Inflection point in psychiatric genetics

Incl. replication (~100K)

Freeze May 2013 (~80K)

Freeze Jan. 2013 (~70K)

WCPG Hamburg 2012 (~65K)

Incl. SWE + CLC (~60K)

loci

loci

loci!

120

100

80

60

40

20

0

2006 2007 2008 2009 2010 2011 2012 2013 2014

Genome-wide association analysis identifies 13 new risk loci for schizophrenia

NATURE GENETICS | LETTER

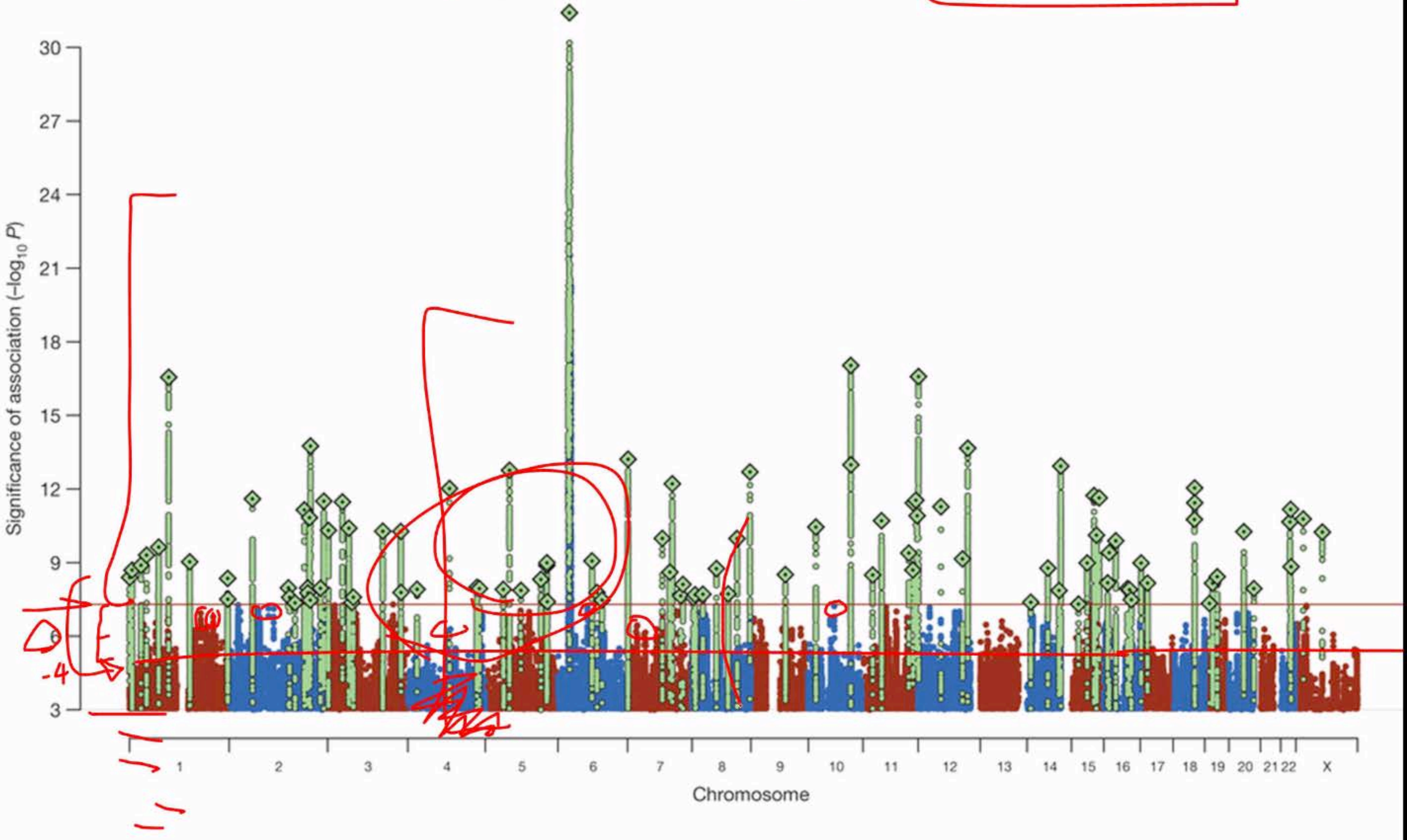
Genome-wide association study identifies five new schizophrenia loci

