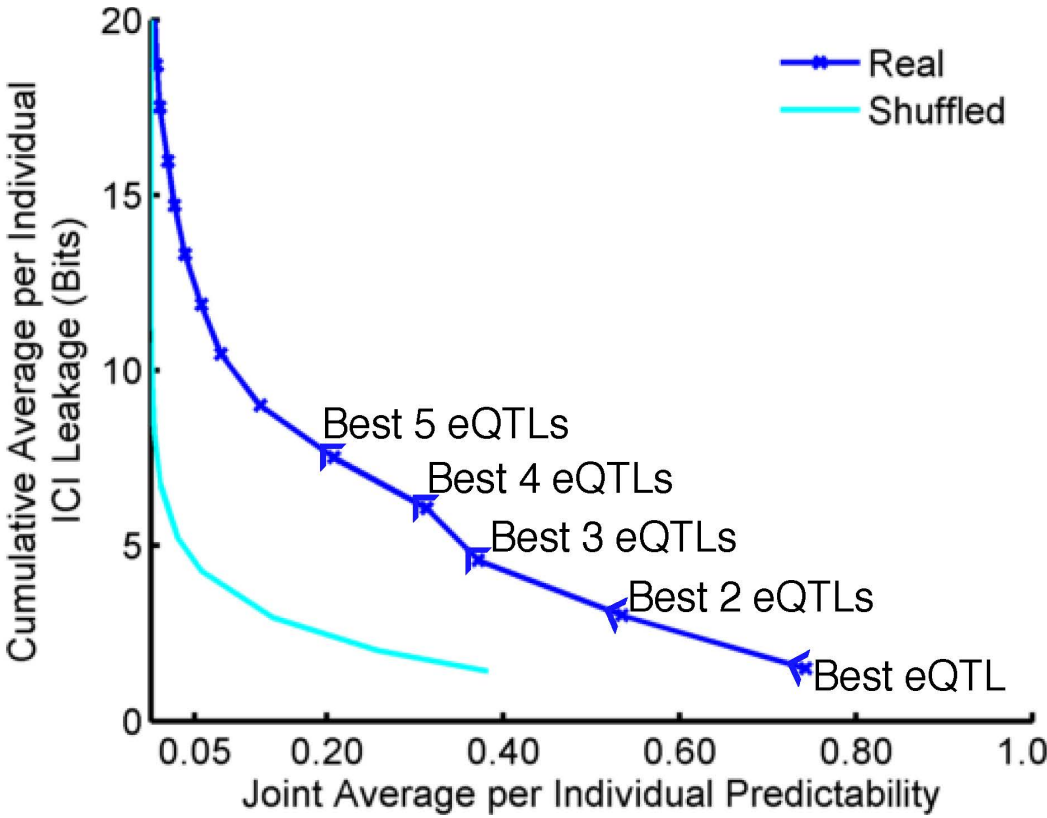
$$\pi\left(V \mid E = e\right) = e^{-H\left(V \mid E = e\right)}$$

- Condition specific entropy
- Higher cond. entropy: Lower predictability
- Additive for multiple eQTLs

[Harmanci et al. Nat. Meth. 2016]

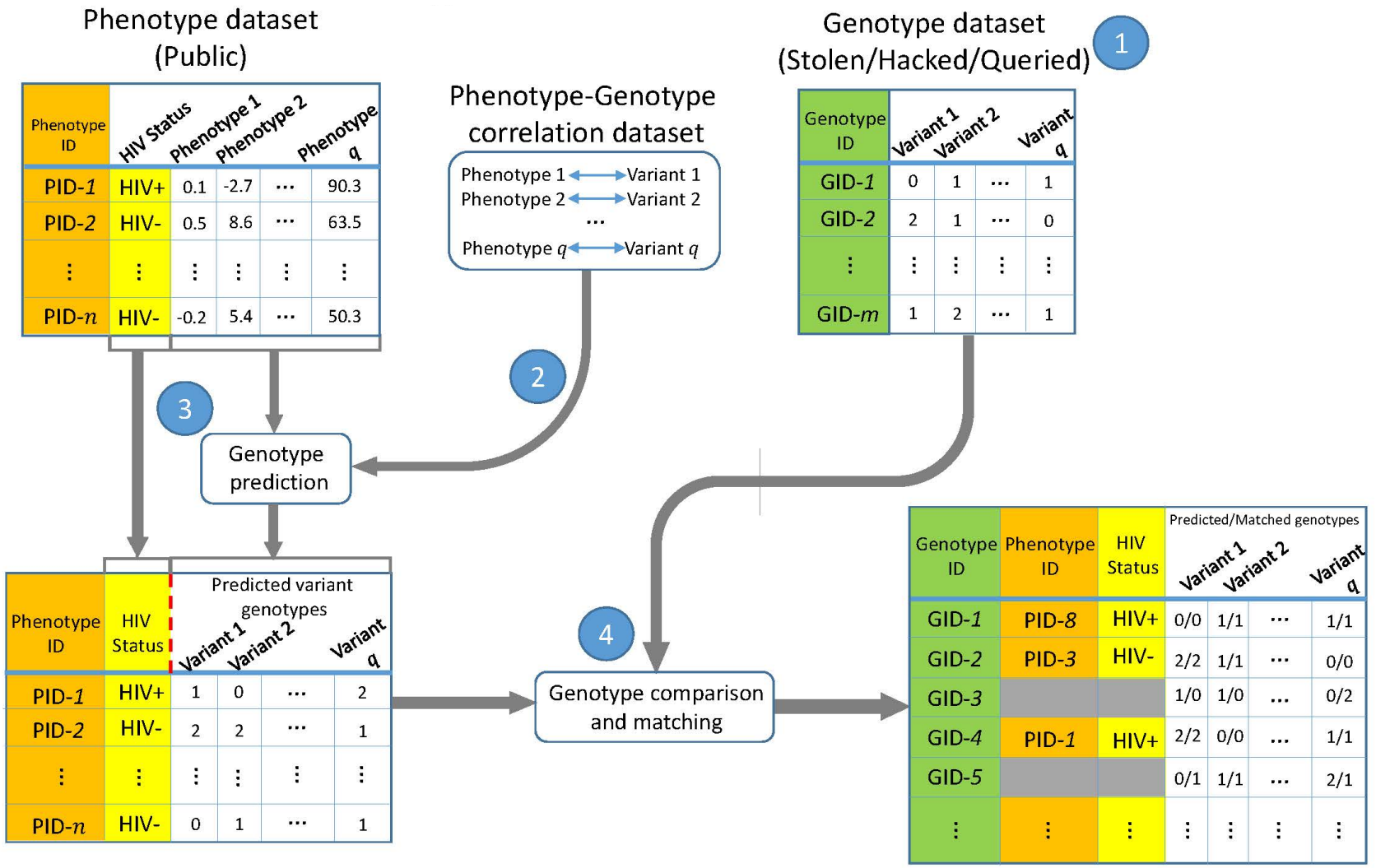
[Harmanciet al. Nat. Meth. (‘16]





