

Co-expression patterns define epigenetic regulators associated with neurological dysfunction

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Other Stuff

Neuronal brain-region-specific DNA methylation and chromatin accessibility are associated with neuropsychiatric trait heritability

Lindsay F. Rizzardi, Peter F. Hickey, Varenka Rodriguez DiBlasi, Rakel Tryggvadóttir, Colin M. Callahan, Adrian Idrizi, Kasper D. Hansen ✉ & Andrew P. Feinberg ✉

Nature Neuroscience **22**, 307–316 (2019) | Download Citation ↓

WGBS in 4 brain regions and 2 cell populations (NeuN +/-)
(supplemented with ATAC-seq and RNA-seq)

Testing the Regulatory Consequences of 1,049 Schizophrenia Associated Variants With a Massively Parallel Reporter Assay

Leslie Myint, Ruihua Wang, Leandros Boukas, Kasper D Hansen, Loyal A Goff, Dimitrios Avramopoulos

doi: <https://doi.org/10.1101/447557>

MPRA for 1,049 variants in 108 loci.

Tested in K562 and SK-SY5Y

Linear models enable powerful differential activity analysis in massively parallel reporter assays

Leslie Myint,  Dimitrios G Avramopoulos,  Loyal A Goff,  Kasper D Hansen

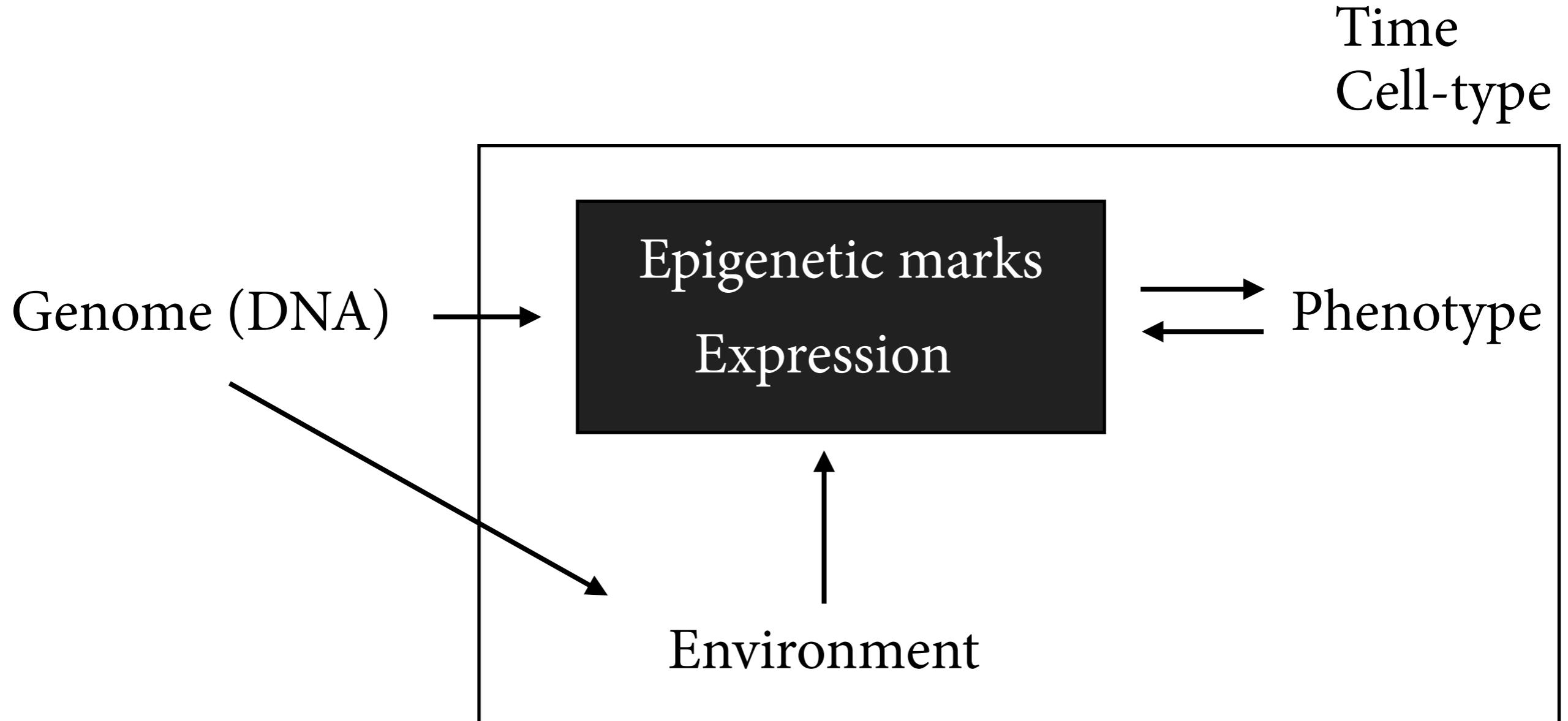
doi: <https://doi.org/10.1101/196394>

Back to the Epigenetic Machinery

Genetics

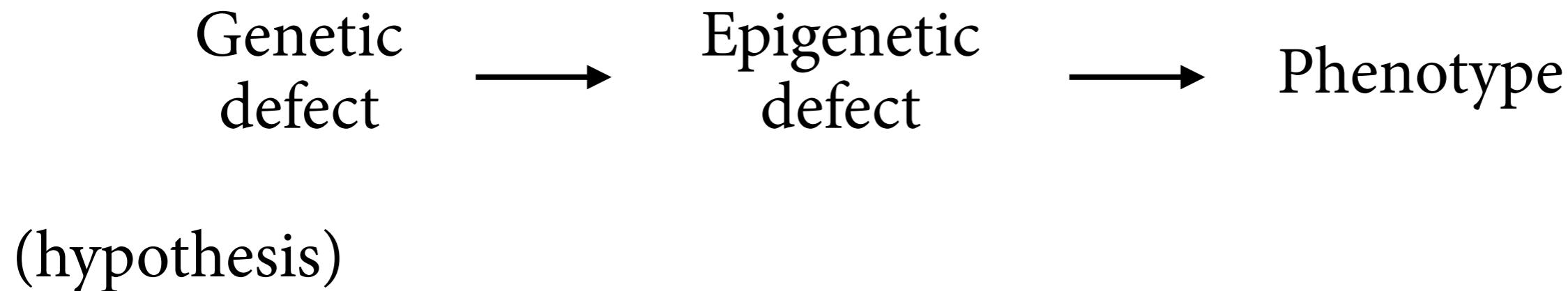
Genome (DNA) —————→ Phenotype

Epigenetics (transcriptomics)