Letter

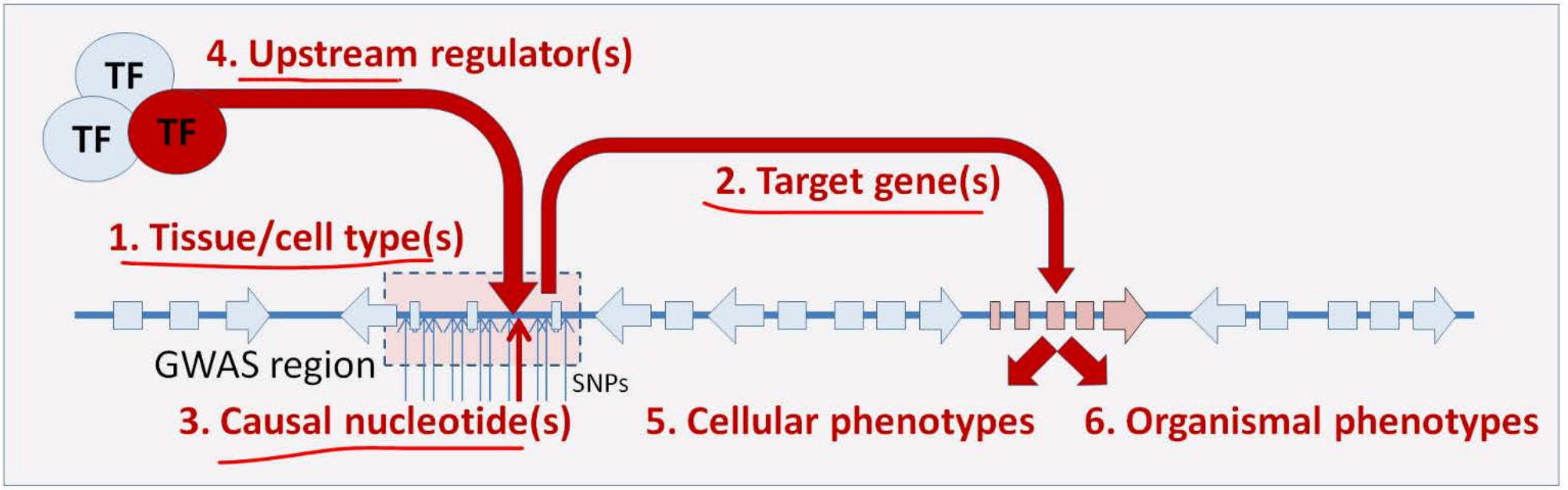
Nature **460**, 748-752 (6 August 2009) | doi:10.1038/nature08185; Received 11 February 2009; Accepted 8 June 2009; Published online 1 July 2009; Corrected 6 August 2009

Common polygenic variation contributes to risk of schizophrenia and bipolar disorder

