Co-expression patterns define epigenetic regulators associated with neurological dysfunction

Kasper Daniel Hansen

< khansen@jhsph.edu | www.hansenlab.org >

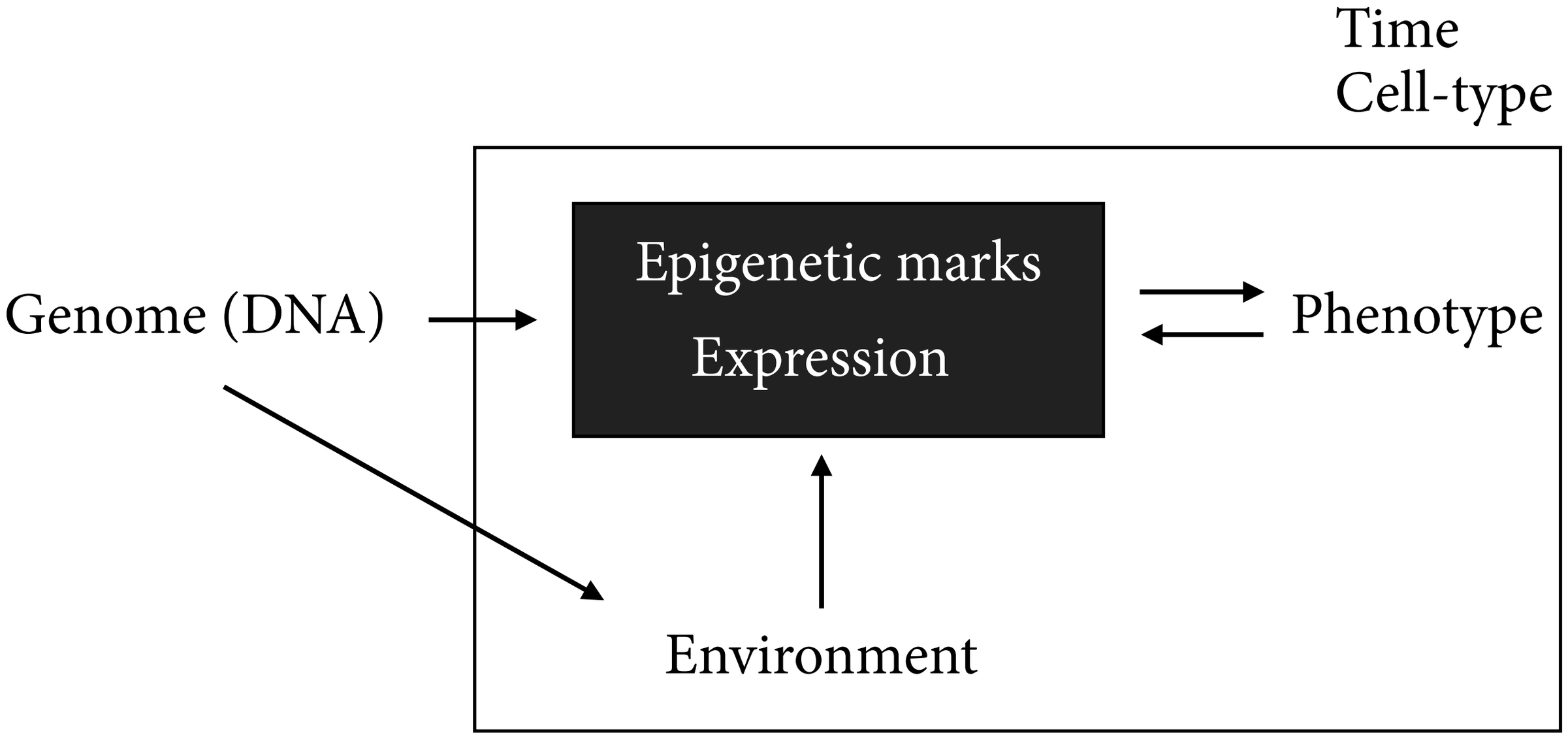
Department of Biostatistics

McKusick-Nathans Institute of Genetic Medicine

Johns Hopkins University

Genetics

Epigenetics (transcriptomics)



Mendelian disorders of the epigenetic machinery

EM: genes involved in DNA methylation or histone modifications

Genetic defect → Epigenetic defect → Phenotype

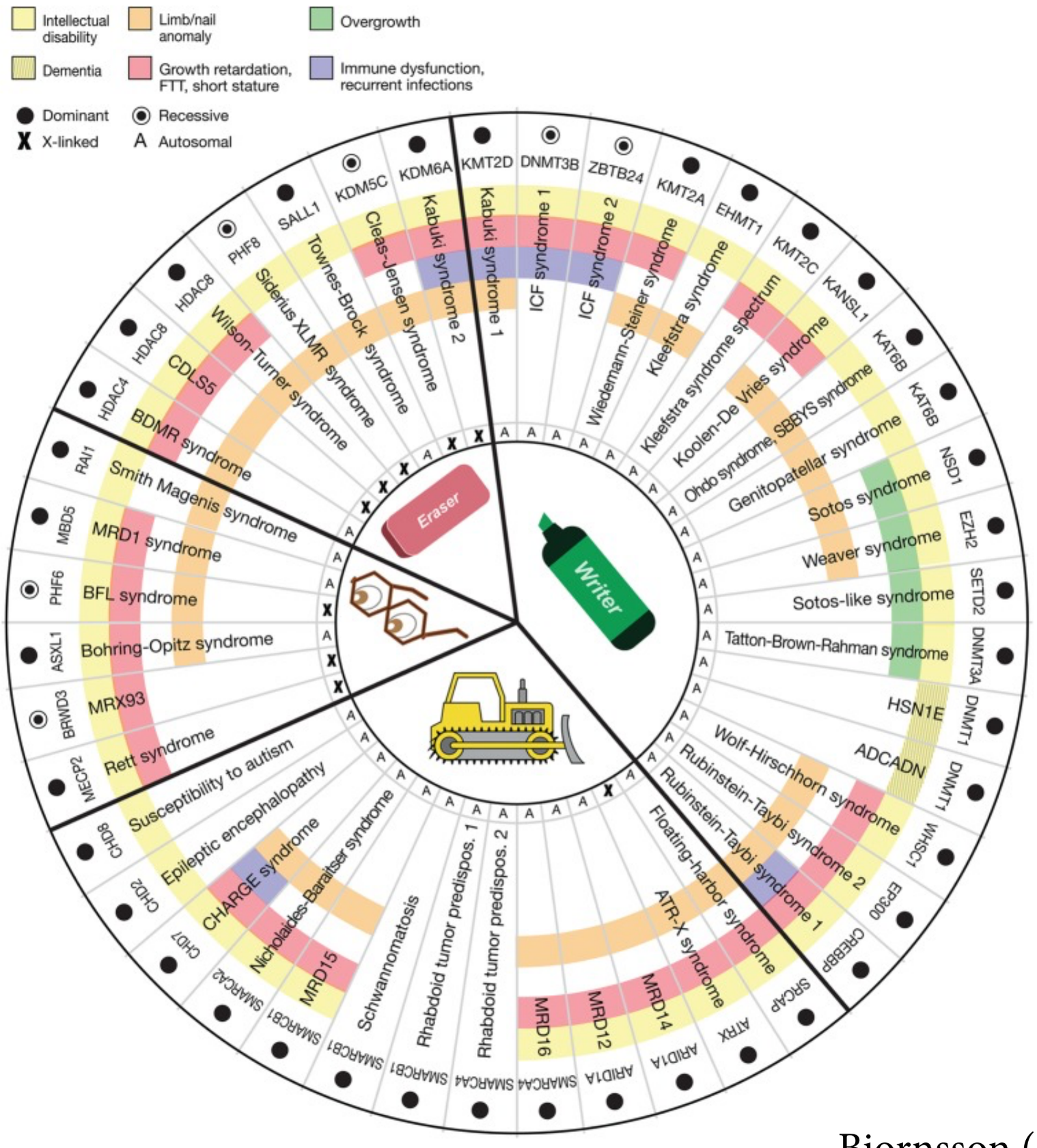
(hypothesis)

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 intellectual disability associated with Kabuki syndrome be reversed by changing the epigenome?

The answer is yes
(caveats: short-term, in mice, Kabuki type I)

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.

Questions

1. Characterize the EM
2. Is the epigenetic function of the EM genes, the most likely cause of disease?
3. Are there expression signatures characteristic of disease candidates?
4. Are there distinct expression signatures between the EM genes involved in neurological dysfunction and cancer?

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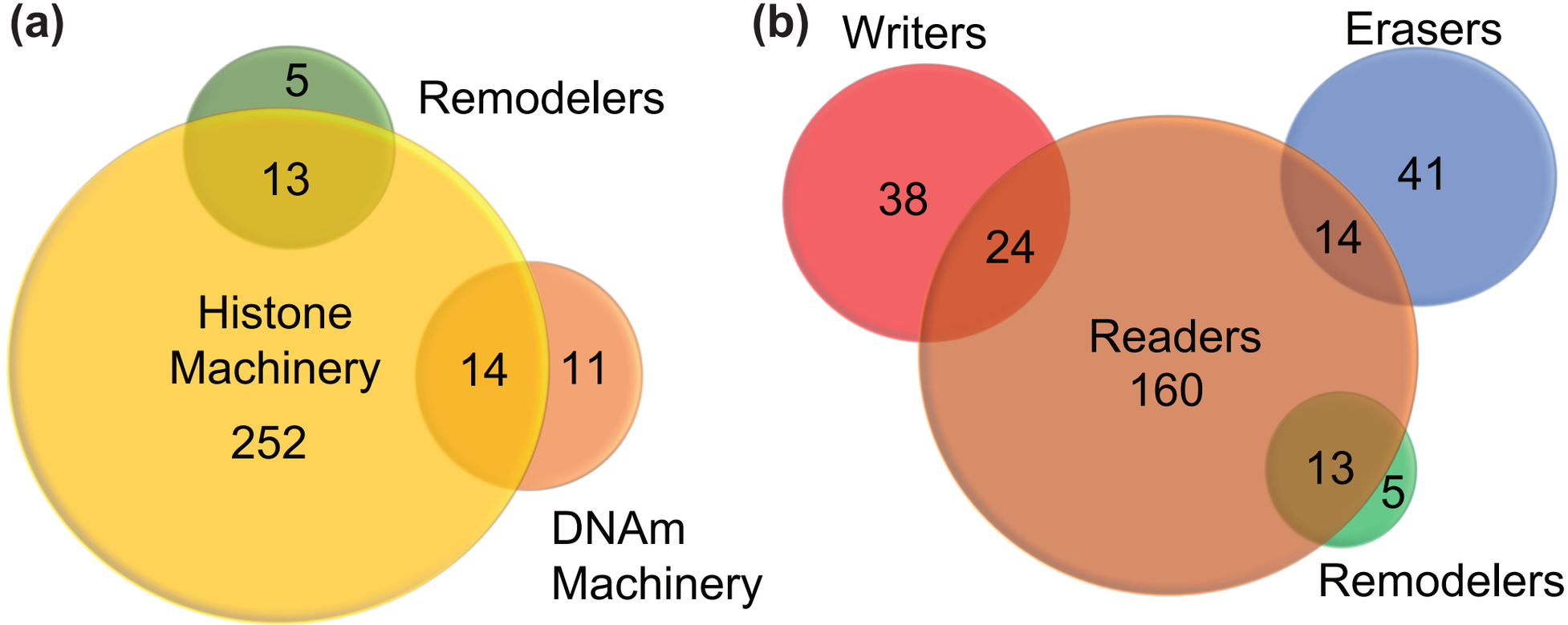
doi: https://doi.org/10.1101/219097

