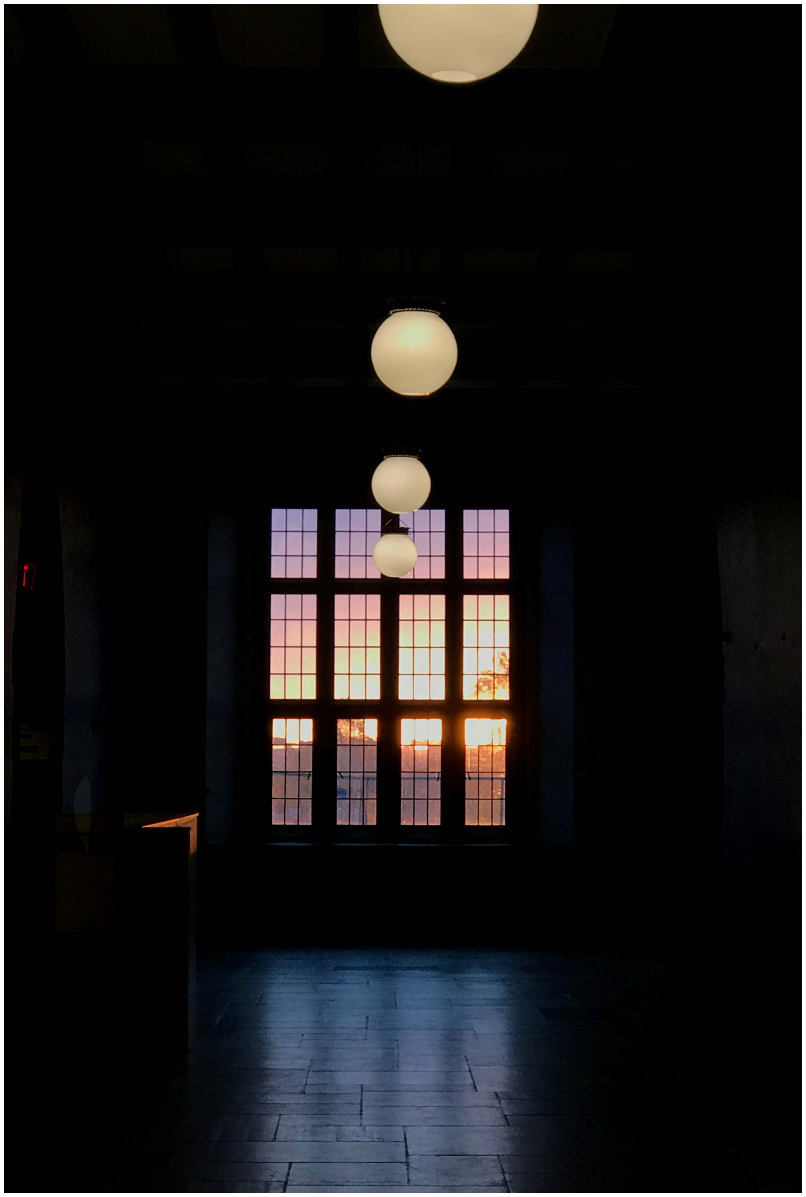


Personal Genomics

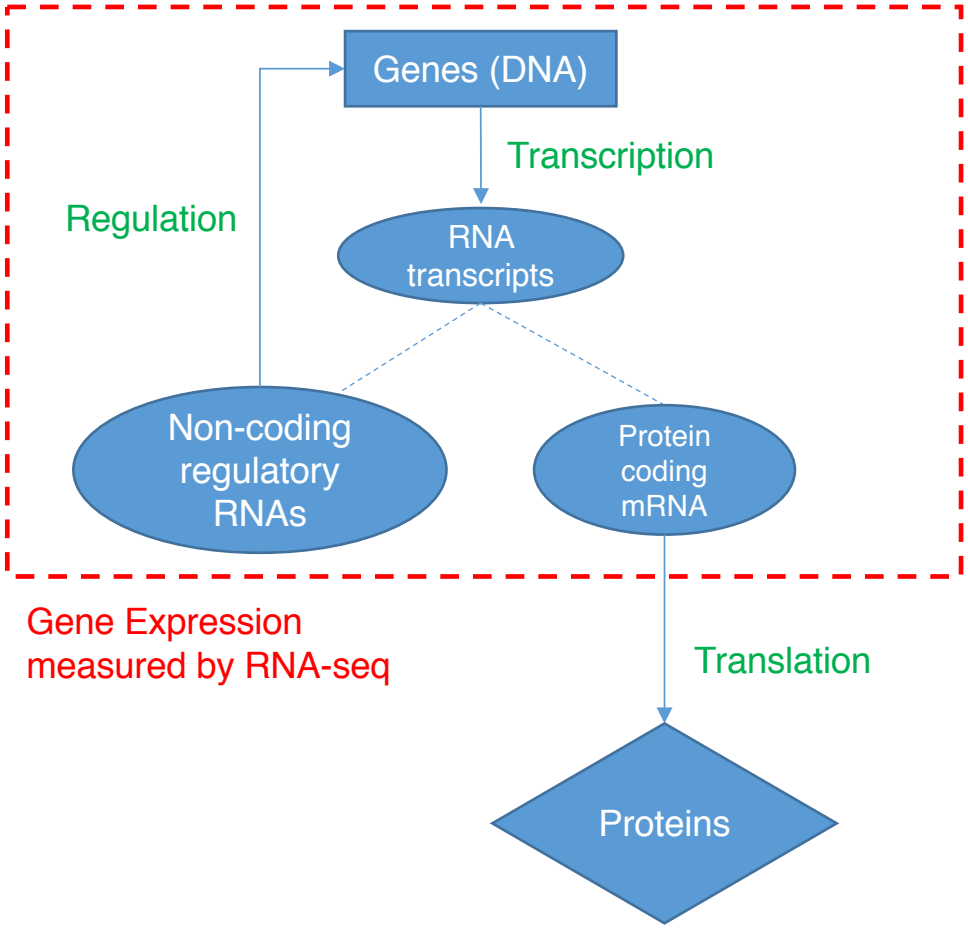
& Data Science:

Using population-scale functional genomics to understand neuropsychiatic disease & interpreting the data exhaust from this activity

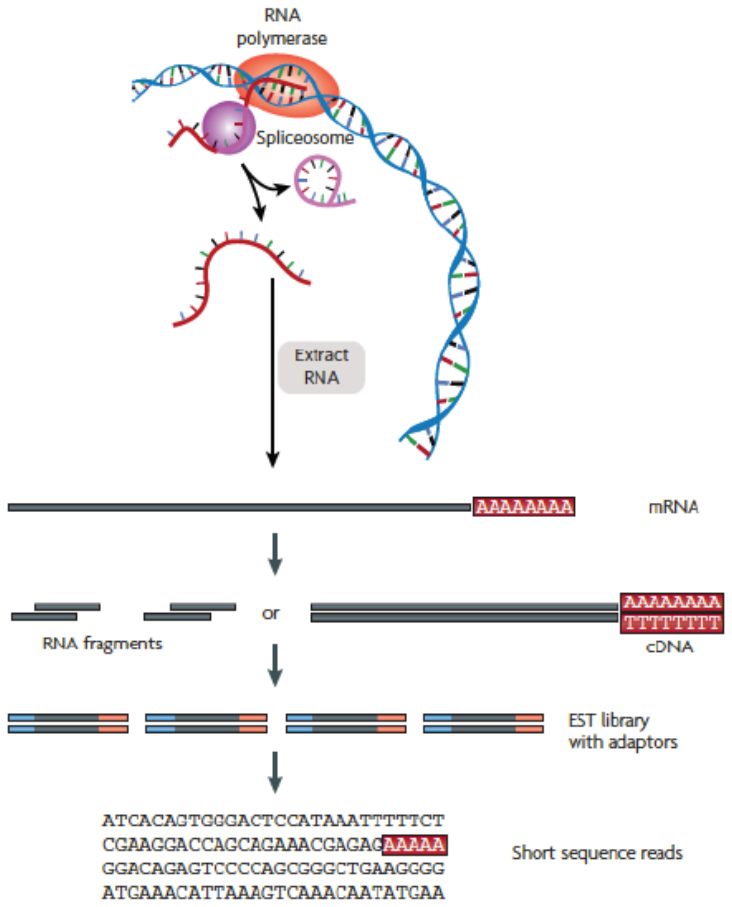
Mark Gerstein
Yale

Slides freely downloadable from
Lectures.GersteinLab.org
& "tweetable" (via **@markgerstein**).
See last slide for more info.

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

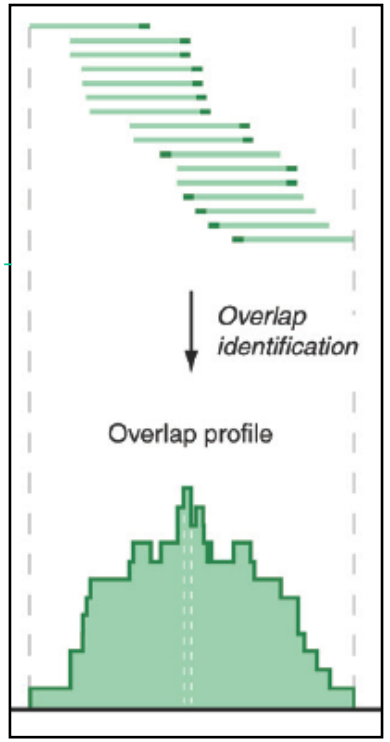
Fastq sequence files
~5-10 GB

```
ATACAAGCAAGTATAAGTTCGTATGCCGTCTT
GGAGGCTGGAGTTGGGGACGTATGCGGCATAG
TACCGATCGAGTCGACTGTAAACGTAGGCATA
ATTCTGACTGGTGTCATGCTGATGTACTTAAA
```

Index-building + Alignment to reference genome

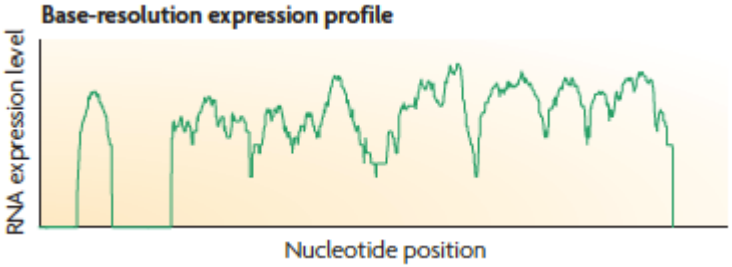
BAM files
~1-2-fold reduction

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

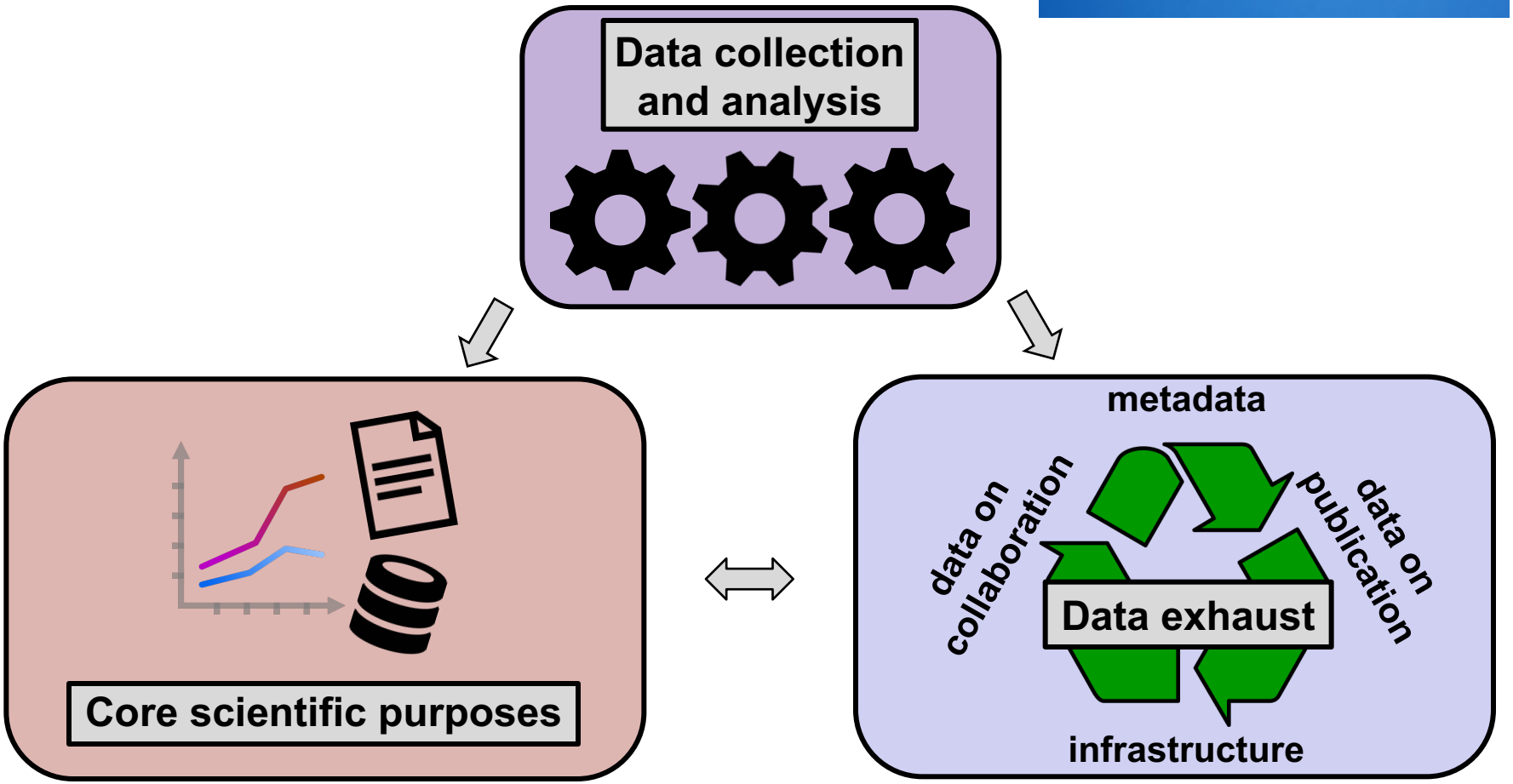
Some Core Science Qs Addressed by RNA-seq

- 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?

Data Exhaust

- Creative use of data is key to data science!
- Data exhaust = exploitable byproducts of big data collection and analysis



[photos: wikipedia/wikimedia]

Using population-scale functional genomics to understand neuropsychiatic disease & interpreting the data exhaust from this activity

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  - The **Dilemma**
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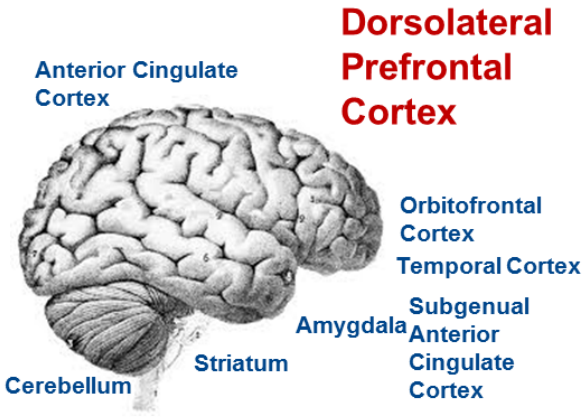
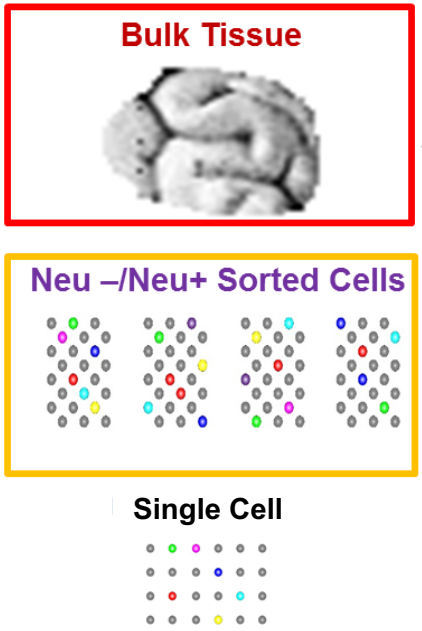
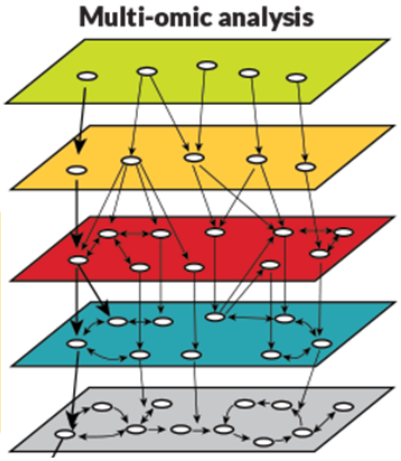
Sample Sources: >2,500 brains

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





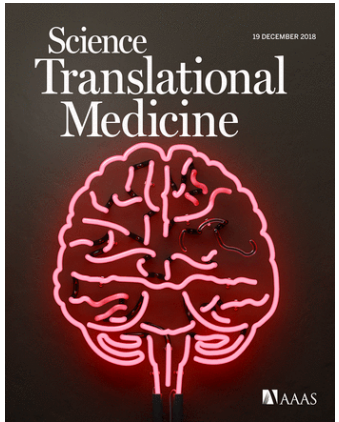


Genome:
WGS, genotype

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

Transcriptome:
RNA-seq, lncRNAseq,

Proteome:
MWP, LC-MS/MS



PsychENCODE

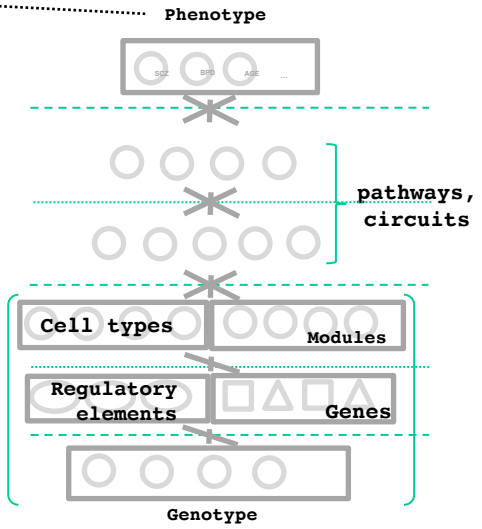
’18 rollout in Science

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

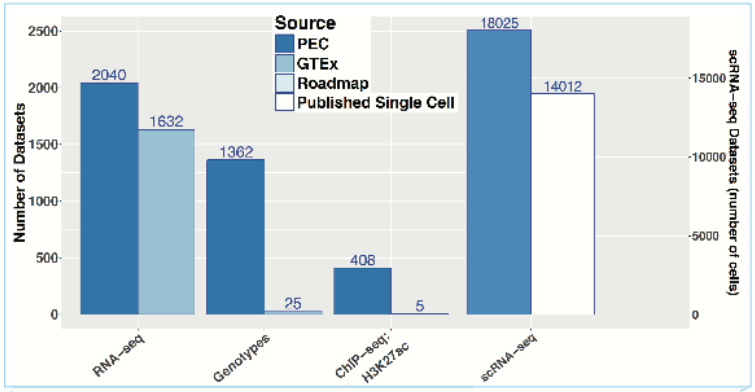
Schizophrenia: up to 80%

But we don't understand basic molecular mechanisms underpinning this association (in contrast to many other diseases such as cancer & heart disease)

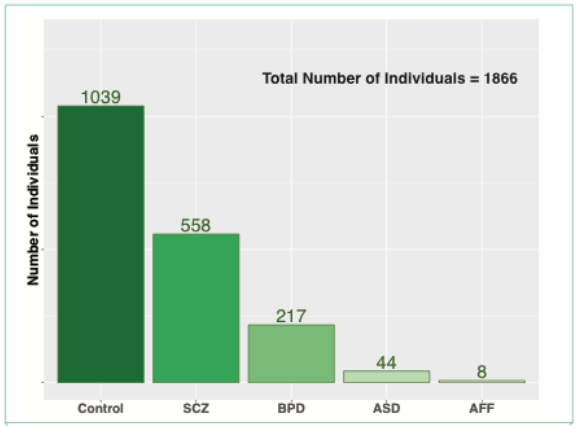
Thus, interested in developing predictive models of psychiatric traits which:

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

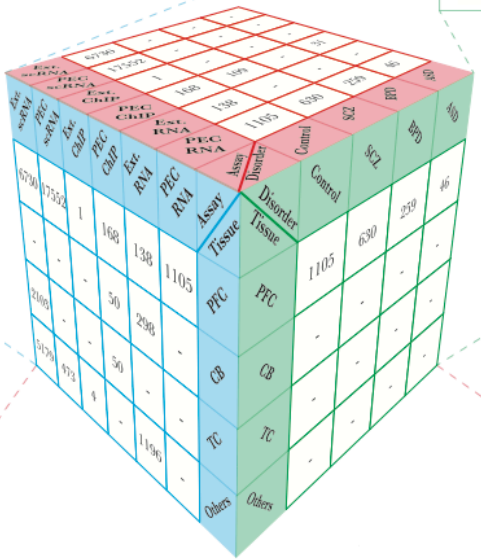


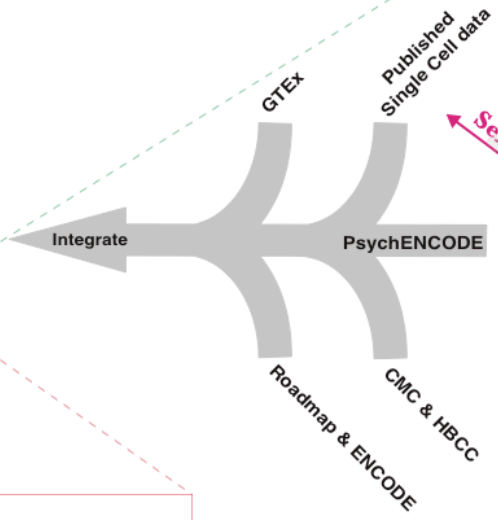
Assay

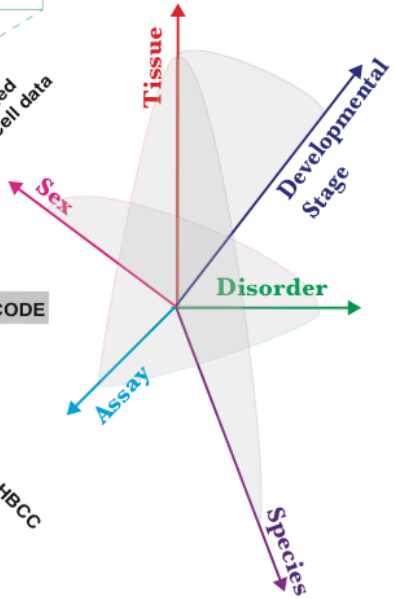


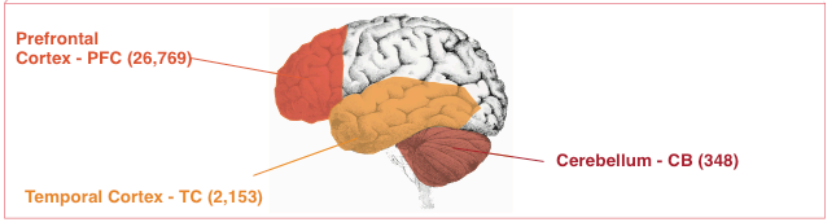
Disorder

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









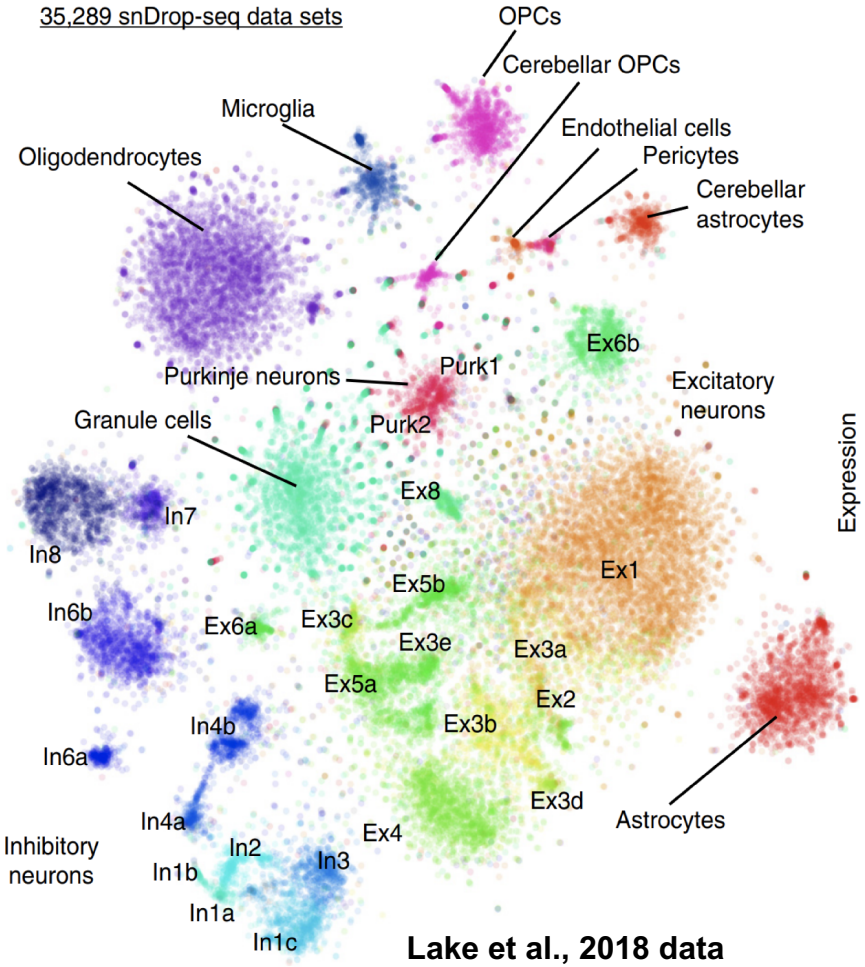
Collecting functional genomic datasets for the adult brain

from PsychENCODE, other large consortia & single cell studies

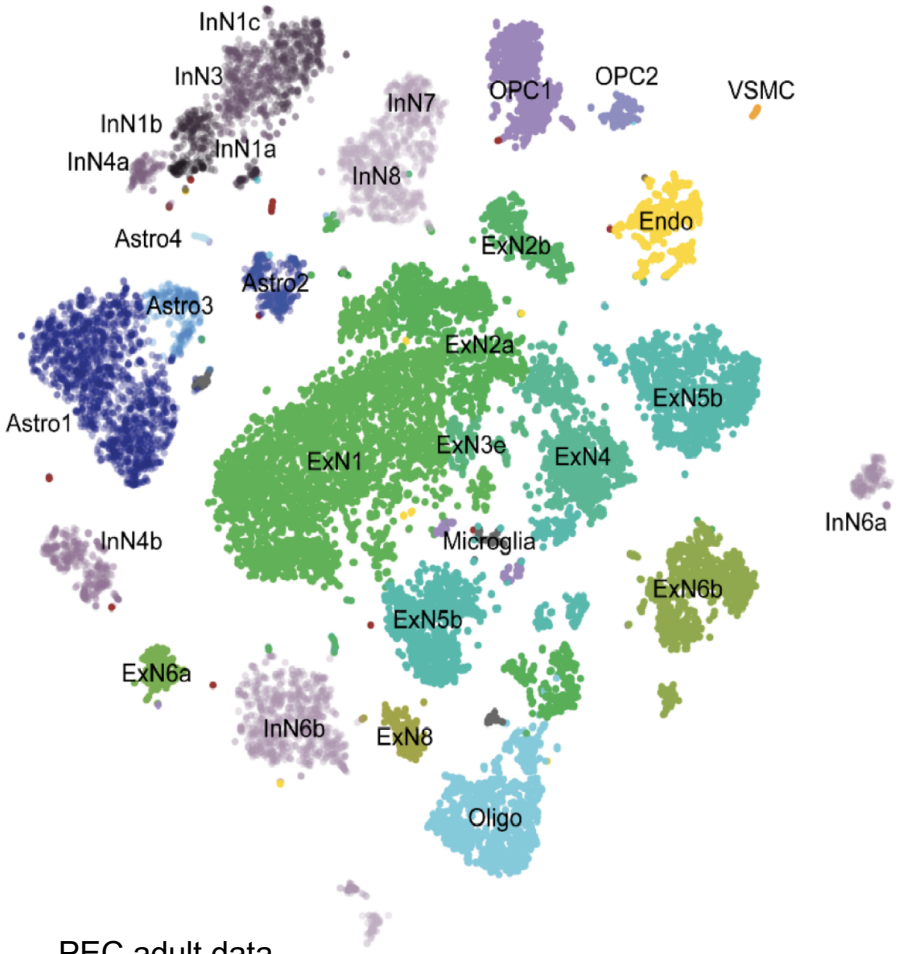
Merging & Clustering Single Cell Data Sets

Single cell signatures, from:

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



Lake et al., 2018 data

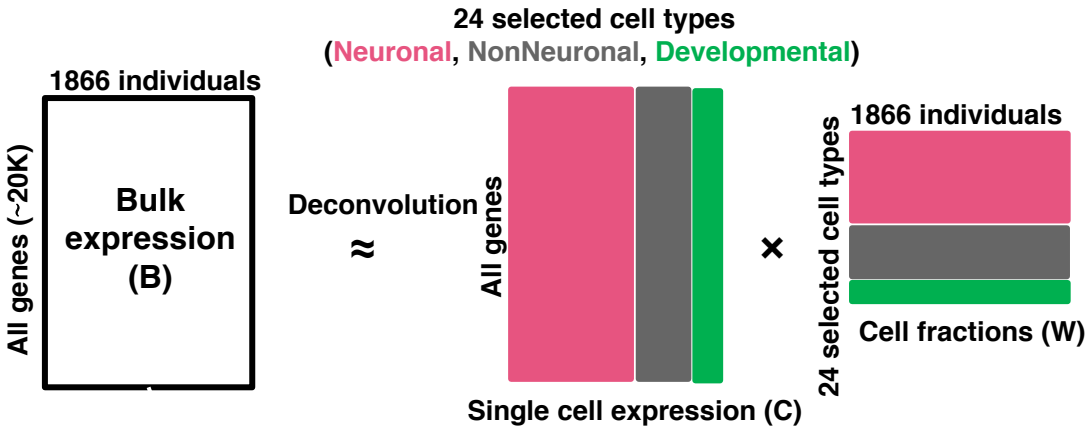


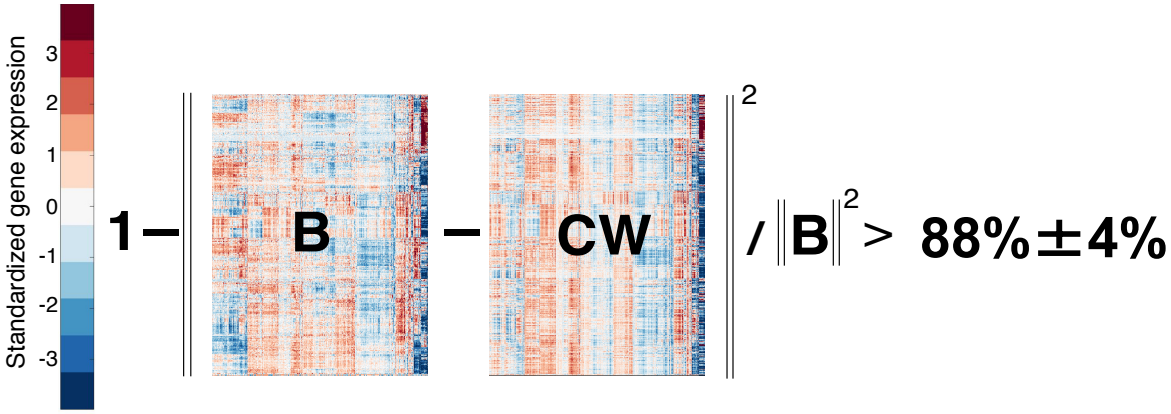
PEC adult data
[Li et al. ('18), Science. Wang et al. ('18). Science]

Single-cell deconvolution

Step 1:

Supervised learning to estimate cell fractions

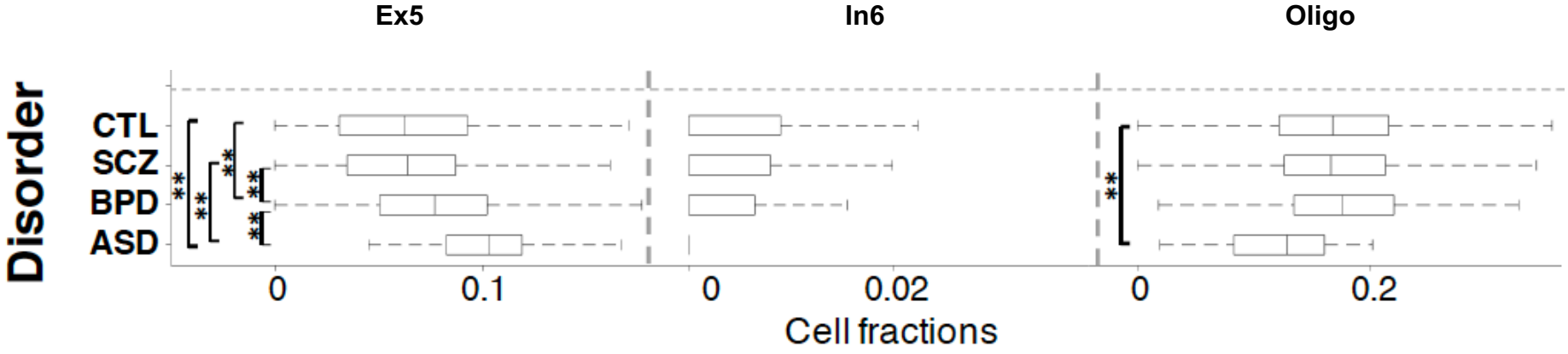




Individual and cross-population reconstruction accuracy via deconvolution

[Wang et al. ('18) Science]

Different neuronal & glial cell fractions across disorders

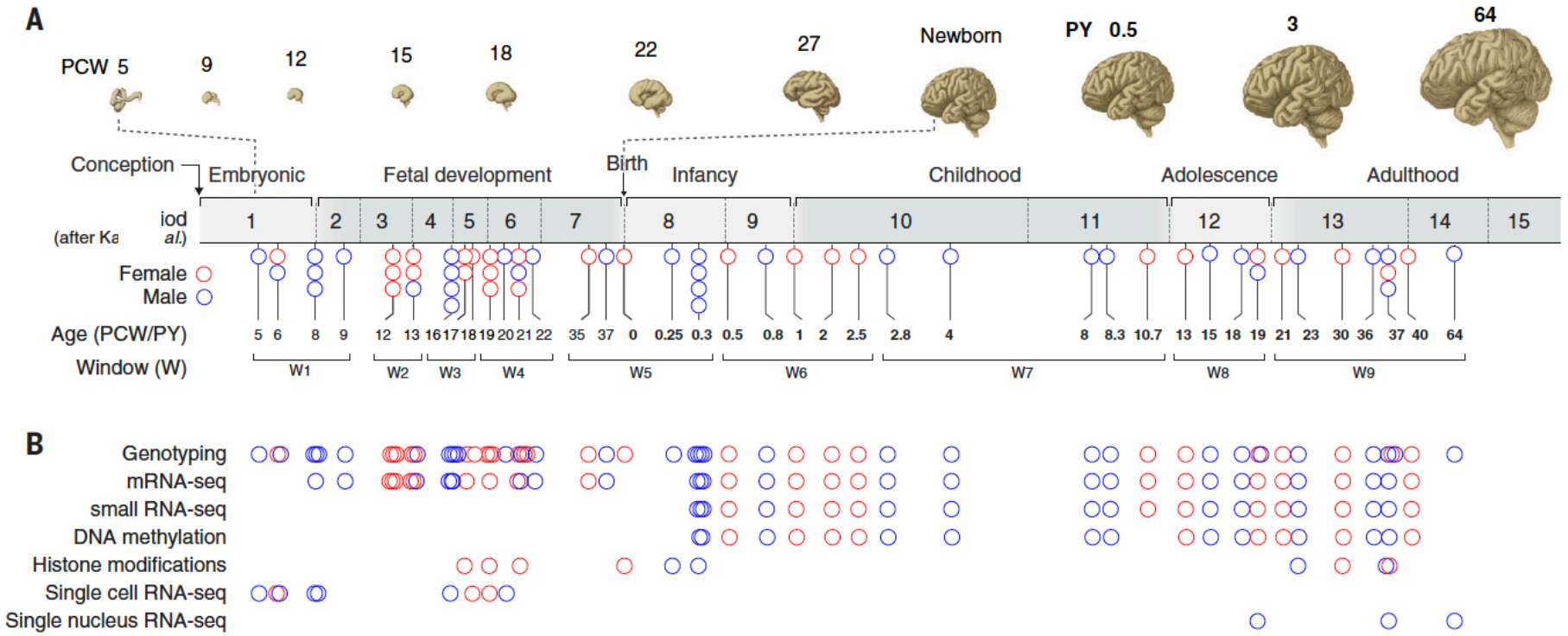


Excitatory to Inhibitory imbalance at neuronal subtype level for ASD*

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

[Wang et al. (‘18) Science]

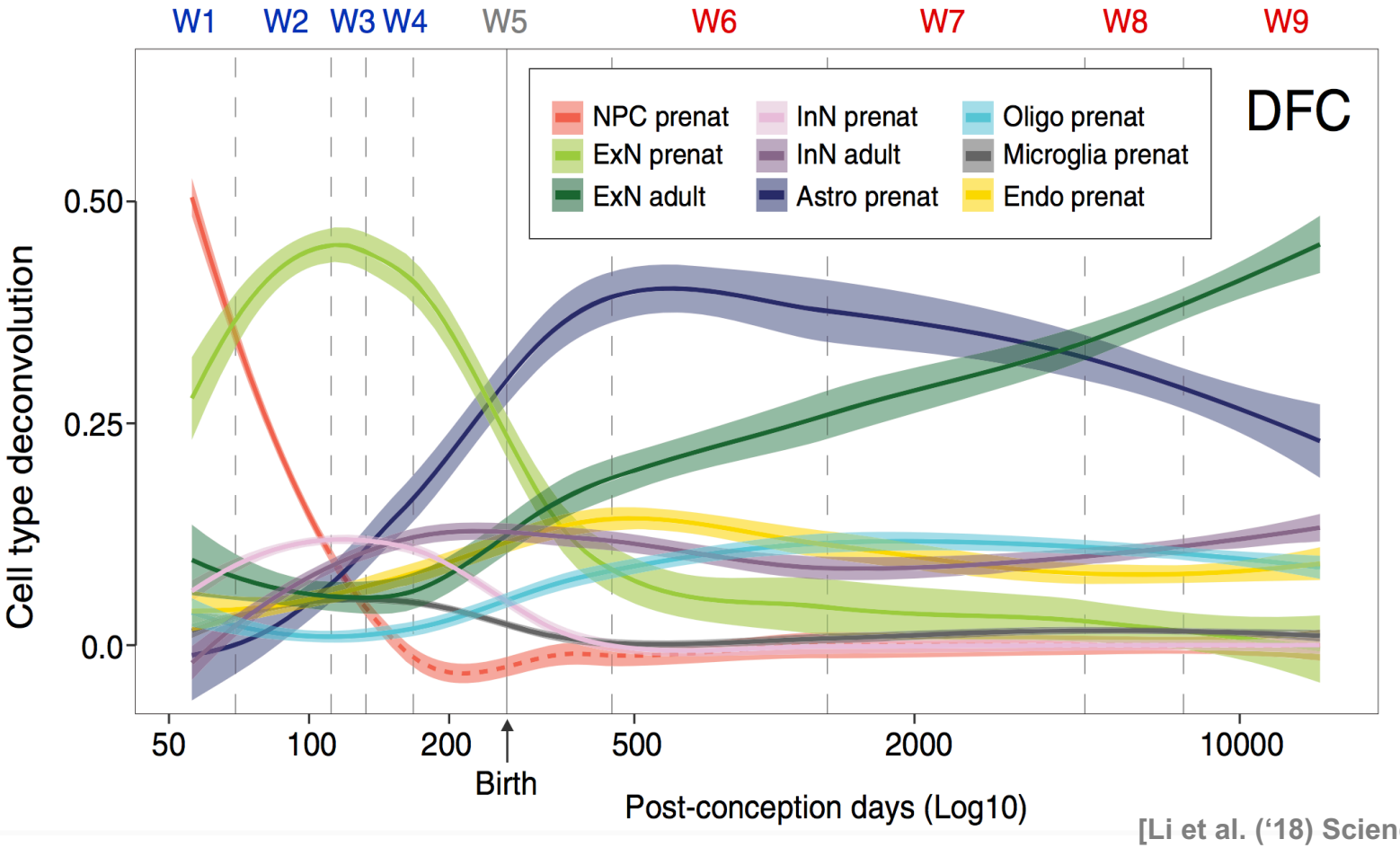
Developmental Capstone Data Set



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

[Li et al. (‘18) Science]

Different neuronal & glial cell fractions across ages



[Li et al. ('18) Science]

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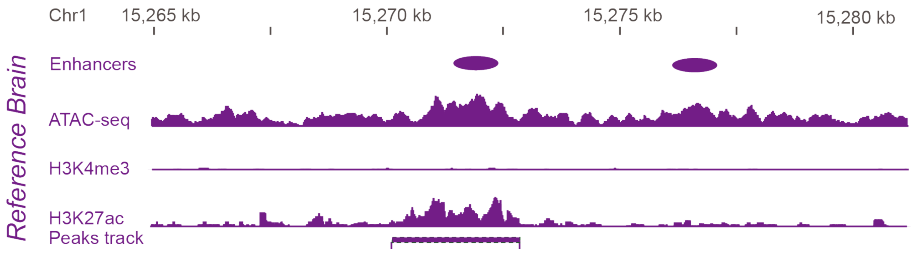
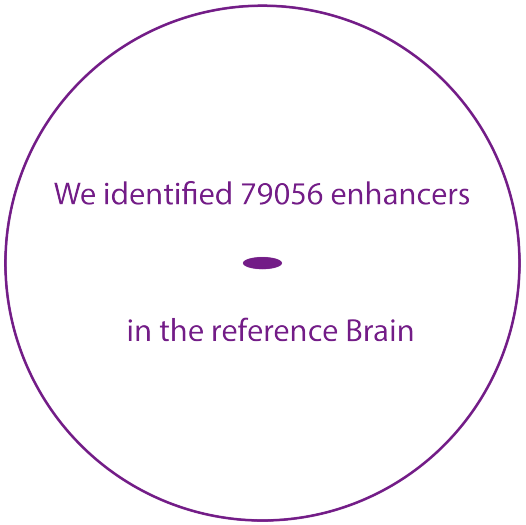
Developing a Reference Set of ~79K PFC Enhancers & Studying Their Population Variation



Consistent with ENCODE, active enhancers are identified as open chromatin regions enriched in H3K27ac and depleted in H3K4me3



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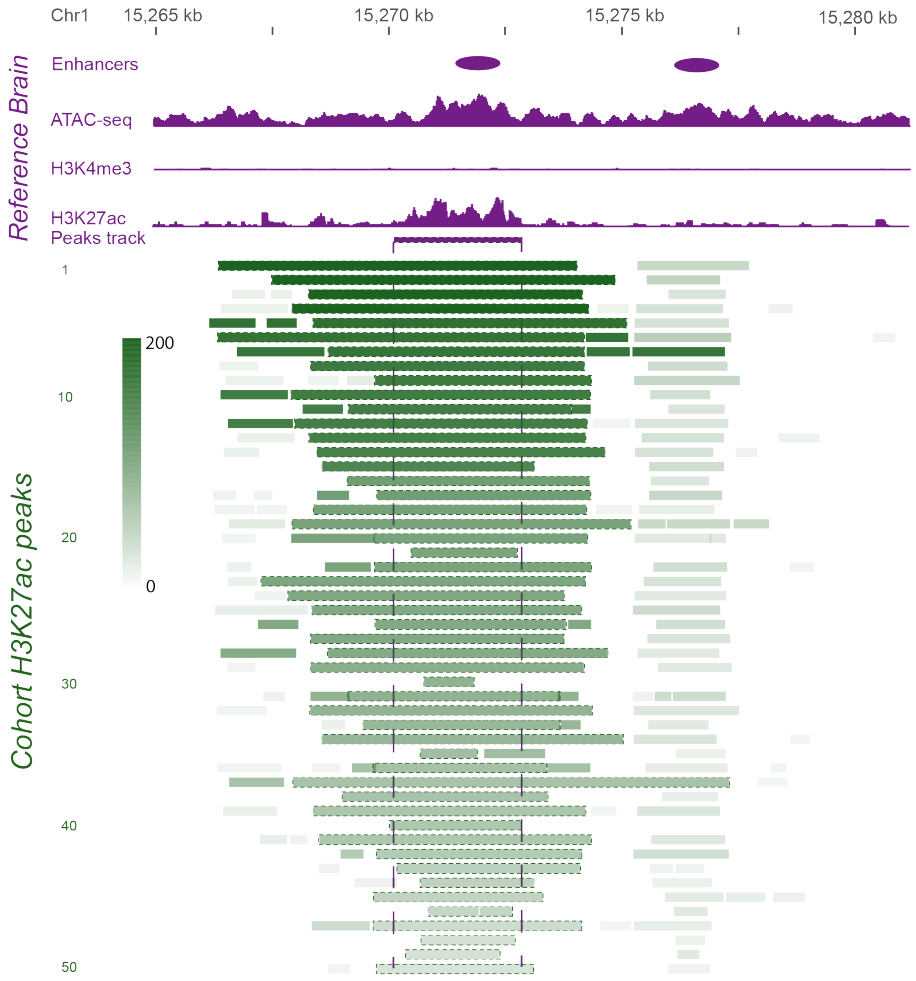
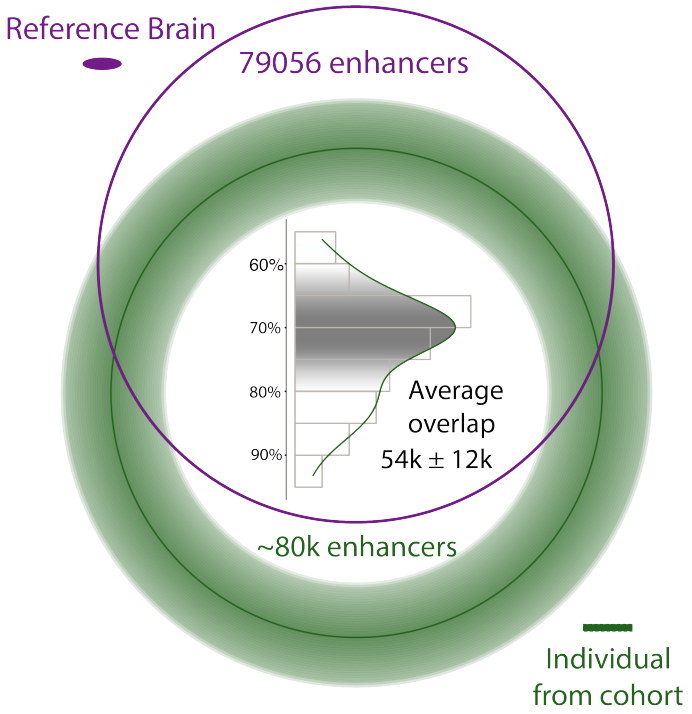
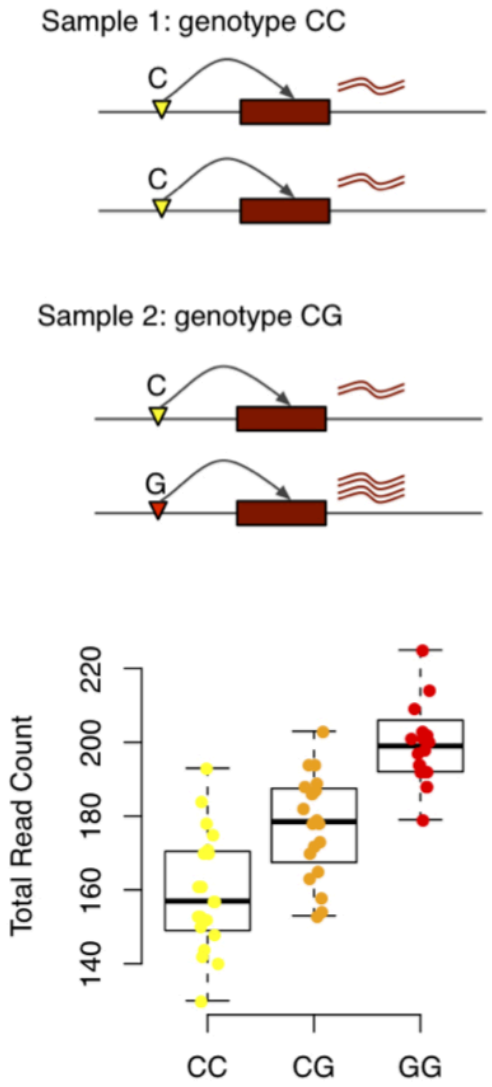