Today: 35,000 cases ⇔ 108 loci

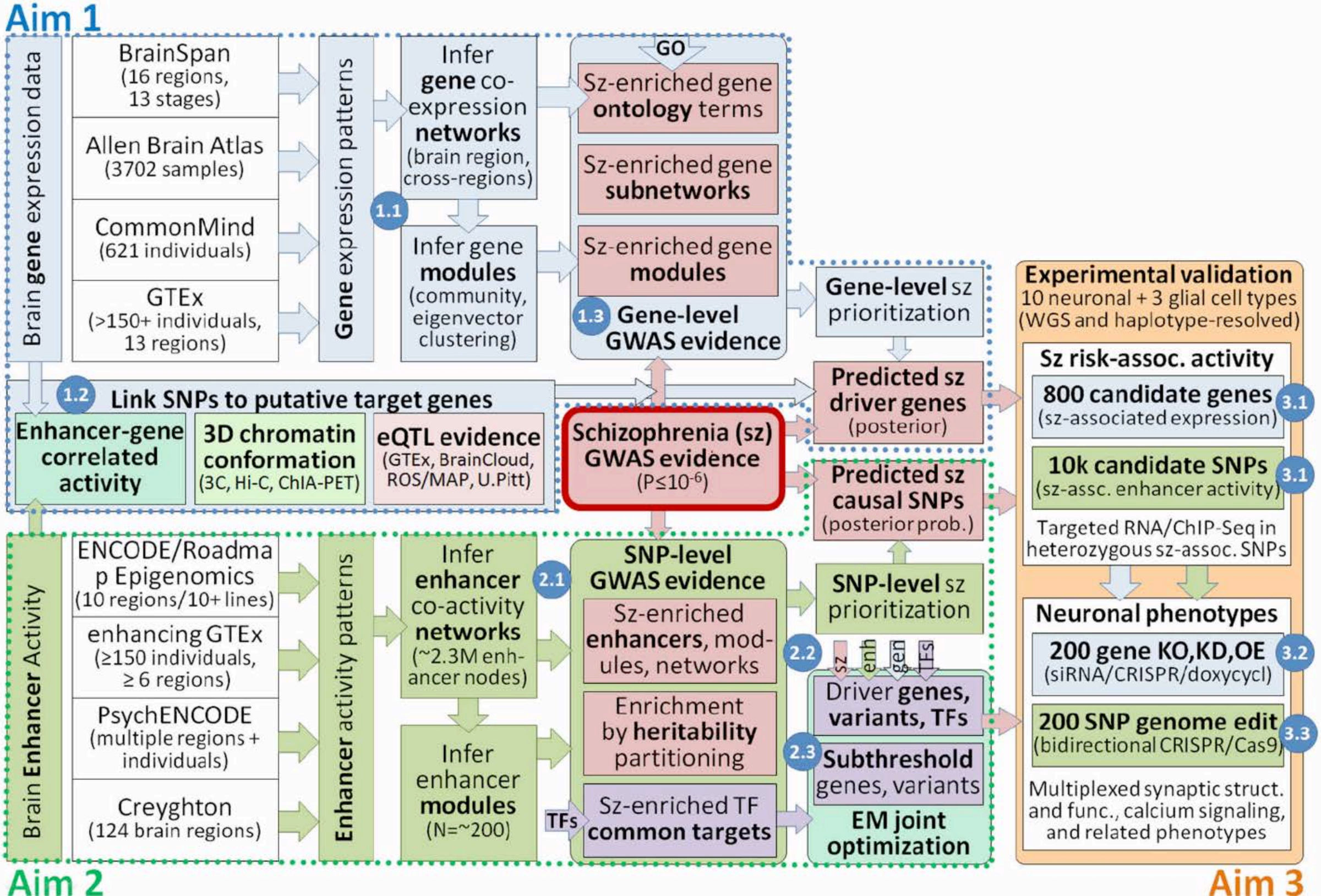


Dissecting non-coding genetic associations

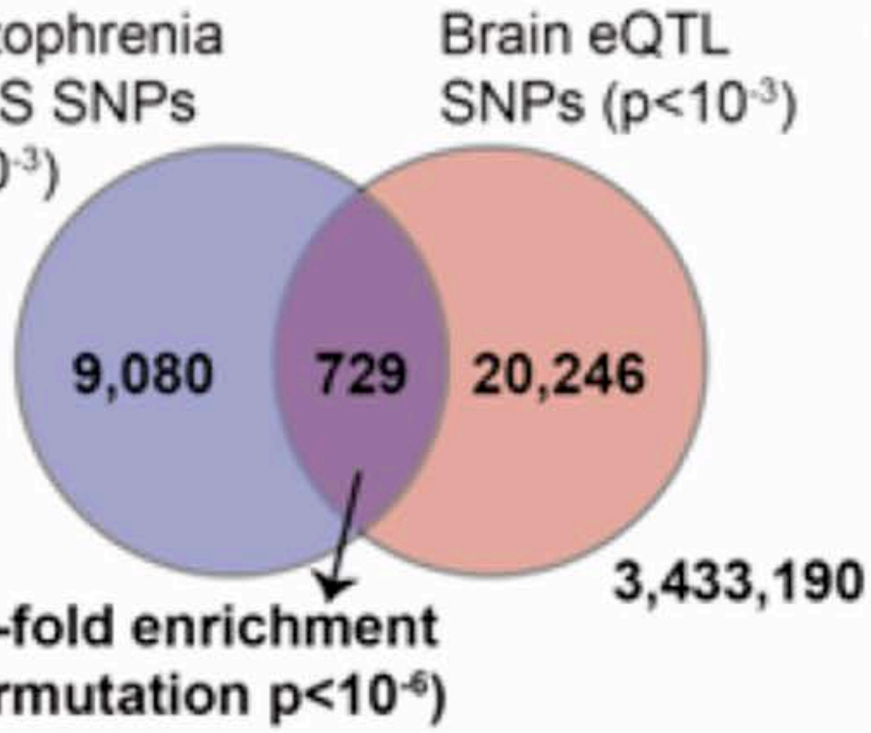


1. Establish relevant **tissue/cell type**
2. Establish downstream **target** gene(s)
3. Establishing **causal** nucleotide variant
4. Establish upstream **regulator** causality
5. Establish **cellular** phenotypic consequences
6. Establish **organismal** phenotypic consequences

Eggan Kellis R01 - Overview of Aims



a.



b.

	Pittsburgh	BrainCloud	ROS/MAP	GTEx
Pittsburgh	2255	400	1142	117
BrainCloud	317	1953	527	92
ROS/MAP	898	676	7362	220
GTEx	59	58	68	958

c.