Defining the Epigenetic Machinery using protein domains

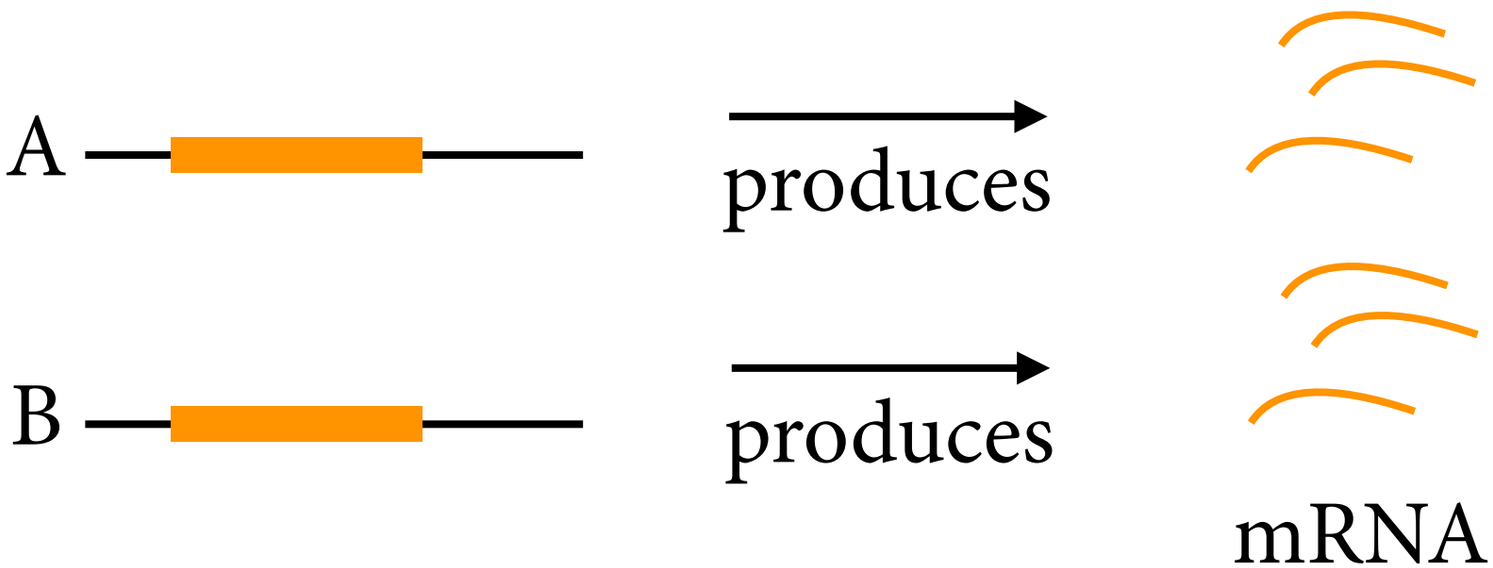
Any gene encoding a protein with a domain which can act as
- Reader / Writer / Eraser of DNA methylation.
- Reader / Writer / Eraser of histone methylation / acetylation.
- Chromatin remodeler

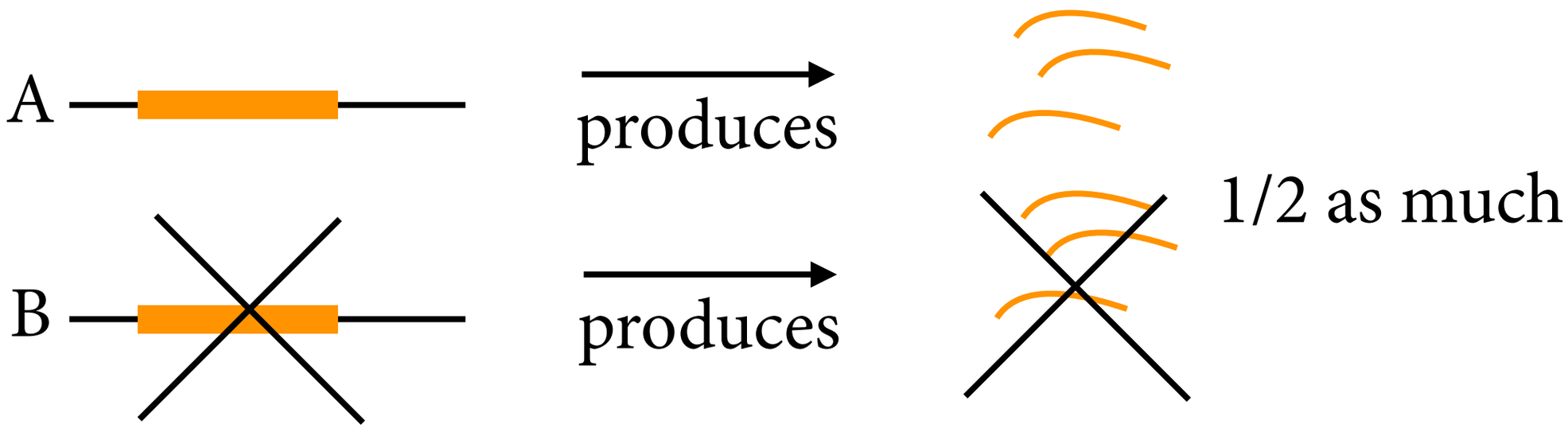
295 EM genes



Loss of function (LOF) mutations

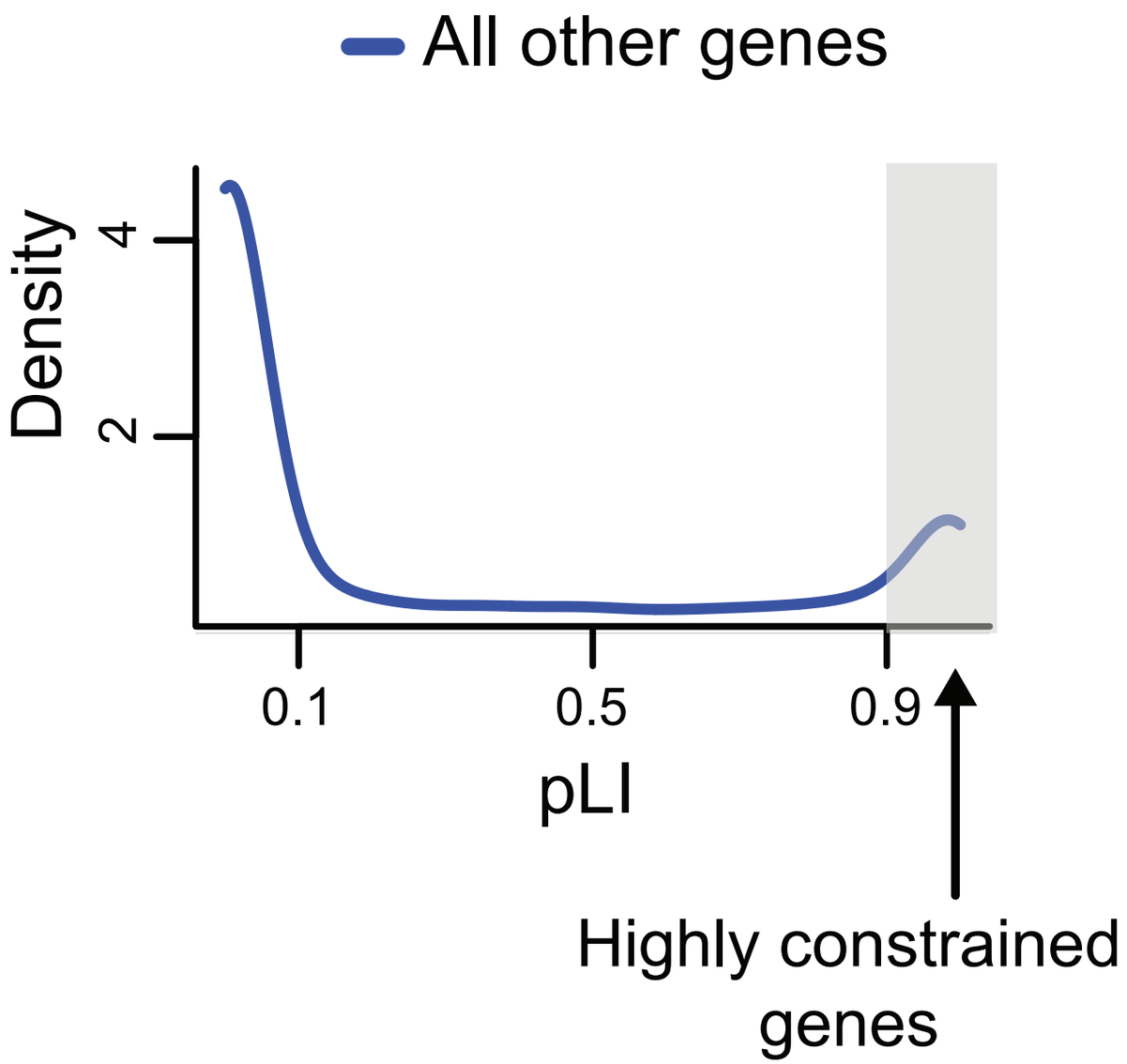
We have two copies of each gene.
Each copy produces mRNA at the same rate