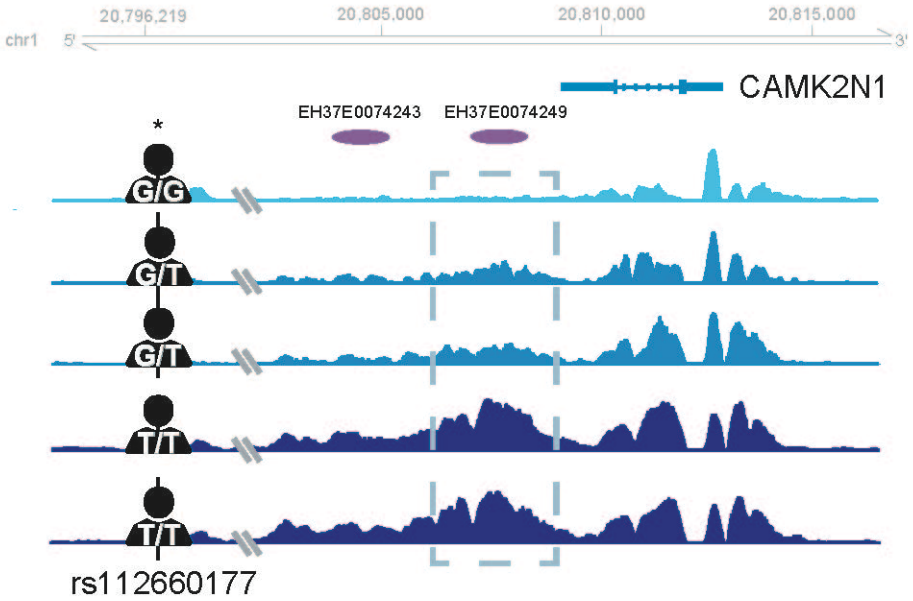
[Wang et al. ('18) Science]

Quantitaive Trait Loci (QTLs) associated with variation

Gene expression (eQTL)



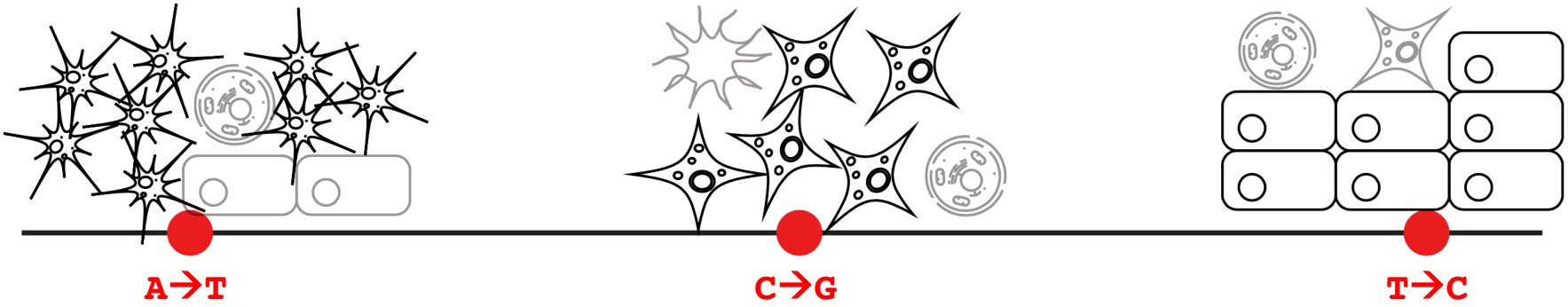
Chromatin (cQTL)

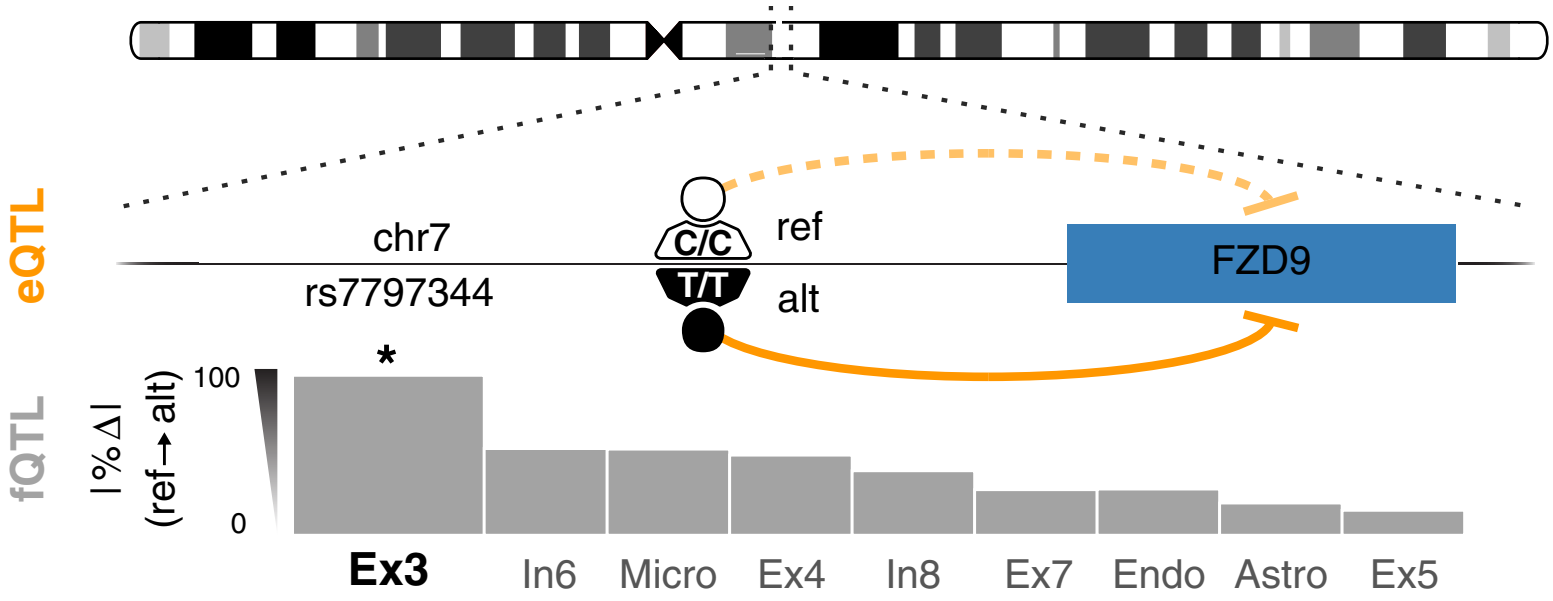


[Wang et al. ('18) Science]

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

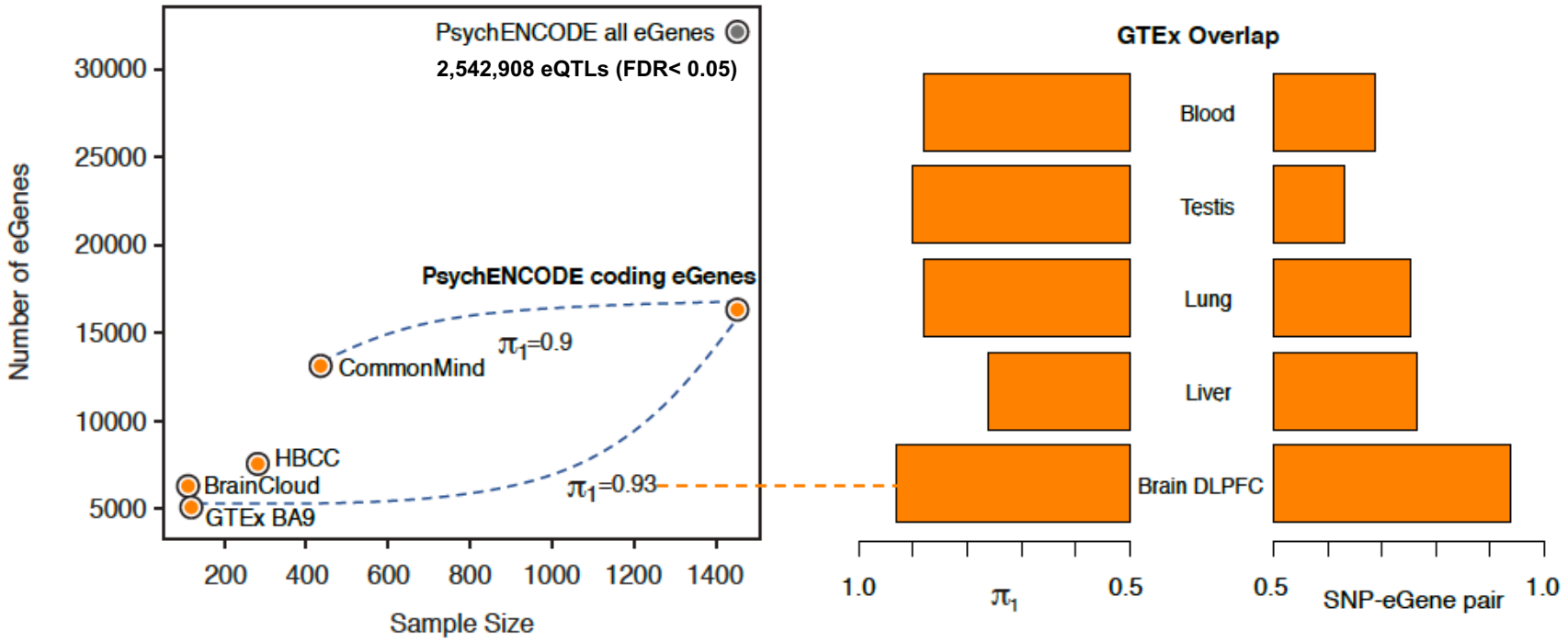
Cell fraction QTLs (fQTLs)





[Wang et al. ('18) Science]

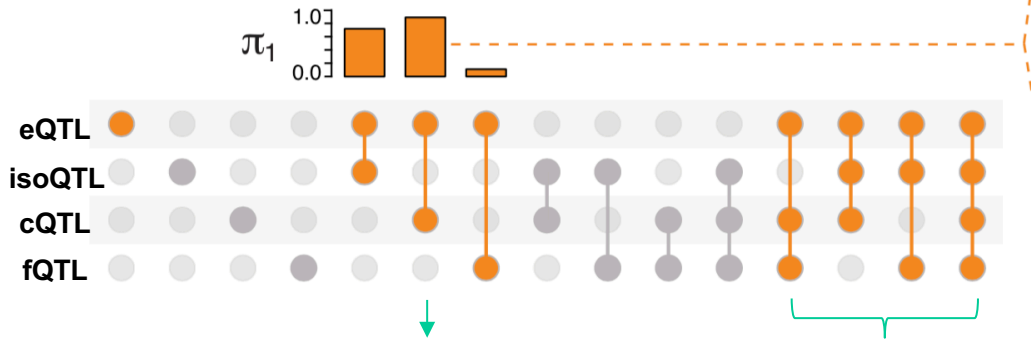
Larger brain eQTL sets than previous studies, but strong overlap with them



[Wang et al. ('18) Science]

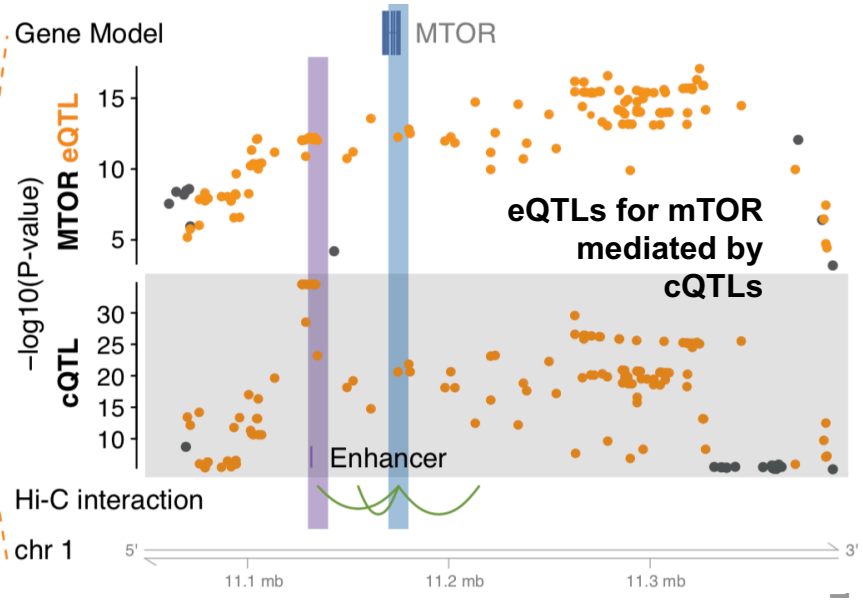
multi-QTLs from overlapping different types of QTLs: cQTL, fQTL, eQTL & isoQTL

	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



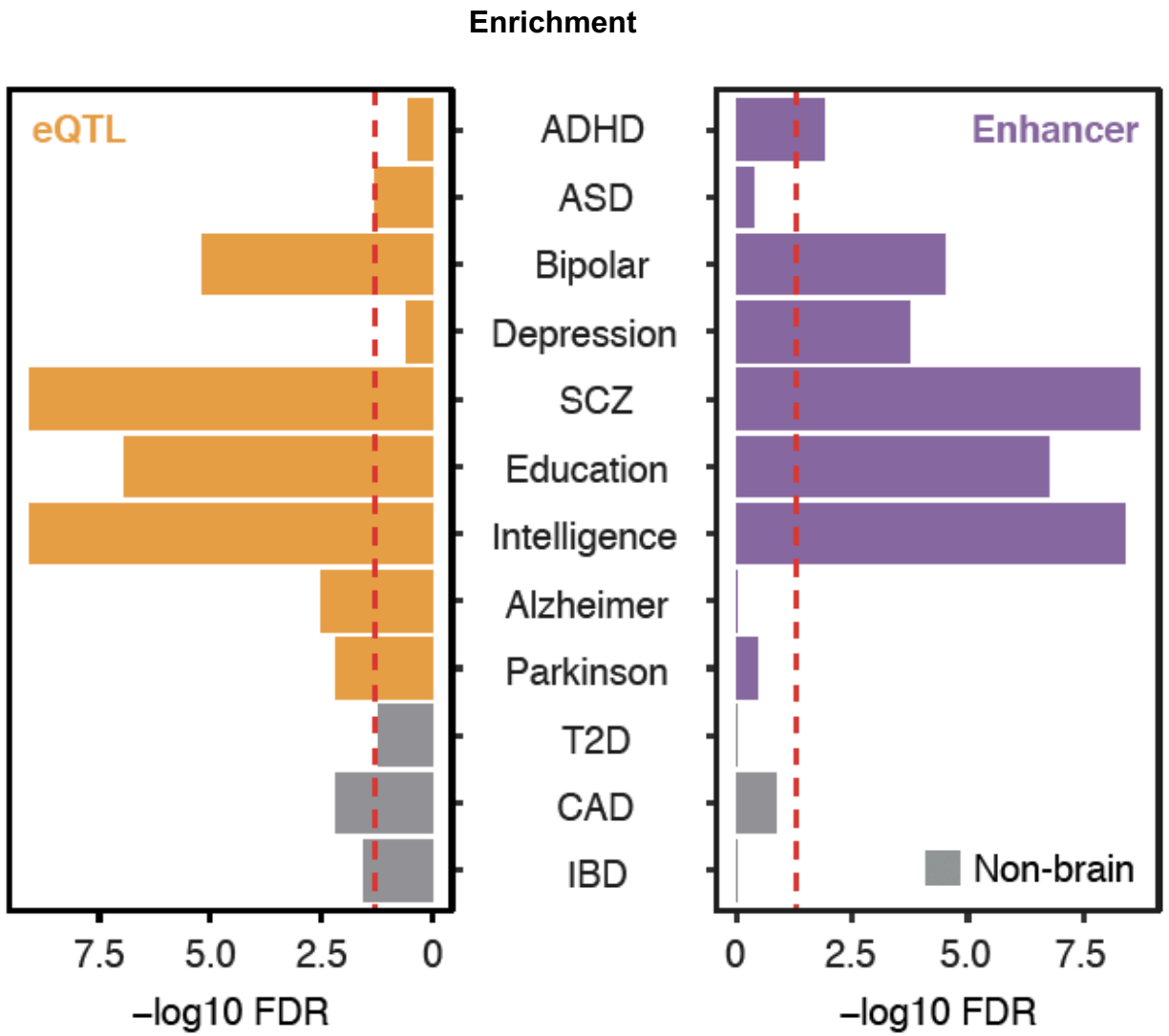
eQTLs and cQTLs significantly overlap

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



[Wang et al. ('18) Science]

Brain eQTLs and enhancers enriched with GWAS SNPs for brain disorders



Wang, et al., *Science*, 2018

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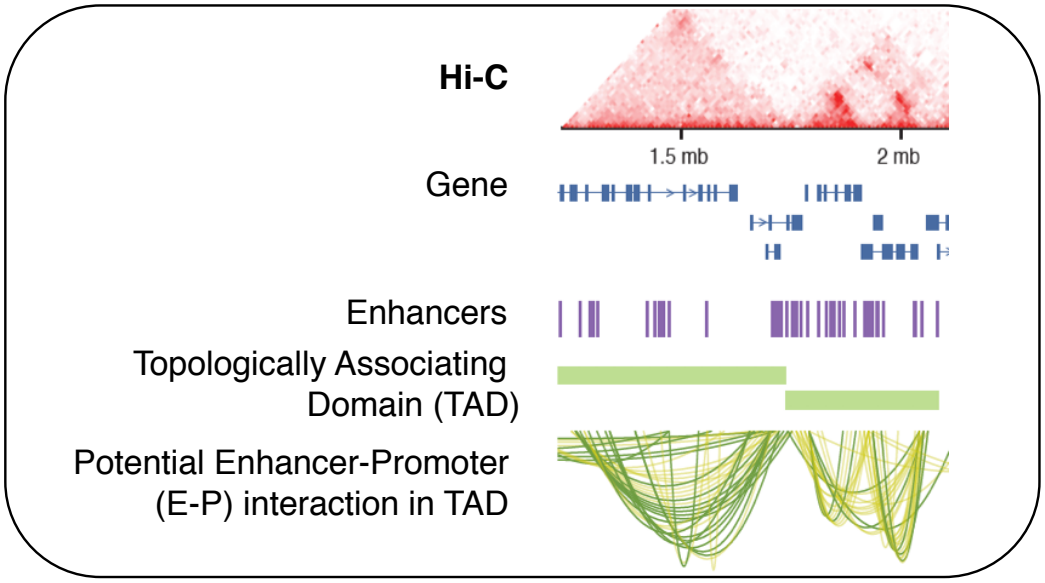
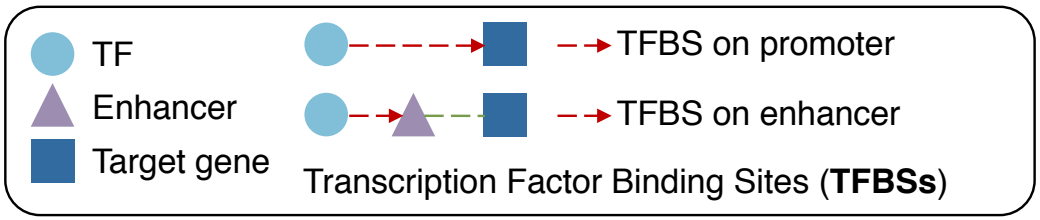
Gene regulatory network inference from Hi-C, QTLs & Activity Correlations

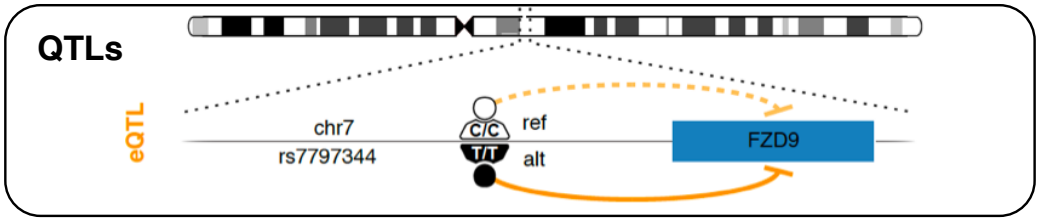




Expression activity relationship

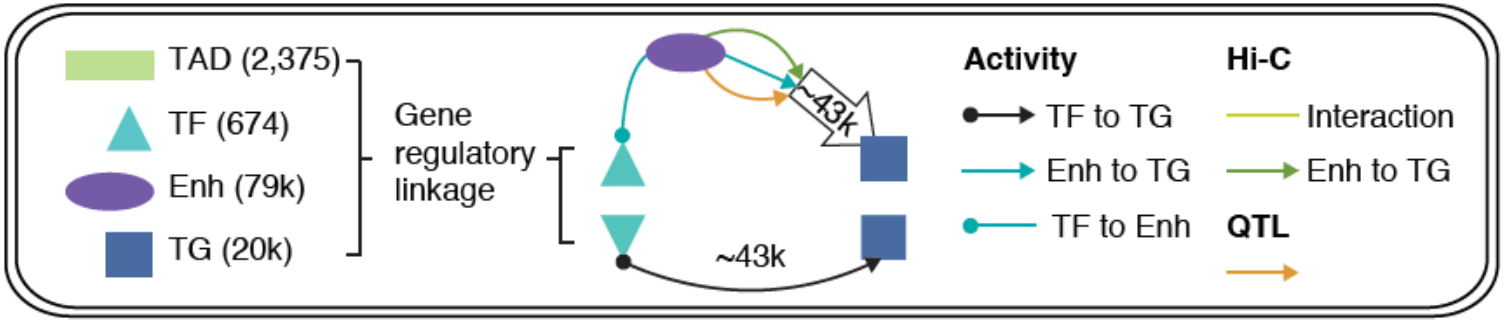
$C^* = argmin_C(\|Y - XC\|^2 + a\|C\|^2 + b\|C\|_{L1})$