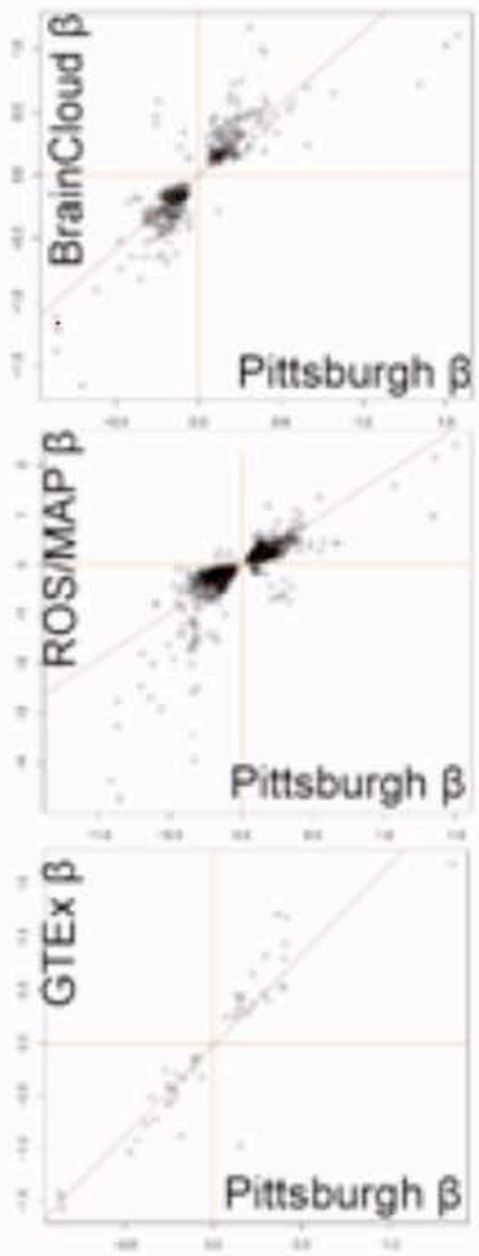
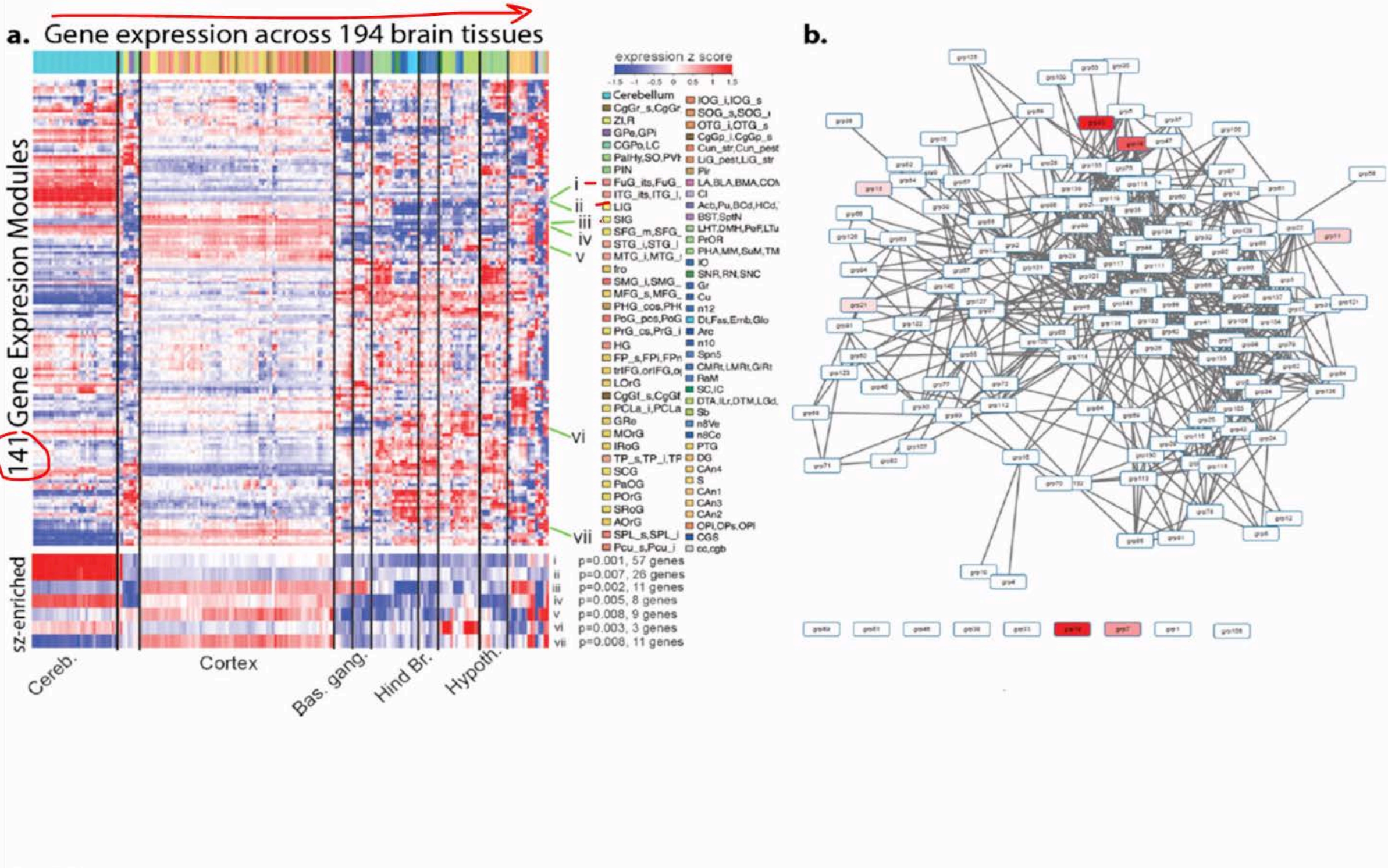


Figure 4. Brain eQTL enrichment in schizophrenia. **a.** Enrichment of Schizophrenia GWAS hits in Brain eQTL SNPs (17-fold, $P<10^{-6}$). **b.** Agreement in eQTLs called between four different brain eQTL datasets, for all SNPs (top right) and independent loci after LD pruning (bottom left). **c.** Agreement in the directionality of effect between brain eQTL datasets.