Mendelian disorders of the epigenetic machinery

EM: genes involved in DNA methylation or histone modifications

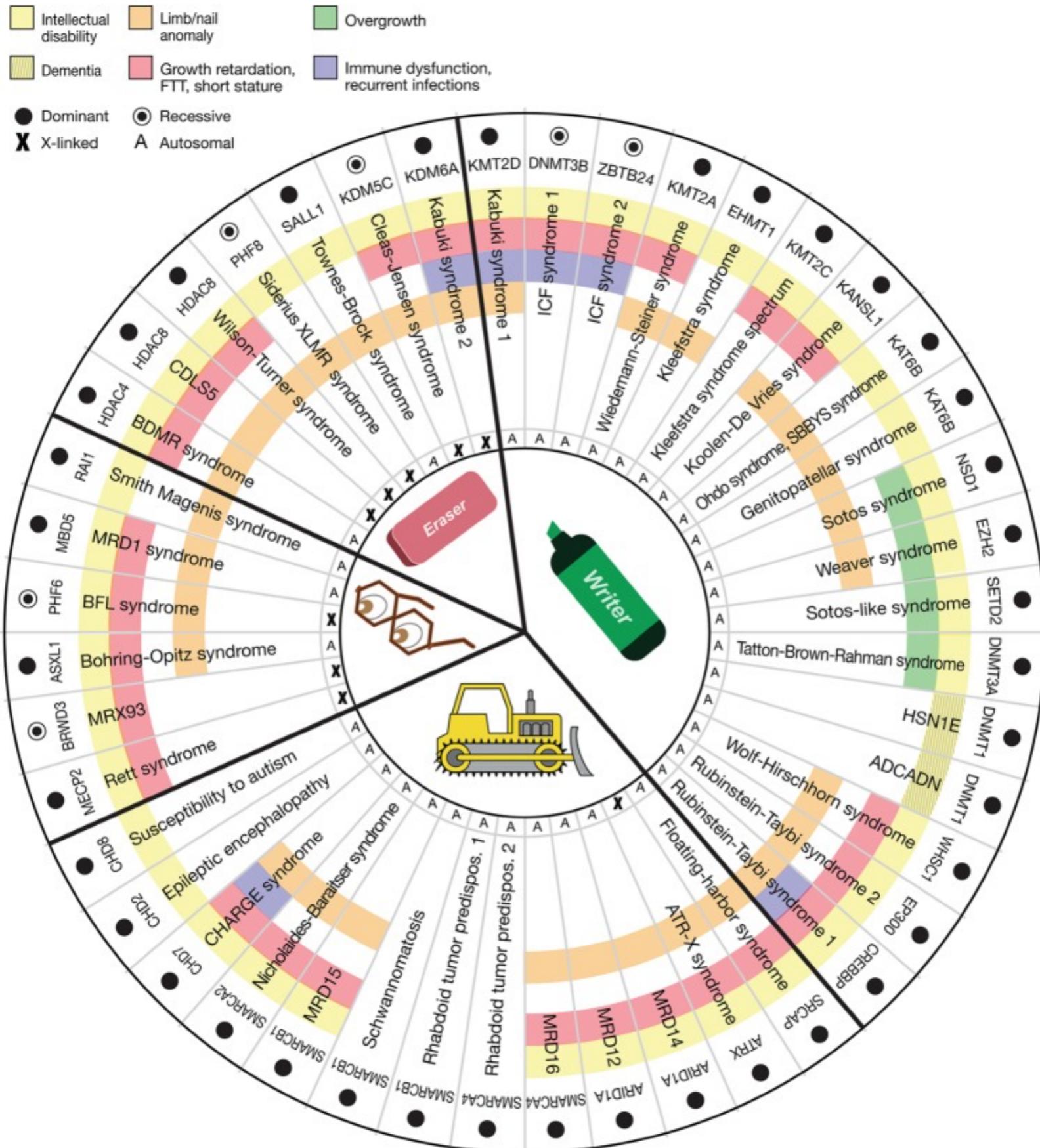


Recent interest in the epigenetic machinery

Cancer: Somatic mutations in EM genes are frequent in many cancers.

Neurological: GWAS and rare variant analysis has implicated EM genes in various neurological disorders incl. sz. and autism.

Shared phenotypes in EM disorders



Bjornsson (2015) Genome Research

Kabuki syndrome / intervening on the epigenome

Caused by LOF in KMT2D or KDM6A.

Can the learning disability associated with Kabuki syndrome be reversed?

The answer is yes

(caveats: short-term, in mice, Kabuki type I, MWM)

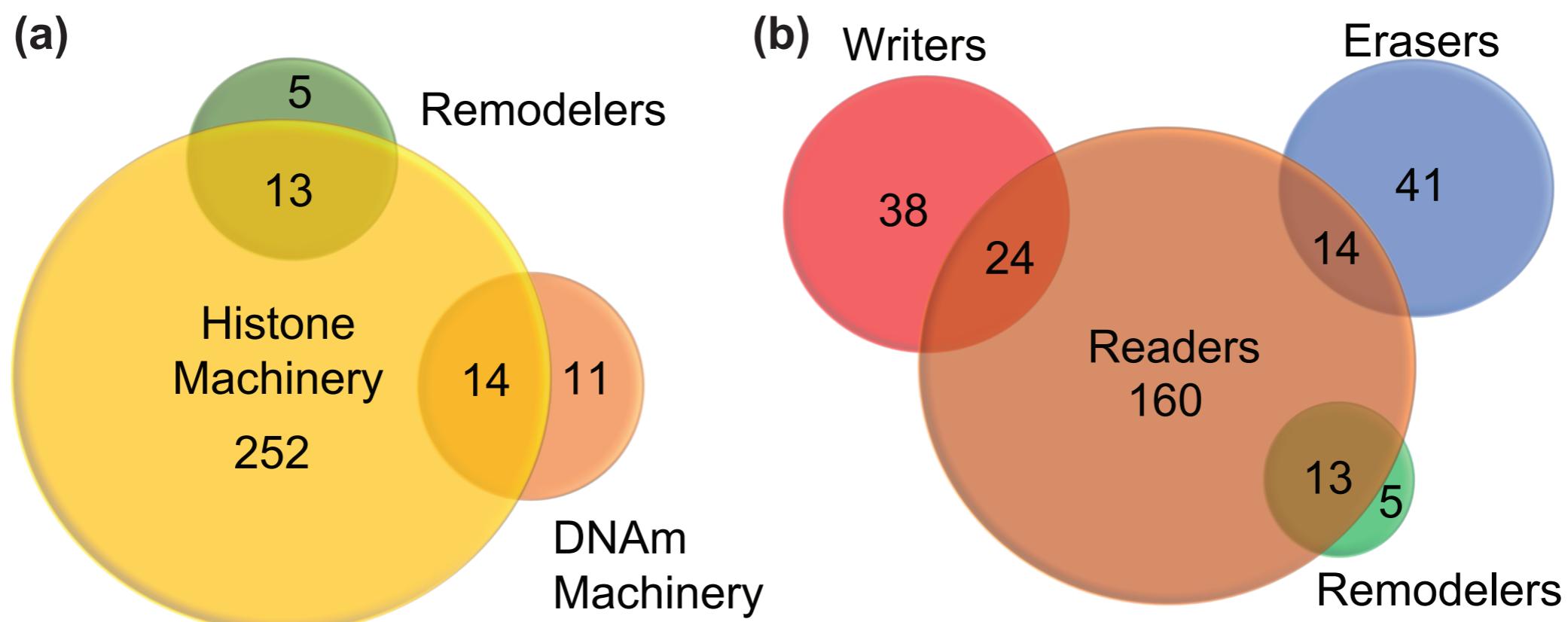
1. (with HDACi): “Histone deacetylase inhibition rescues structural and functional brain deficits in a mouse model of Kabuki syndrome” Bjornsson et al (2014) Sci Trans Med.
2. (with diet): “A ketogenic diet rescues hippocampal memory defects in a mouse model of Kabuki syndrome”, Benjamin et al (2017) PNAS.

Defining the Epigenetic Machinery using protein domains

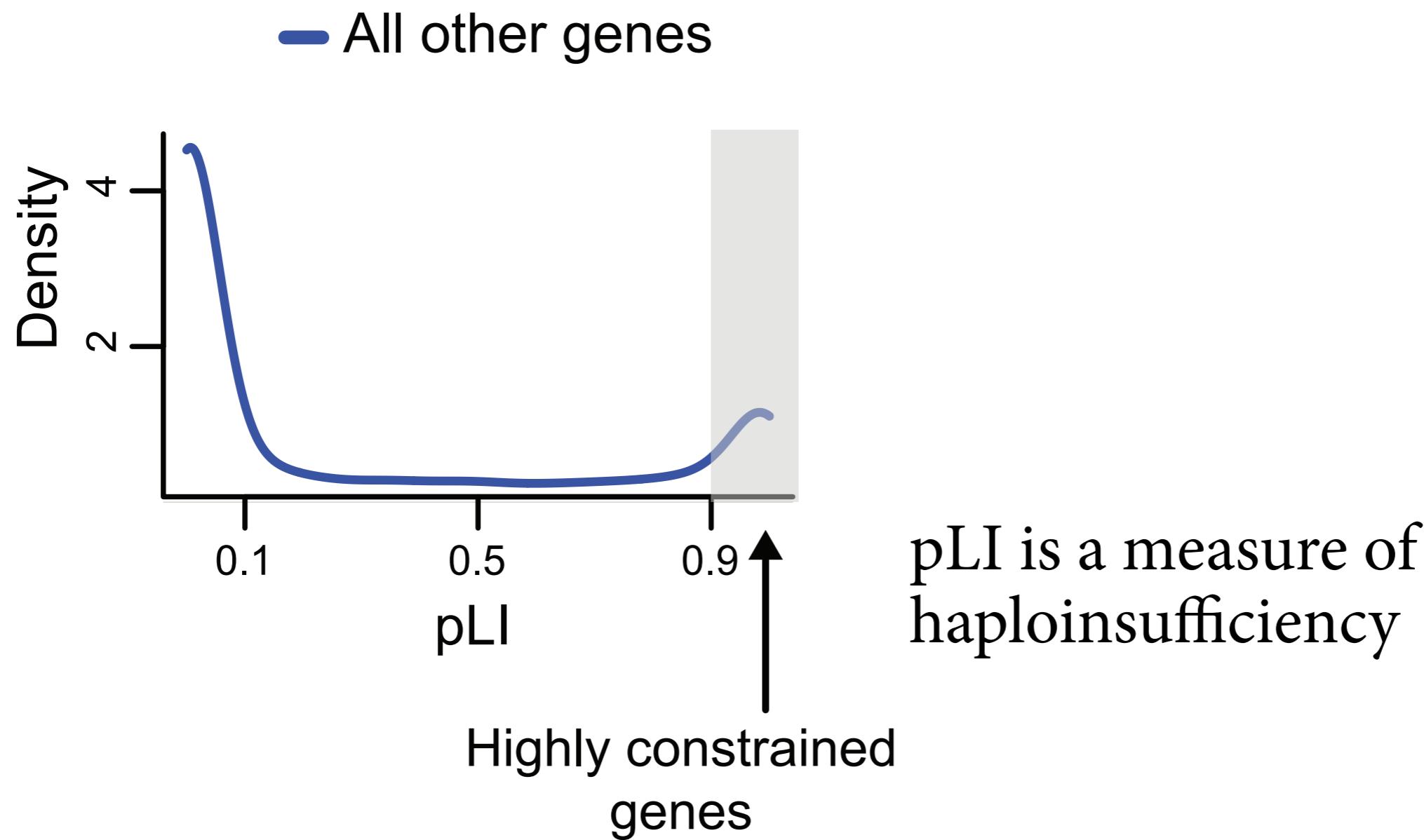
Any gene encoding a protein with a domain which can act as