ICI Leakage versus Genotype Predictability

Linking Attack Scenario



[Harmanciet al. Nat. Meth. (in revision)]

Linking Attacks: Case of Netflix Prize

User (ID)	Movie (ID)	Date of Grade	Grade [1,2,3,4,5]
NTFLX-0	NTFLX-19	10/12/2008	1
NTFLX-1	NTFLX-116	4/23/2009	3
NTFLX-2	NTFLX-92	5/27/2010	2
NTFLX-1	NTFLX-666	6/6/2016	5
…	…	…	…
…	…	…	…

Names available for many users!

User (ID)	Movie (ID)	Date of Grade	Grade [0-10]
IMDB-0	IMDB-173	4/20/2009	5
IMDB-1	IMDB-18	10/18/2008	0
IMDB-2	IMDB-341	5/27/2010	-
…	…	…	…
…	…	…	…
…	…	…	…

- **Many users are shared**
- **The grades of same users are correlated**
- **A user grades one movie around the same date in two databases**

Anonymized Netflix Prize Training Dataset made available to contestants

Linking Attacks: Case of Netflix Prize

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- **IMDB users are public**

- **NetFLIX and IMdB moves are public**

Linking Attacks: Case of Netflix Prize

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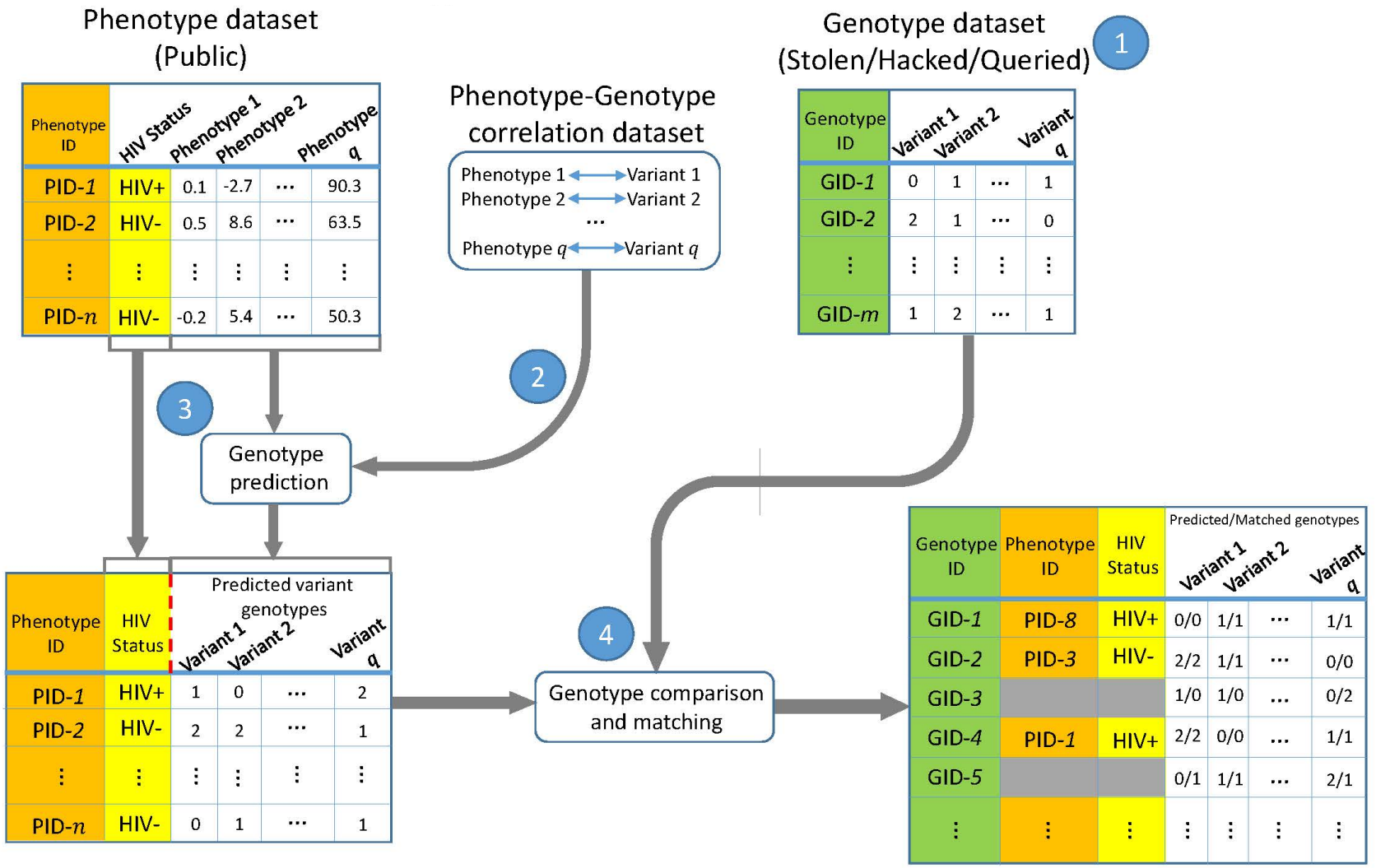