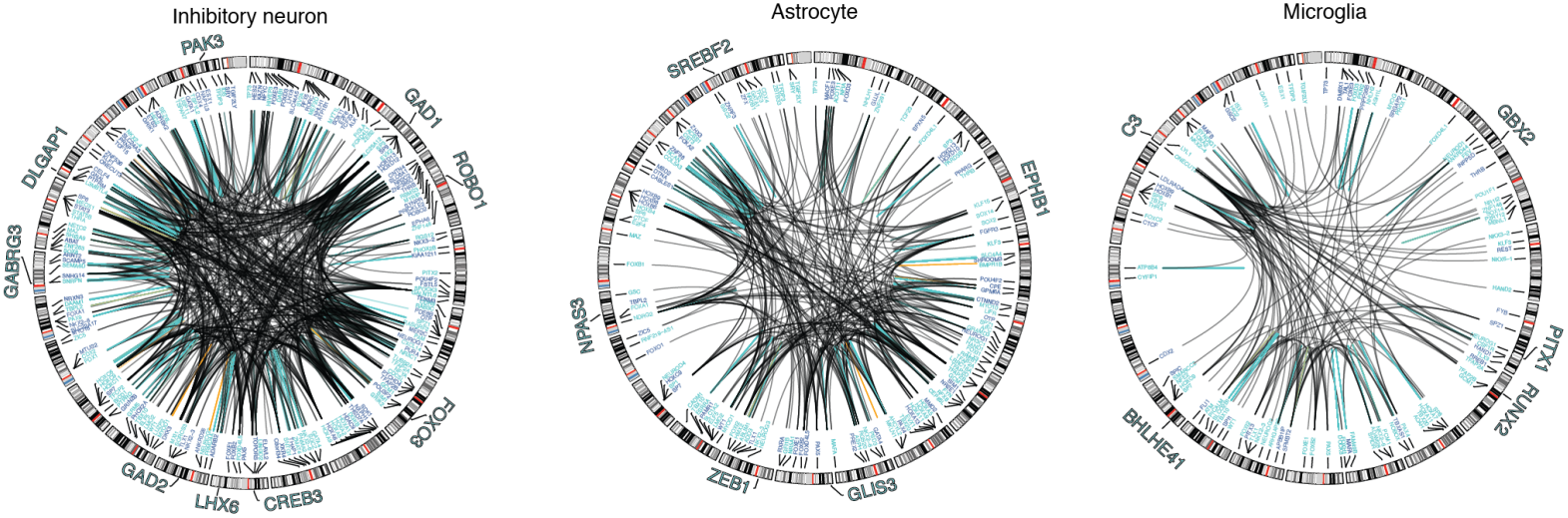
TF expression (X) to predict target gene expression (Y) using Elastic net regression



[Wang et al. ('18) Science]

Imputed gene regulatory network for the human brain

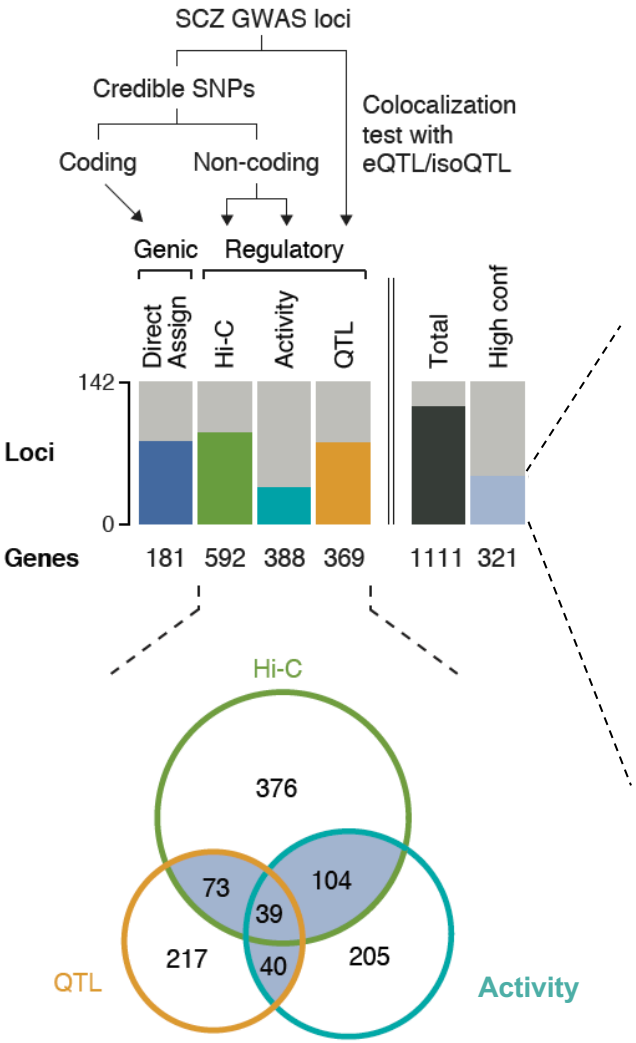


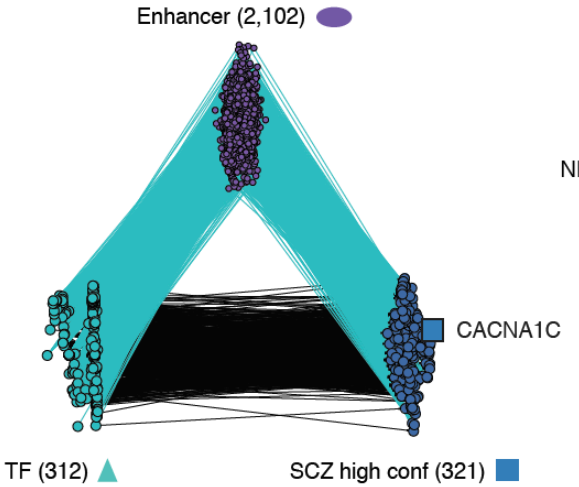


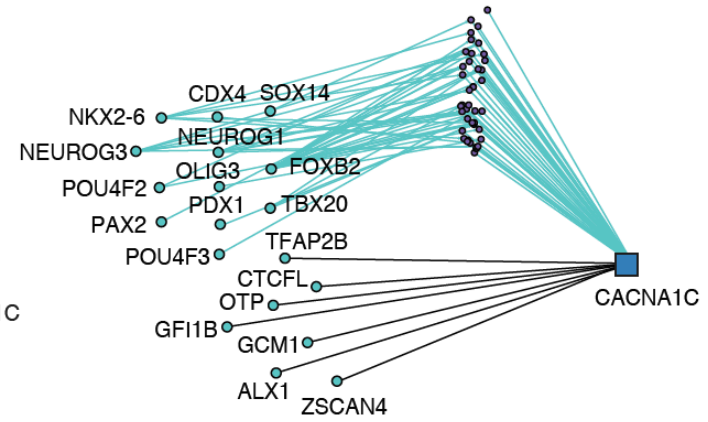
subnetworks targeting single cell marker genes

[Wang et al. ('18) Science]

Linking GWAS SNPs to disease genes using the regulatory network



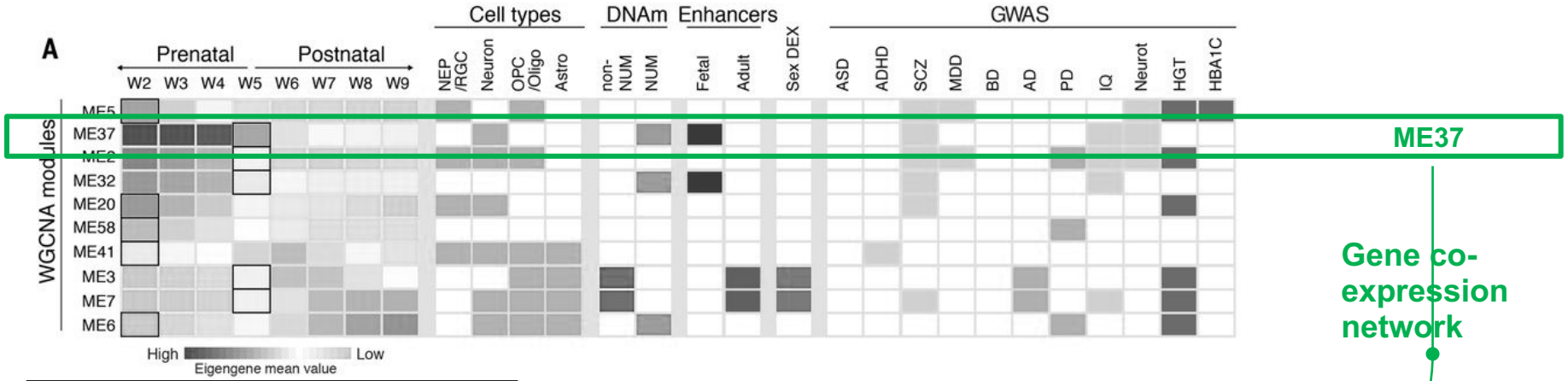


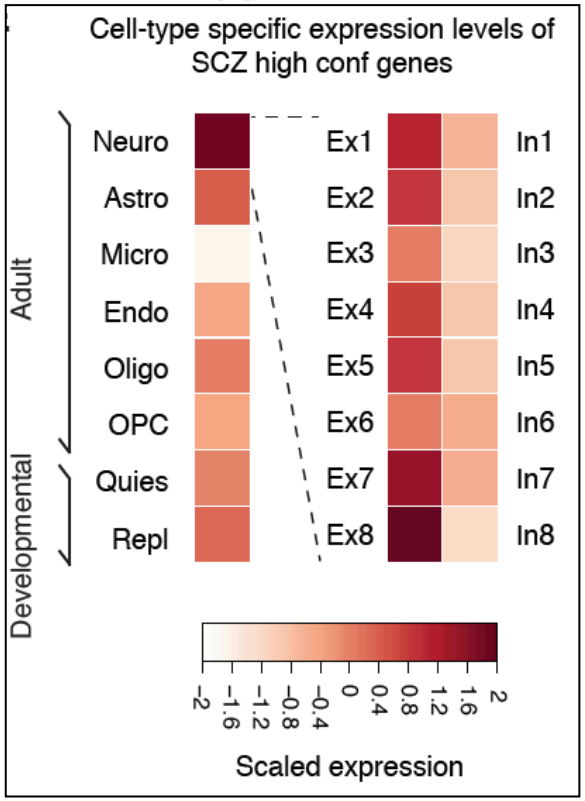


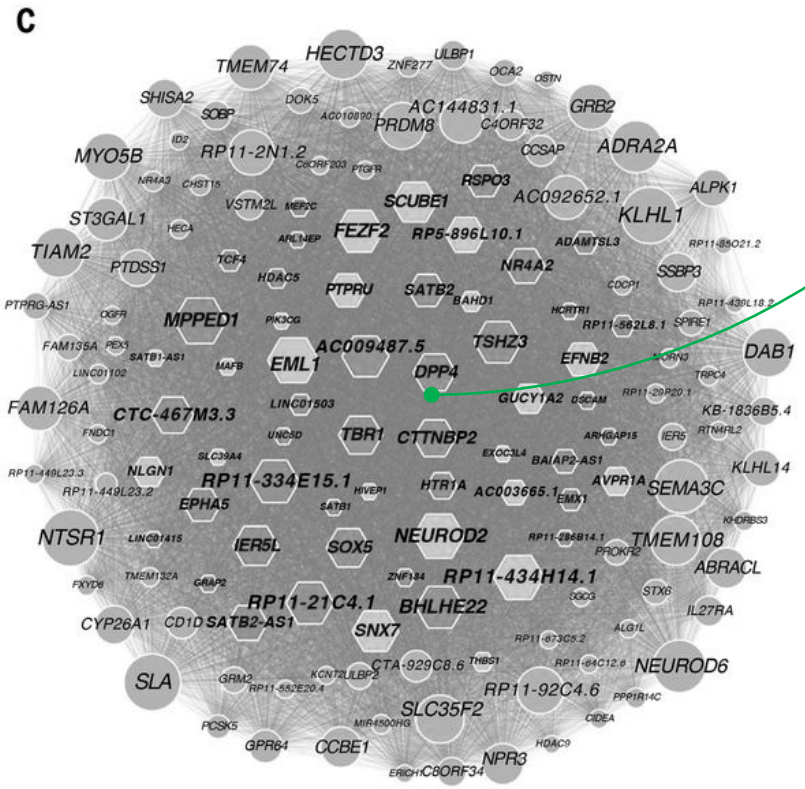
321
high-confident SCZ genes

[Wang et al. ('18) Science]

Genes associated with SCZ enriched in specific neuronal cell types & co-expression modules, active prenatally







Mingfeng Li et al. Science 2018

Wang, et al., Science, 2018

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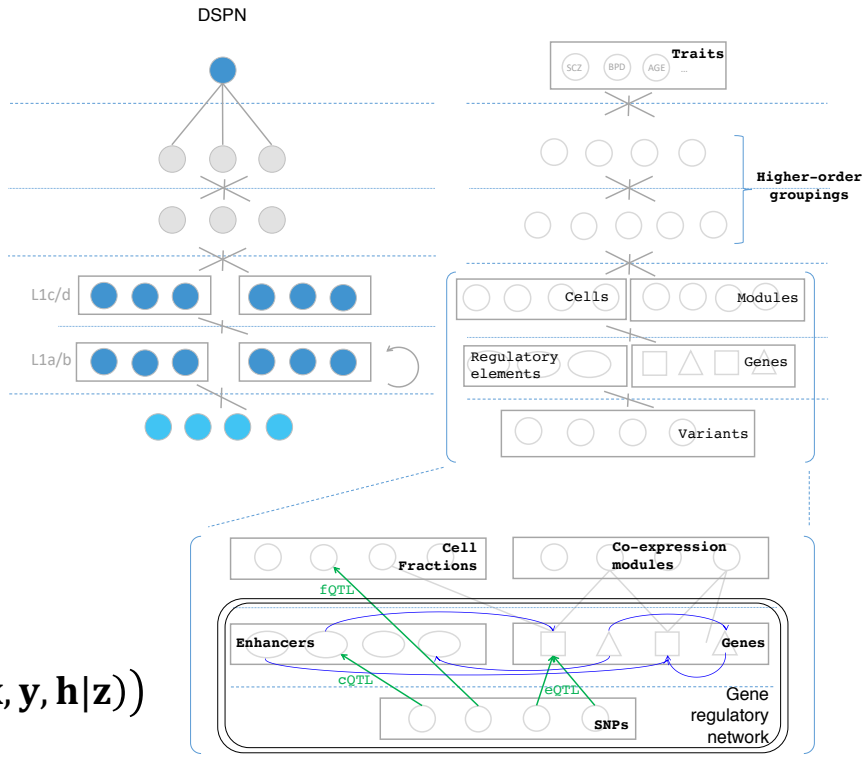
Deep Structured Phenotype Network (DSPN)

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)

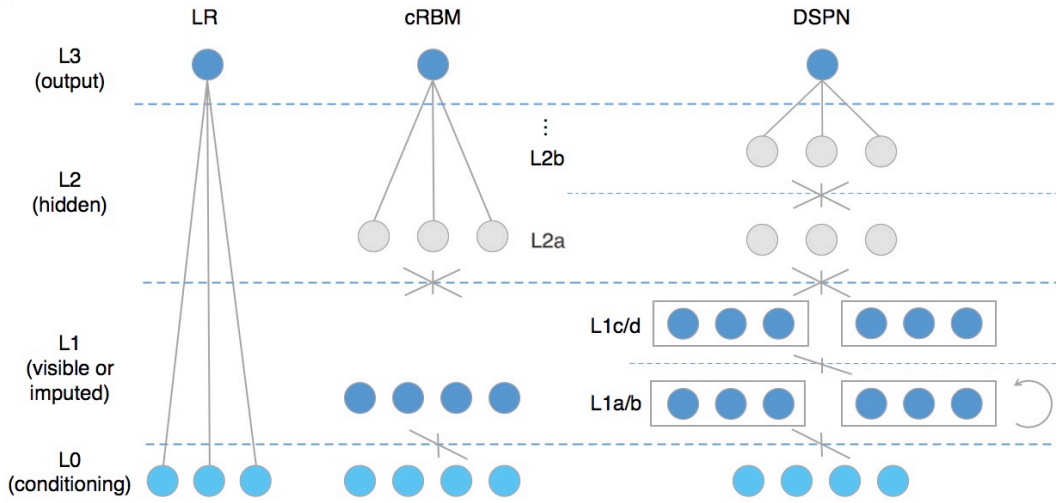
Energy model:

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

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

[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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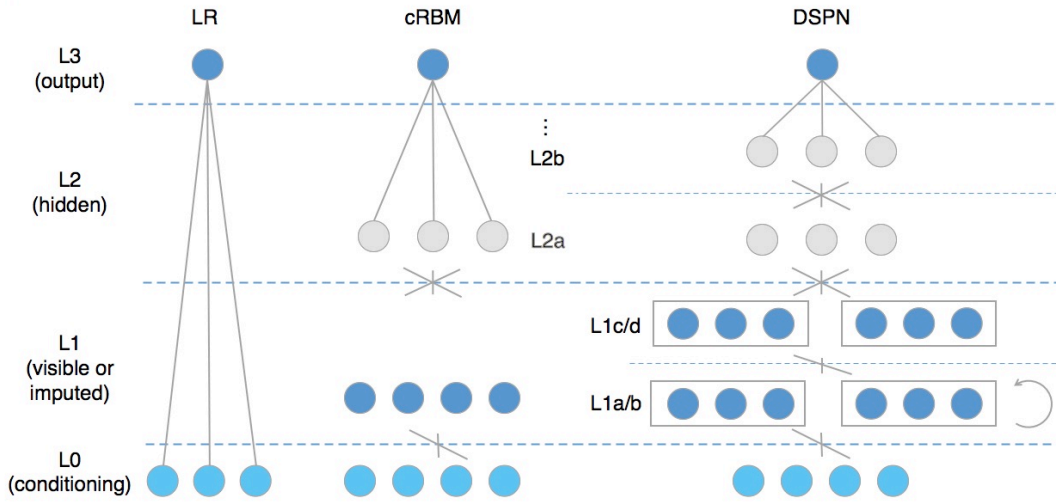

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X 2.5

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[Wang et al. ('18) Science]

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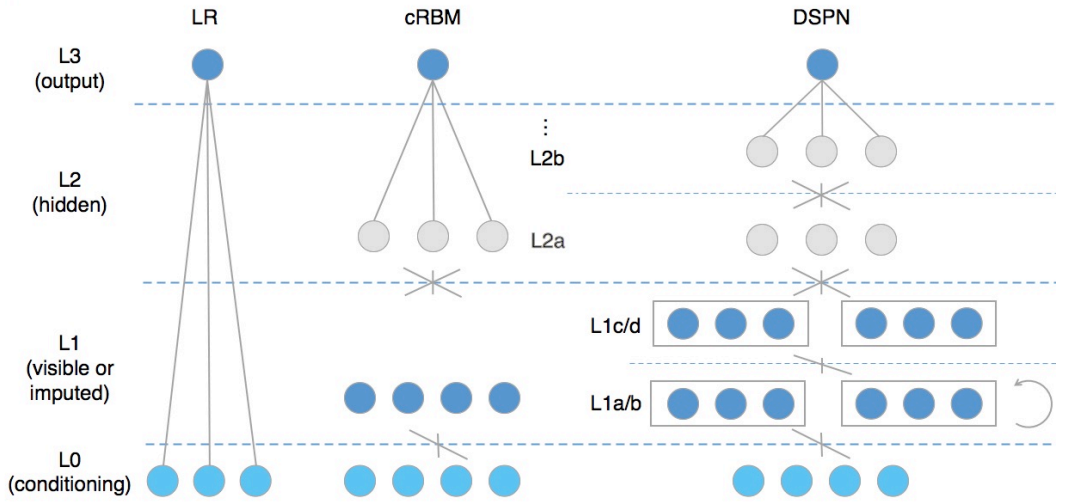

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X 3.1

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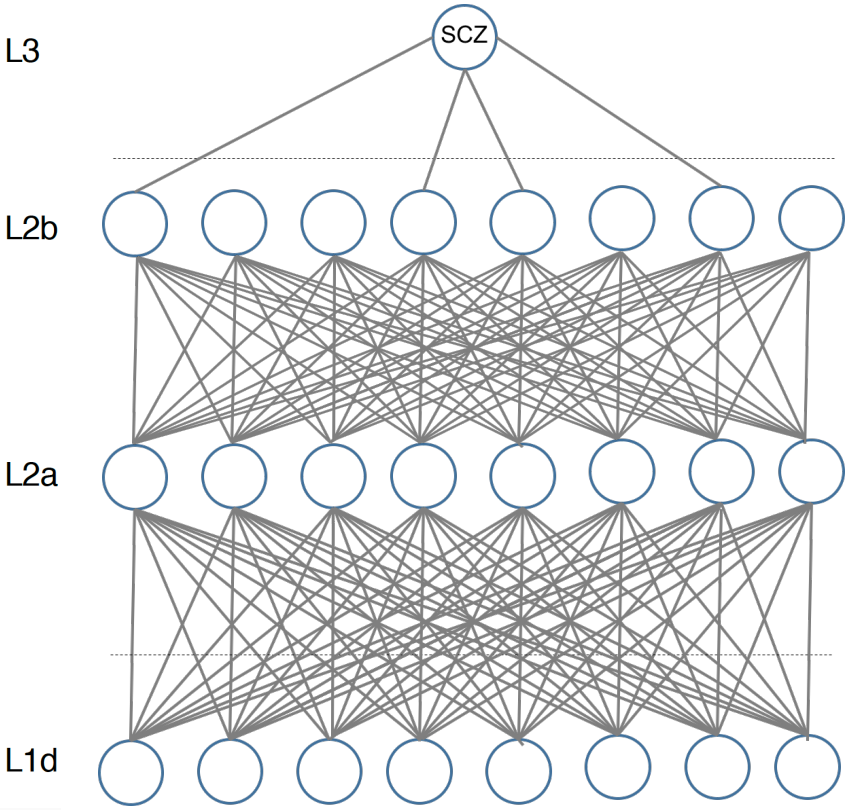
[Wang et al. ('18) Science]