- Reader / Writer / Eraser of DNA methylation.
- Reader / Writer / Eraser of histone methylation / acetylation.
- Chromatin remodeler

295 EM genes (www.epigeneticmachinery.org)

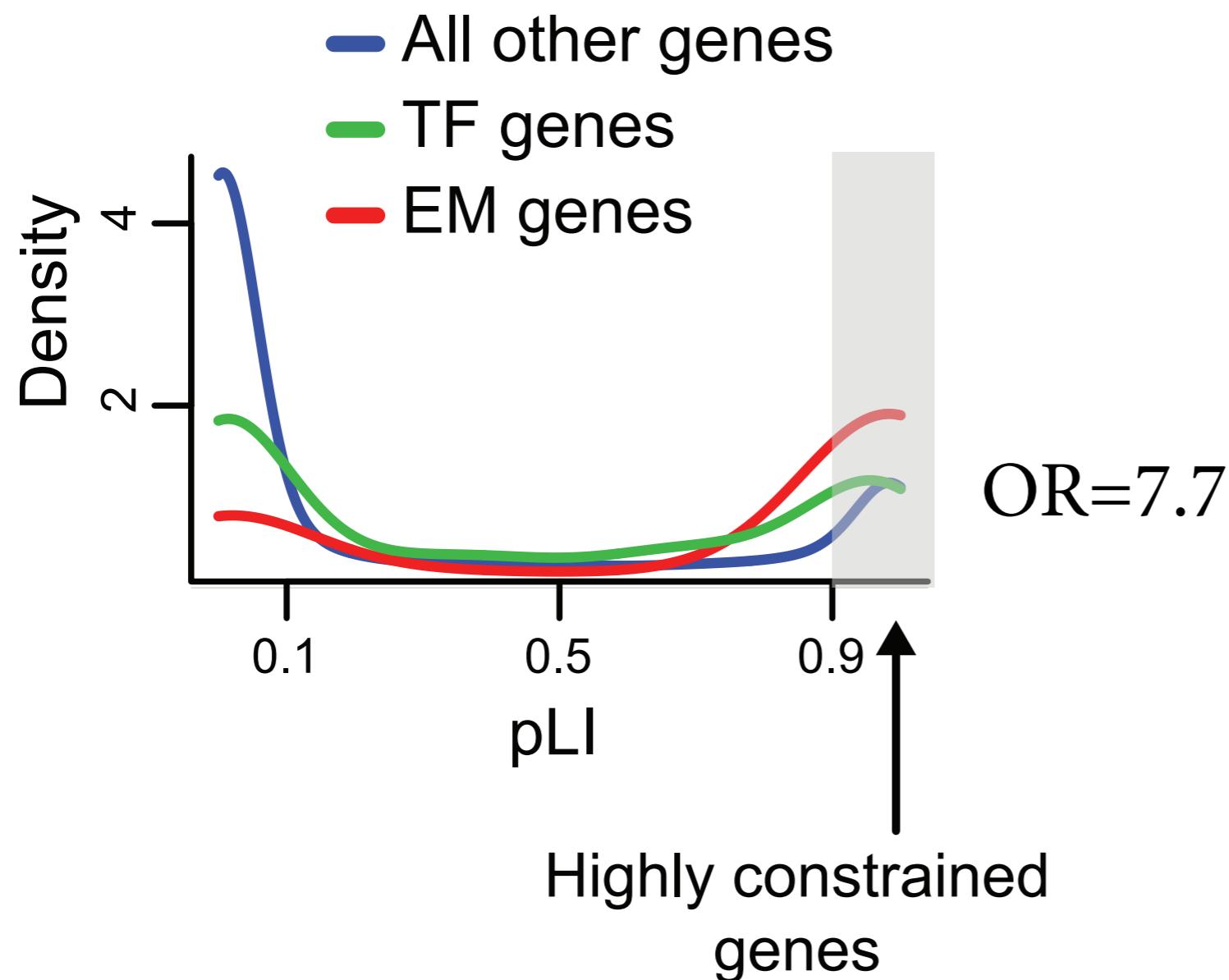


EM genes are highly intolerant to LOF mutations



Using ExAC (Lek et al. 2016)

EM genes are very intolerant to LOF mutations

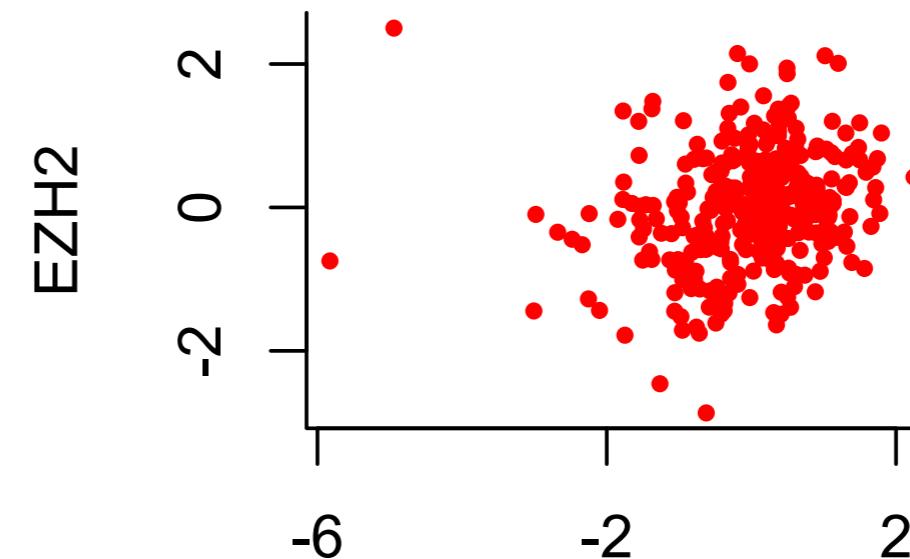
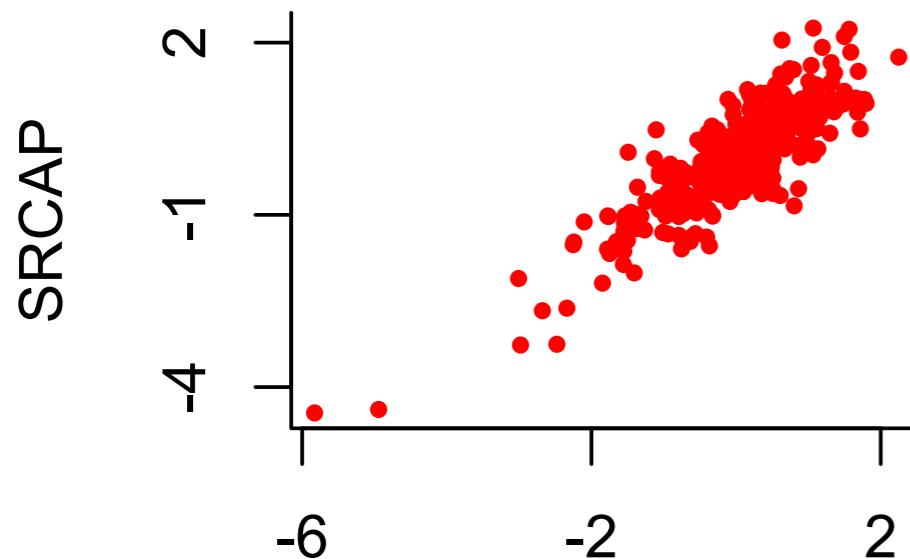


This is driven by the “epigenetic” protein domain
(see paper)