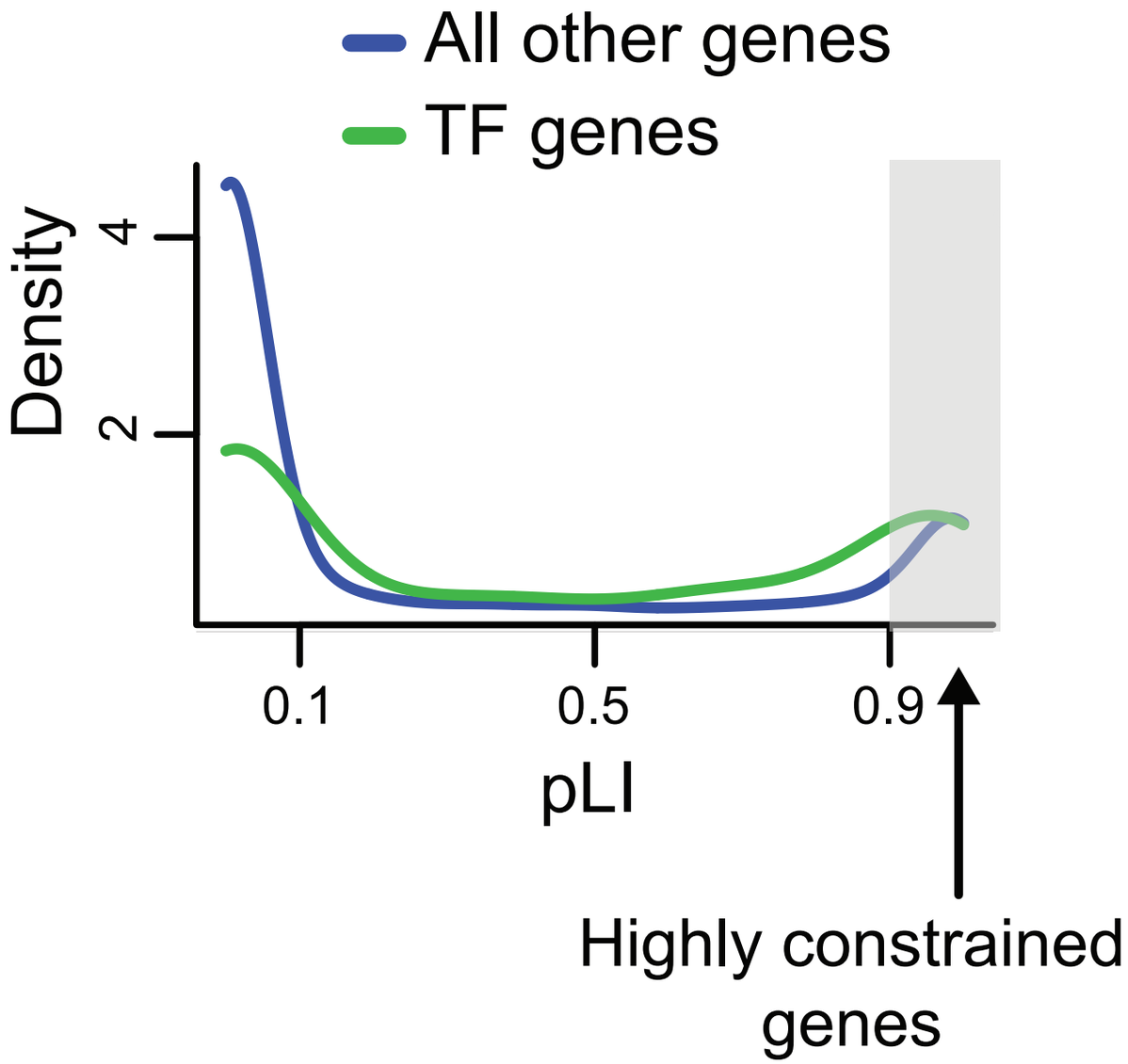
"dosage sensitive" or "haploinsufficient"

EM genes are highly intolerant to LOF mutations

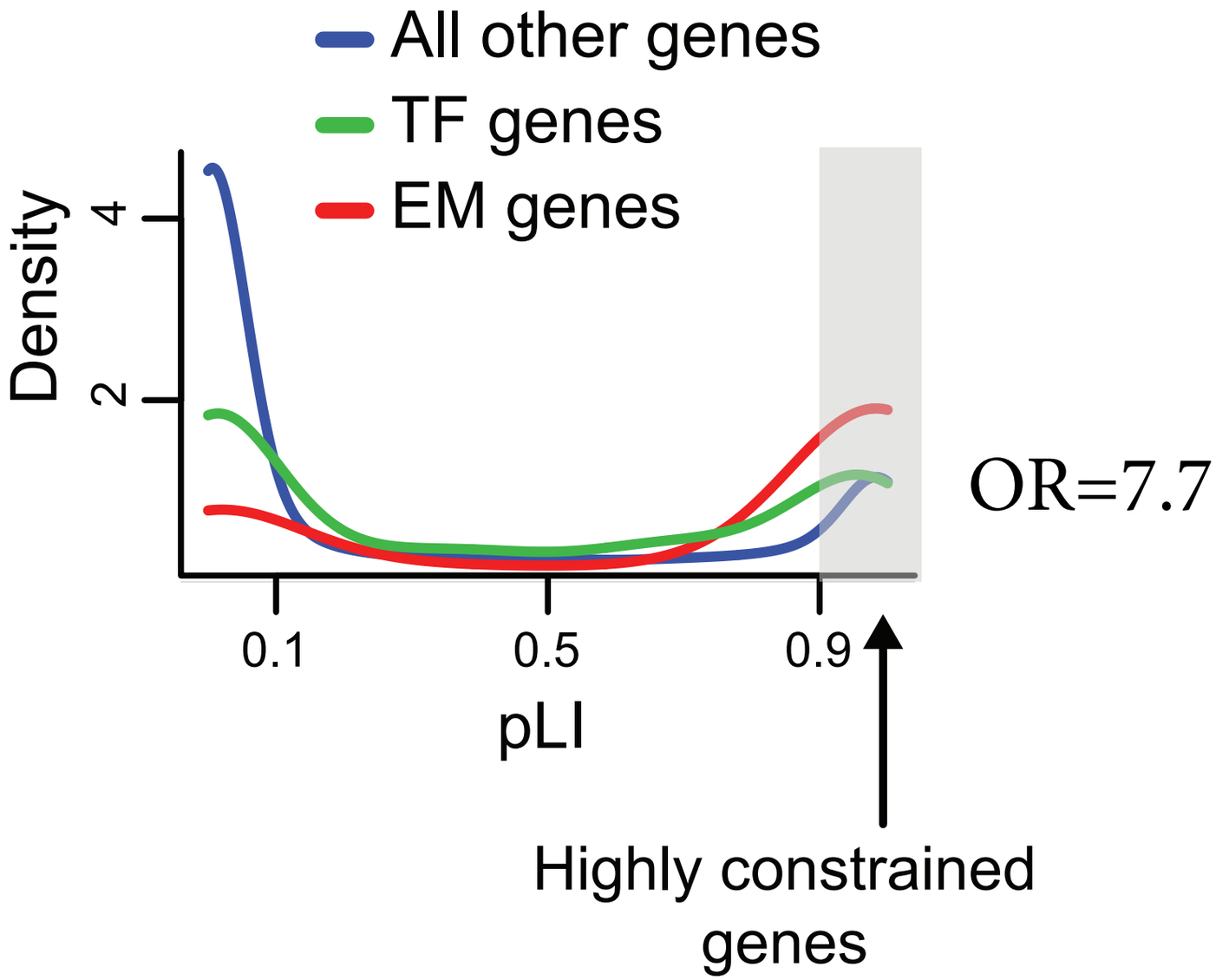


Using ExAC (Lek et al. 2016)