Aim 1: Sz gene modules



Aim 2: Sz enhancer enrichments

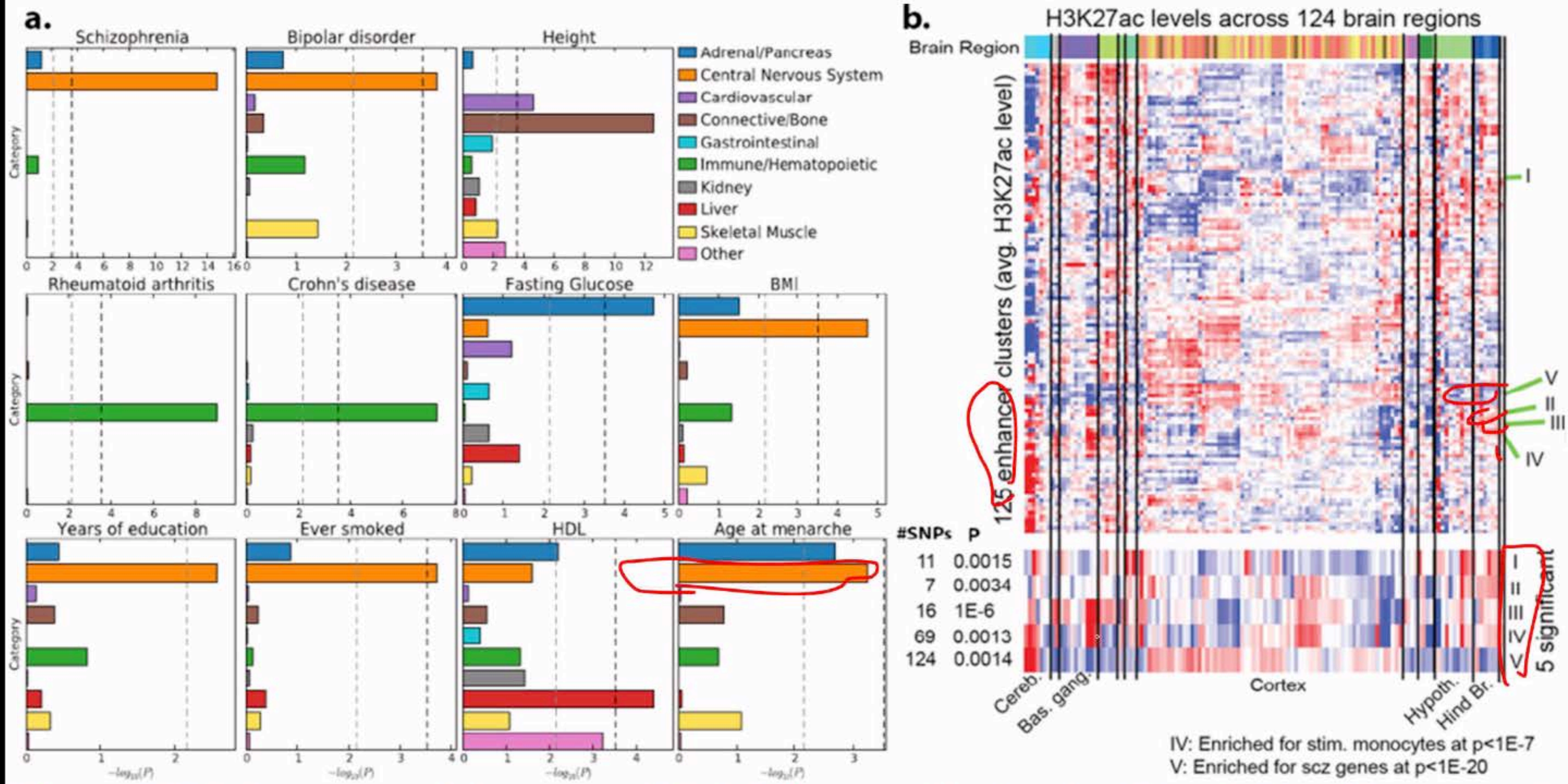
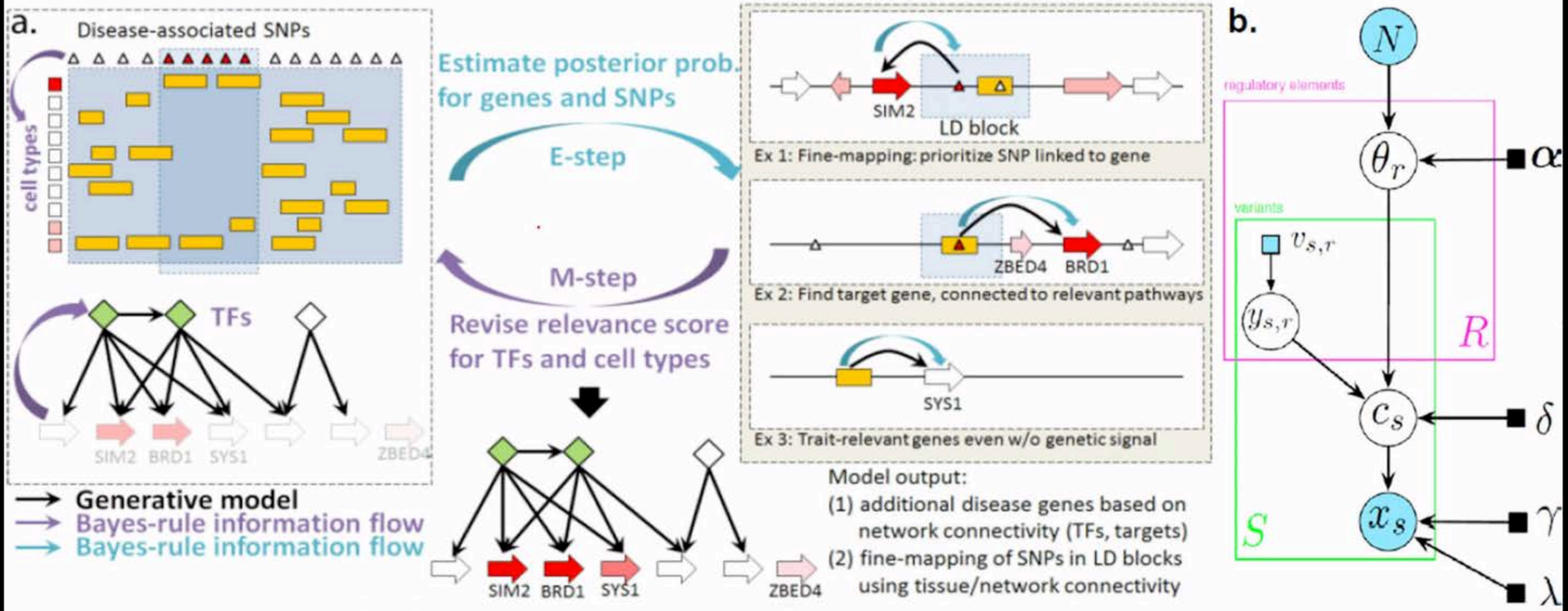