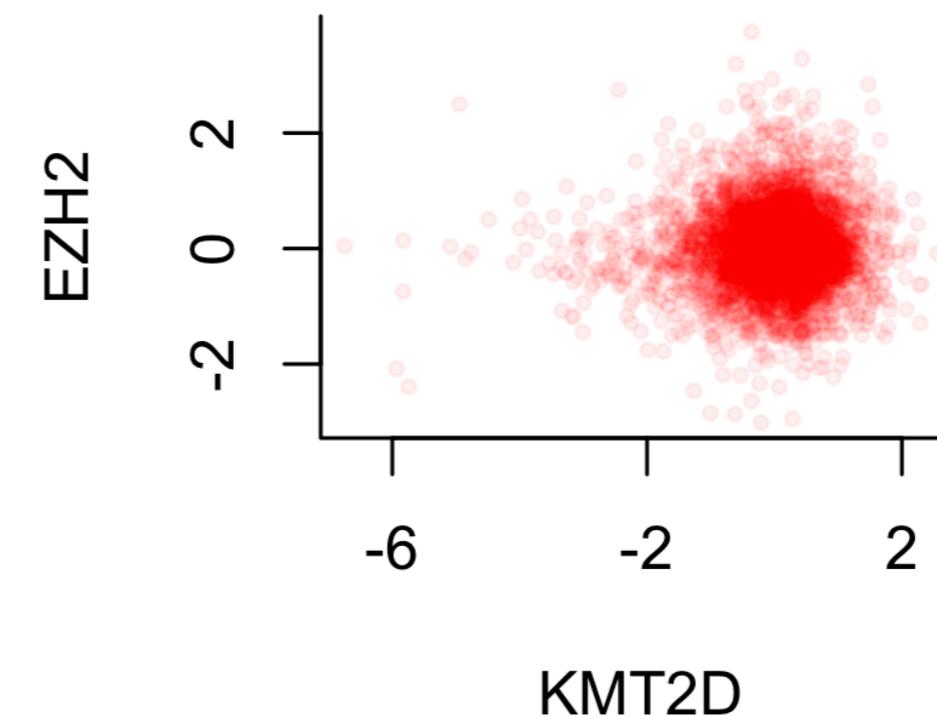
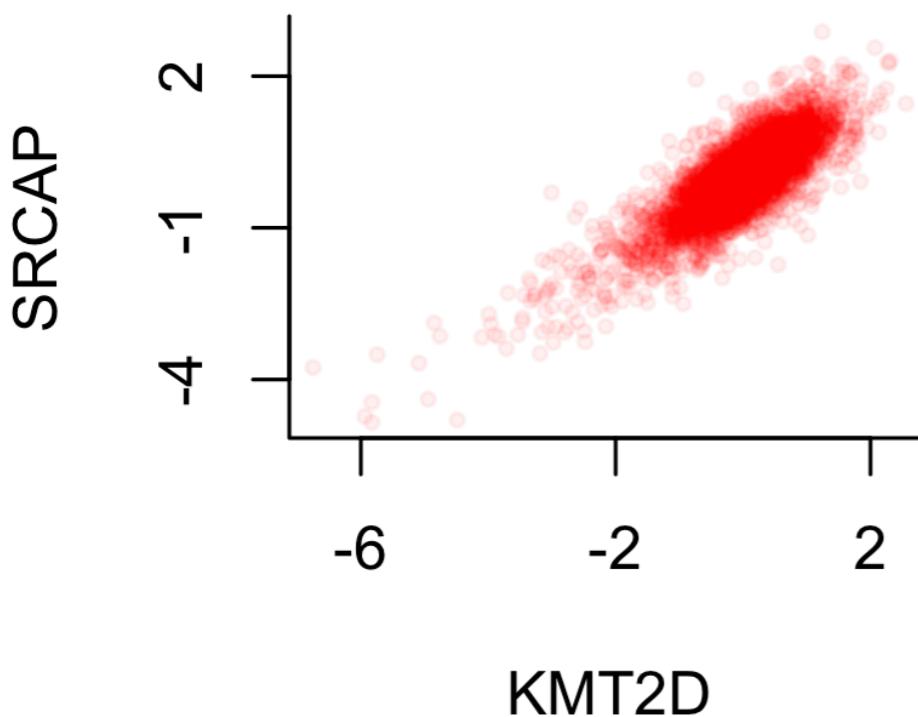
Expression of EM genes