EM genes are very intolerant to LOF mutations



EM genes are very intolerant to LOF mutations



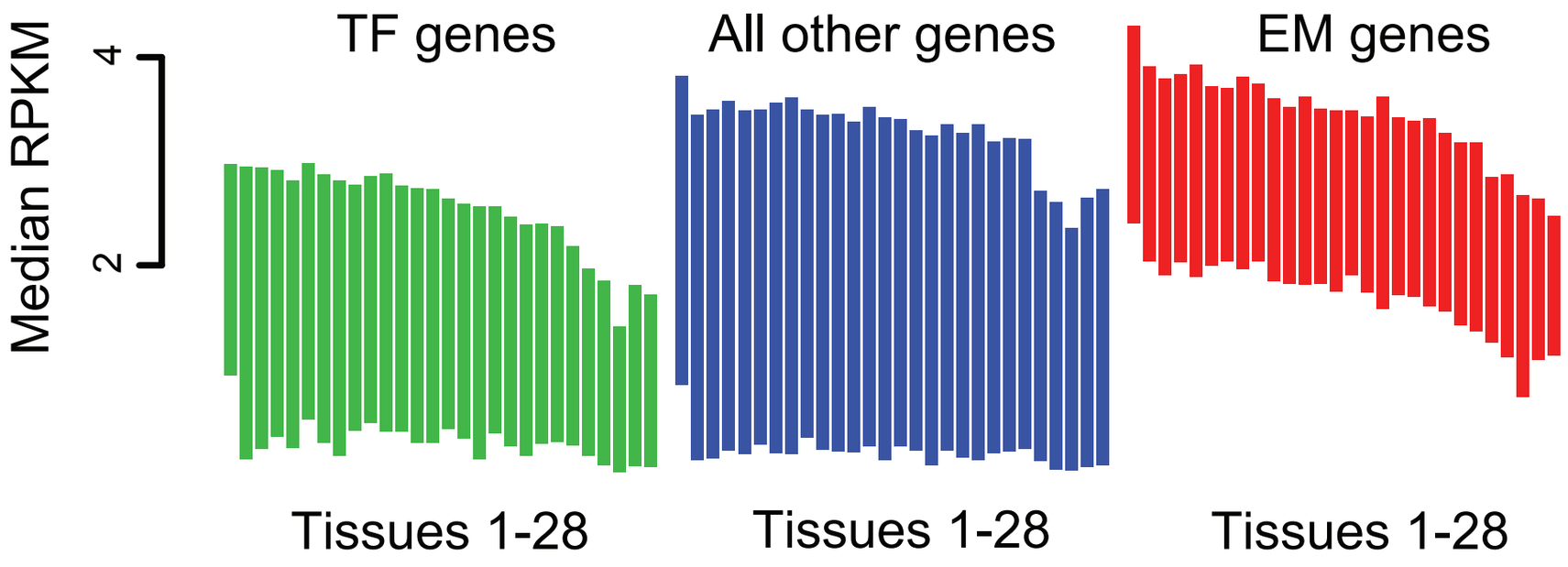
OR=7.7

The epigenetic machinery and tissue expression

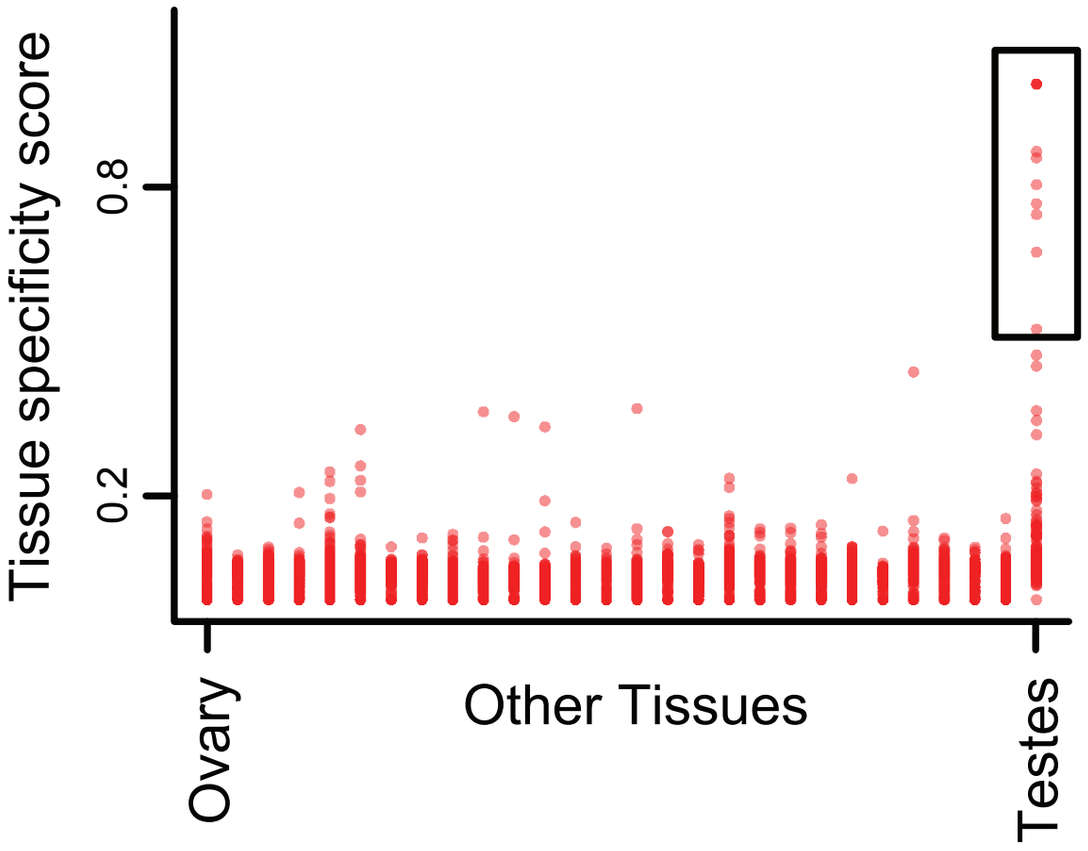
These epigenetic marks are present in every cell type and at every time point.

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

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



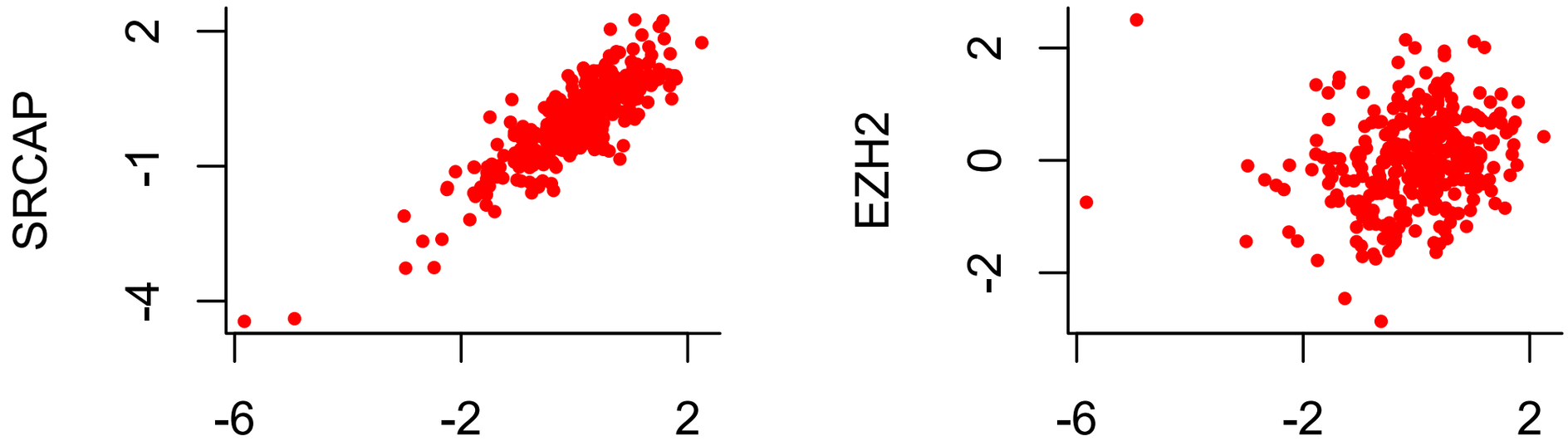
Testis is an outlier tissue



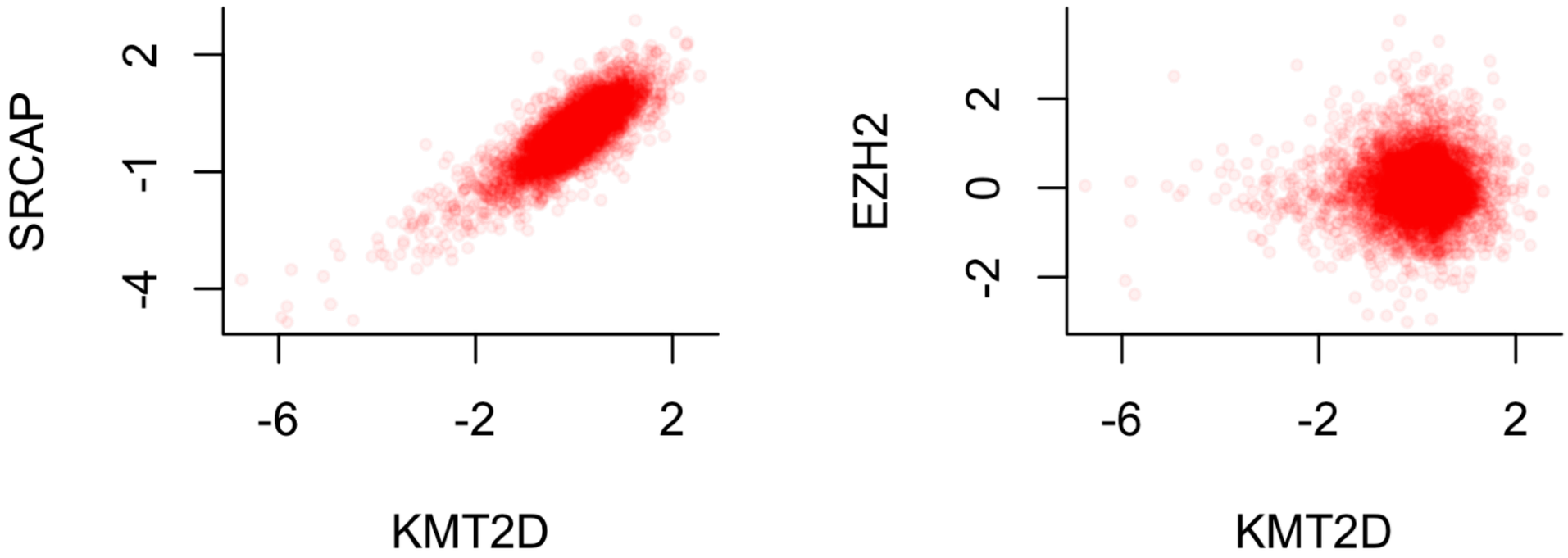
Gene name	Testis specificity score
PRDM9	1
PRDM13	1
PRDM14	1
CDY2A	1
BRDT	0.87
RNF17	0.86
HDGFL1	0.81
PRDM7	0.77
MORC1	0.75
TDRD15	0.67
TDRD1	0.52