Multilevel Network Interpretation

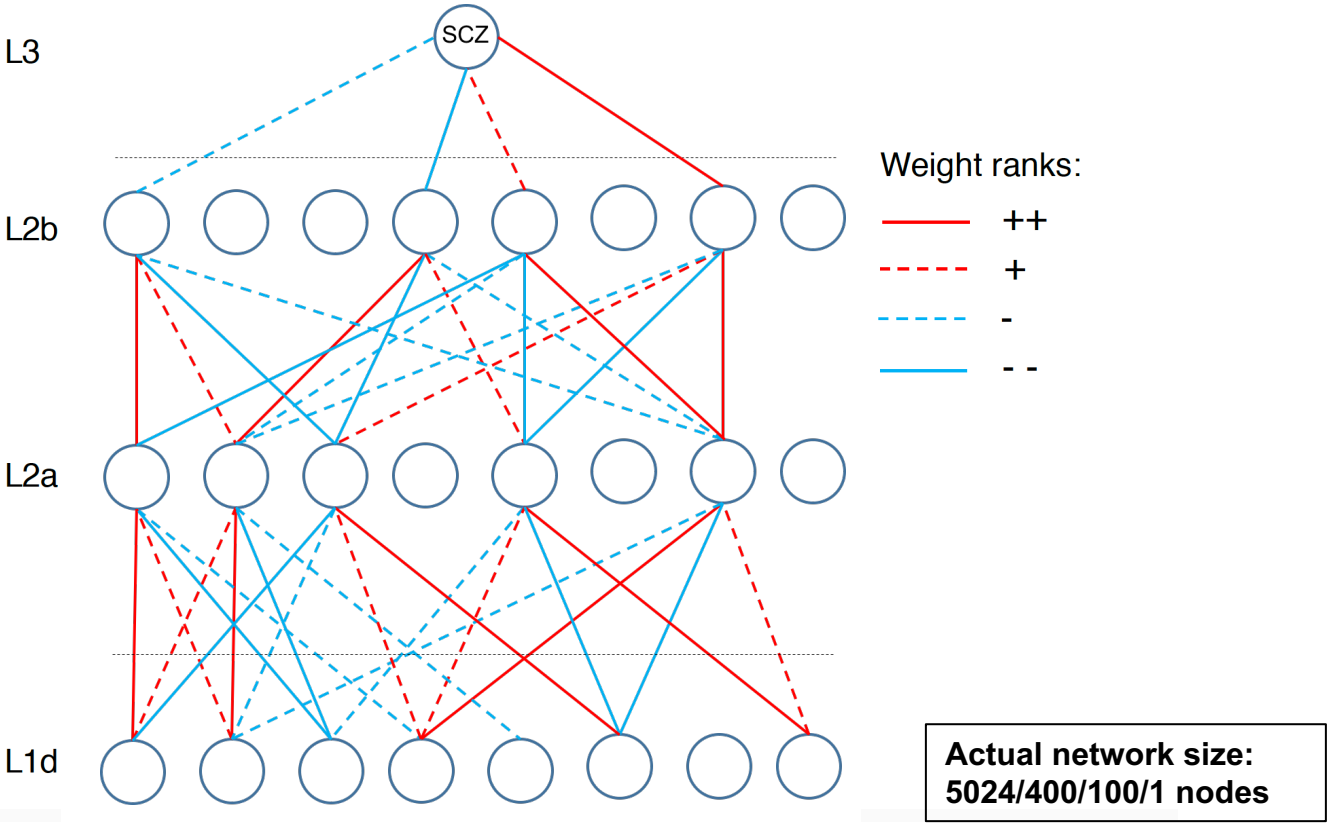


Actual network size:
5024/400/100/1 nodes

- Start with a fully connected trained network

[Wang et al. (‘18) Science]

Multilevel Network Interpretation



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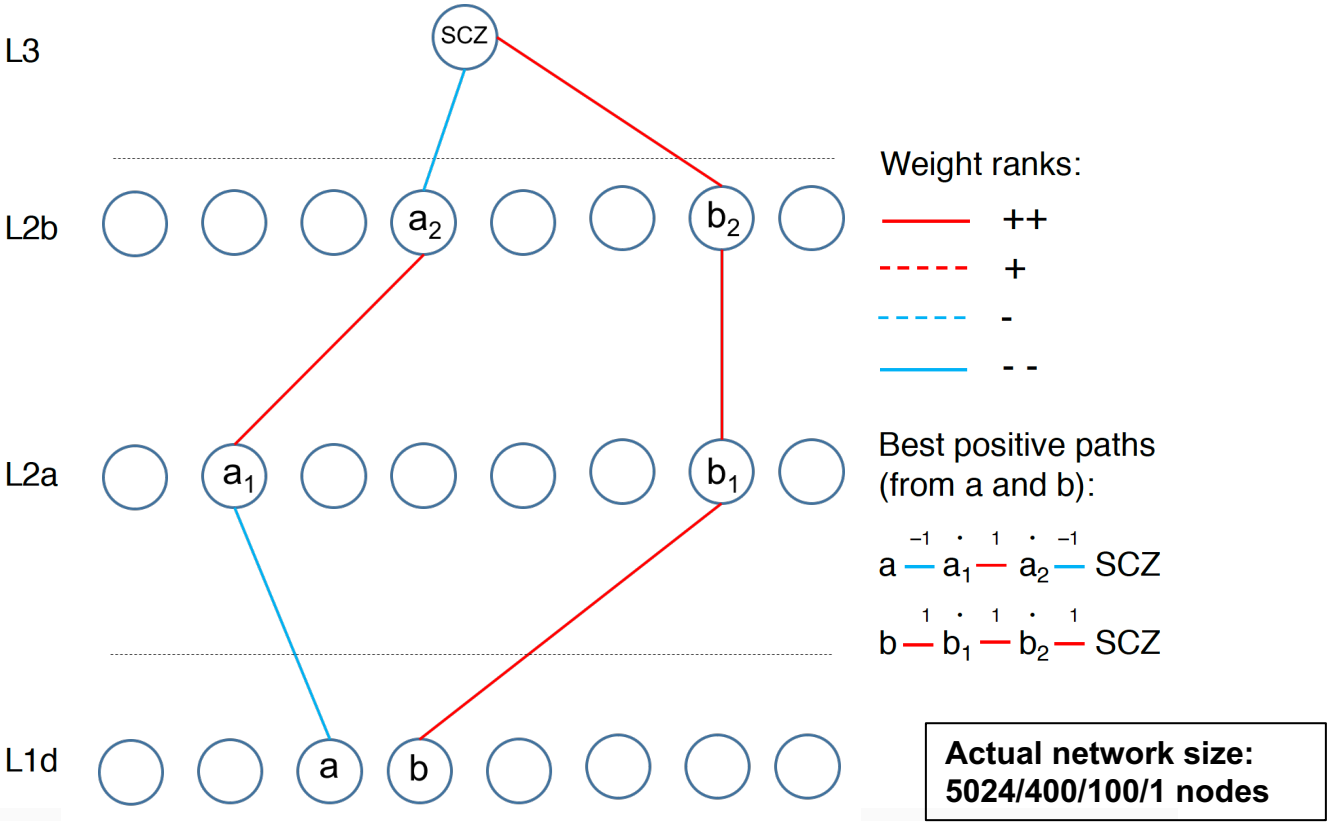
[Wang et al. ('18) Science]

Multilevel Network Interpretation

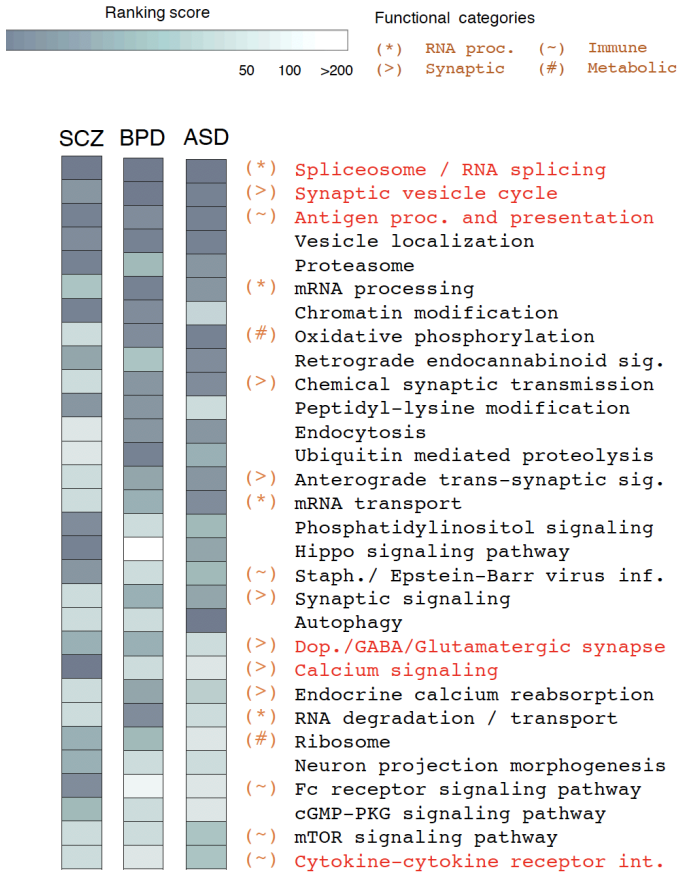


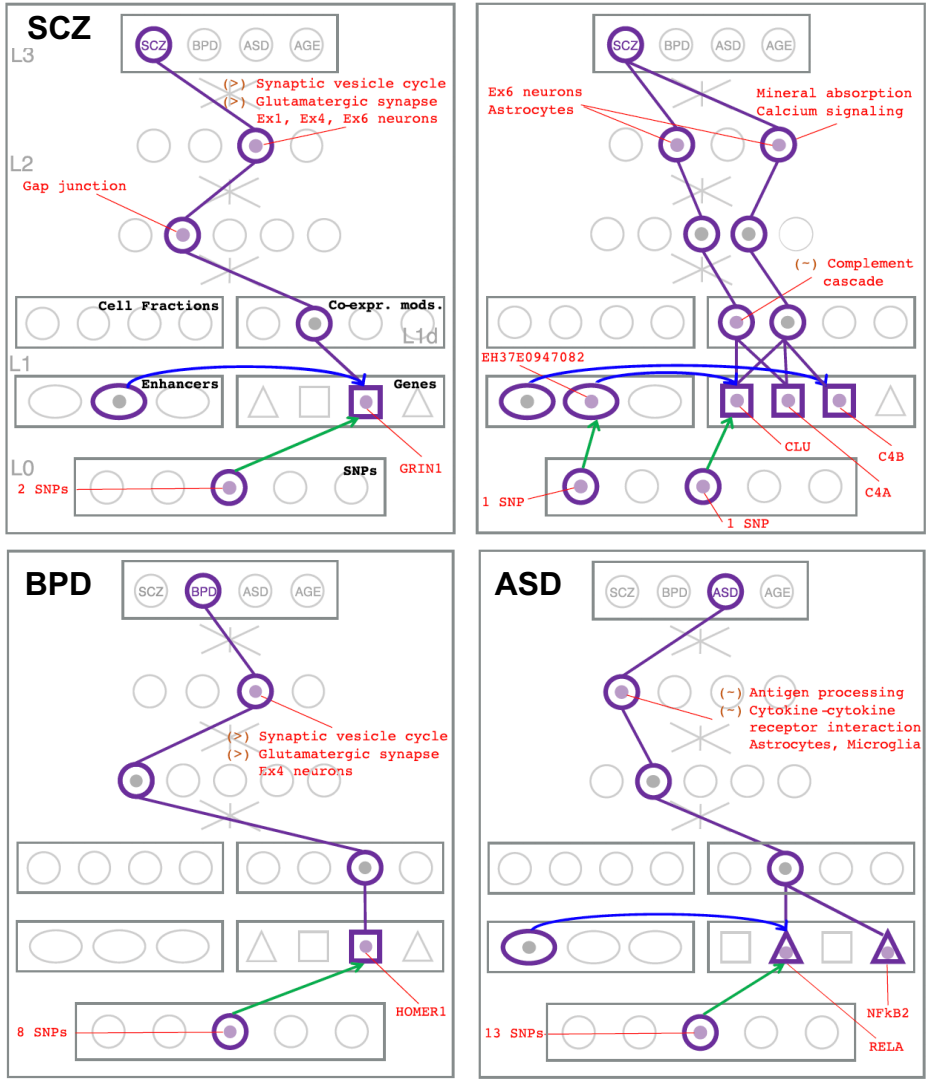
- Start with a fully connected trained network
- Sparsify network using edges with largest absolute weights (+/-)
- Extract 'best positive paths' to each prioritized module (e.g. a-a_1-a_2-SCZ) by summing weights and multiplying signs

[Wang et al. ('18) Science]

DSPN discovers enriched pathways and linkages to genetic variation

Cross-disorder MOD/HOG enrichment ranking





[Wang et al. ('18) Science]

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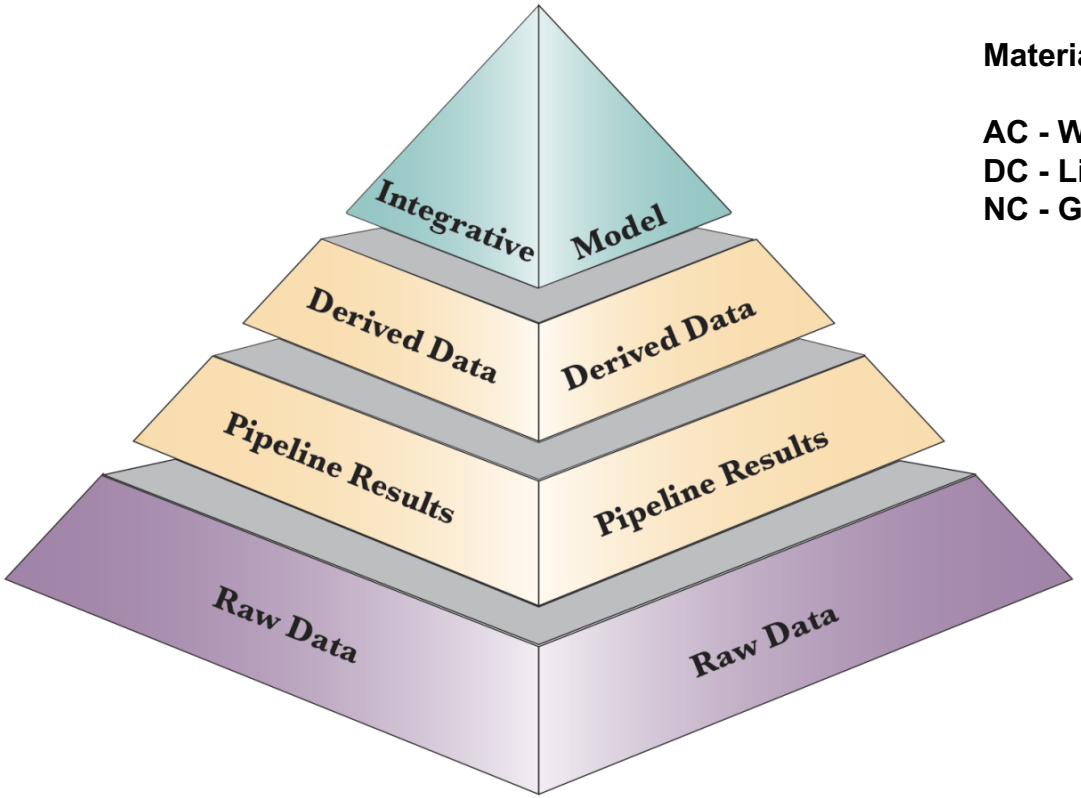
Phase 1 PsychENCODE capstone resource: Layers of distributed information



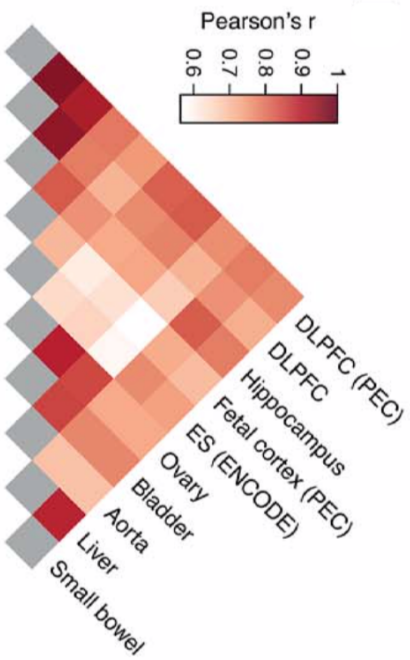
Material in the 3 capstones:

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

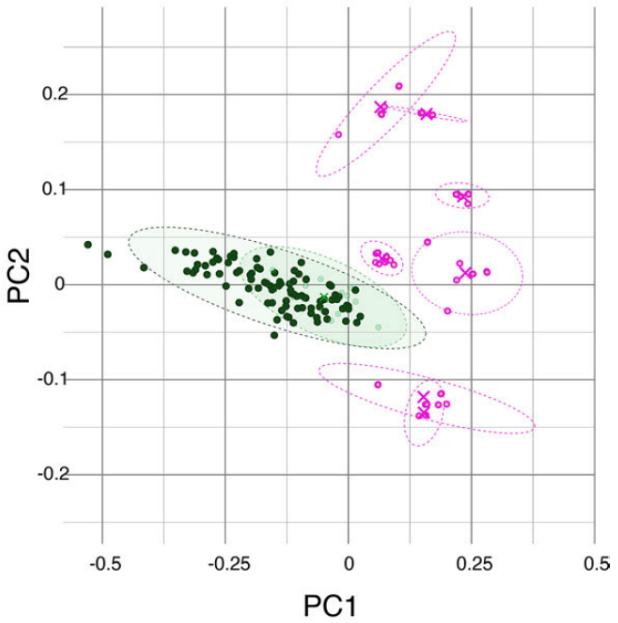
Resource.psychencode.org
Development.psychencode.org

Cross tissue variation in Chromatin & Expression

Placing the Brain in context of all other Body Tissues

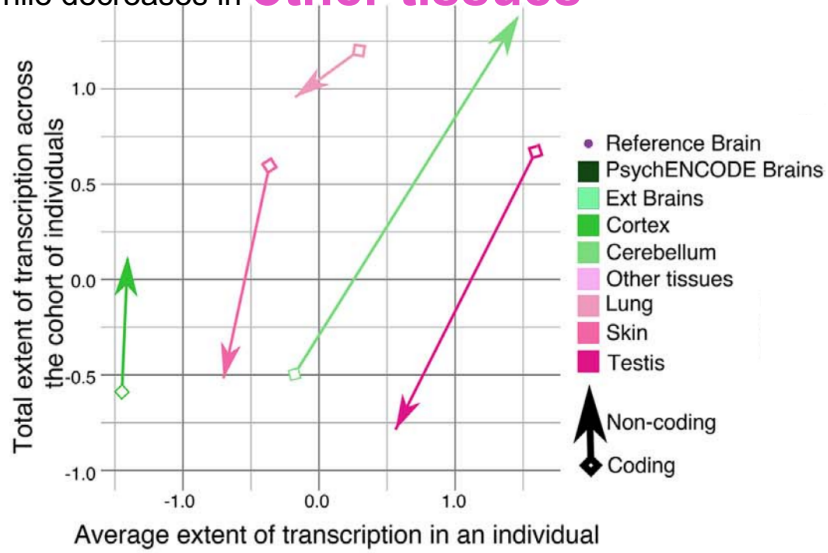


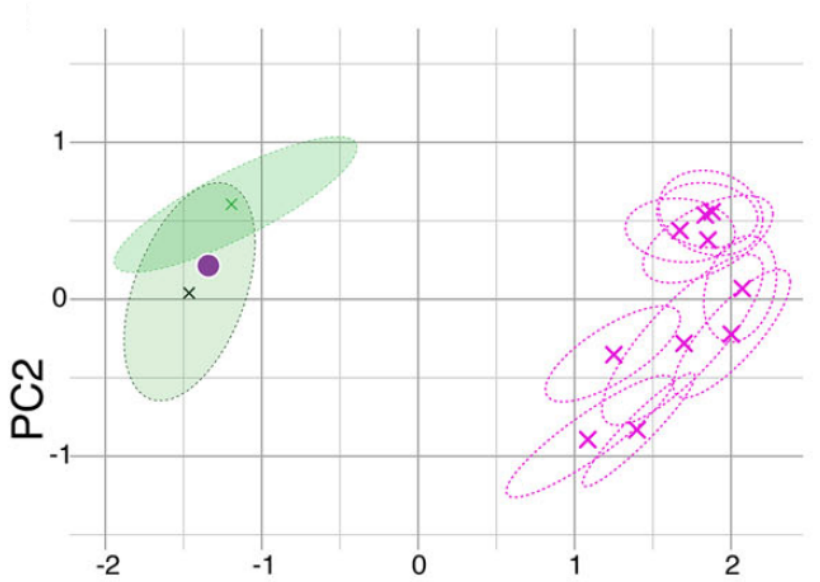
Hi-C



Chromatin

Transcriptome diversity increases in the non-coding portion of the **brain genome** while decreases in **other tissues**



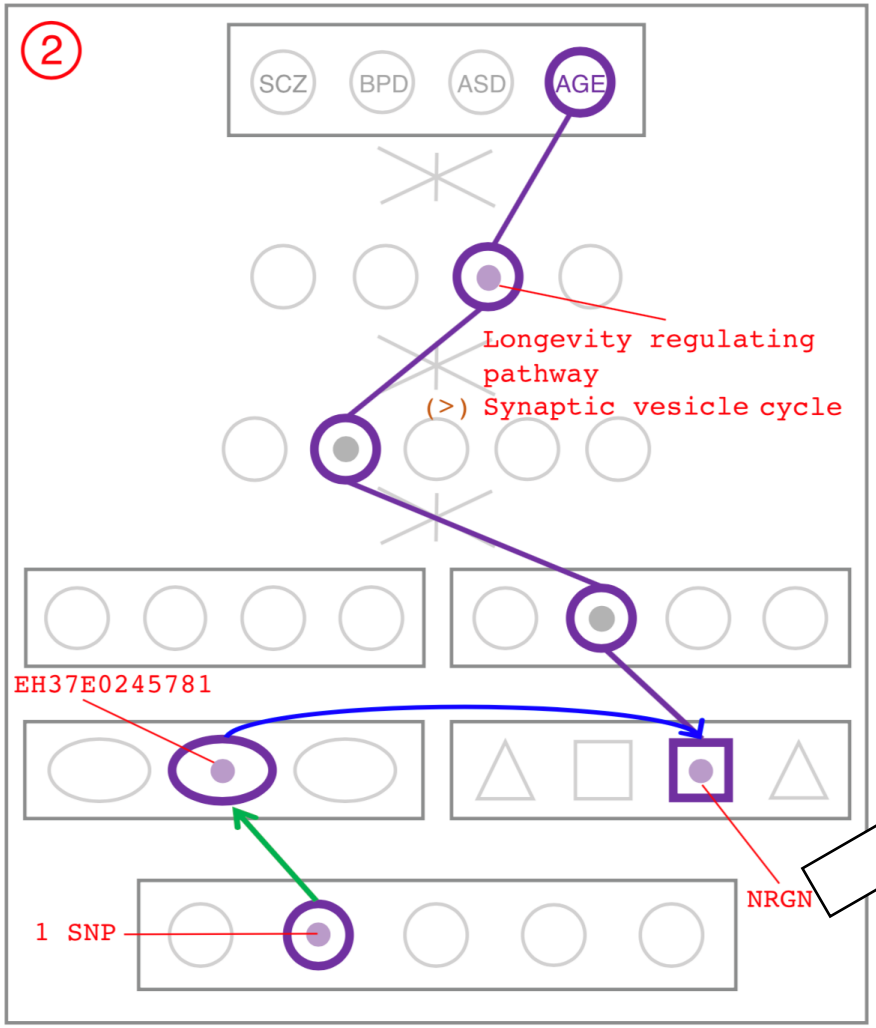


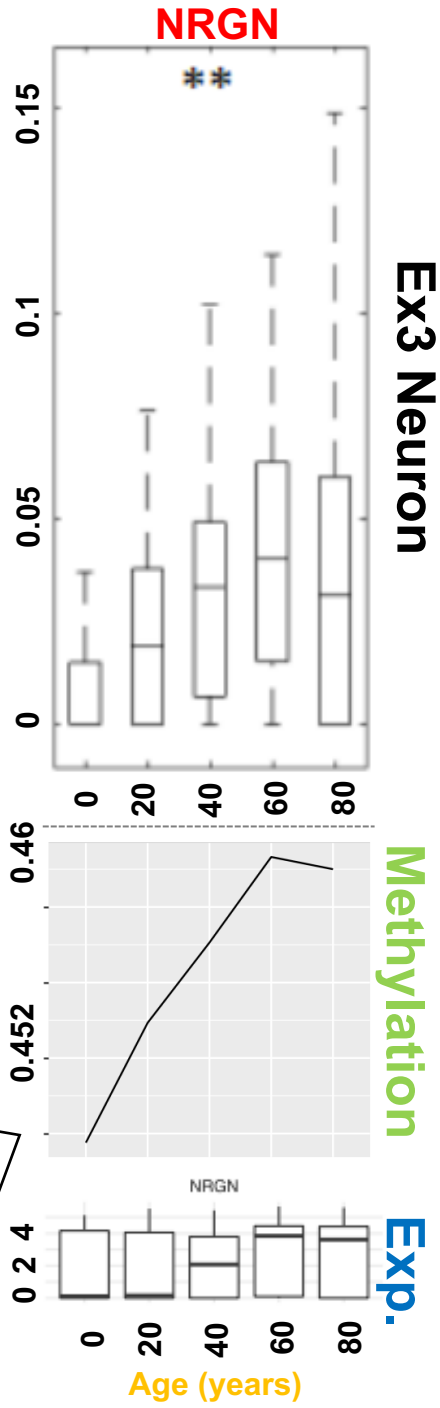
Expression

[Wang et al. ('18) Science]