Figure 5. Enhancer enrichment. a. Heritability partitioning for 11 traits in enhancers of 10 tissue groups shows that schizophrenia heritability is primarily explained by SNPs residing in central nervous system enhancers. **b.** Clustering of enhancer activity across 124 brain regions reveals significant schizophrenia enrichment for five clusters (I-V) with diverse activity patterns, including both higher (cortex) and lower (cerebellum). Genes near clusters IV & V are enriched in monocytes and schizophrenia, respectively.


a.
Disease-associated SNPs
cell types
TFs
SIM2
BRD1
SYS1
ZBED4
Generative model
Bayes-rule information flow
Bayes-rule information flow
Estimate posterior prob. for genes and SNPs
E-step
M-step
Revise relevance score for TFs and cell types
SIM2
BRD1
SYS1
ZBED4
SIM2
LD block
Ex 1: Fine-mapping: prioritize SNP linked to gene
ZBED4
BRD1
Ex 2: Find target gene, connected to relevant pathways
SYS1
Ex 3: Trait-relevant genes even w/o genetic signal
Model output:
(1) additional disease genes based on network connectivity (TFs, targets)
(2) fine-mapping of SNPs in LD blocks using tissue/network connectivity
b.
N
regulatory elements
θ_r
α
variants
$v_{s,r}$
$y_{s,r}$
R
c_s
δ
x_s
γ
S
λ

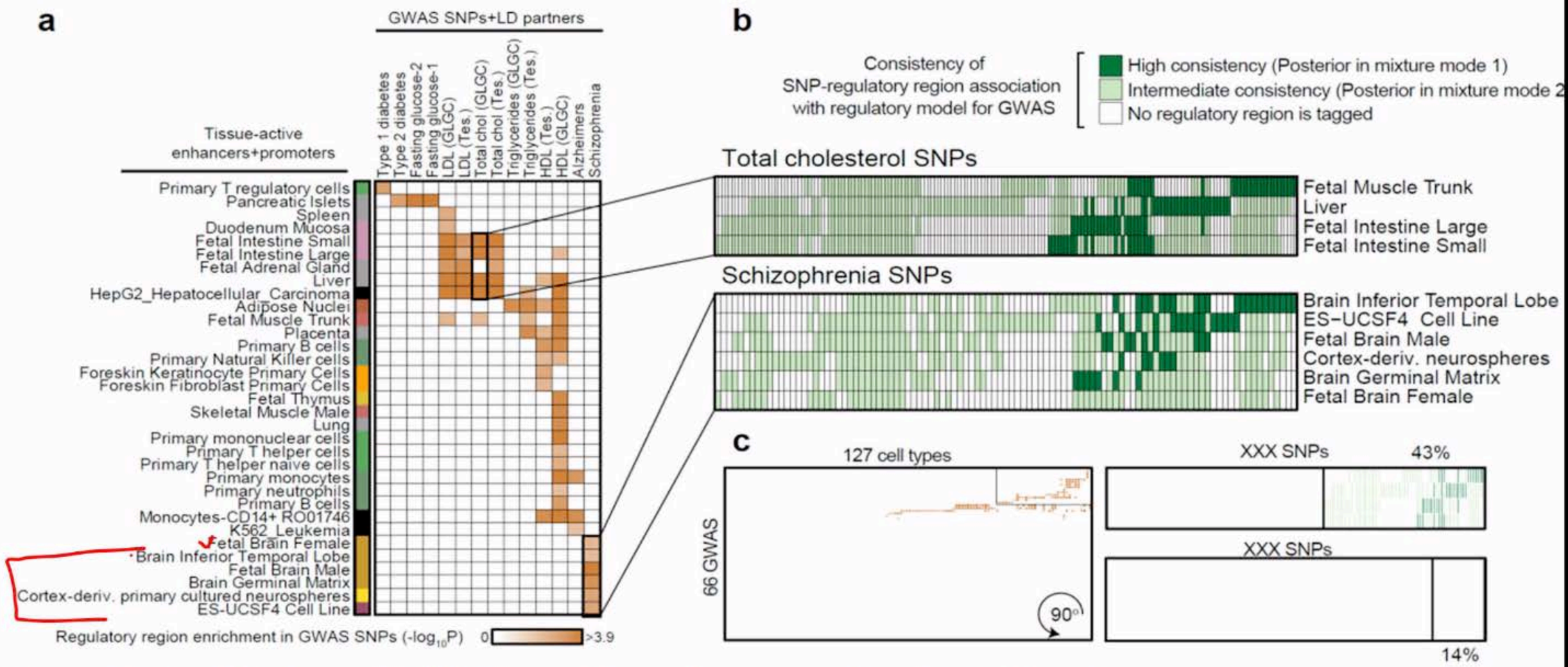


Figure 7: Identification of GWAS target regulatory modules in Schizophrenia and comparison with diverse traits. (a) Variant-regulatory region edges of the network highlight cell types enriched for GWAS regulatory variants. (b) GWAS variants target distinct regulatory modules in different cell types, partitioning GWAS variants into: variants which did not tag any regulatory region in that cell type (white); variants which showed lower priority (light green); and variants with high priority (dark green). (c) Large heatmaps show all GWAS variants that tag a regulatory region in at least one target cell type.