Motivation for co-expression

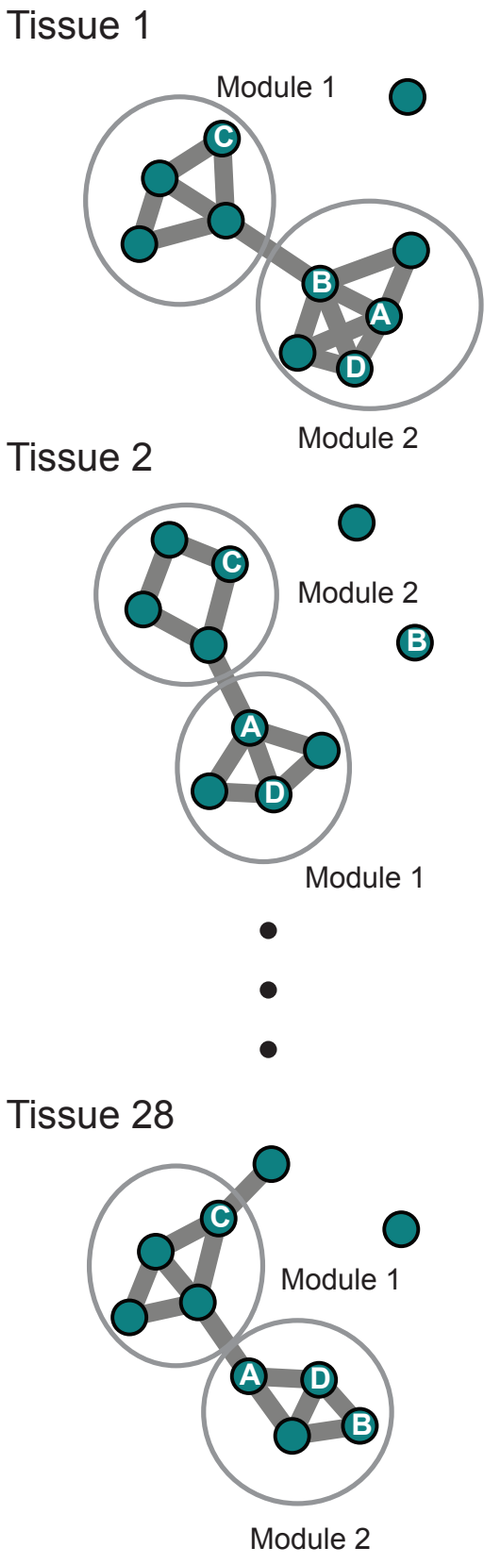
1 tissue in GTEx



All of GTEx



Co-expression; tissue-specific networks and modules



WGCNA

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

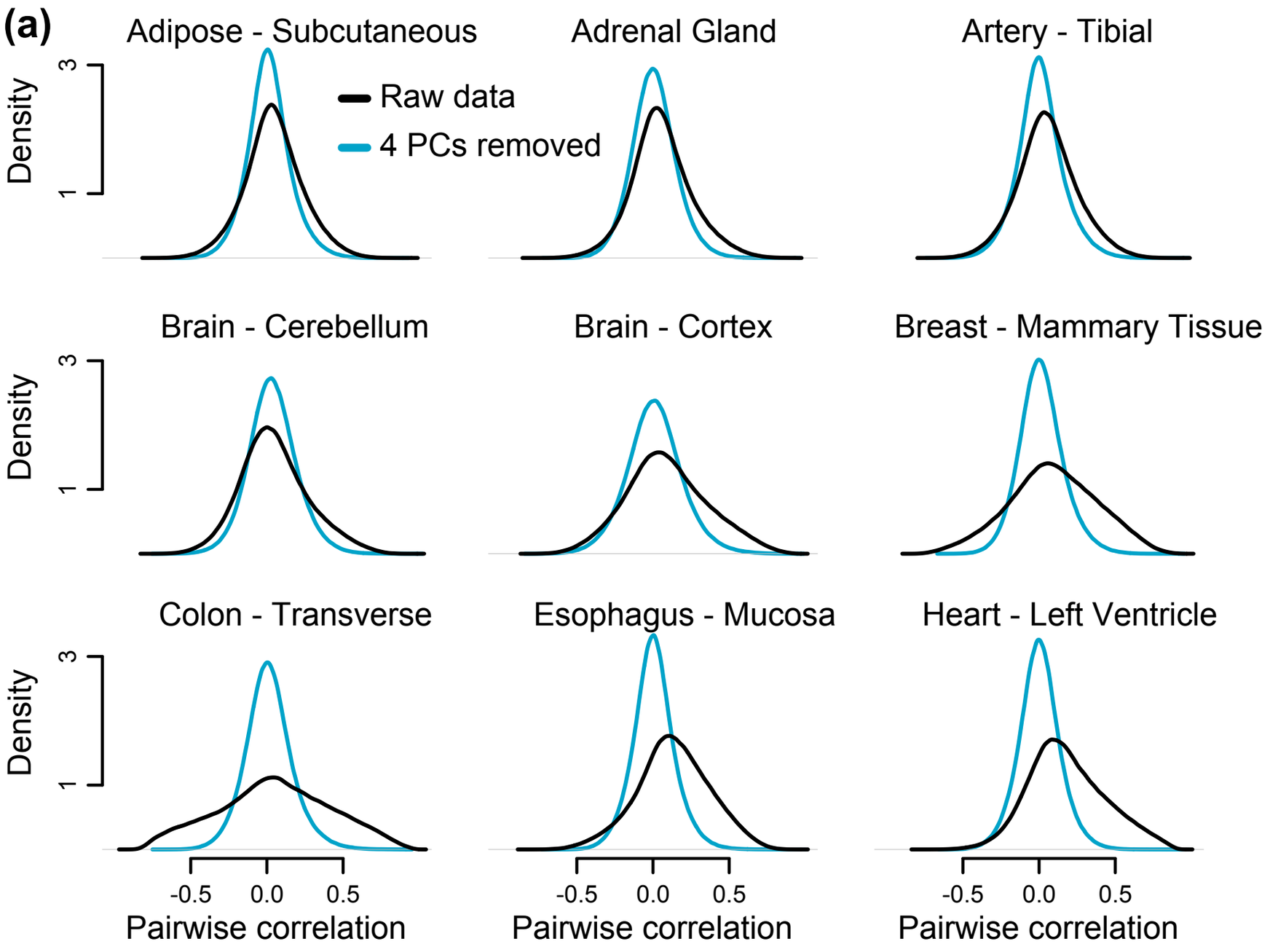
RESEARCH ARTICLE Open Access

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

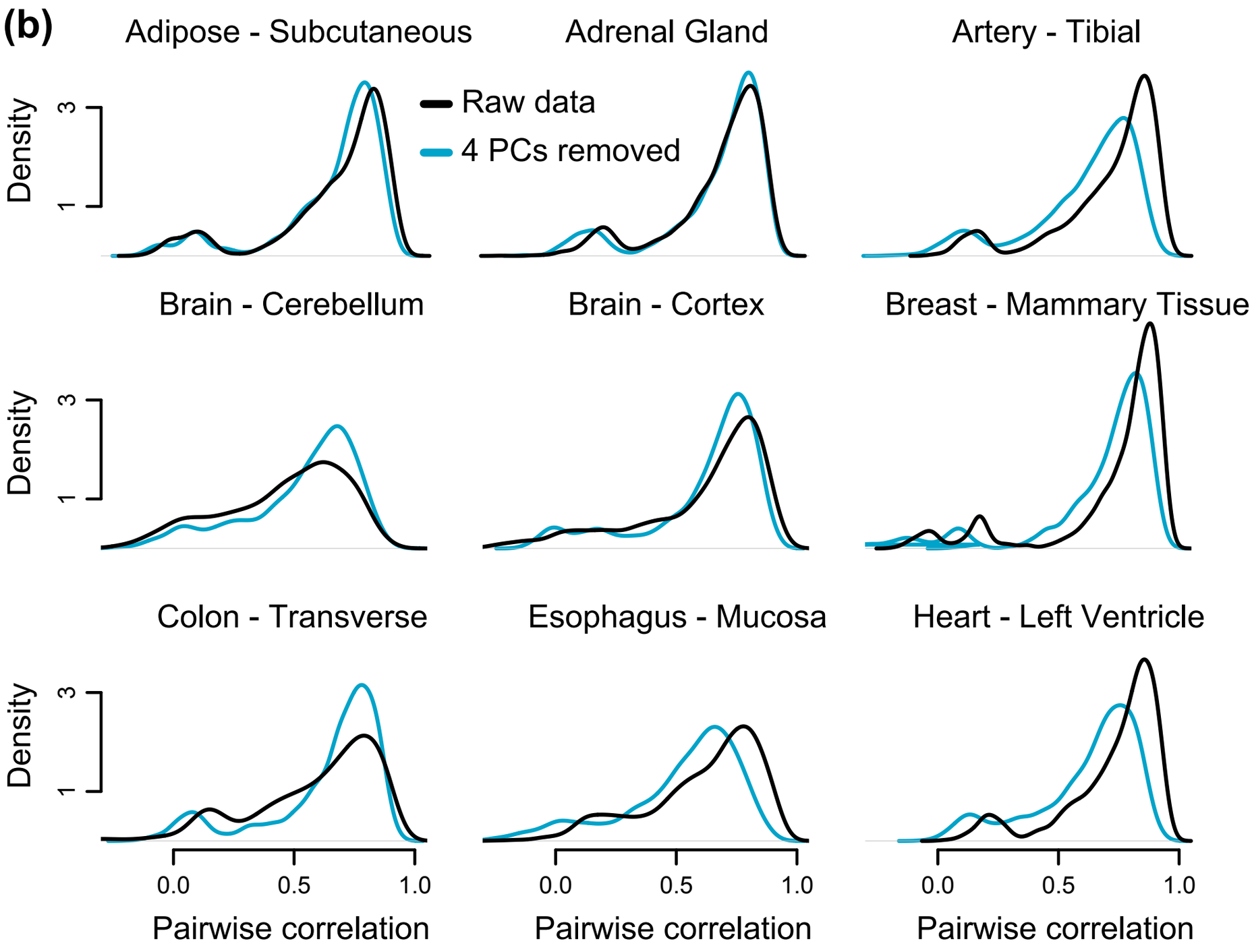
Saskia Freytag[1,2*], Johann Gagnon-Bartsch[3], Terence P. Speed[1,2,3] and Melanie Bahlo[1,2,4]

How do we measure if it works?