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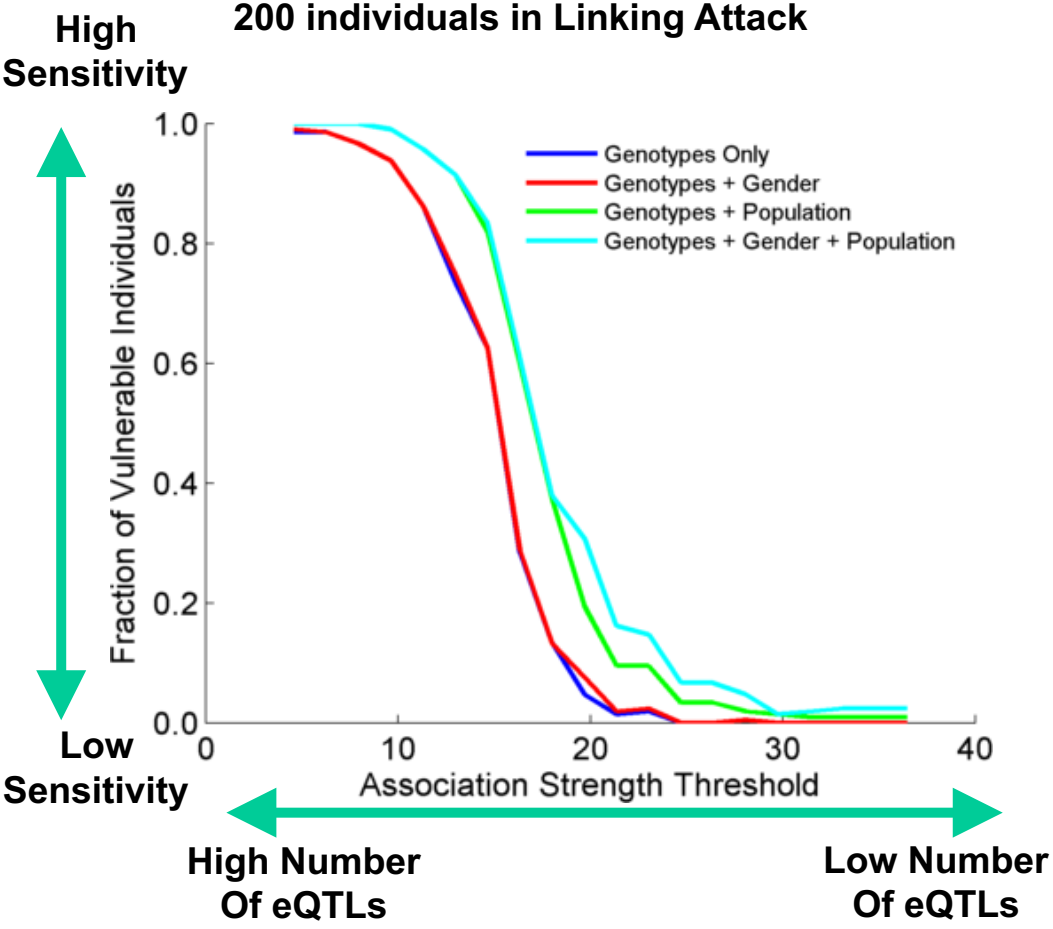
Success in Linking Attack with Extremity based Genotype Prediction

200 individuals eQTL Discovery
200 individuals in Linking Attack



[Harmanci et al. *Nat. Meth.* (16)]