Motivation for co-expression

1 tissue in GTEx



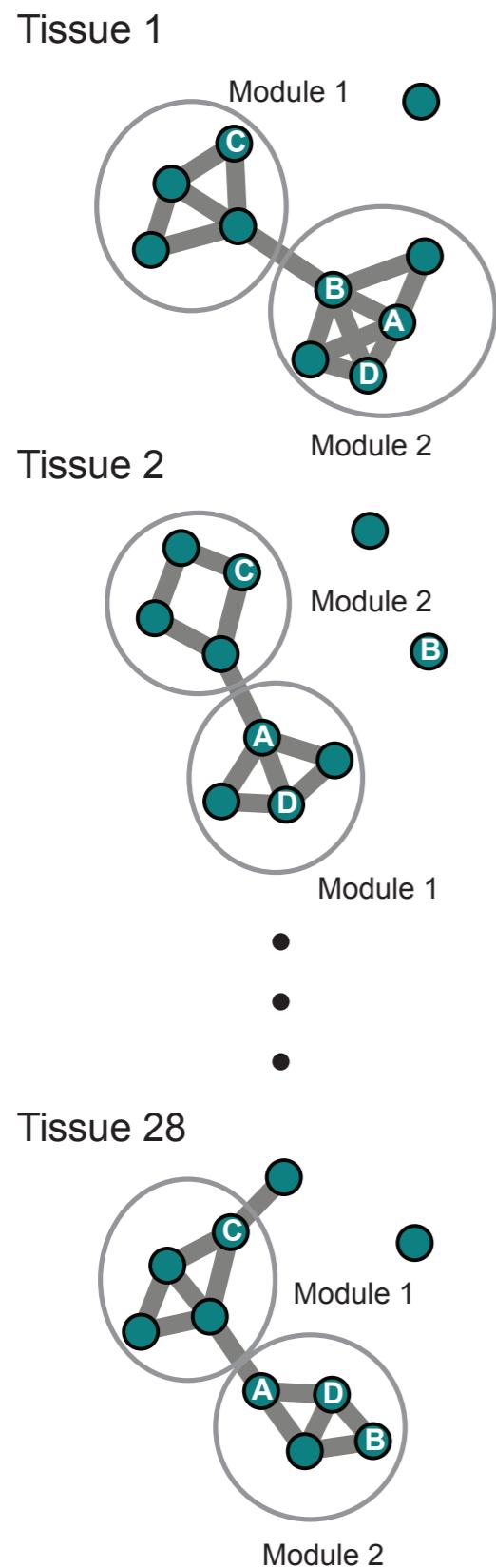
All of GTEx



KMT2D

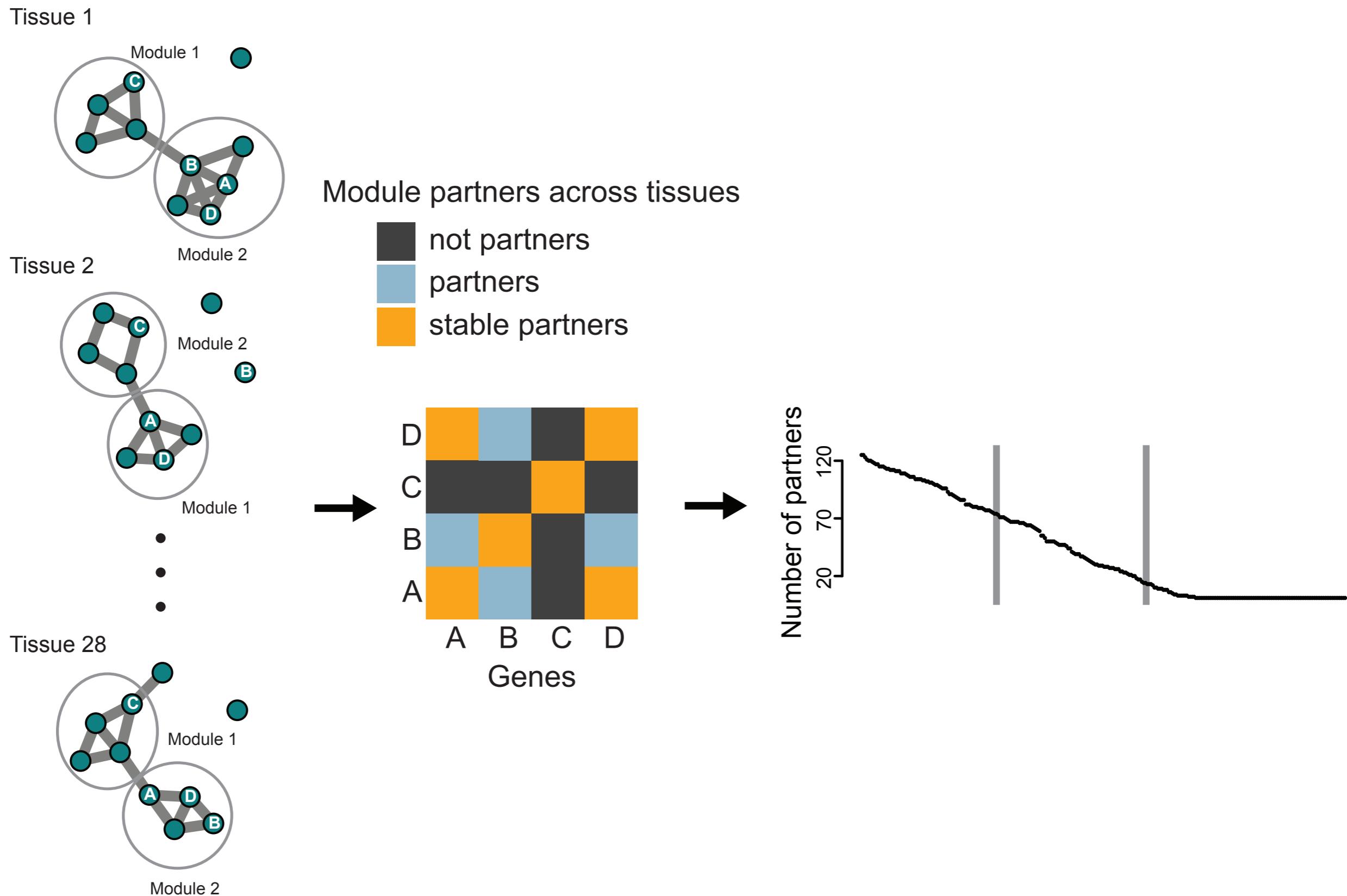
KMT2D

Co-expression; tissue-specific networks and modules

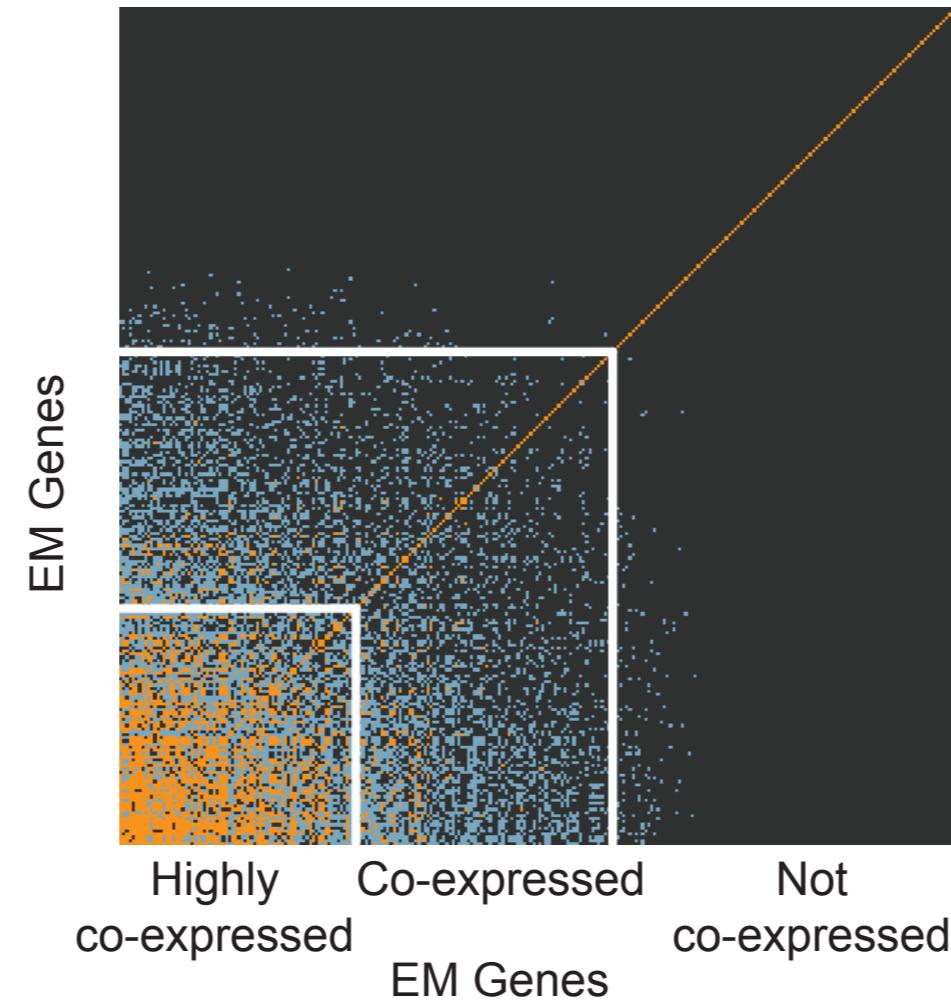


WGCNA

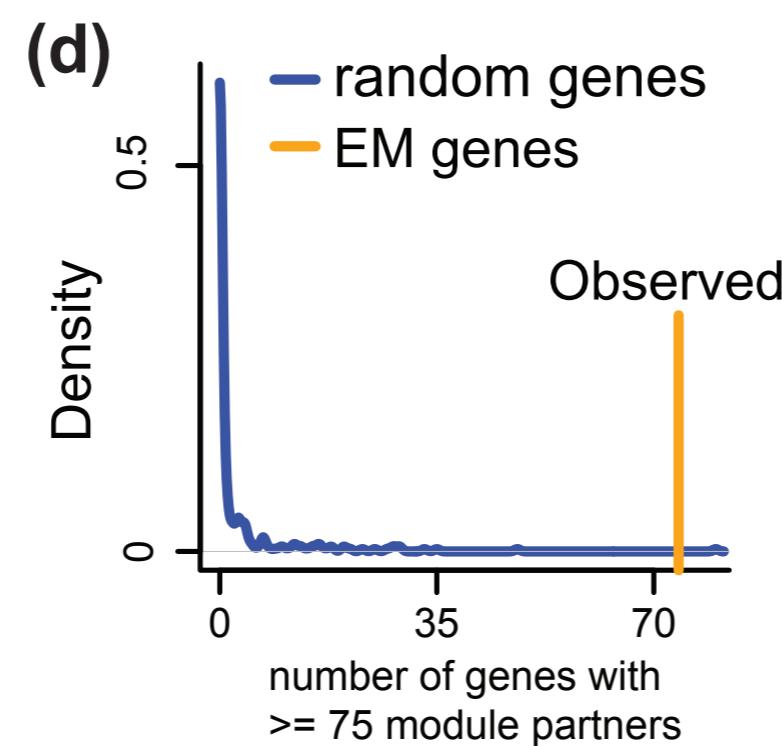
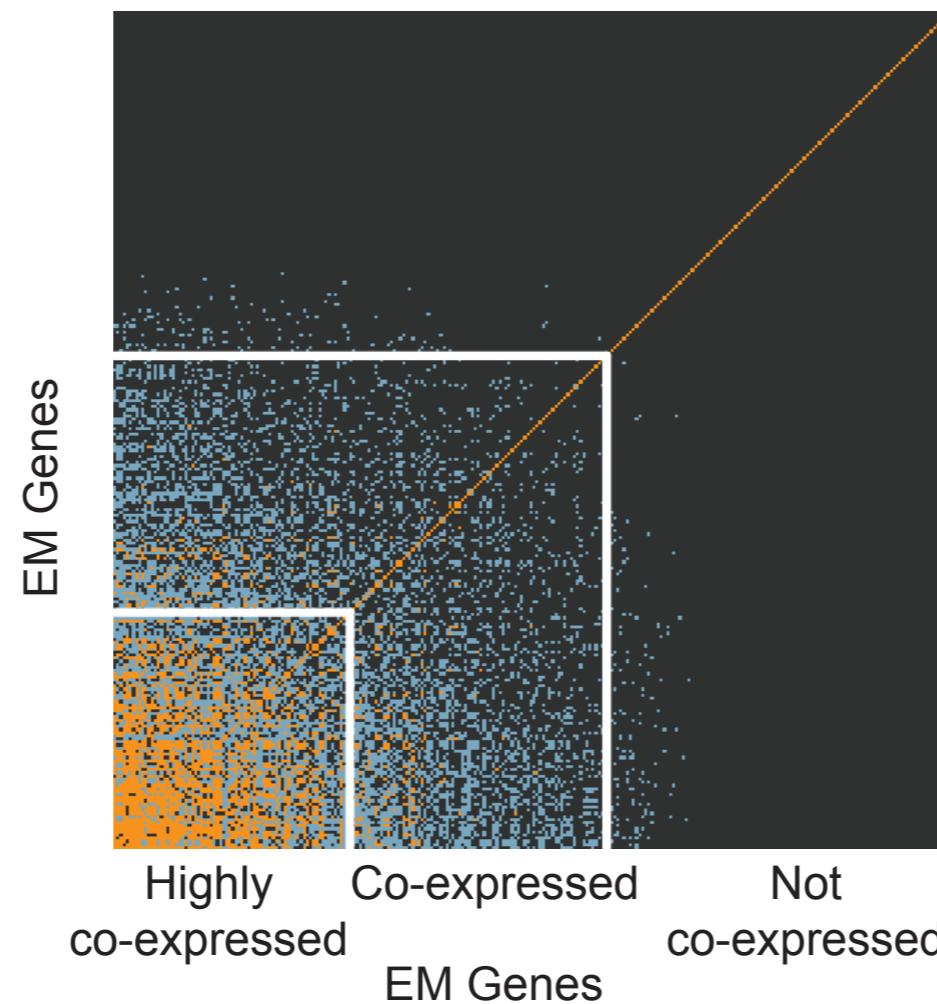
Co-expression; tissue-specific networks and modules