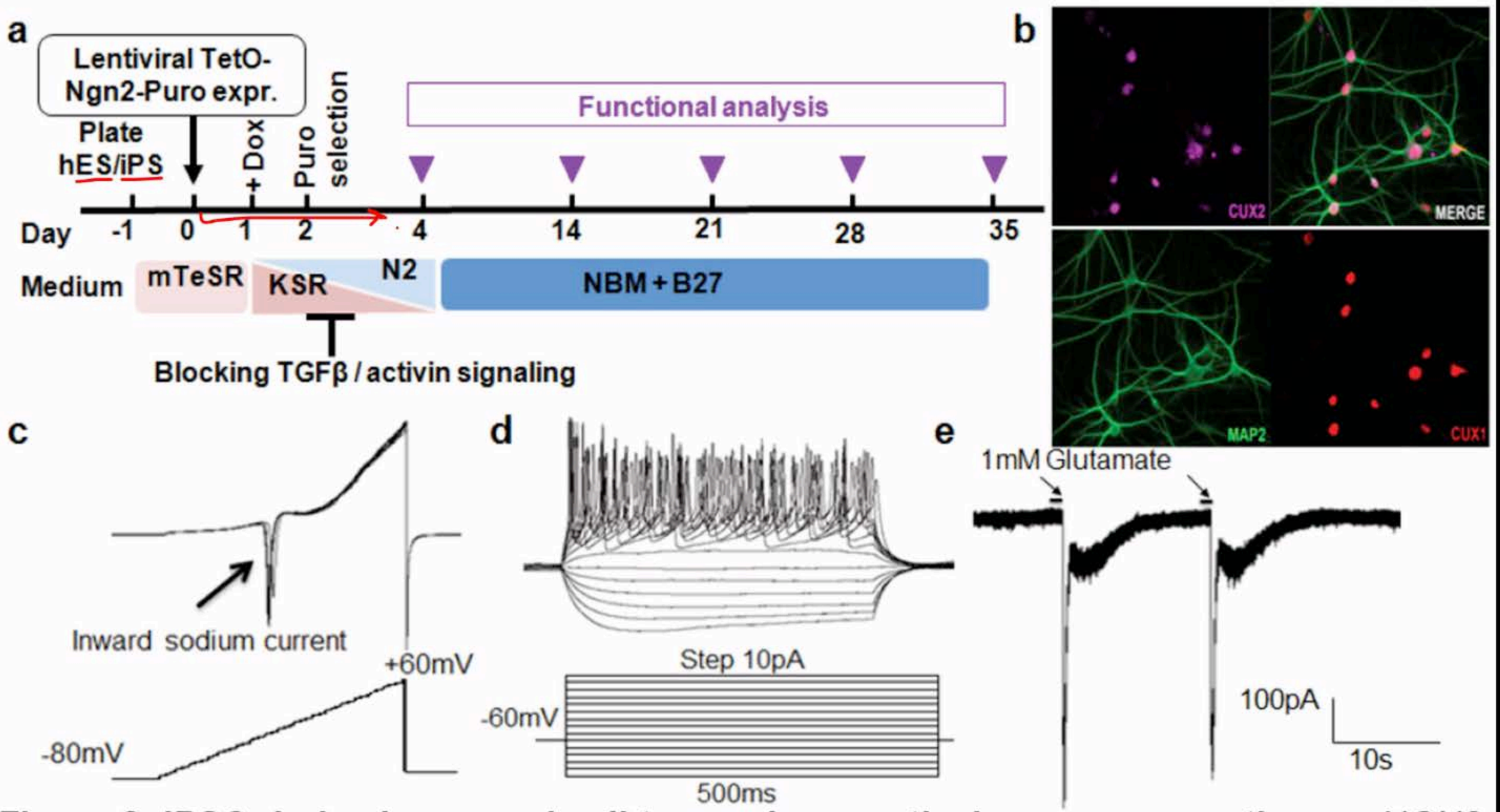


Figure 8. iPSC-derived neuronal cell types show cortical neuron properties. a. NGN2 neural induction used to produce and QC cortical excitatory neurons from iPSCs. iPSC-derived neu-rons show several cortical properties, including: **b.** TF expression patterns indicating cortical identity; **c.** inward sodium current in ramp-voltage tests; **d.** repetitive action potentials induced by step depolarization current injection; **e.** AMPAR and NMDAR mediated currents, in response to 1mM glutamate receptor applied by pressure injection.