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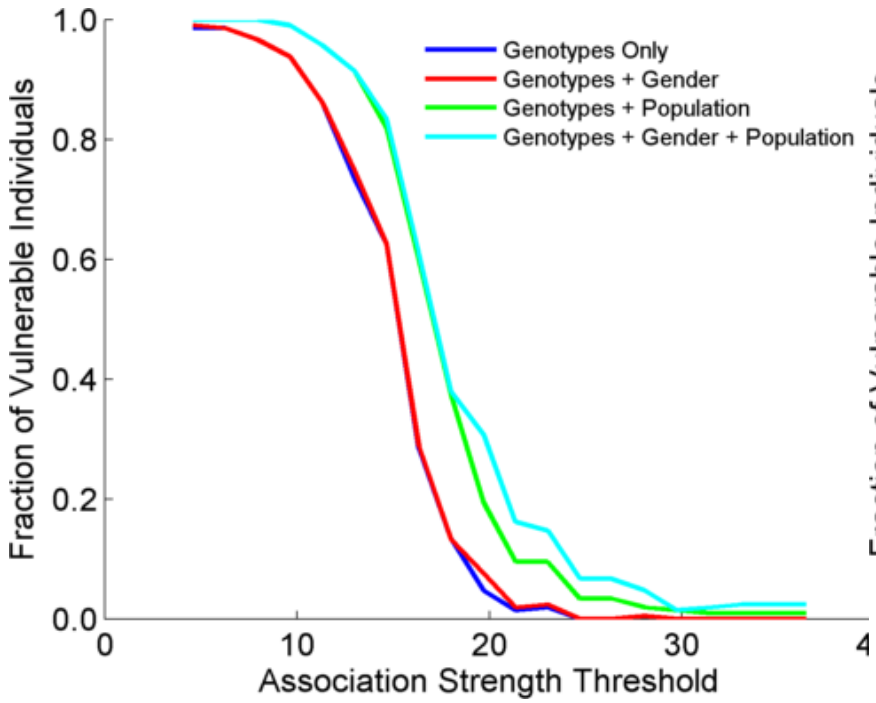
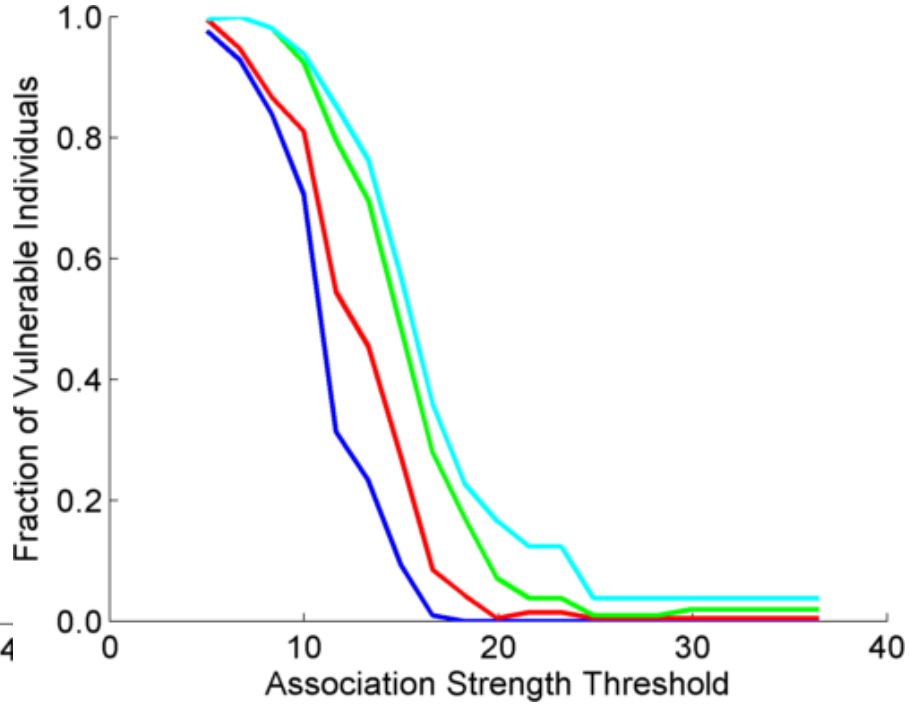


200 individuals eQTL Discovery
100,200 individuals in Linking Attack



[Harmanci et al. *Nat. Meth.* (16)]

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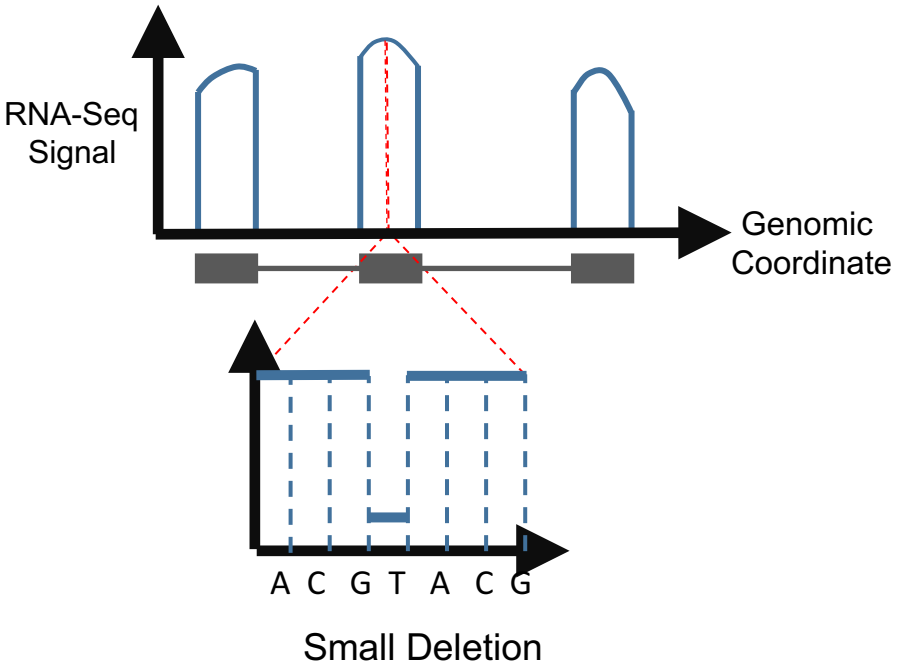
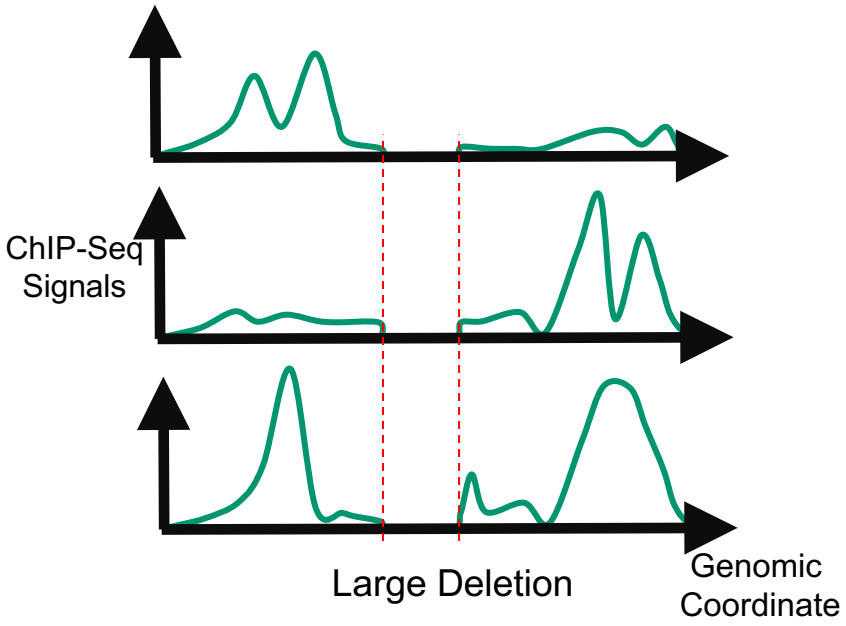
Detection & Genotyping of small & large SV deletions from signal profiles