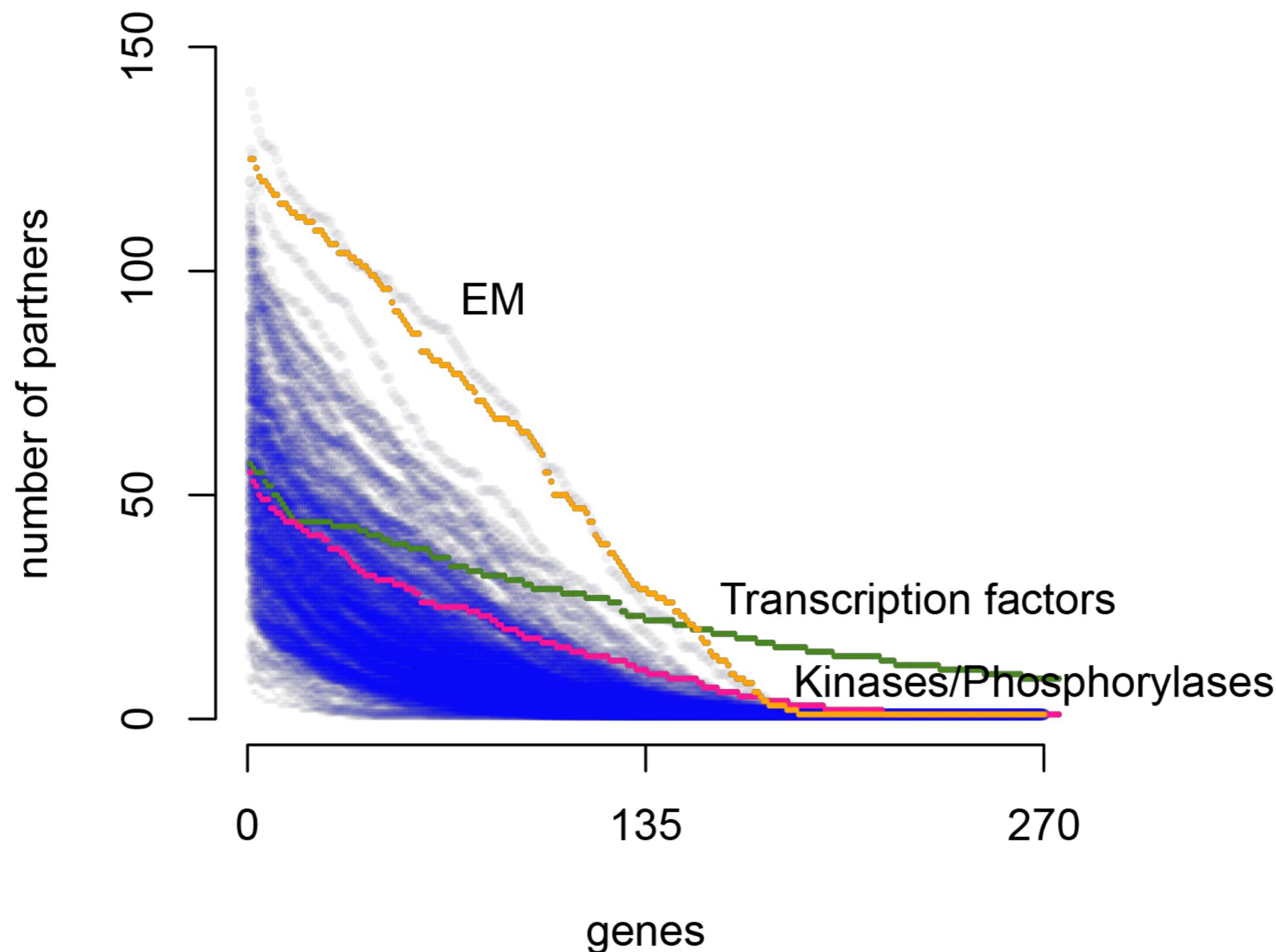
Co-expression is associated with LOF intolerance



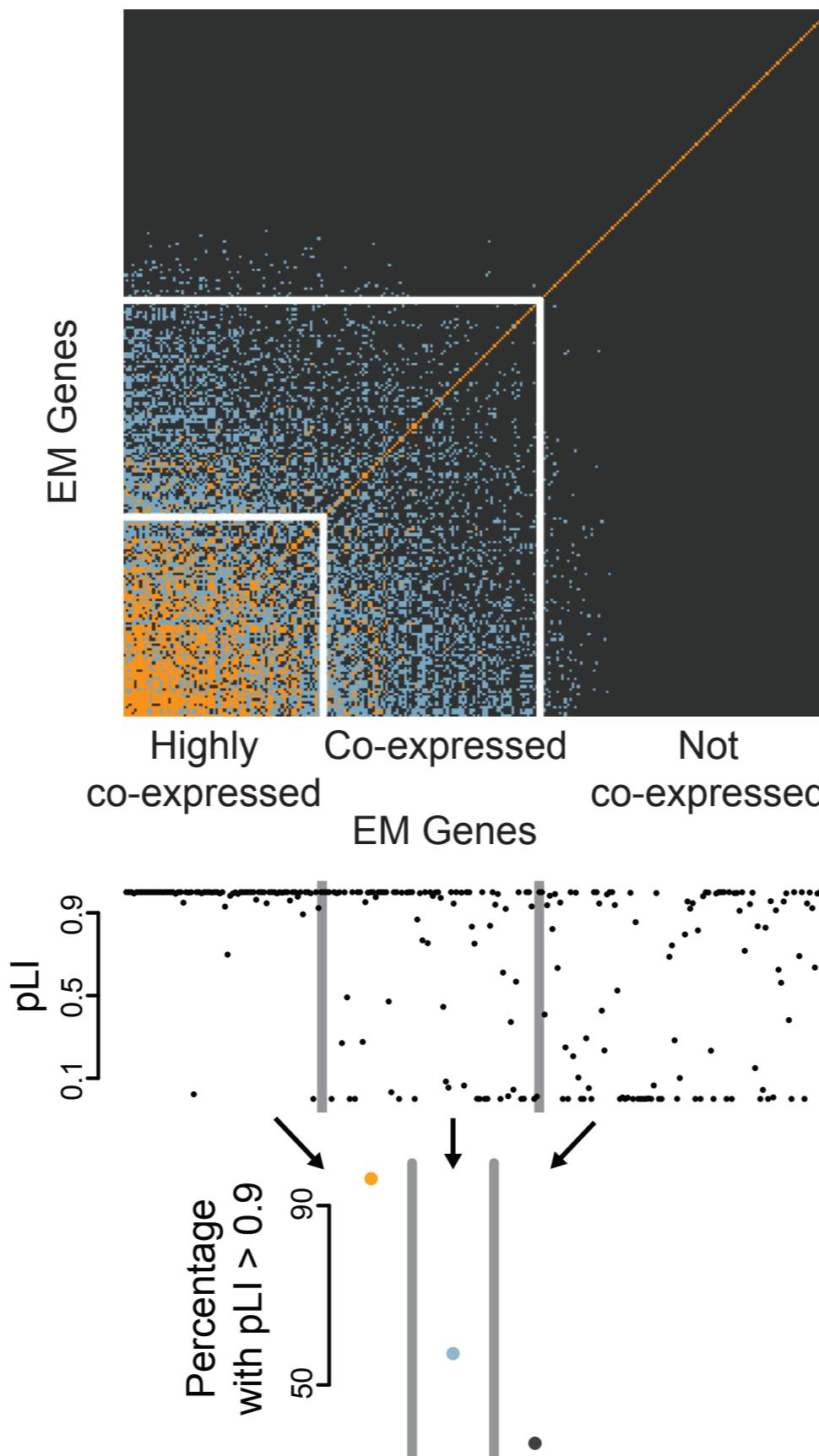
Co-expression is associated with LOF intolerance



