INFERRING THE SHARED NONCODING REGULATORY MECHANISMS UNDERLYING GENETIC SUSCEPTIBILITY TO ALZHEIMER'S AND PARKINSON'S DISEASES

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INFERNO

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Outline

- Noncoding genetics / enhancer background
- INFERNO methodology
- AD and PD individual INFERNO results
- Shared AD/PD signals

Vast majority of GWAS signals are noncoding

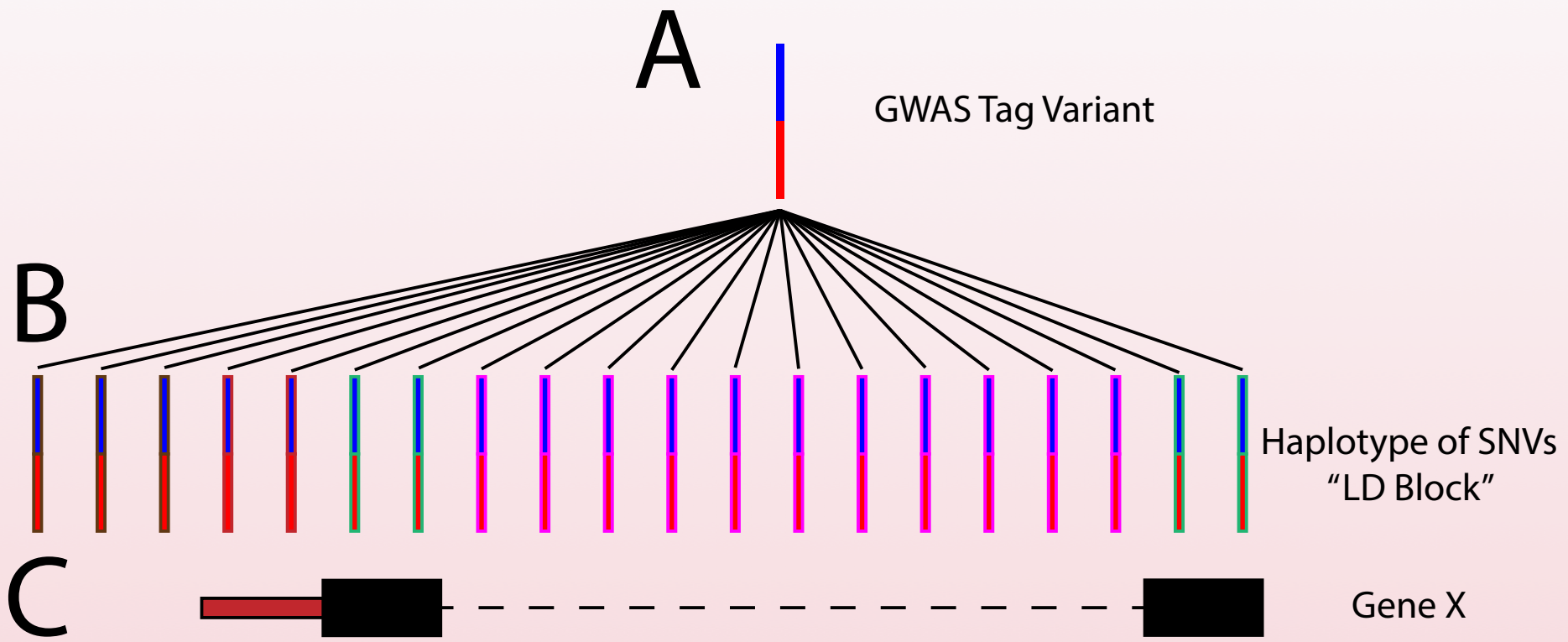
- Need to characterize:
  - Affected regulatory mechanism
  - Relevant tissue context
  - Target genes
  - Downstream biological processes

NIH National Human Genome Research Institute

EMBL-EBI

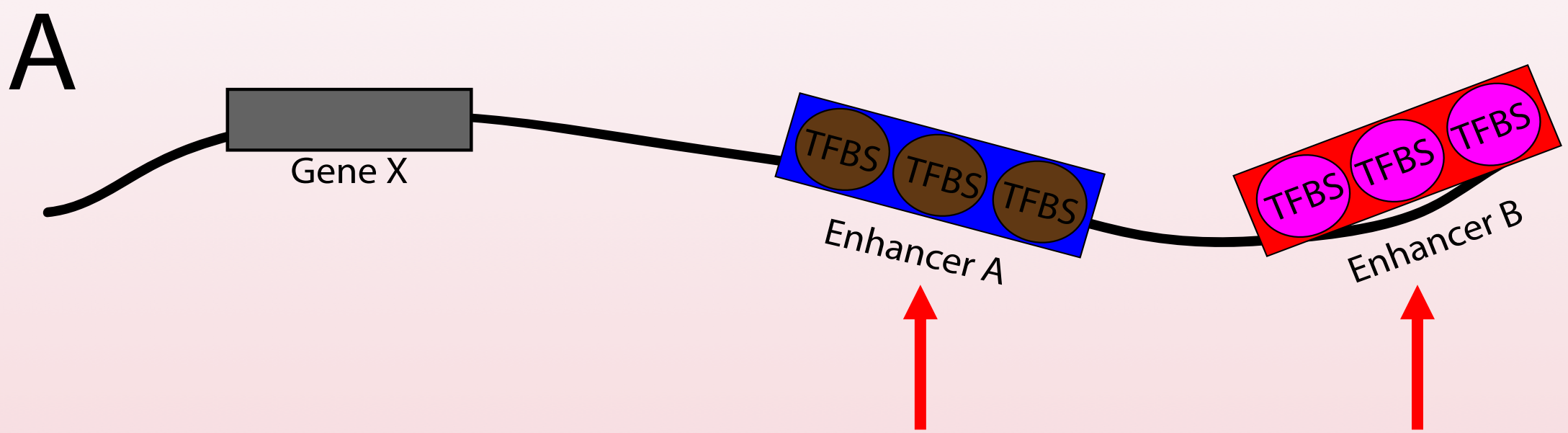
NHGRI-EBI GWAS Catalog
www.ebi.ac.uk/gwas