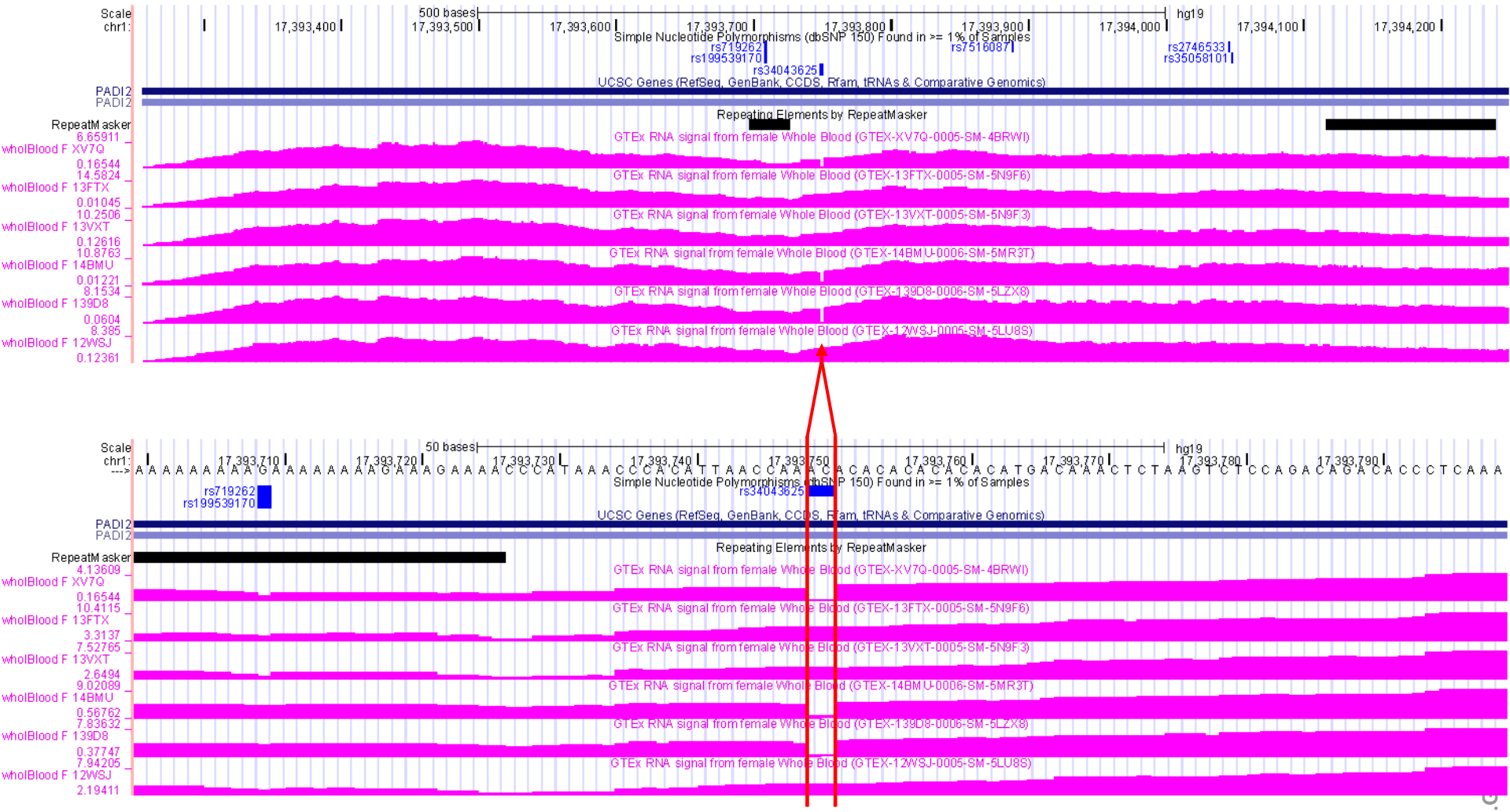




RNA-seq also shows large deletions

[Harmanci & Gerstein, *Nat. Comm.* ('18)]

Example of Small Deletion Evident in Signal Profile



[Harmanci & Gerstein, *Nat. Comm.* ('18)]