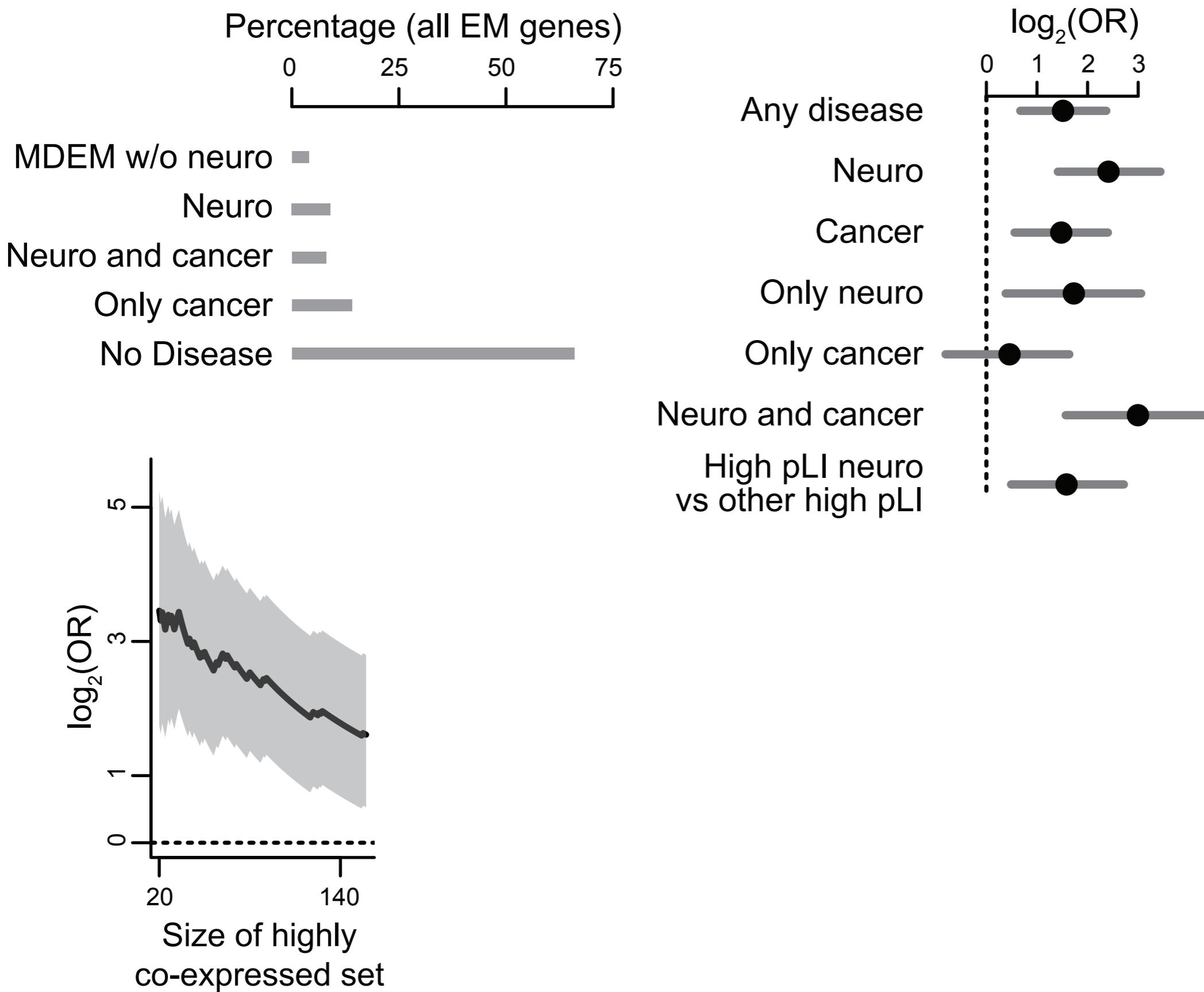
Permutations



Co-expression is associated with LOF intolerance

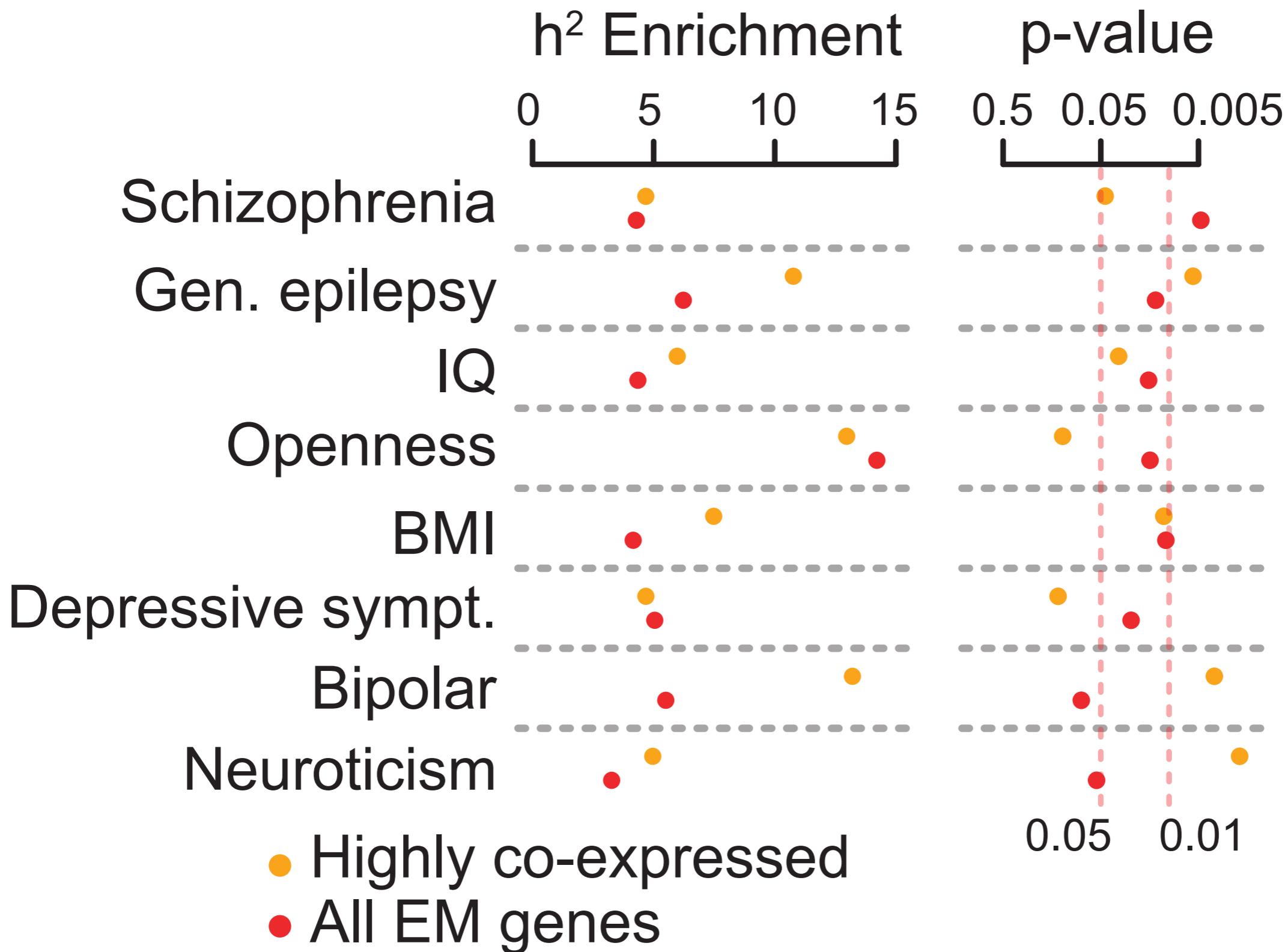


Co-expression is associated with neurological dysfunction



Common genetic variation

Using SLDSC on brain-specific enhancers within 1MB of EM genes



Acknowledgements



Leandros Boukas



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Peter Hickey

Co-expression patterns define epigenetic regulators associated with neurological dysfunction

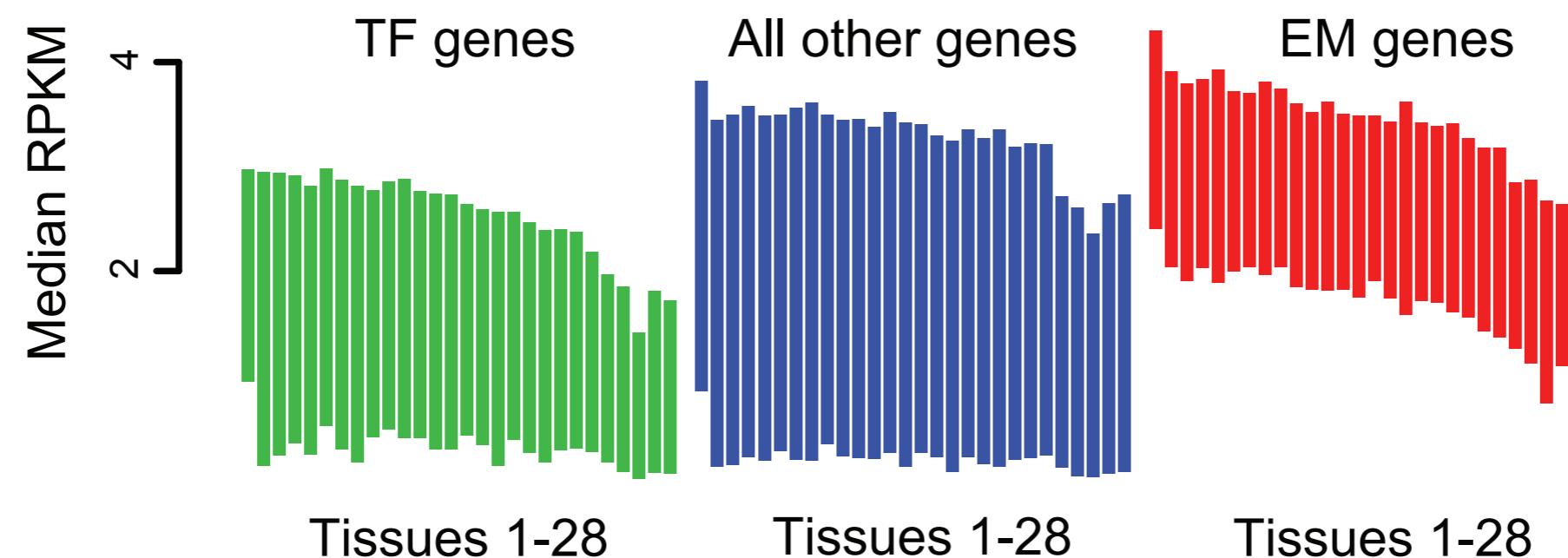
Leandros Boukas, James M Havrilla, Aaron R Quinlan, Hans T Bjornsson, Kasper D Hansen
doi: <https://doi.org/10.1101/219097>