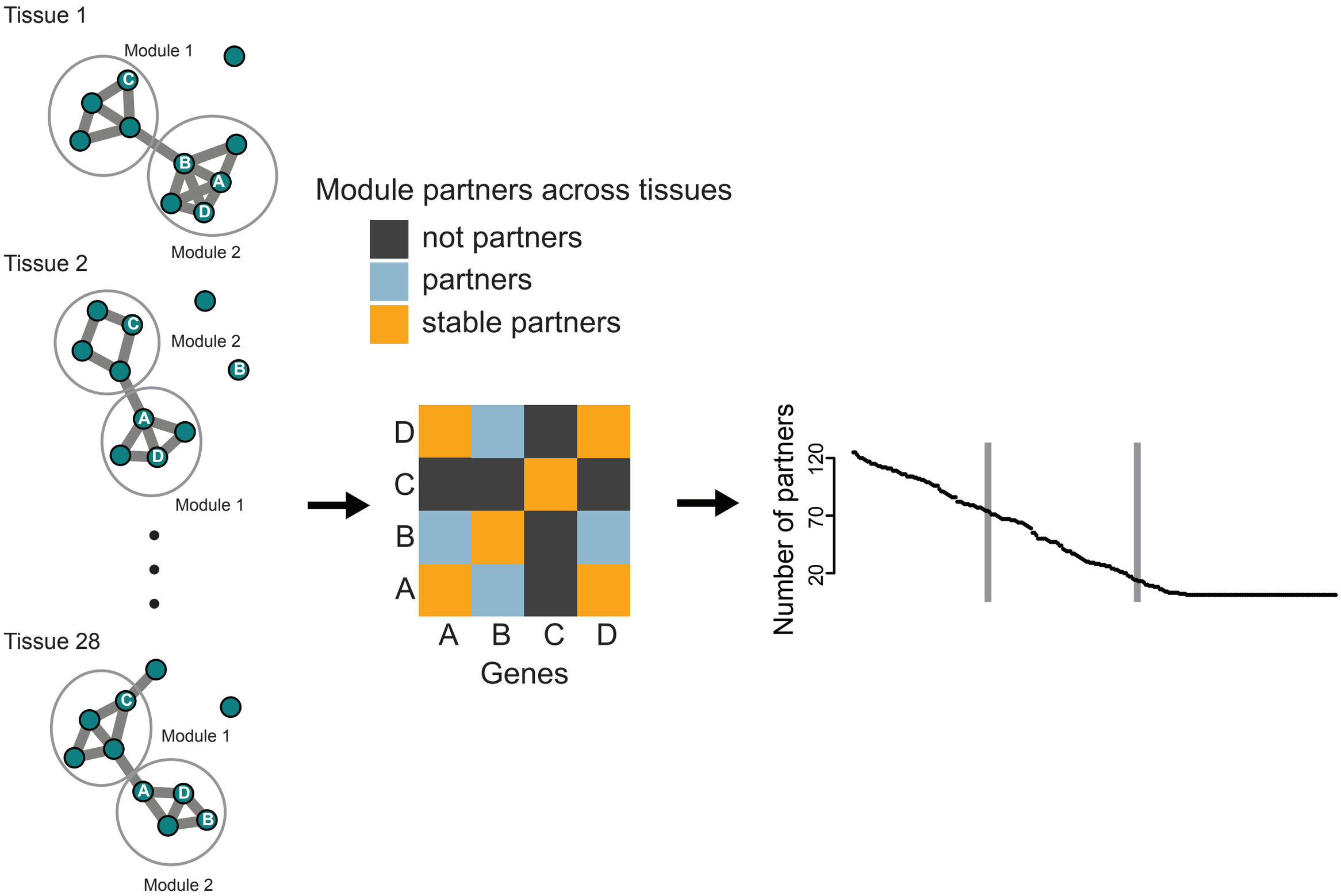
Random groups of genes



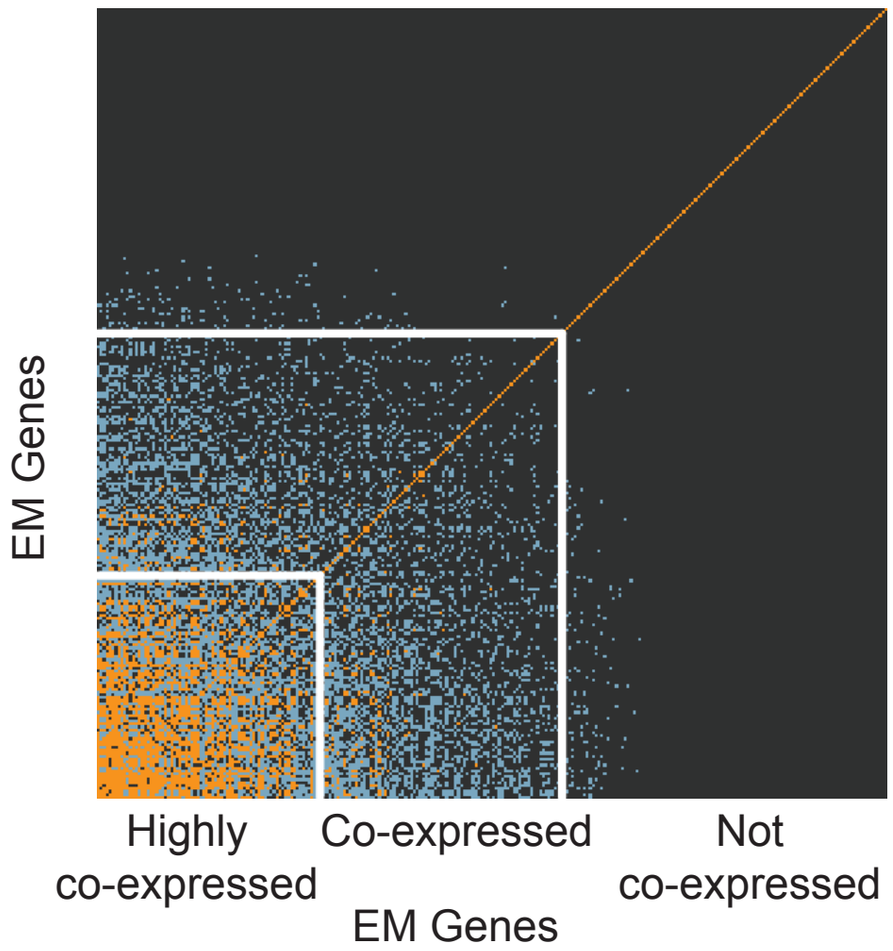
Positive controls



Co-expression; tissue-specific networks and modules