NRGN has variable expression over age and is in Synaptic vesicle cycle pathway is enriched in SCZ, BPD, ASD

NGRN is a gene associated with the **Synaptic vesicle pathway** and NGRN **expression** and **methylation** is correlated with **Age**





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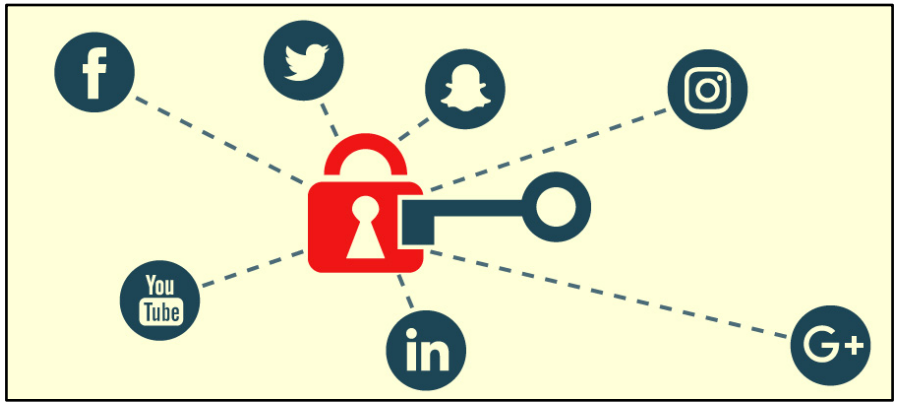
2-sided nature of functional genomics data: Analysis can be very General/Public or Individual/Private

- **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)

Privacy: Does Genomics has similar "Big Data" Dilemma as in the Rest of Society?



- We confront privacy risks every day we access the internet (e.g., social media, e-commerce).
- Sharing & "peer-production" is central to success of many new ventures, with analogous risks to genomics
  - **EG web search**: Large-scale mining essential

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?

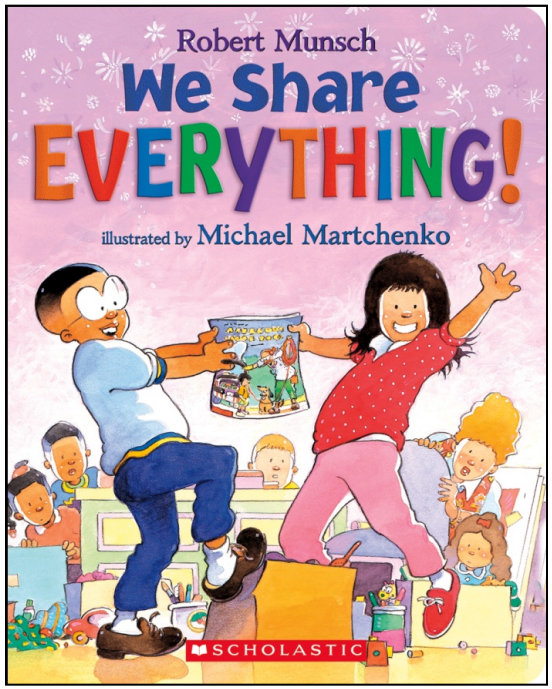
Once put on the web it can't be taken back

Ethically challenged history of genetics

Ownership of the data & what consent means (Hela)

Could your genetic data give rise to a product line?

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

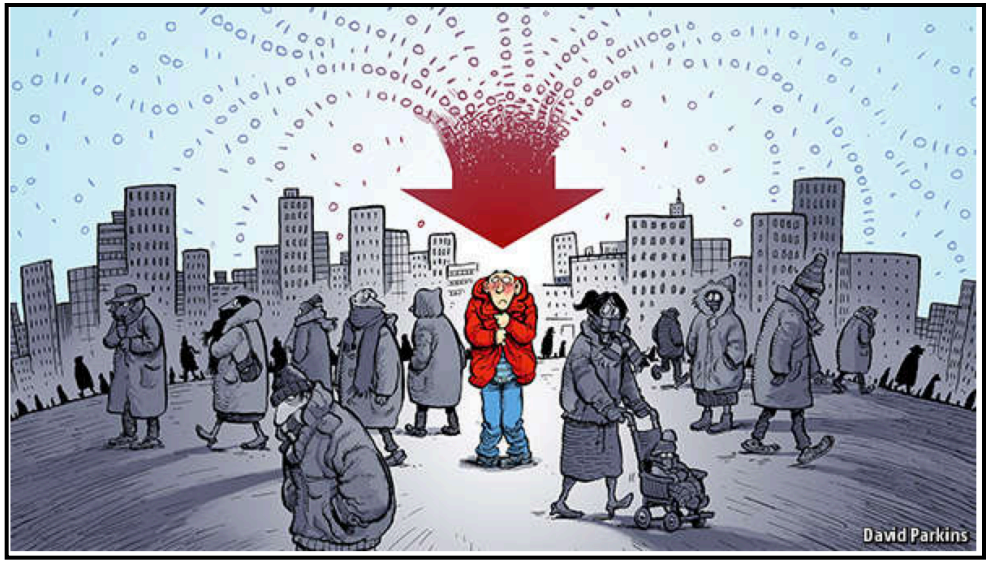


The Dilemma

- The individual (harmed?) v the collective (benefits)
  - But do sick patients care about their privacy?
- How to balance risks v rewards
  – Quantification

The Other Side of the Coin for Genomics: Why we should share

- Sharing helps **speed research**
  - Large-scale mining of this information is important for medical research
  - Statistical power
  - Privacy is cumbersome, particularly for big data



[Economist, 15 Aug '15]

[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)]

Current Social & Technical Solutions: The quandary where are now

- **Closed Data** Approach
  - Consents
  - "Protected" distribution via dbGAP
  - Local computes on secure computer
- Issues with Closed Data
  - Non-uniformity of consents & paperwork
    - Different, confusing int'l norms
  - Computer security is burdensome
  - Many schemes get "hacked" .
  - **Tricky aspects of high-dimensional data** (leakage & ease of creating quasi-identifiers)
- **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; Photo: futurism.com]

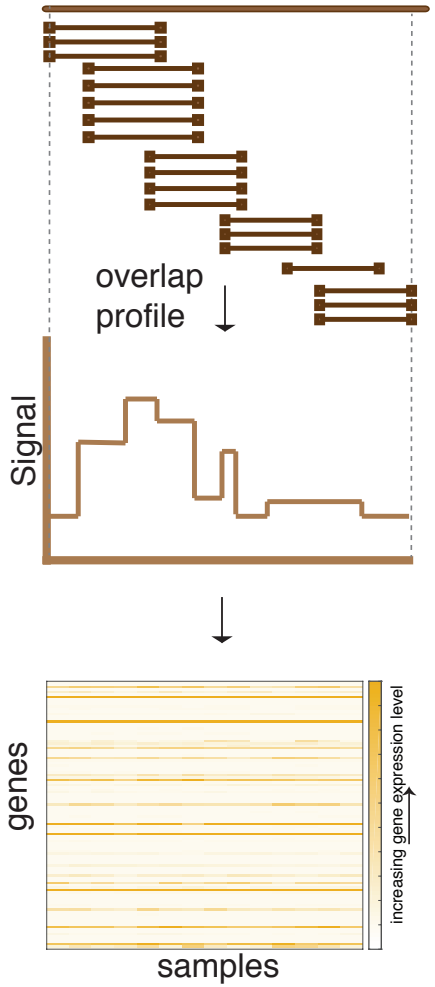
Strawman Hybrid Social & Tech Proposed Solution?

- 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”

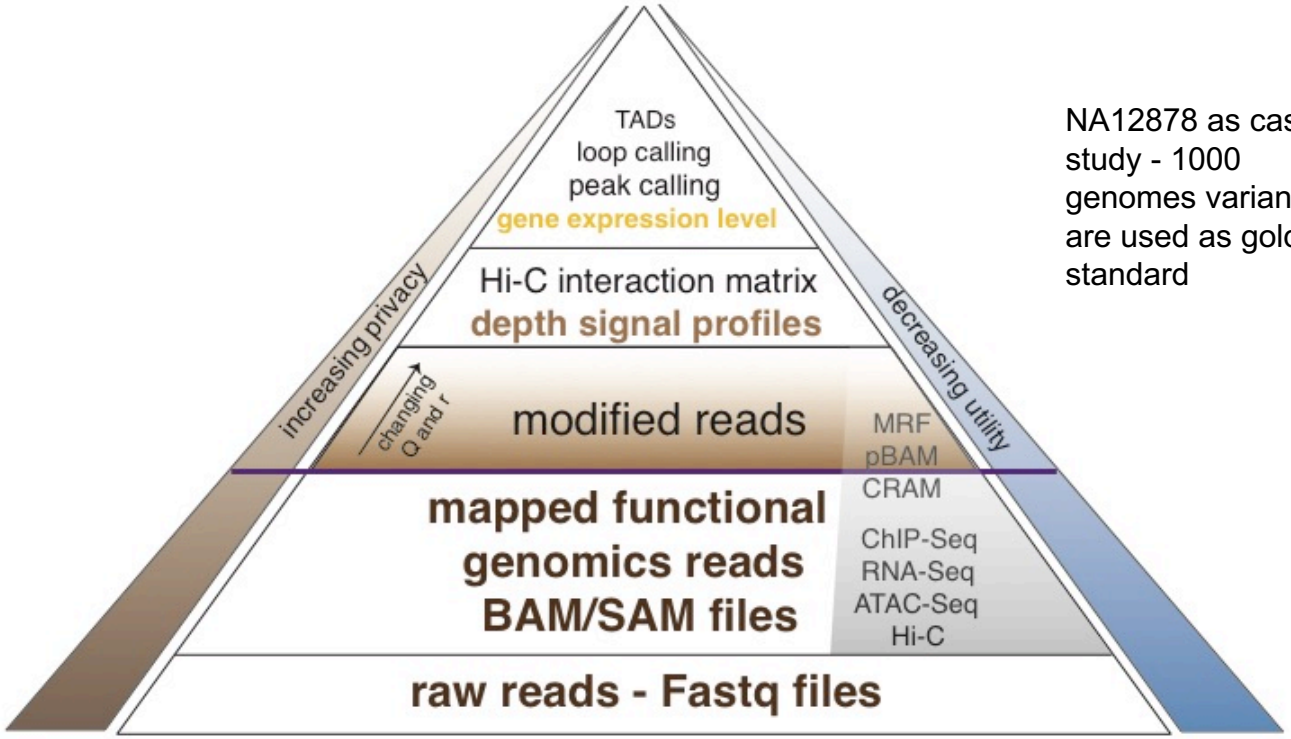
- **Quantifying Leakage & allowing a small amounts of it**
- **Careful separation & coupling of private & public data**
  - **Lightweight, freely accessible secondary datasets coupled to underlying variants**
  - Selection of stub & "test pilot" datasets for benchmarking
  - Develop programs on public 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)]

Functional genomics data comes with a great deal of sequencing; We can quantify amount of leakage at every step of the data summarization process.



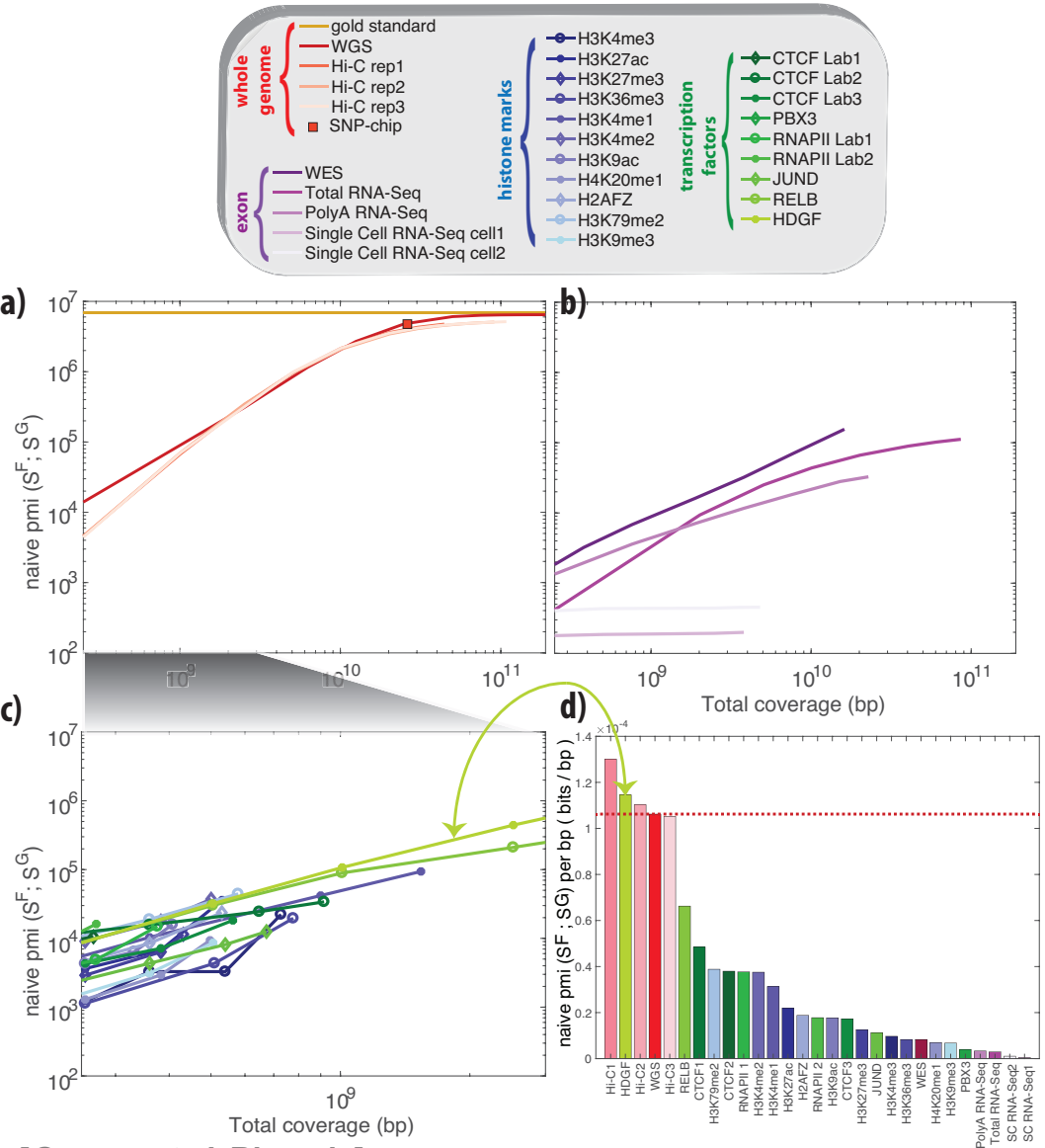
[*Gursoy et al*, Bioarvix]



NA12878 as case study - 1000 genomes variants are used as gold standard

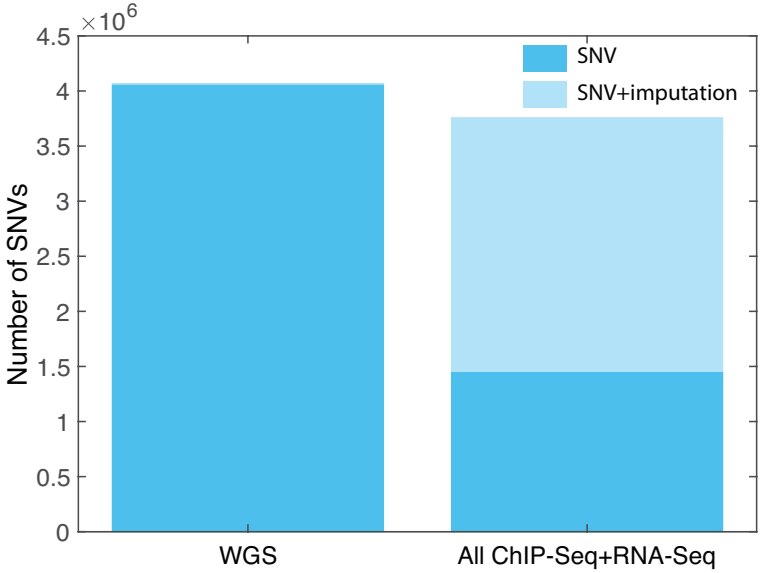
Leakage Source	Leaking Variants	# of potential variants	Average leakage per variant (bits)	Maximum leakage per variant (bits)	# of accessible variants	Total leakage (bits)
Raw reads	Exonic variants	2,682,417	0.10 ± 0.28	9.88 ± 2.12	246,893	24,689
Modified reads Q = {indels}	Exonic SNVs	2,607,969	0.09 ± 0.27	9.95 ± 2.02	231,031	207,92
Modified reads Q = {mismatches}	Exonic indels	51,408	0.33 ± 0.47	7.64 ± 2.42	15,862	5234
Signal profiles	Exonic deletions	48,019	0.29 ± 0.45	7.97 ± 2.42	1,067	298
Gene expression quantification	eQTLs	3,175	1.19 ± 0.36	4.00 ± 1.92	158	188

- **How much information, for example, do RNA-Seq reads (or ChIP-Seq) reads contain? Does that information enough to identify individuals?**



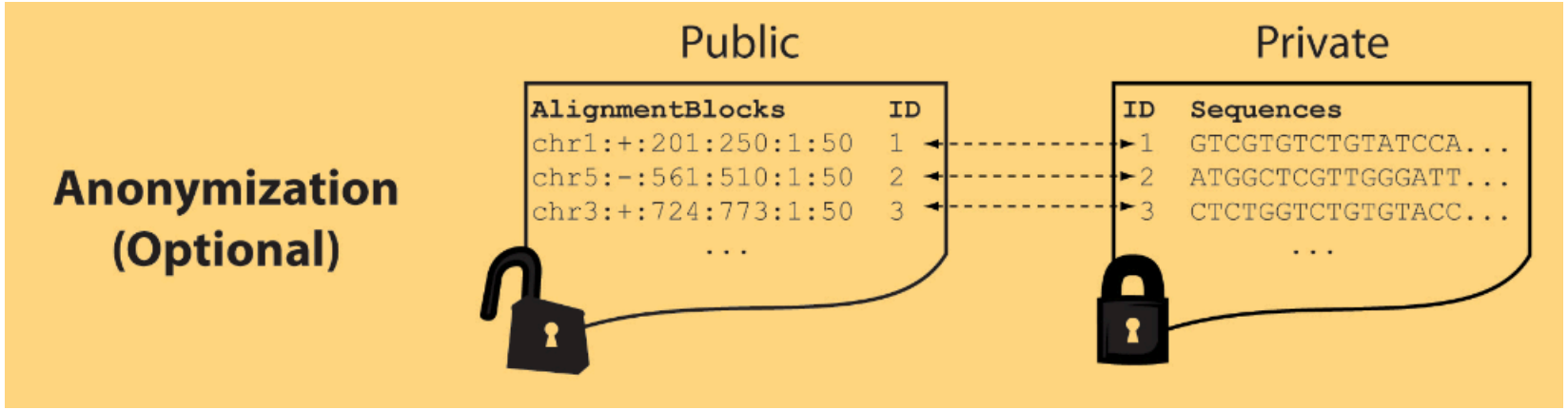
[*Gursoy et al*, Bioarvix]

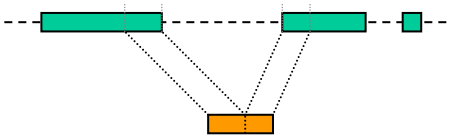
- **It might seem like we don't infer much information from single ChIP-Seq and RNA-Seq experiments compared to WGS**
  - **However putting 10 different ChIP-Seq experiments and RNA-Seq together with imputation provides a great deal of information about the individual**



Light-weight formats to Hide Most of the Read Data (Signal Tracks)

- Some lightweight format clearly separate public & private info., aiding exchange
- Files become much smaller. Similar to CRAM
- Distinction between formats to compute on and those to archive with – become sharper with big data





Mapping coordinates without variants (MRF)

Reads (linked via ID, 10X larger than mapping coord.)