The epigenetic machinery and tissue expression

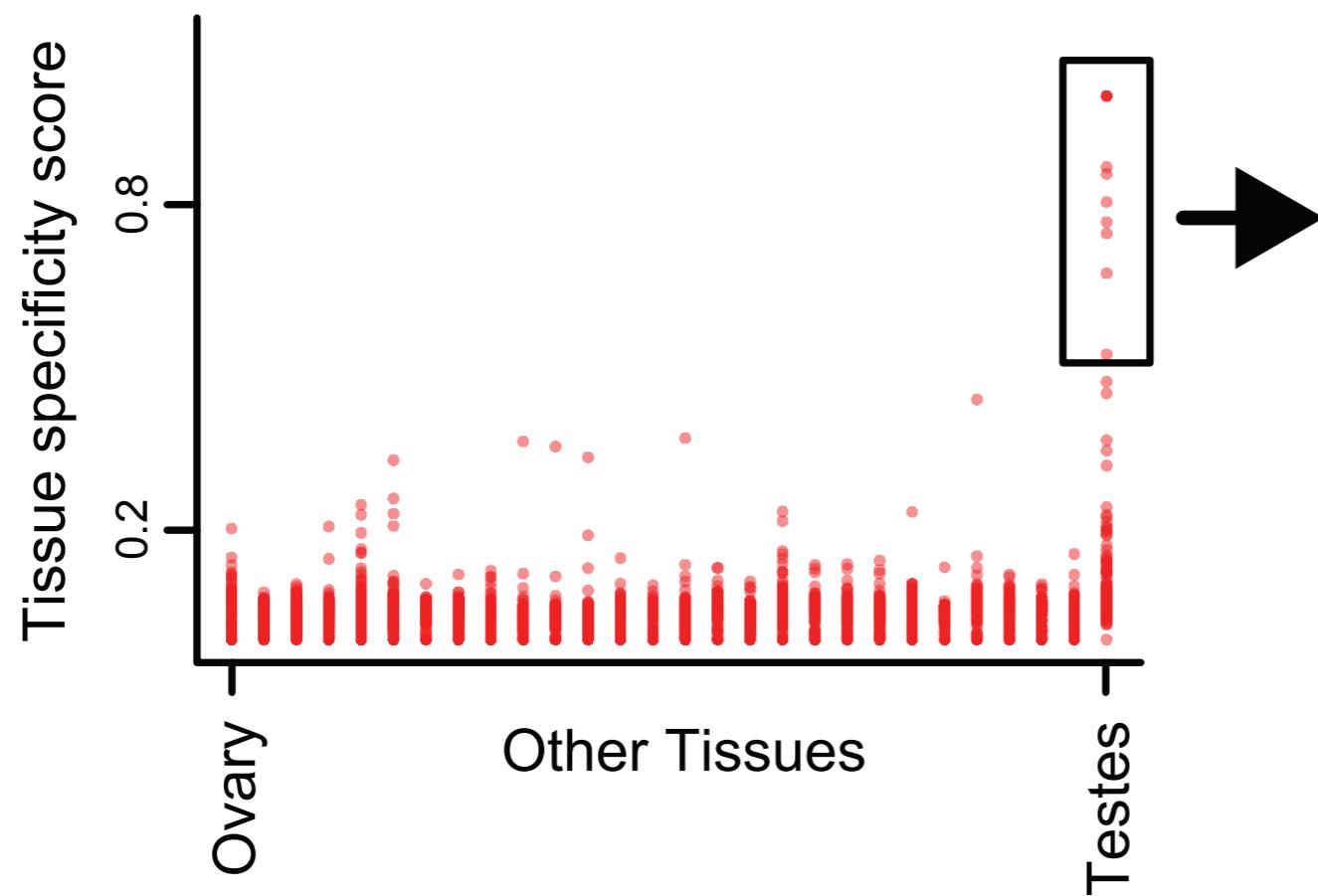
These epigenetic marks are present in every cell type and at every time point.

Genetic defects act in every cell where the gene is expressed.

The GTEx (genotype-tissue expression) project is profiling ~30 tissues in ~1000 people.



Testis is an outlier tissue



Gene name	Testis specificity score
<i>PRDM9</i>	1
<i>PRDM13</i>	1
<i>PRDM14</i>	1
<i>CDY2A</i>	1
<i>BRDT</i>	0.87
<i>RNF17</i>	0.86
<i>HDGFL1</i>	0.81
<i>PRDM7</i>	0.77
<i>MORC1</i>	0.75
<i>TDRD15</i>	0.67
<i>TDRD1</i>	0.52

Removing unwanted variation in co-expression networks

Addressing confounding artifacts in reconstruction of gene co-expression networks

 Princy Parsana, Claire Ruberman, Andrew E. Jaffe, Michael C. Schatz, Alexis Battle, Jeffery T. Leek

doi: <https://doi.org/10.1101/202903>

Simple solution: remove the top singular values; they will represent artifacts

RESEARCH ARTICLE

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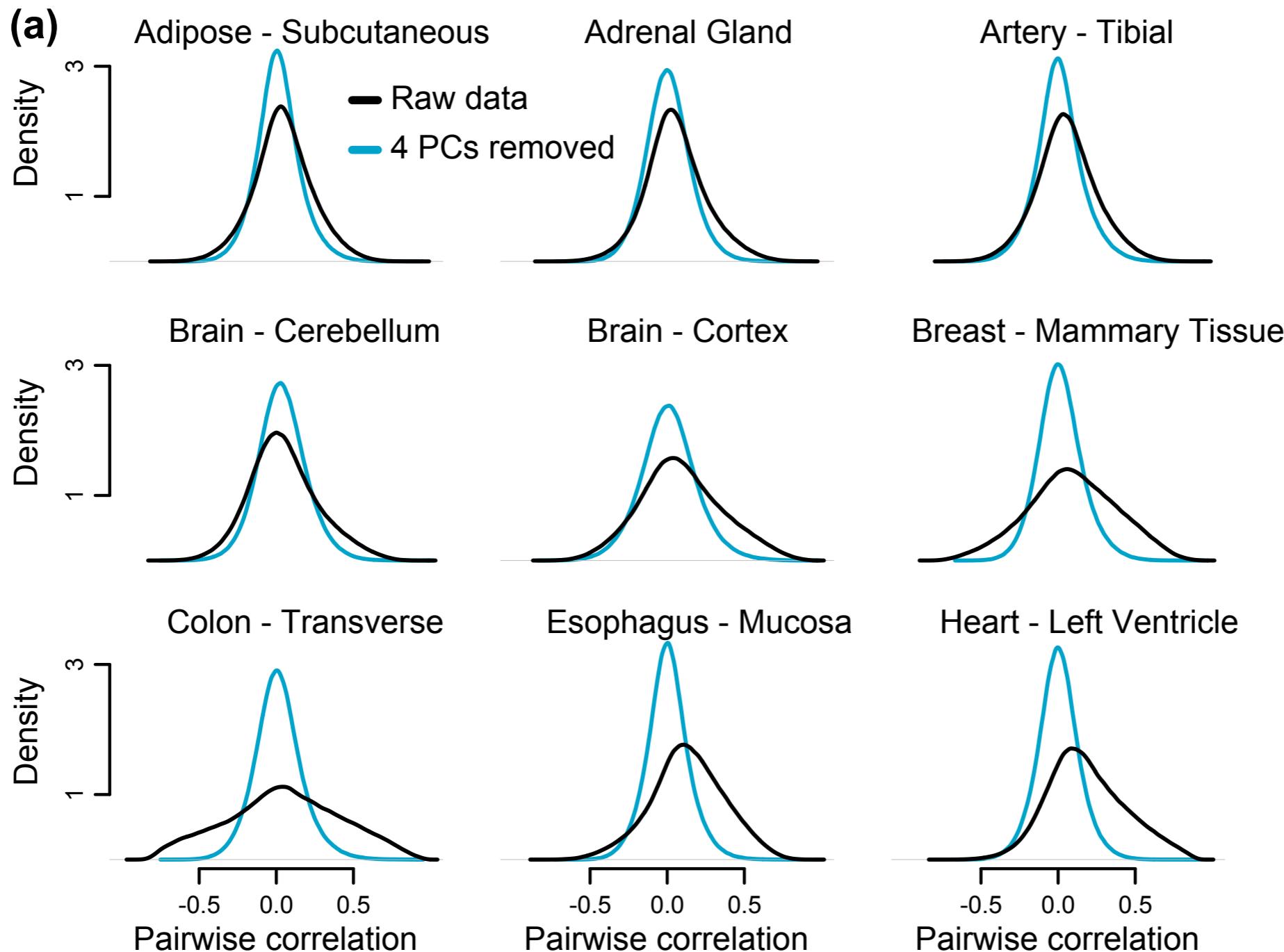


Systematic noise degrades gene co-expression signals but can be corrected

Saskia Freytag^{1,2*}, Johann Gagnon-Bartsch³, Terence P. Speed^{1,2,3} and Melanie Bahlo^{1,2,4}

How do we measure if it works?

Random groups of genes



Positive controls