Co-expression is associated with LOF intolerance



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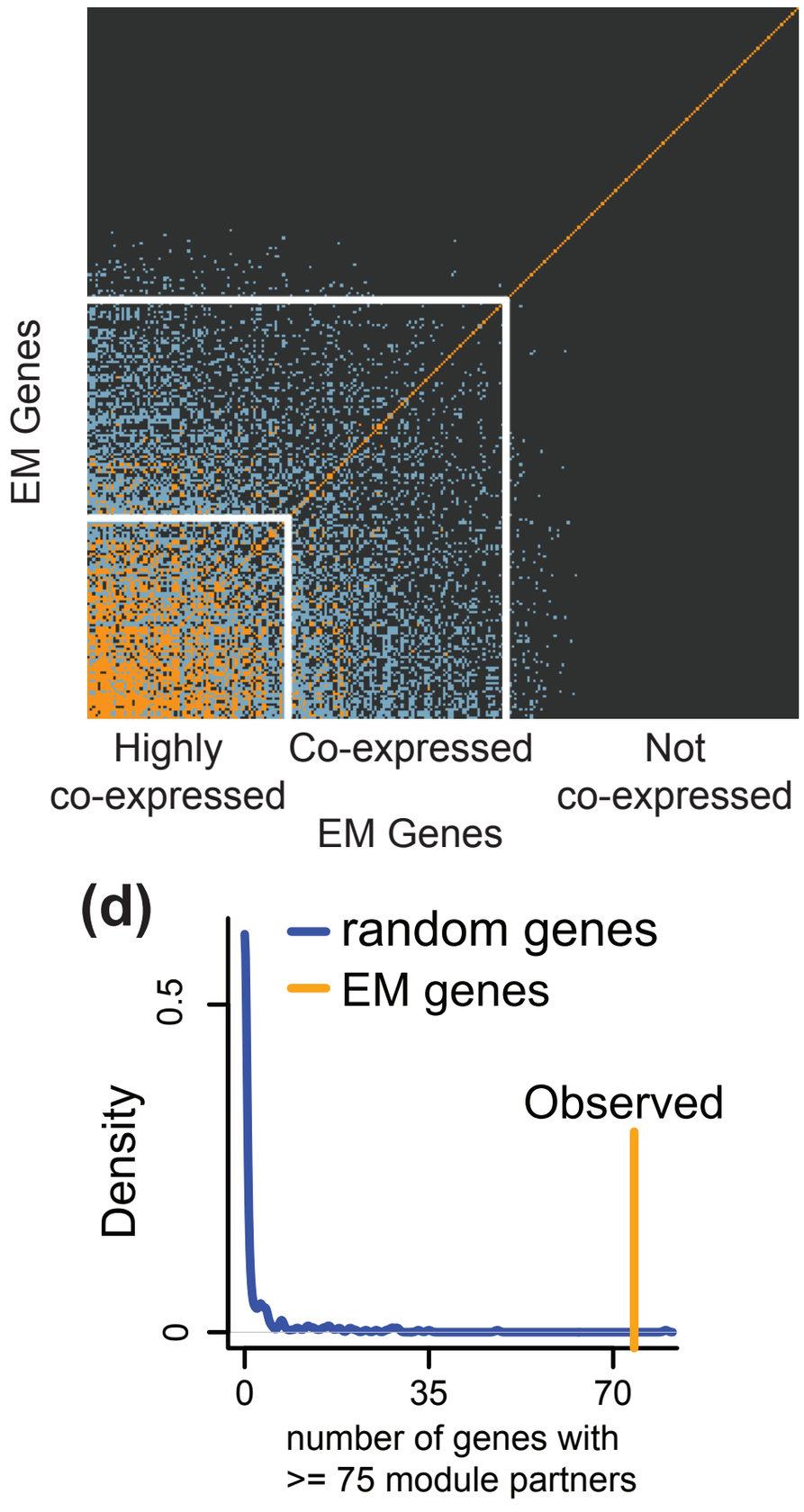
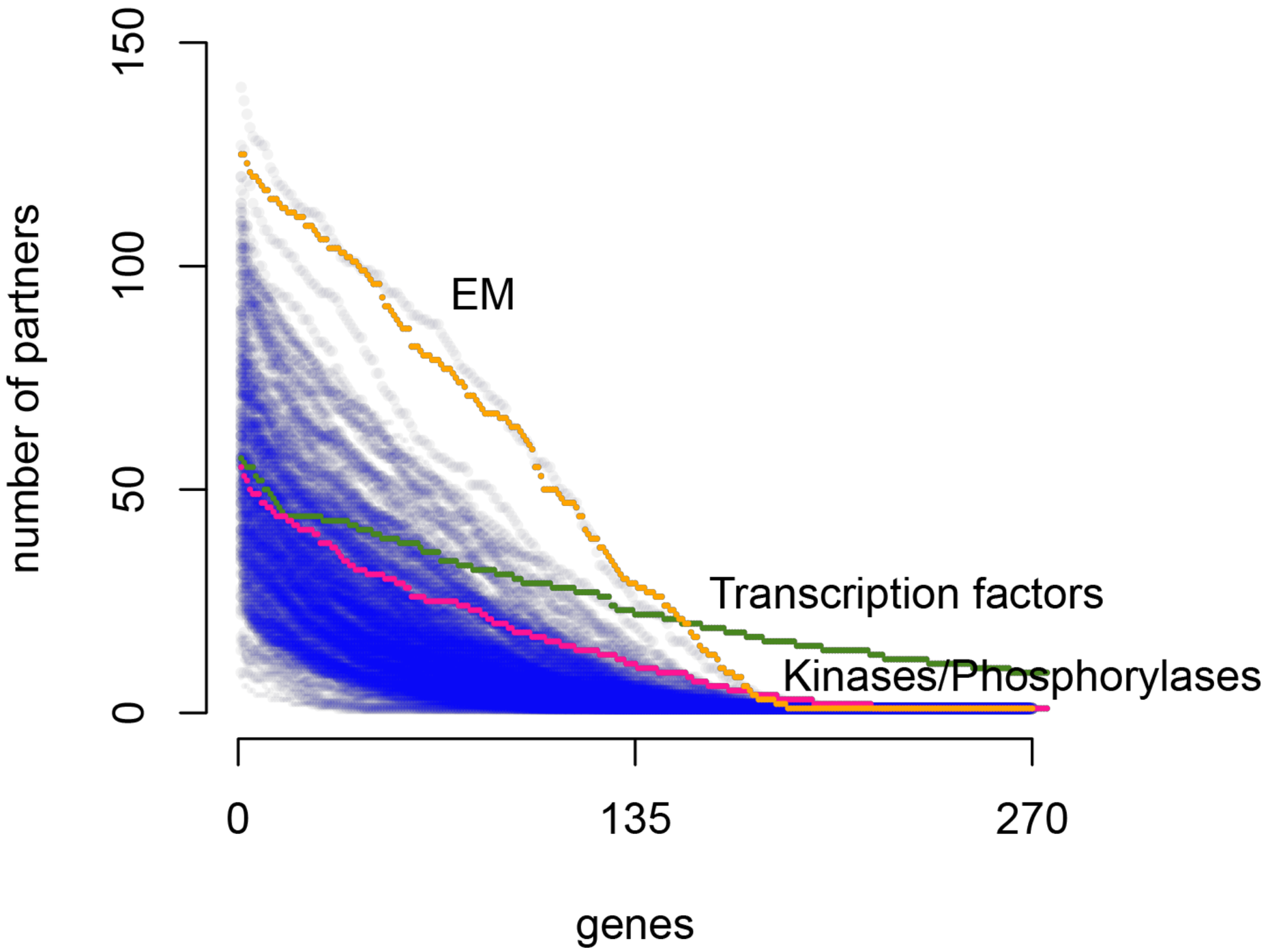
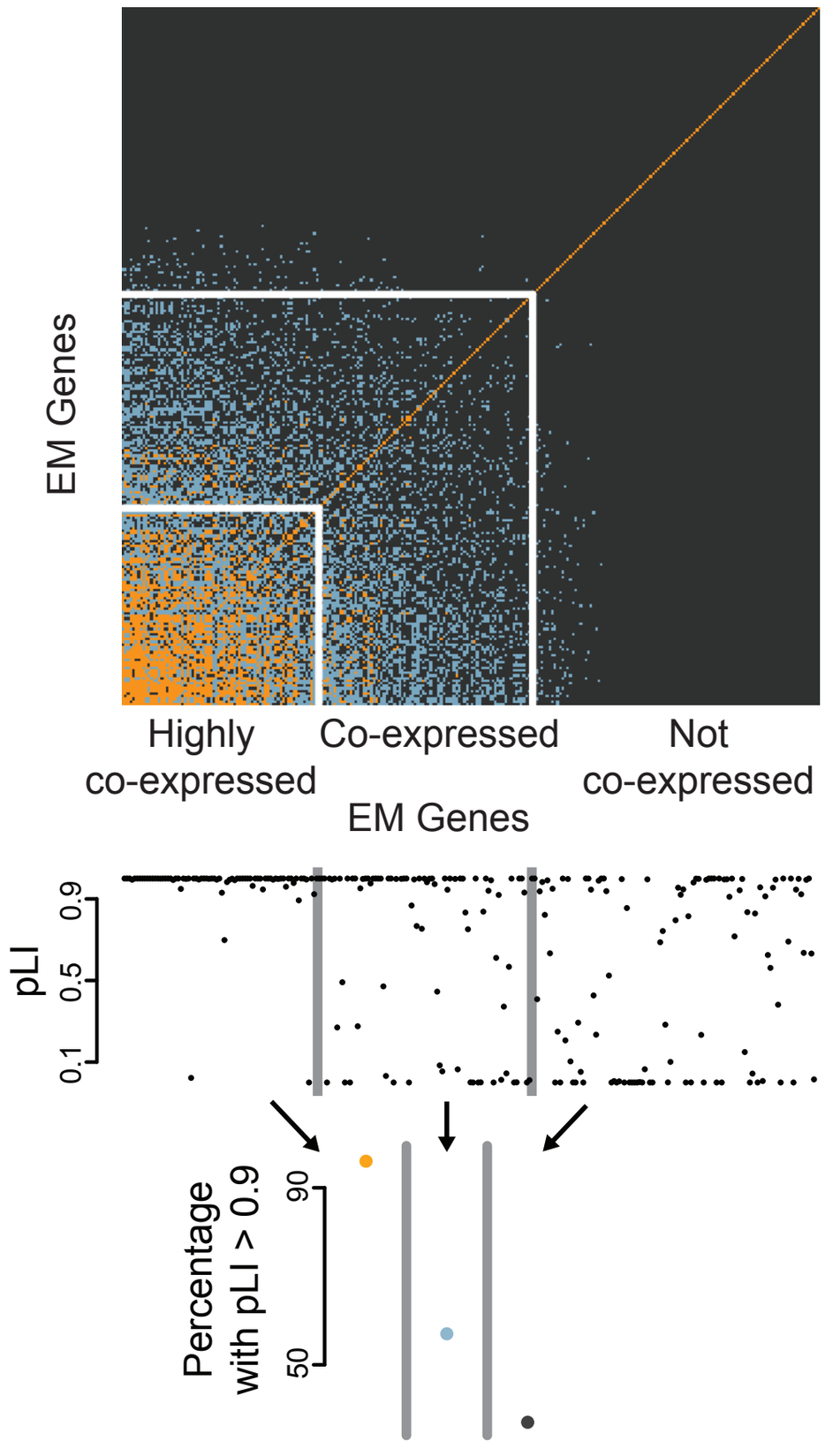