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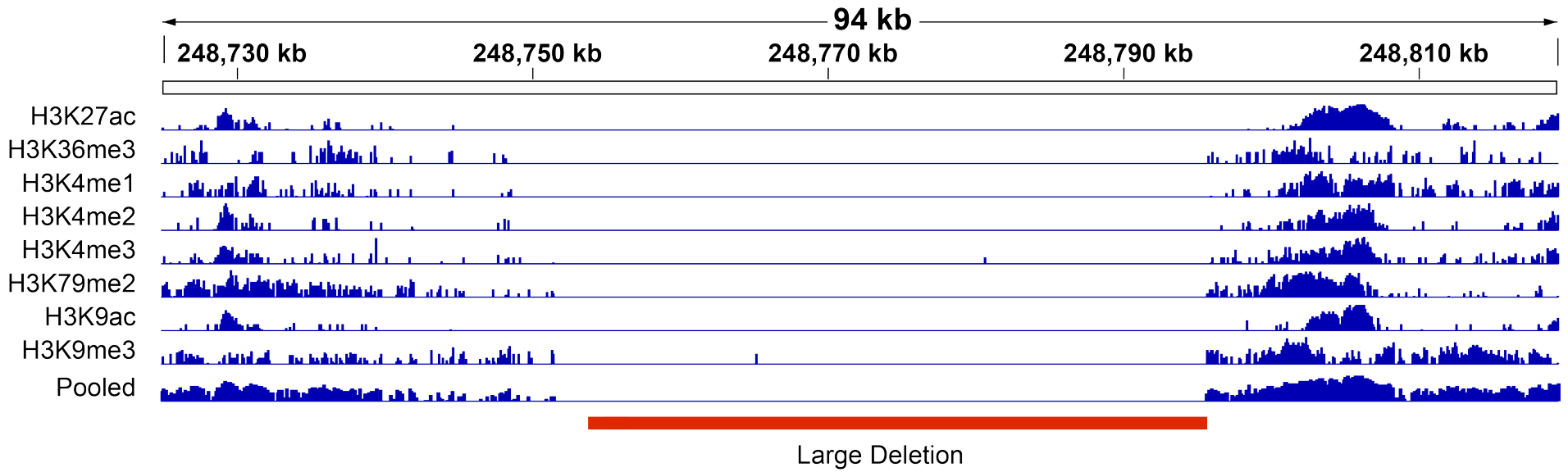
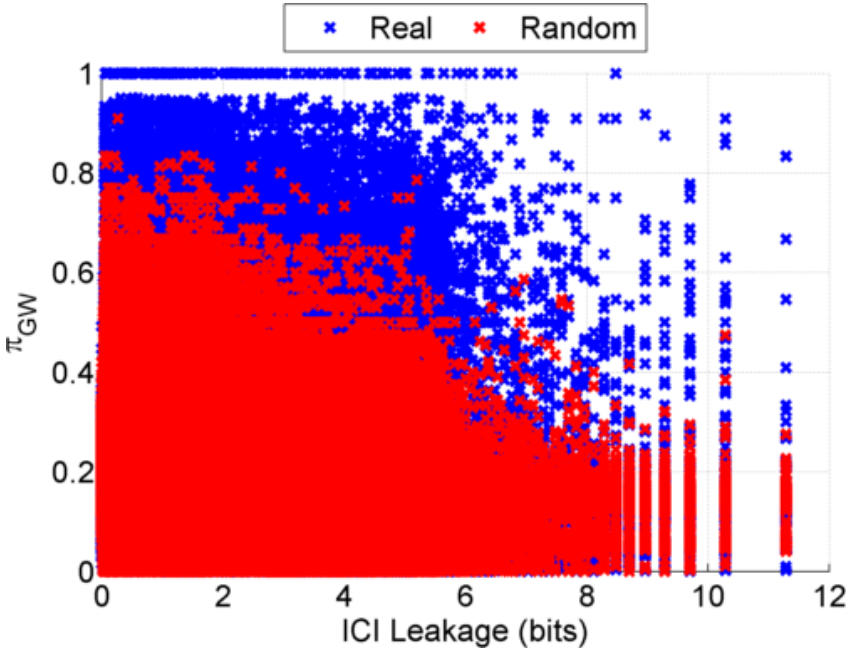


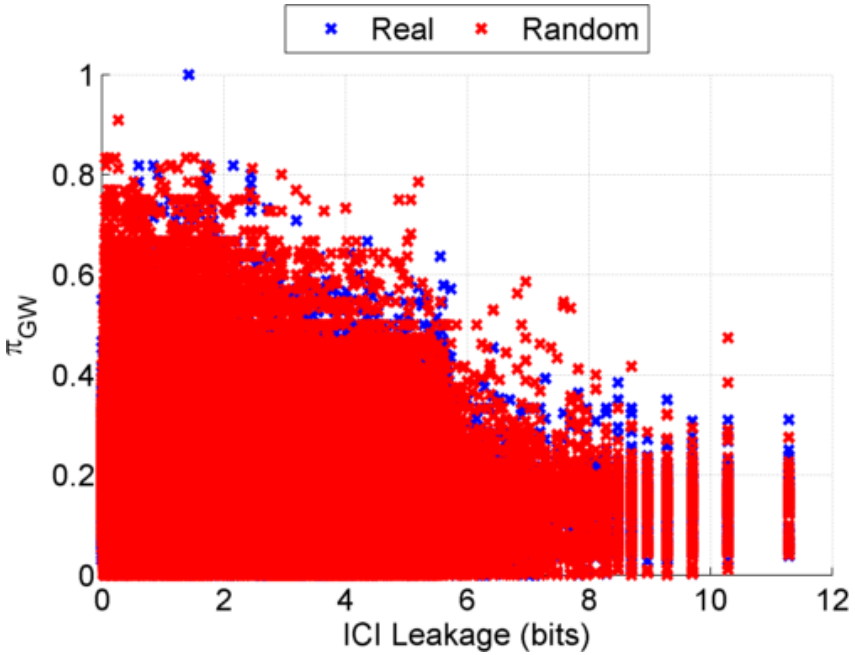
[Harmanci & Gerstein, *Nat. Comm.* ('18)]