[*Bioinformatics* 27: 281]

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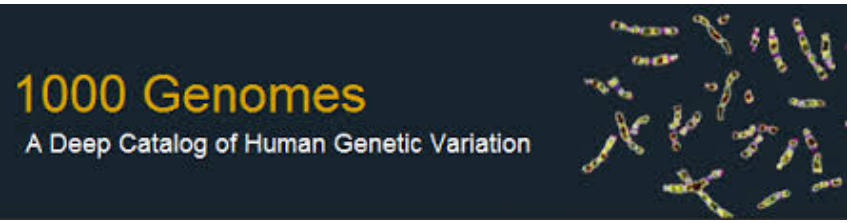
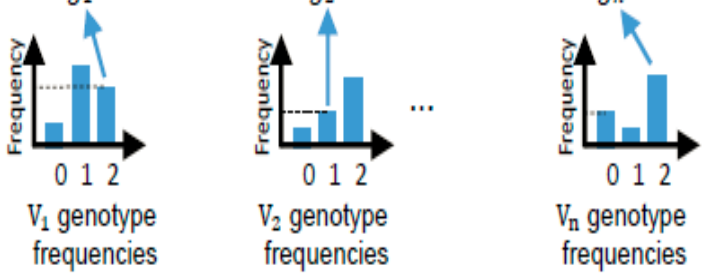
Representative Functional Genomics, Genotype, eQTL Datasets

- 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)

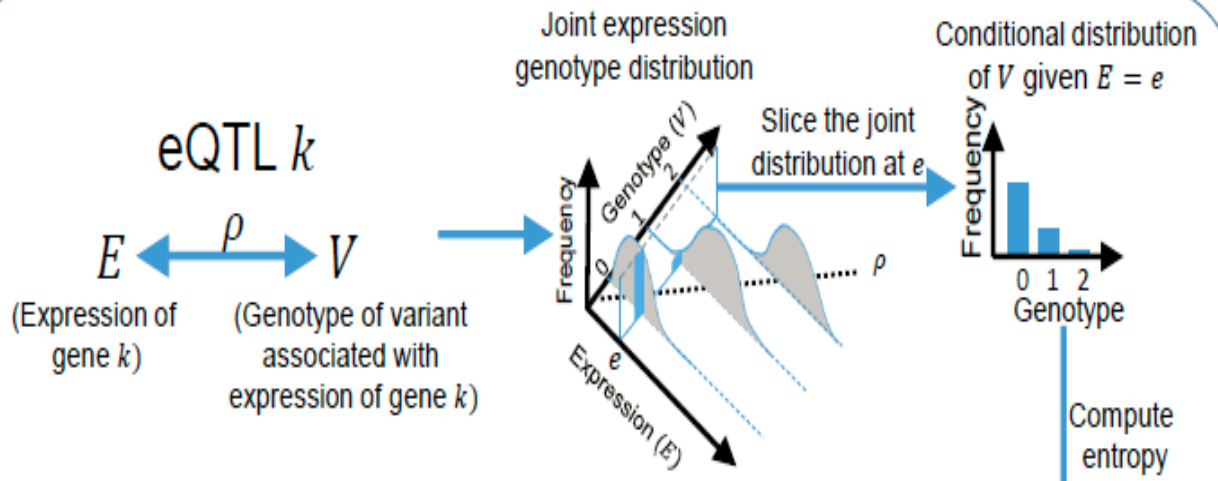


Information Content and Predictability

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



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

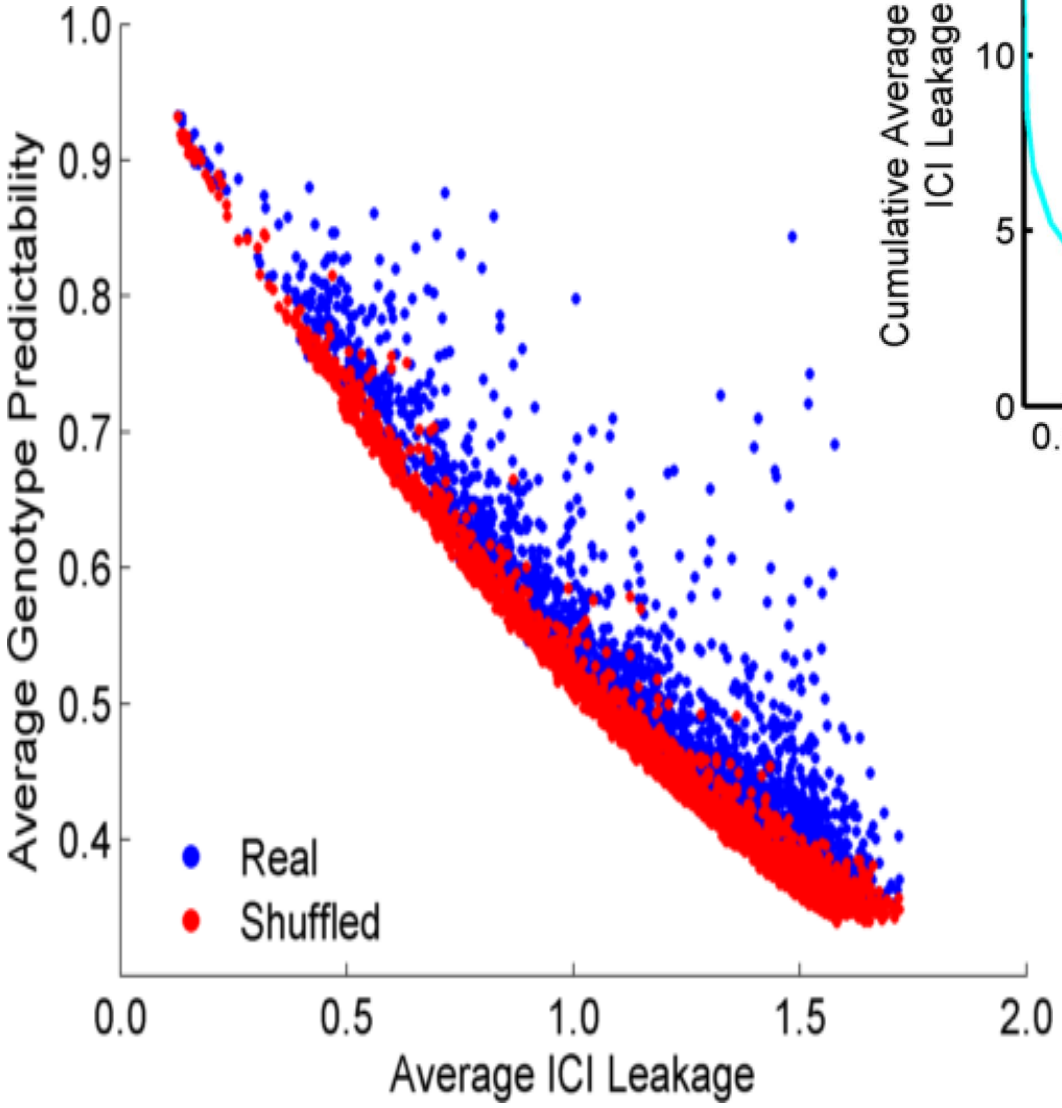


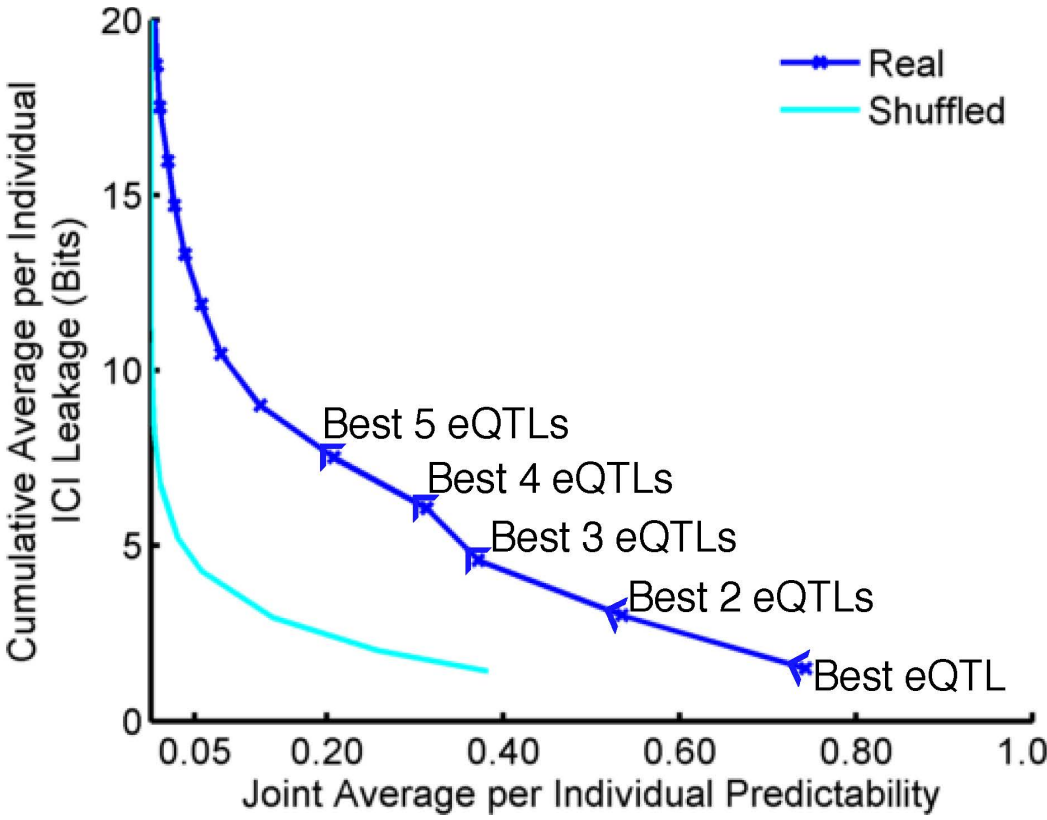
$$\pi\left(V \mid E = e\right) = e^{-H\left(V \mid E = e\right)}$$

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

[Harmanci et al. Nat. Meth. 2016]

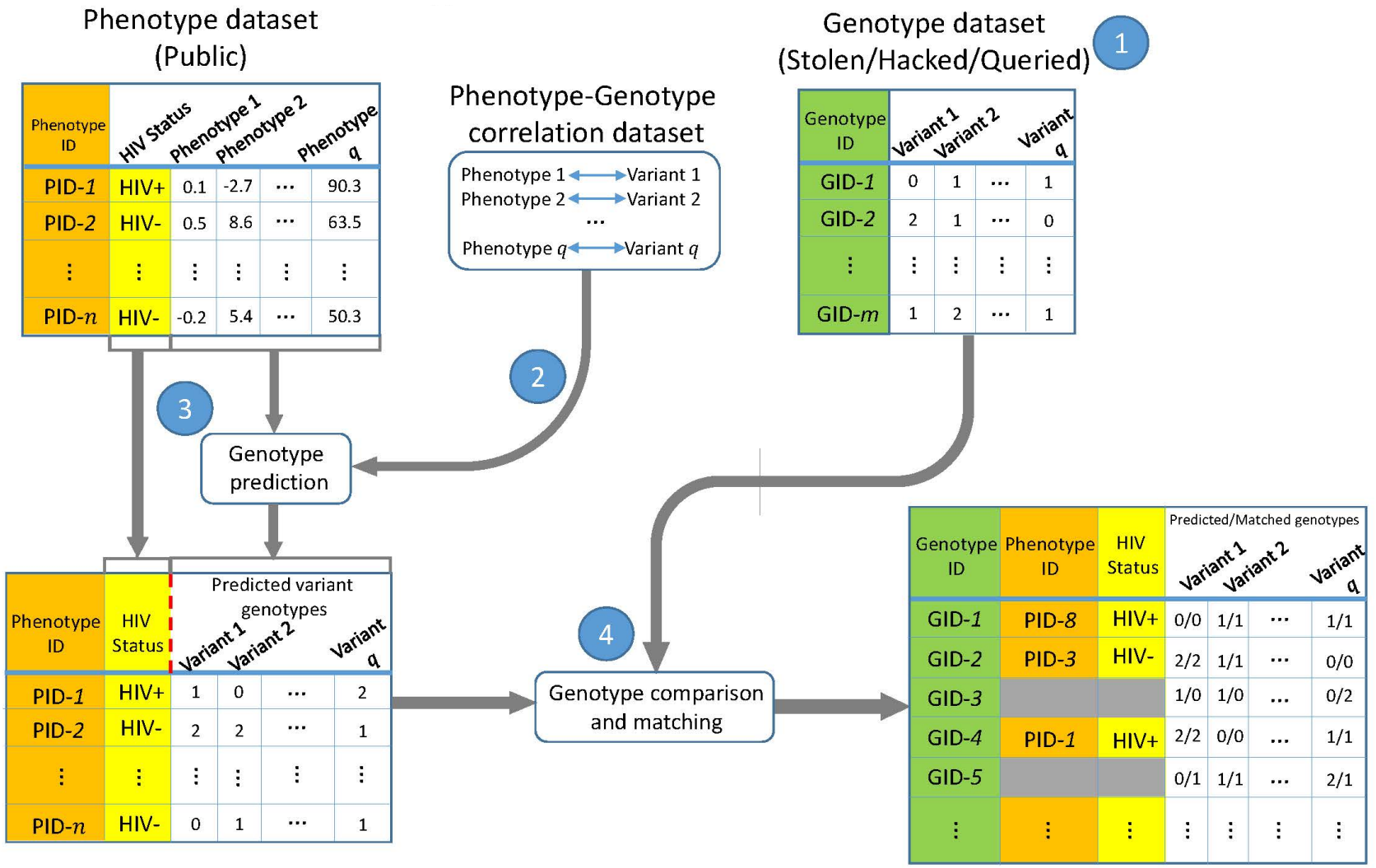
[Harmanciet al. Nat. Meth. (‘16]





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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…	…	…	…
…	…	…	…
…	…	…	…

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- **IMDB users are public**

- **NetFLIX and IMdB moves are public**

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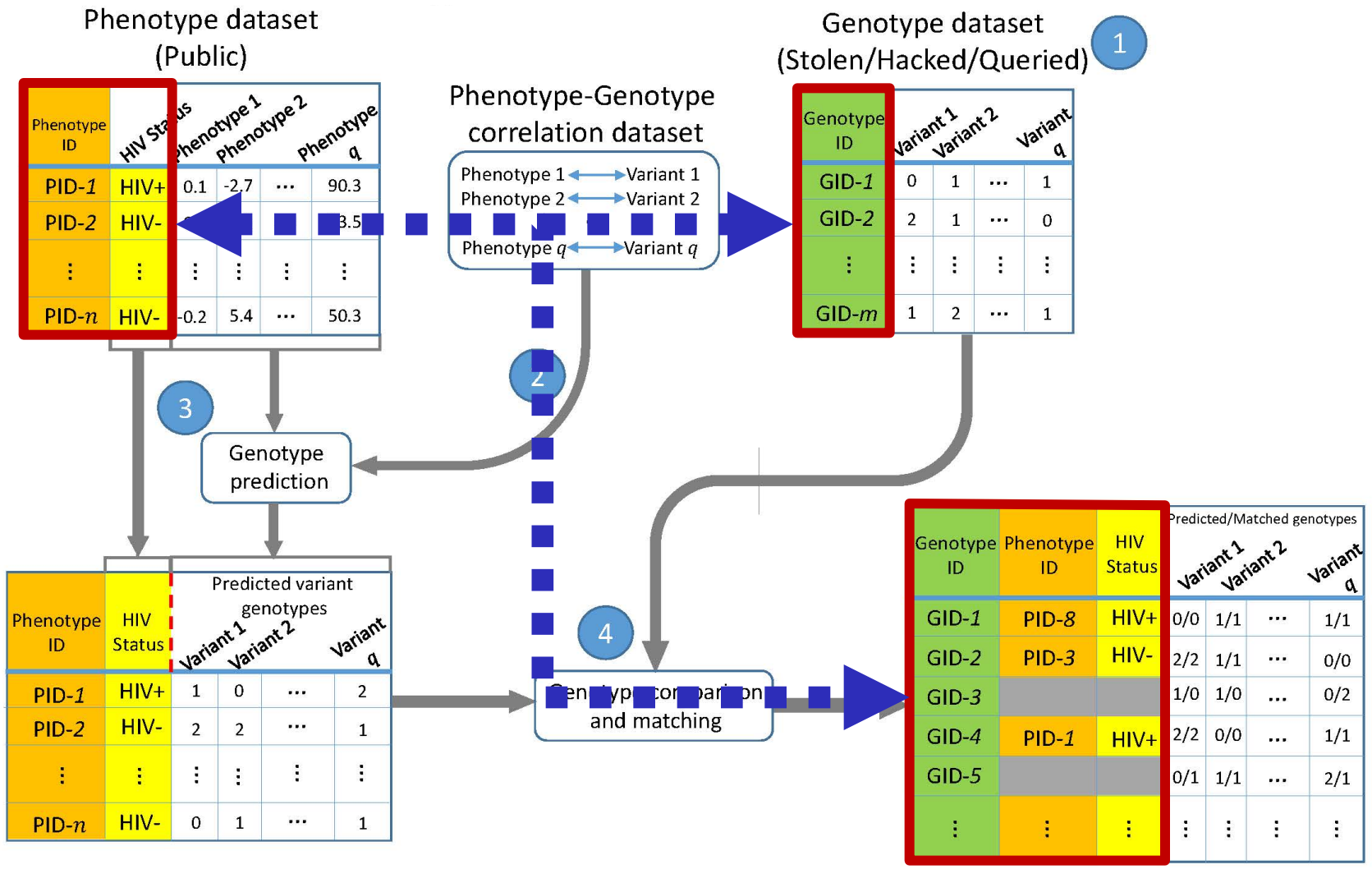
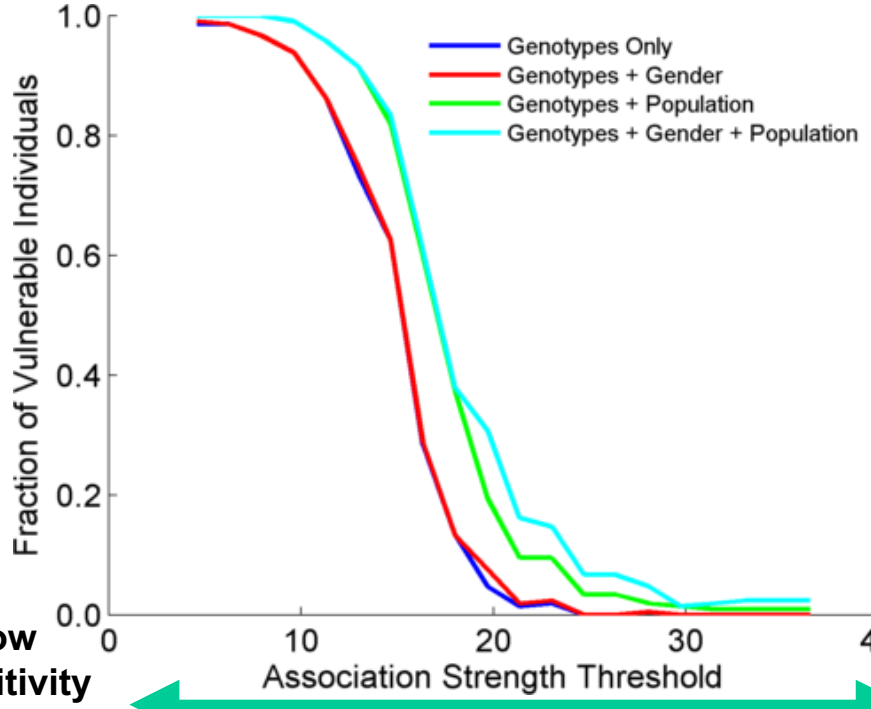


[Harmanciet al. Nat. Meth. (in revision)]

Success in Linking Attack with Extremity based Genotype Prediction

200 individuals eQTL Discovery
200 individuals in Linking Attack

High Sensitivity



Low Sensitivity

High Number Of eQTLs

Low Number Of eQTLs

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

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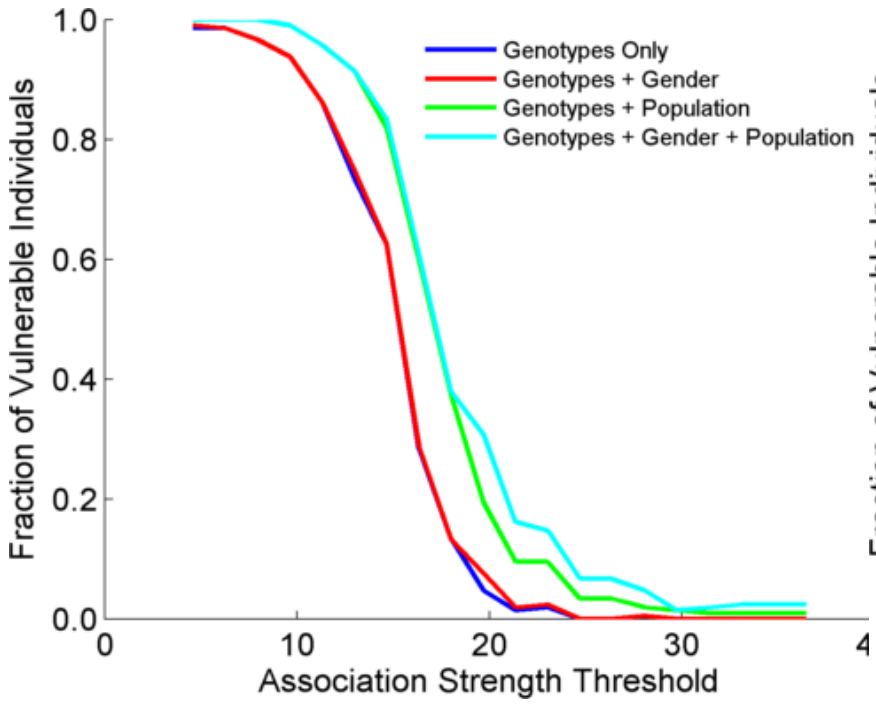
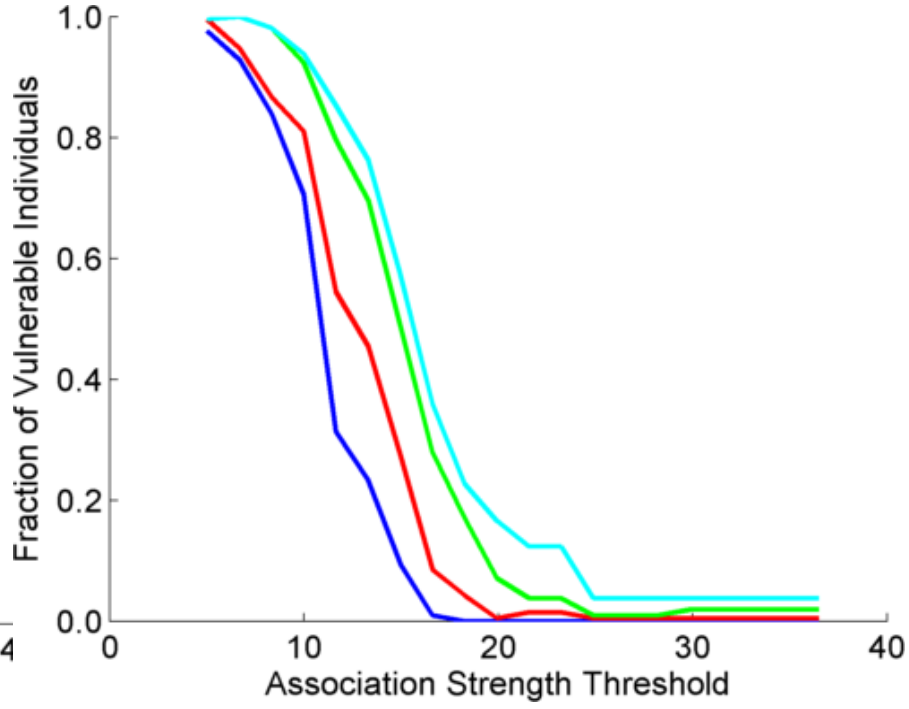