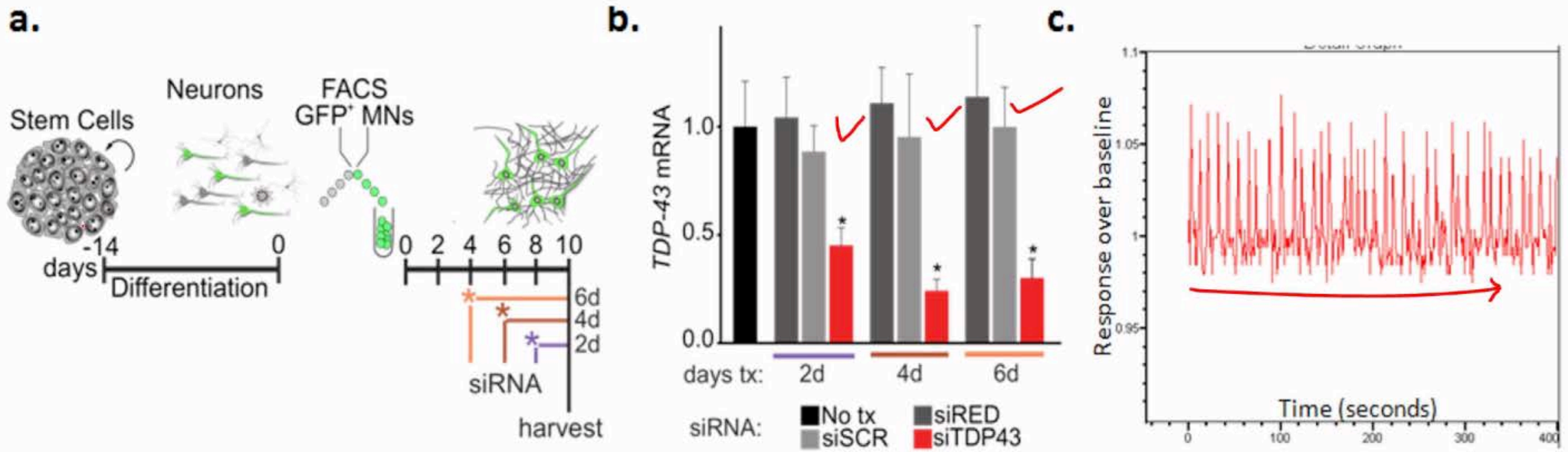
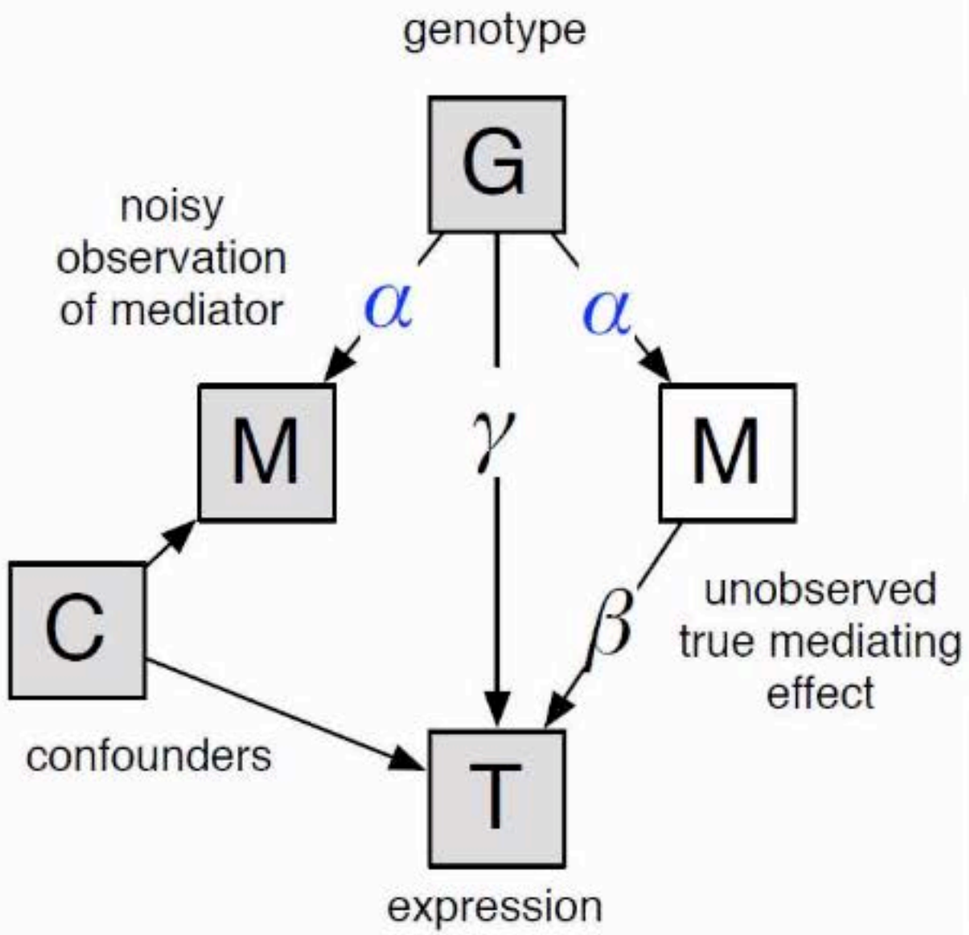


Figure 9. Multiplexed neuronal perturbations. **a.** RNAi knockdown of genes of interest. Differentiated neurons are flow sorted to isolate responding cells and plated at fixed densities. Neurons are repeatedly transfected with target or scambled siRNA. **b.** Quantitative real time PCR demonstrates significant knockdown (e.g. TDP-43, involved in dementia). **c.** Fluorescence imaging of NGN2 neurons transfected with Calcium reporter Synapsin::GCAMP6 into 384 well plates shows synchronous, whole-calcium transients, indicating synaptic connections after 7 days.

Two-stage approach to handle multi-layered regression (mimicking potential mediators)



Step 1. fit observed
argmax P(M | αG + δC)

Step 2. impute
M ~ E[α]G

Step 3. regress on the imputed
argmax P(T | β*M* + γG + δ'C)

Impute disease association by mediated-eQTL, i.e., **w** = E[αβ]

Interesting analysis:
w = E[αβ] vs E[γ]