Information Leakage from SV Deletions

a) Before Anonymization



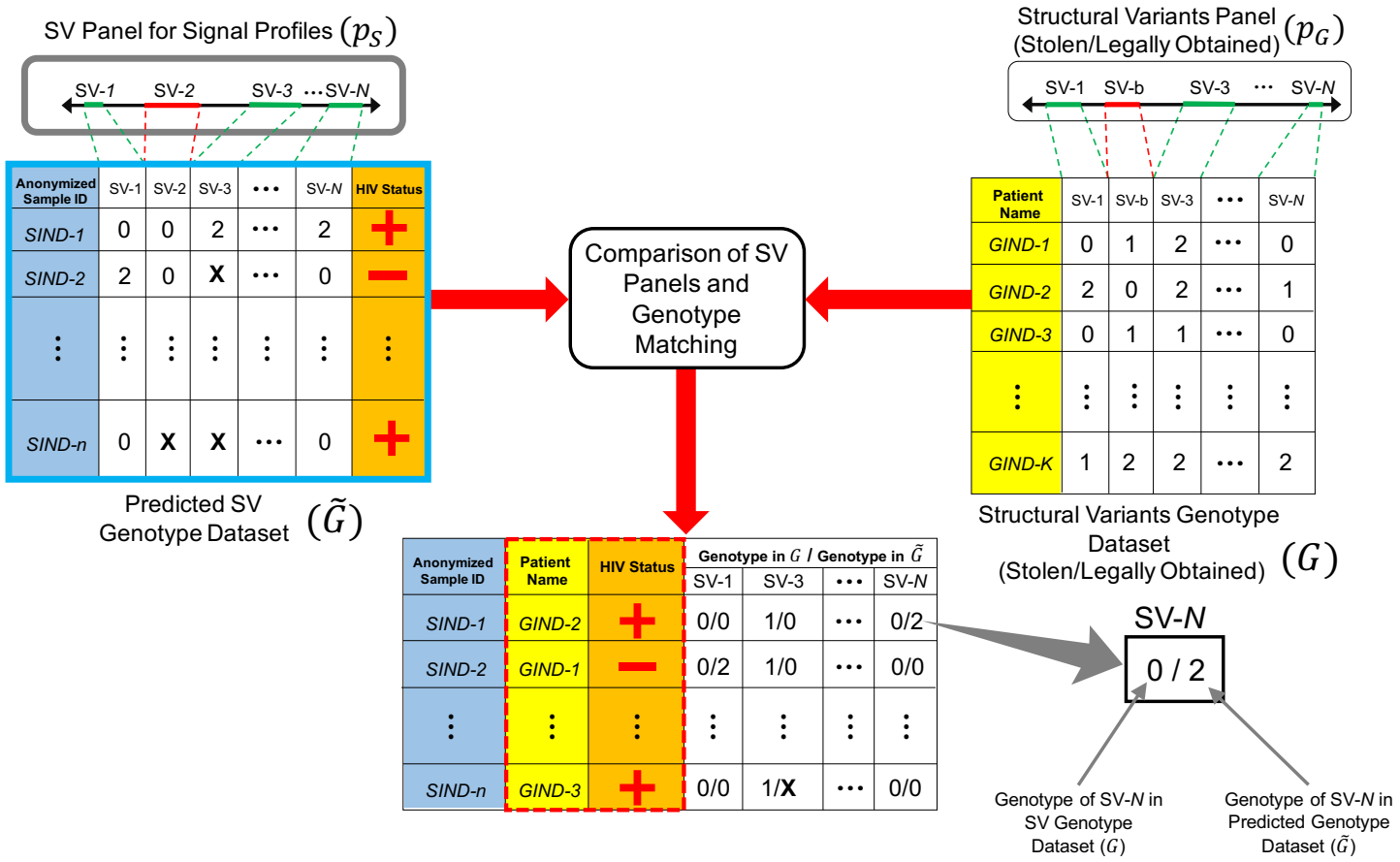
b) After Anonymization



Simple anonymization procedure (filling in deletion by value at endpoints) has dramatic effect

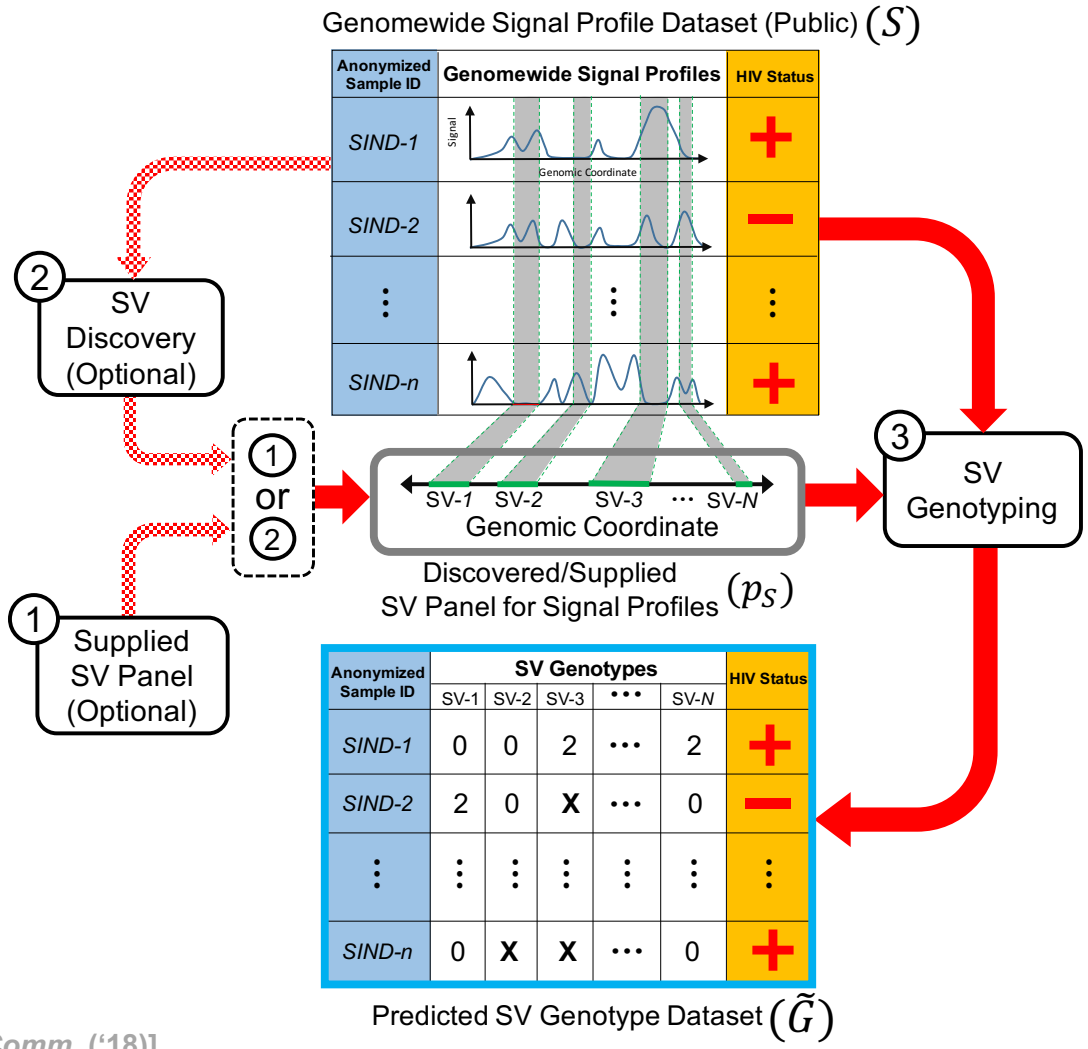
[Harmanci & Gerstein, *Nat. Comm.* ('18)]