200 individuals eQTL Discovery
100,200 individuals in Linking Attack



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

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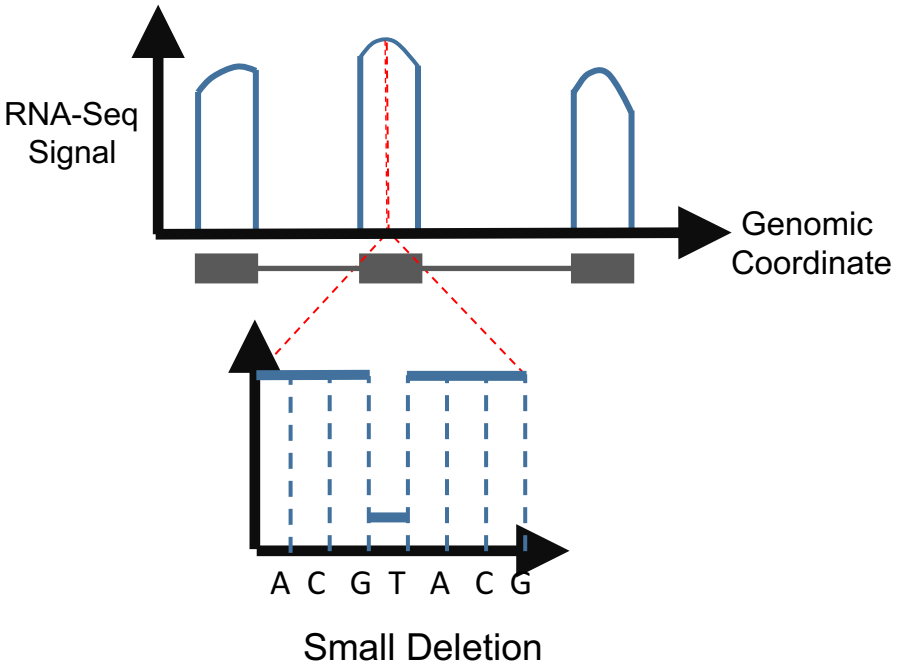
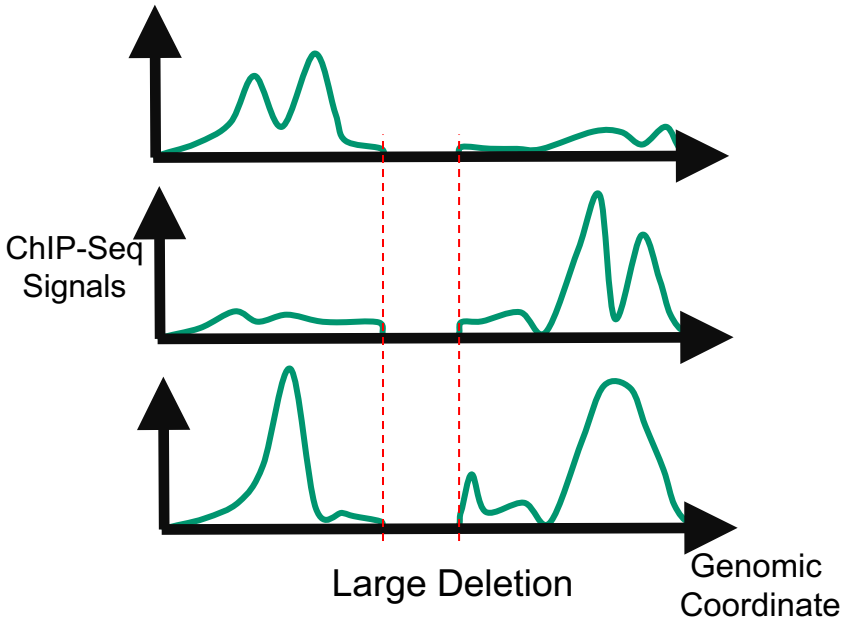
Detection & Genotyping of small & large SV deletions from signal profiles

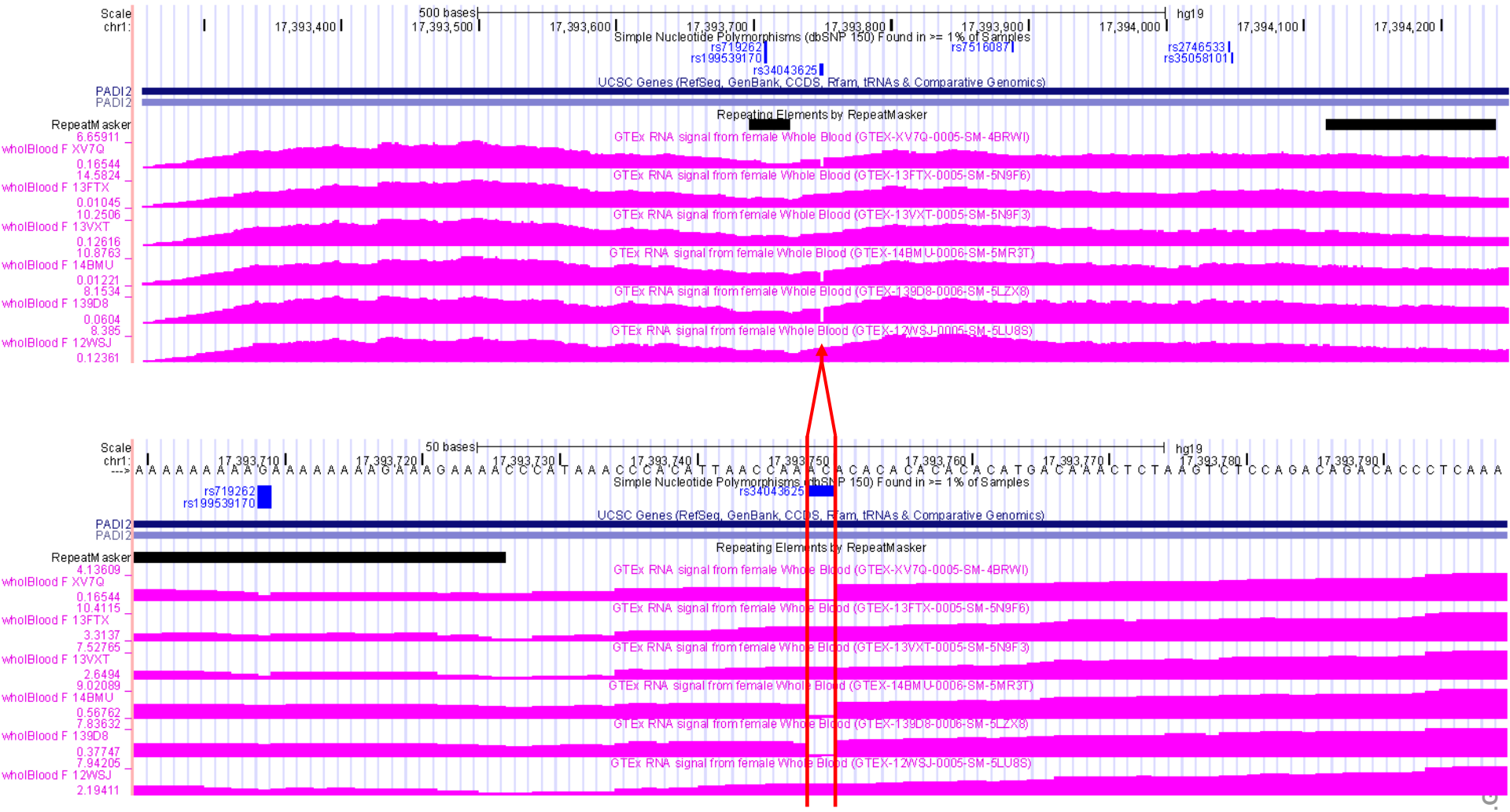




RNA-seq also shows large deletions

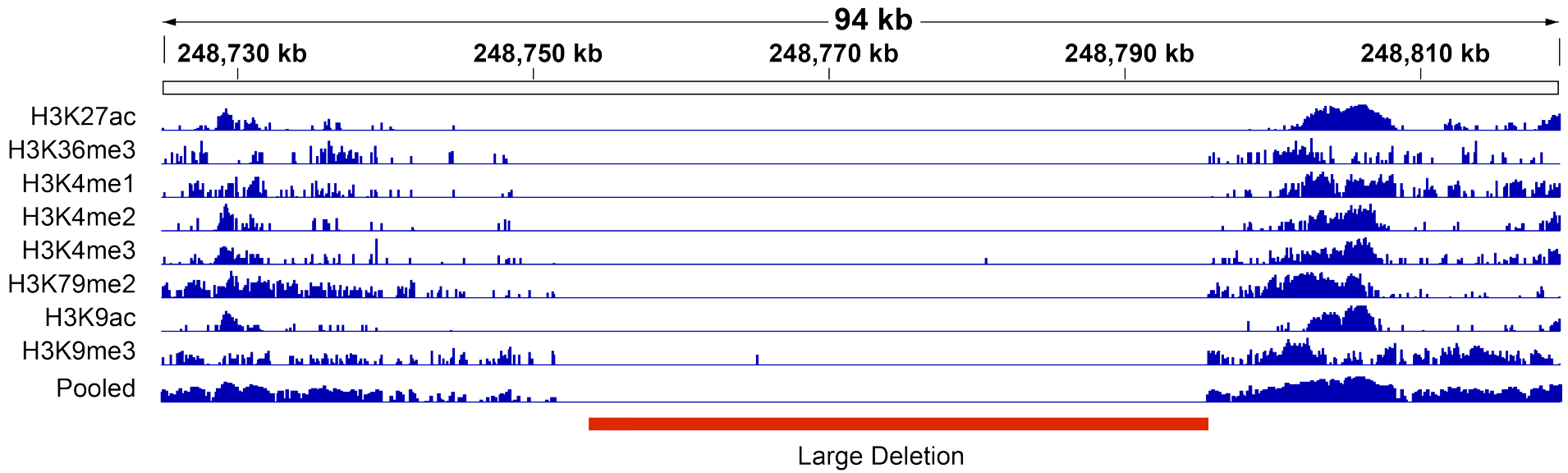
[Harmanci & Gerstein, *Nat. Comm.* ('18)]

Example of Small Deletion Evident in Signal Profile



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

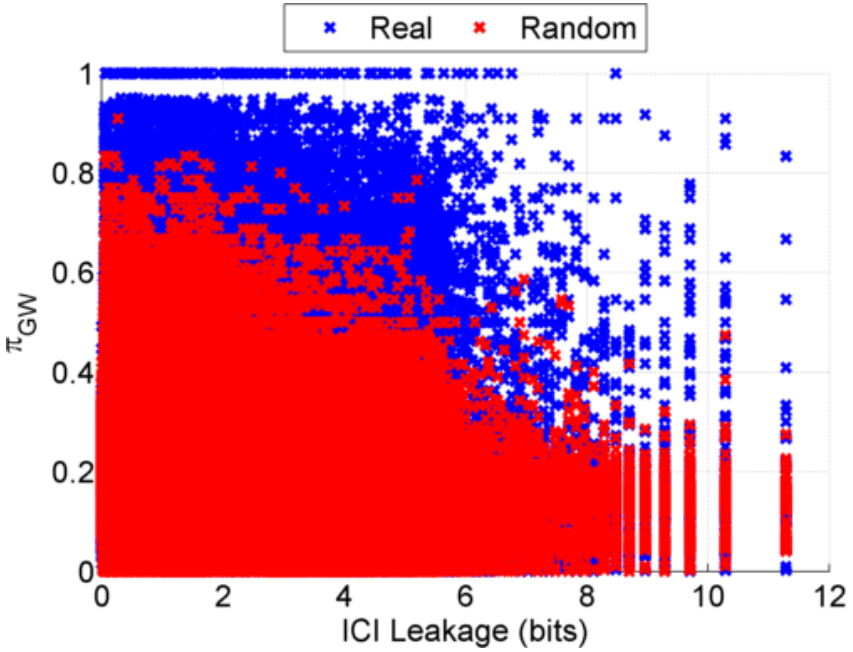
Example of Large Deletion Evident in Signal Profile



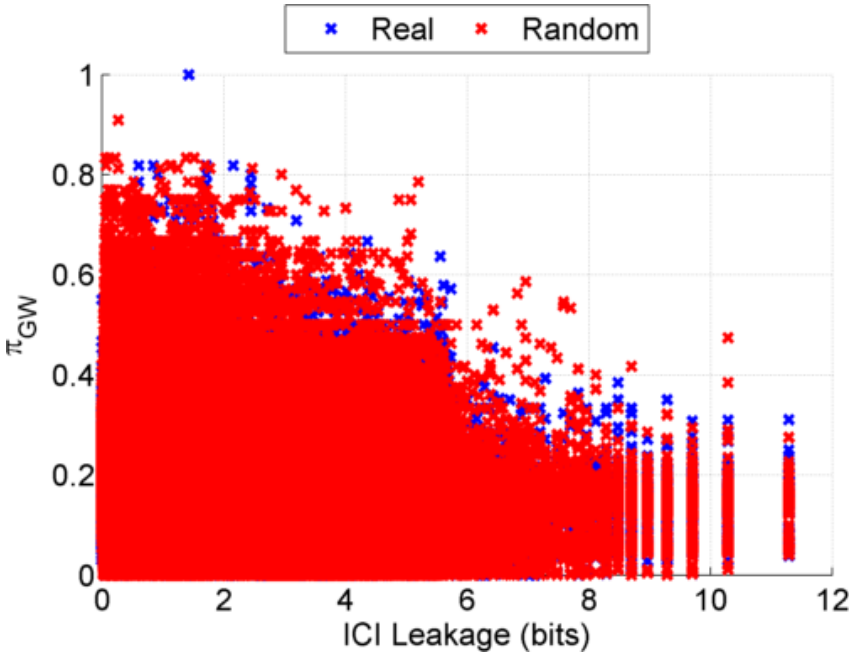
[Harmanci & Gerstein, *Nat. Comm.* ('18)]

Information Leakage from SV Deletions

a) Before Anonymization



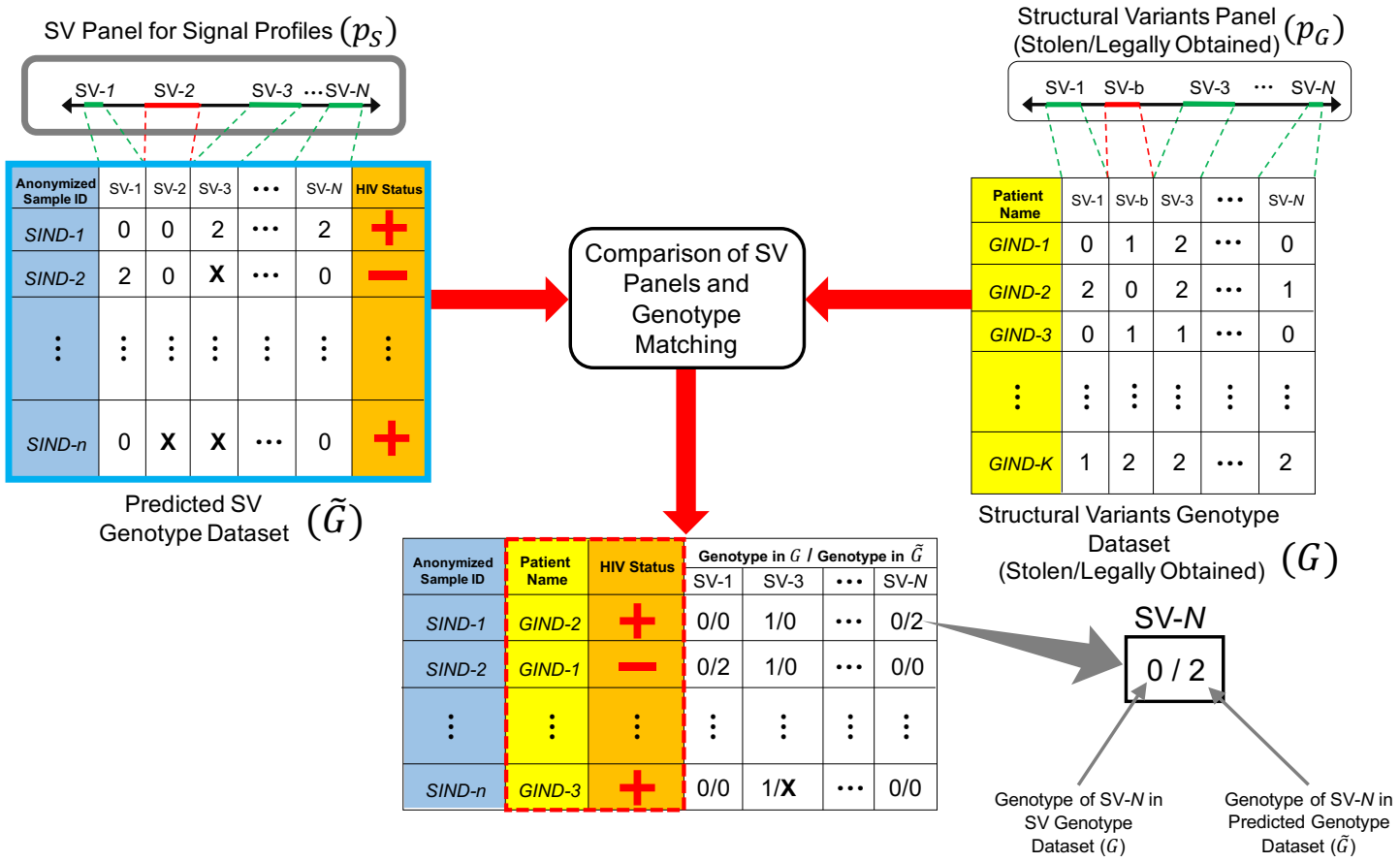
b) After Anonymization



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

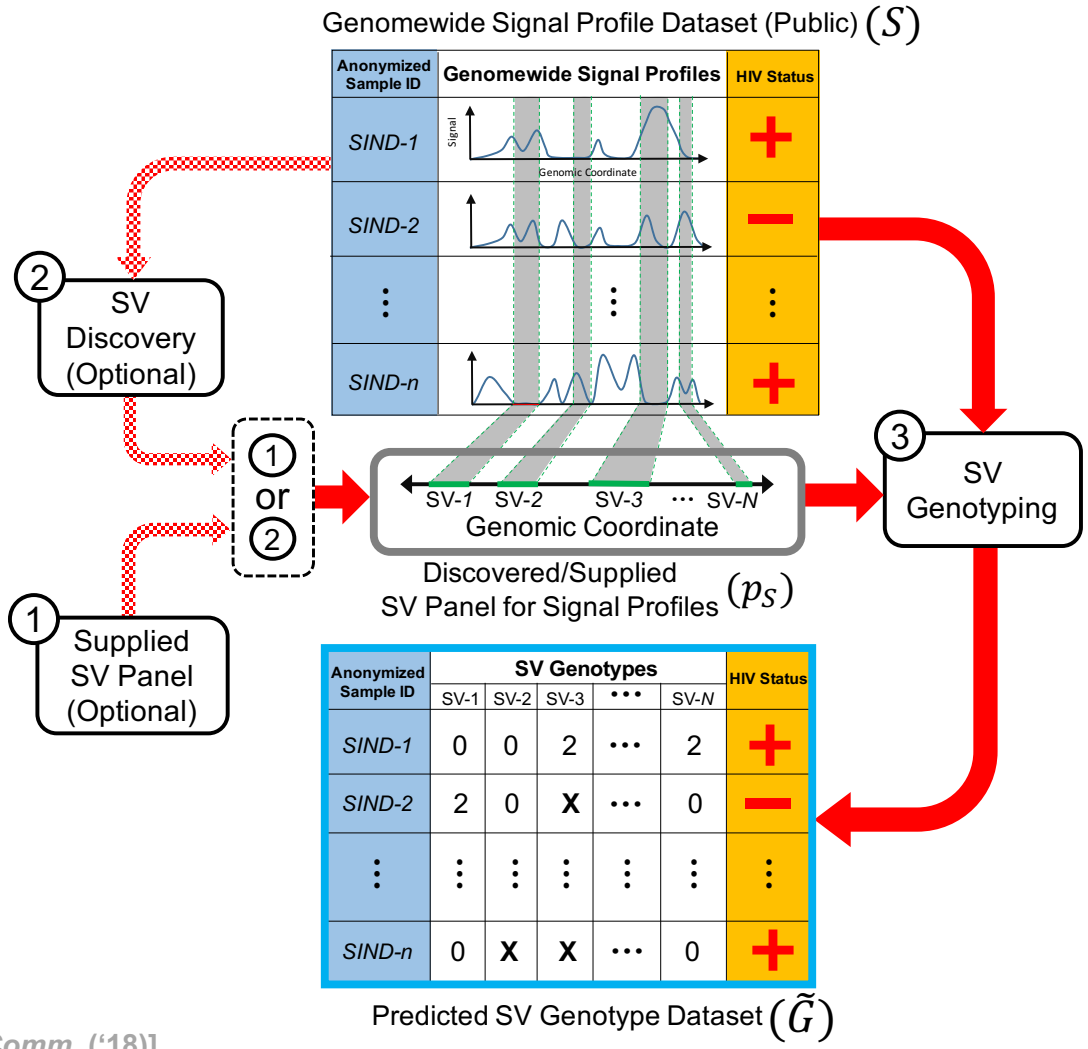
[Harmanci & Gerstein, *Nat. Comm.* ('18)]

Another type of Linking Attack: Linking based on SV Genotyping



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

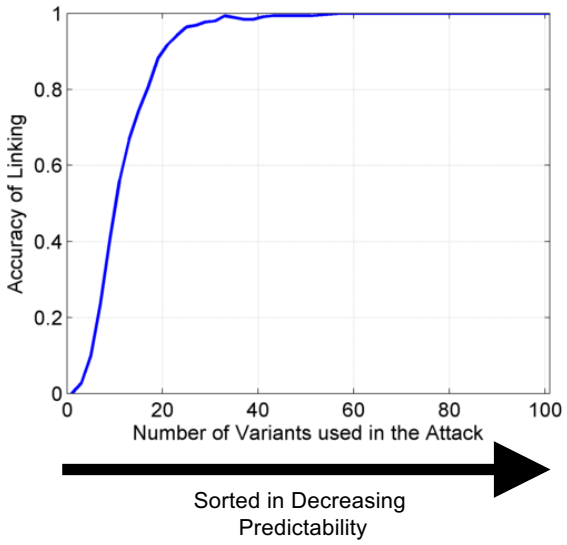
Another type of Linking Attack: First Doing SV Genotyping



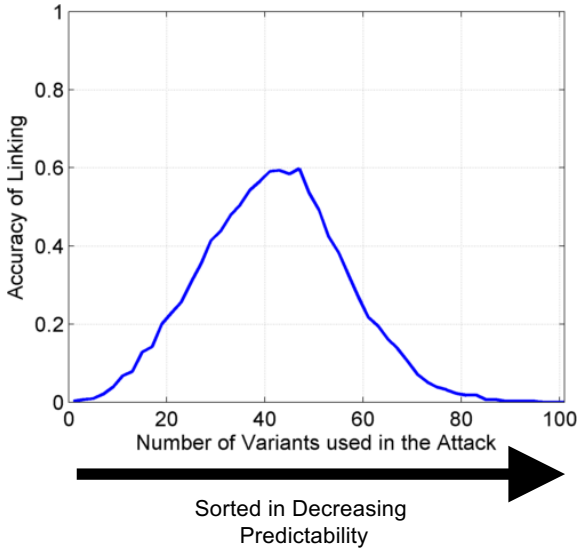
[Harmanci & Gerstein, *Nat. Comm.* ('18)]

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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- Alexander Arguello
- Thomas Lehner

"Adult Capstone" Team – 1 of 3 capstones

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PsychENCODE Consortium,

Panos Roussos, Schahram Akbarian, Andrew E. Jaffe, Kevin White, Zhiping Weng, Nenad Sestan,

Daniel H. Geschwind, James A. Knowles

Dedicated to **Pamela Sklar**

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