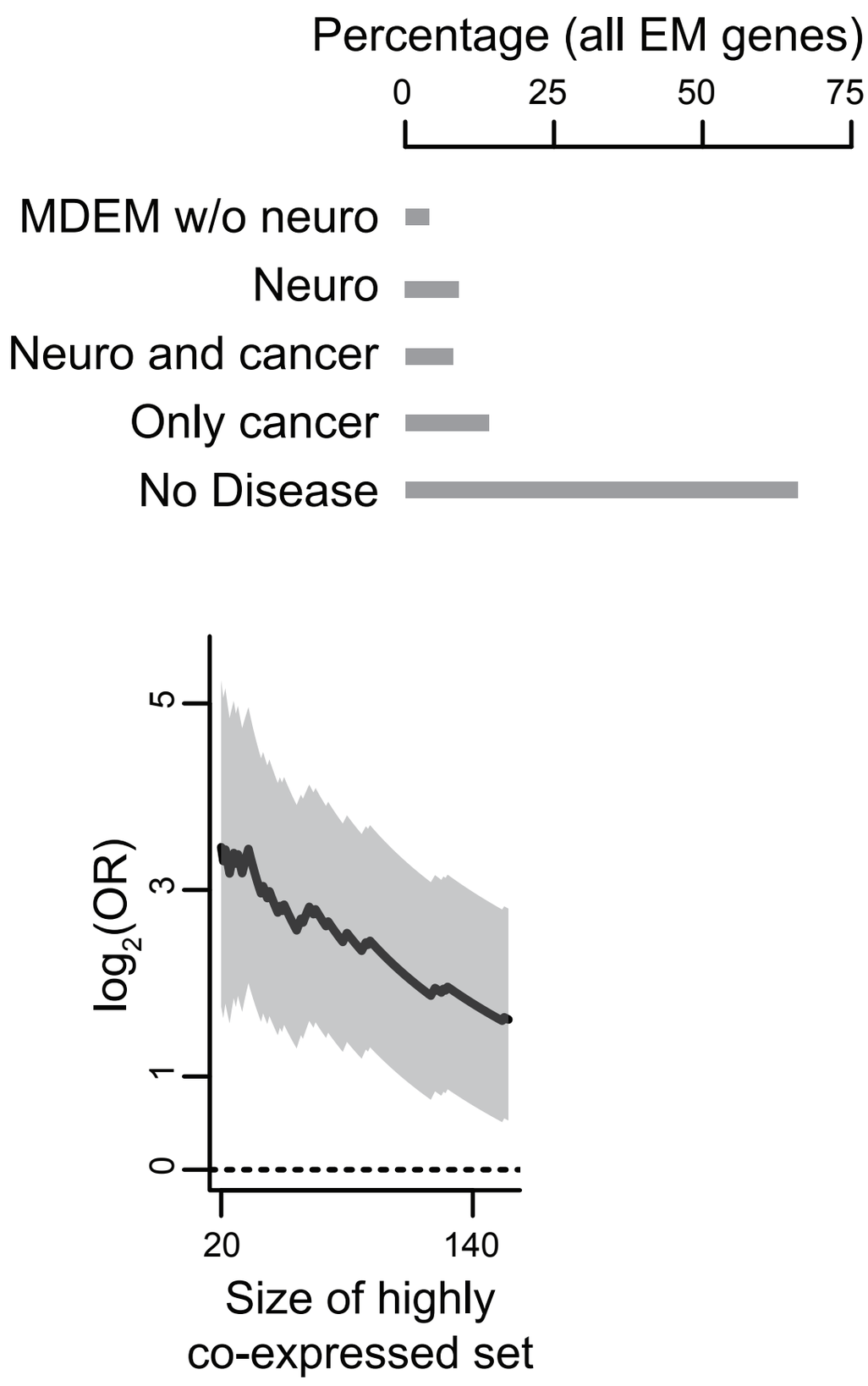
Permutations

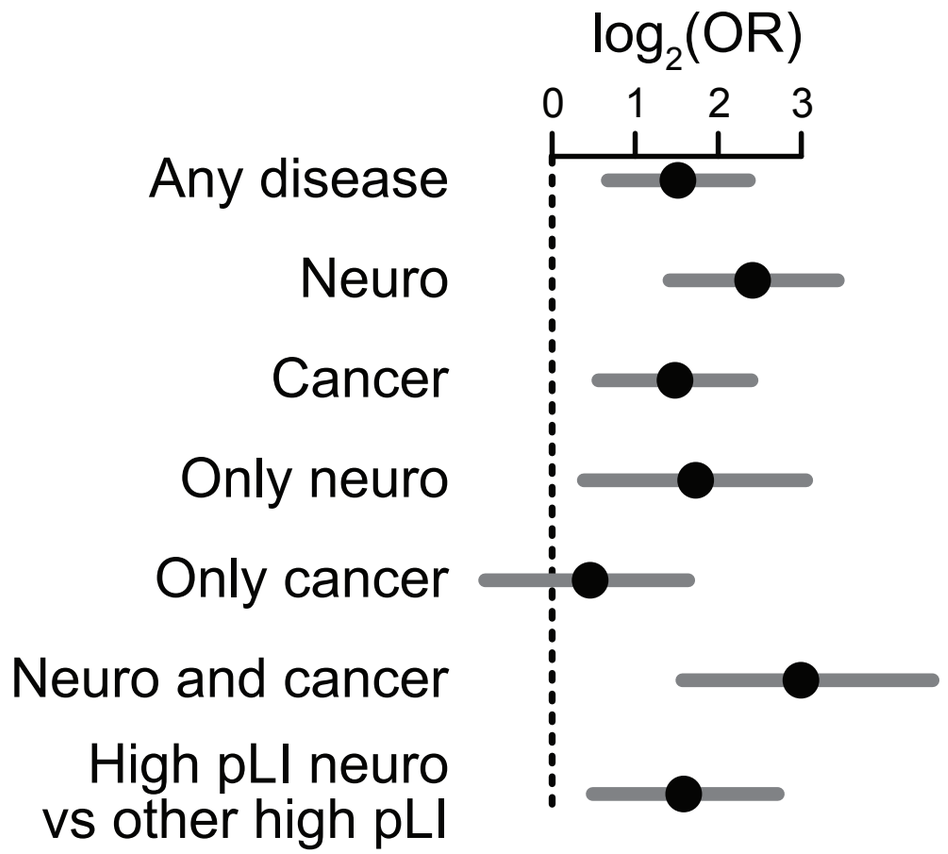


Co-expression is associated with LOF intolerance



Co-expression is associated with neurological dysfunction





Acknowledgements

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Aaron Quinlan

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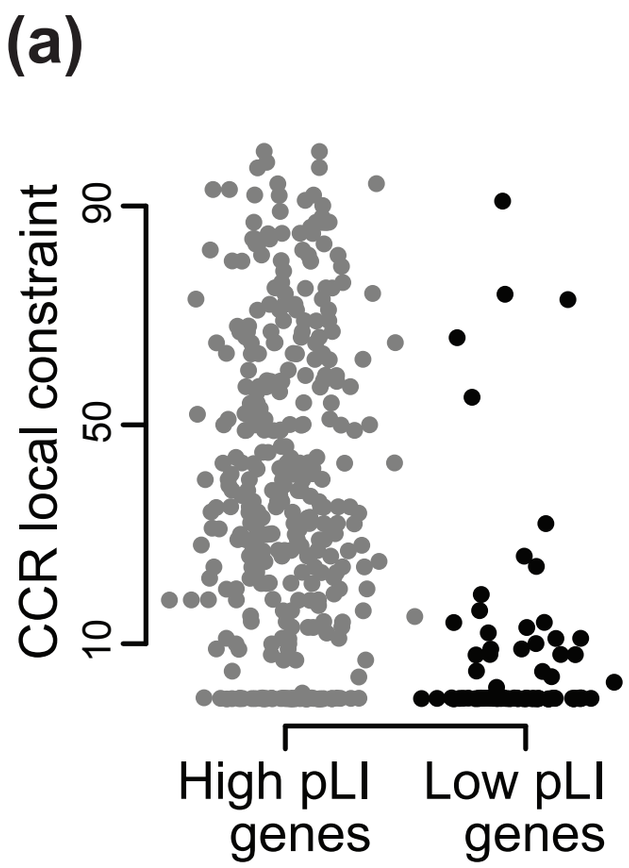
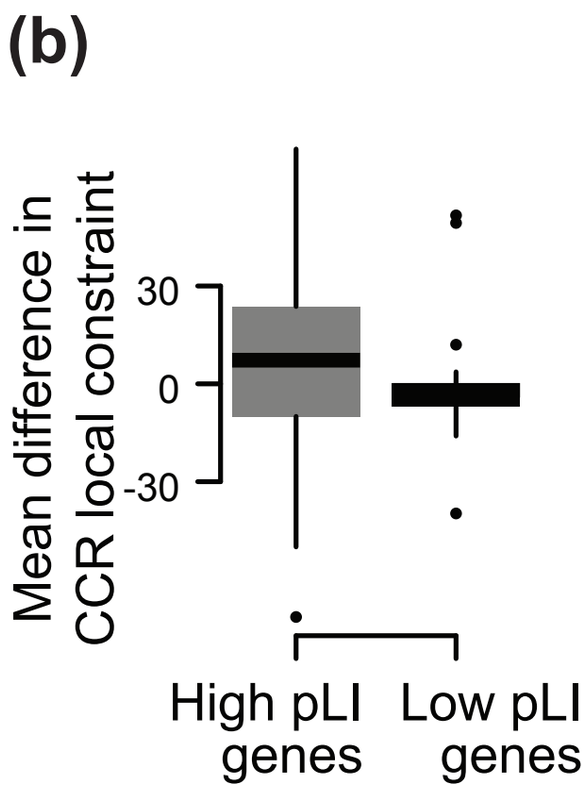
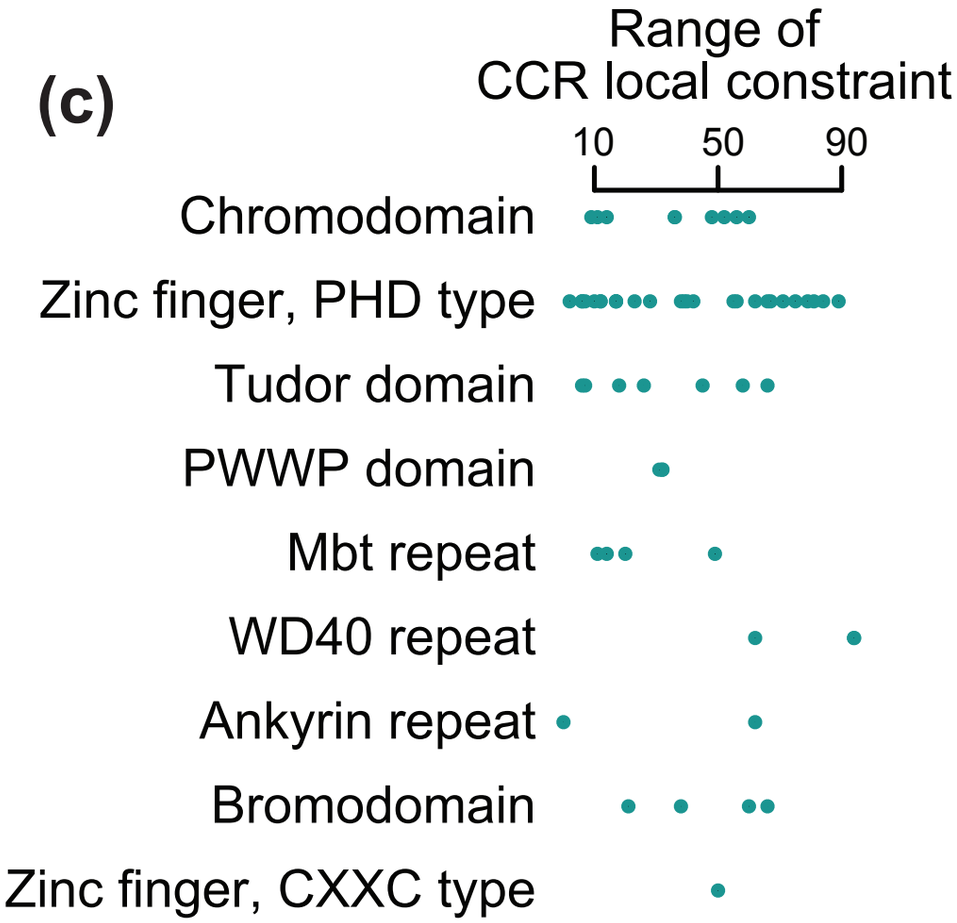
(looking for postdocs)

Domains


(a)
CCR local constraint
90
50
10
High pLI genes
Low pLI genes


(b)
Mean difference in CCR local constraint
30
0
-30
High pLI genes
Low pLI genes


(c)
Range of CCR local constraint
10
50
90
Chromodomain
Zinc finger, PHD type
Tudor domain
PWWP domain
Mbt repeat
WD40 repeat
Ankyrin repeat
Bromodomain
Zinc finger, CXXC type