Another type of Linking Attack: Linking based on SV Genotyping



[Harmanci & Gerstein, *Nat. Comm.* ('18)]

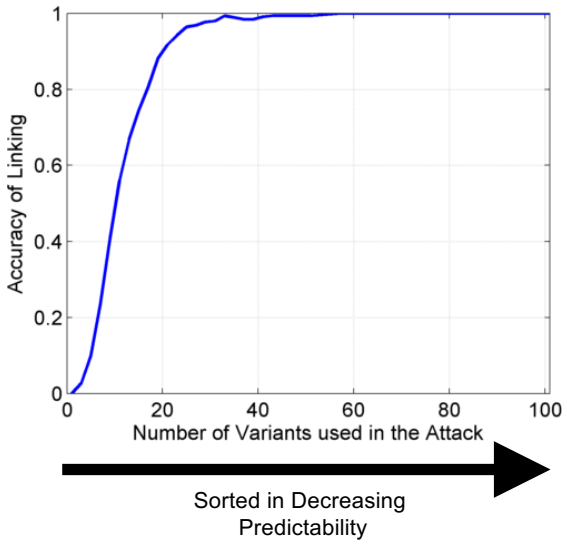
Another type of Linking Attack: First Doing SV Genotyping



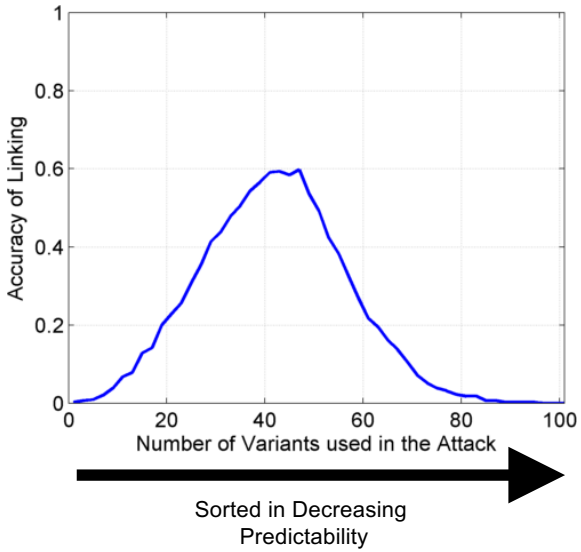
[Harmanci & Gerstein, *Nat. Comm.* ('18)]

Linking Attack Based on SV Deletions in gEUVADIS Dataset

c) Genotyping
(1kG MAF>0.01)



d) Discovery + Genotyping



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PsychENCODE Acknowledgment

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PsychENCODE Consortium,

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Daniel H. Geschwind, James A. Knowles

Dedicated to Pamela Sklar

NIH National Institute of Mental Health

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- Lora Bingaman
- David Panchision
- Alexander Arguello
- Thomas Lehner

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P. Navarro, Yale University; Jonathan Warrell, Yale University; Declan Clarke, Yale University; Prashant S. Emani, Yale University; Mengting Gu, Yale University; Xu Shi, Yale University; Min Xu, Yale University; Yucheng T. Yang, Yale University; Robert R. Kitchen, Yale University; Gamze Gürsoy, Yale University; Jing Zhang, Yale University; Becky C Carlyle, Yale University; Angus C Nairn, Yale University; Mingfeng Li, Yale University; Sirisha Pochareddy, Yale University; Nenad Sestan, Yale University; Mario Skarica, Yale University; Zhen Li, Yale University; Andre M.M. 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Developmental Capstone

- **M Li, G Santpere, Y Imamura Kawasawa, OV Evgrafov, FO Gulden, S Pochareddy, SM Sunkin, Z Li, Y Shin,**

Y Zhu, AMM Sousa, DM Werling, RR Kitchen, HJ Kang, M Pletikos, J Choi, S Muchnik, X Xu, D Wang, B Lorente-Galdos, S Liu, P Giusti-Rodriguez, H Won, CA de Leeuw, AF Pardinas, BrainSpan Consortium,
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M Hu, F Jin, Y Li, MJ Owen, MC O'Donovan, JTR Walters, D Posthuma, MA Reimers, P Levitt, DR Weinberger, TM Hyde, JE Kleinman, DH Geschwind, MJ Hawrylycz, MW State, SJ Sanders, PF Sullivan,

ES Lein, JA Knowles, N Sestan

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D Greenbaum,
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