Linkage disequilibrium and causal variants

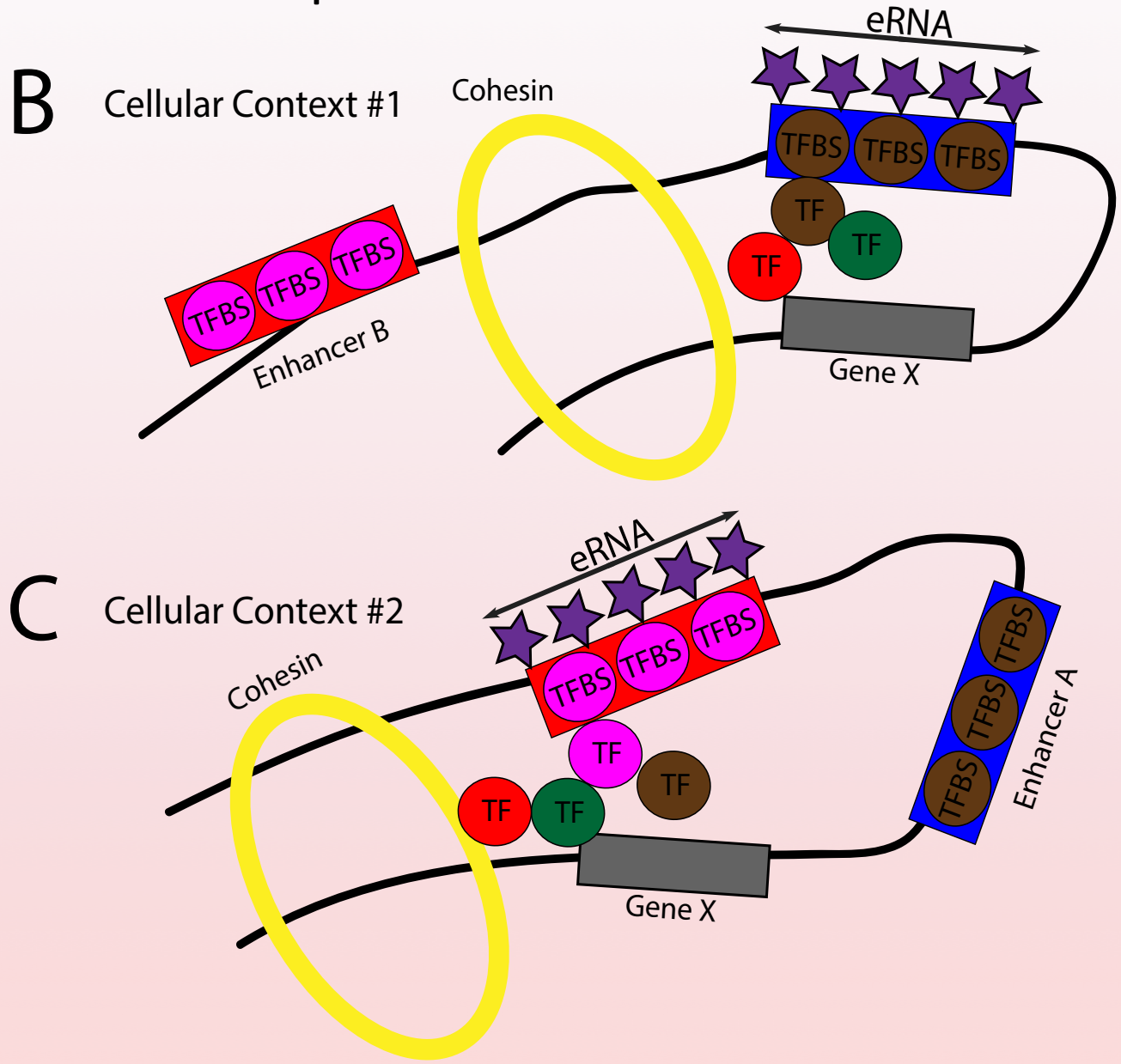


- Brown: intergenic variants
- Red: promoter-overlapping variants
- Green: exon-overlapping (coding) variants
- Pink: intron-overlapping variants

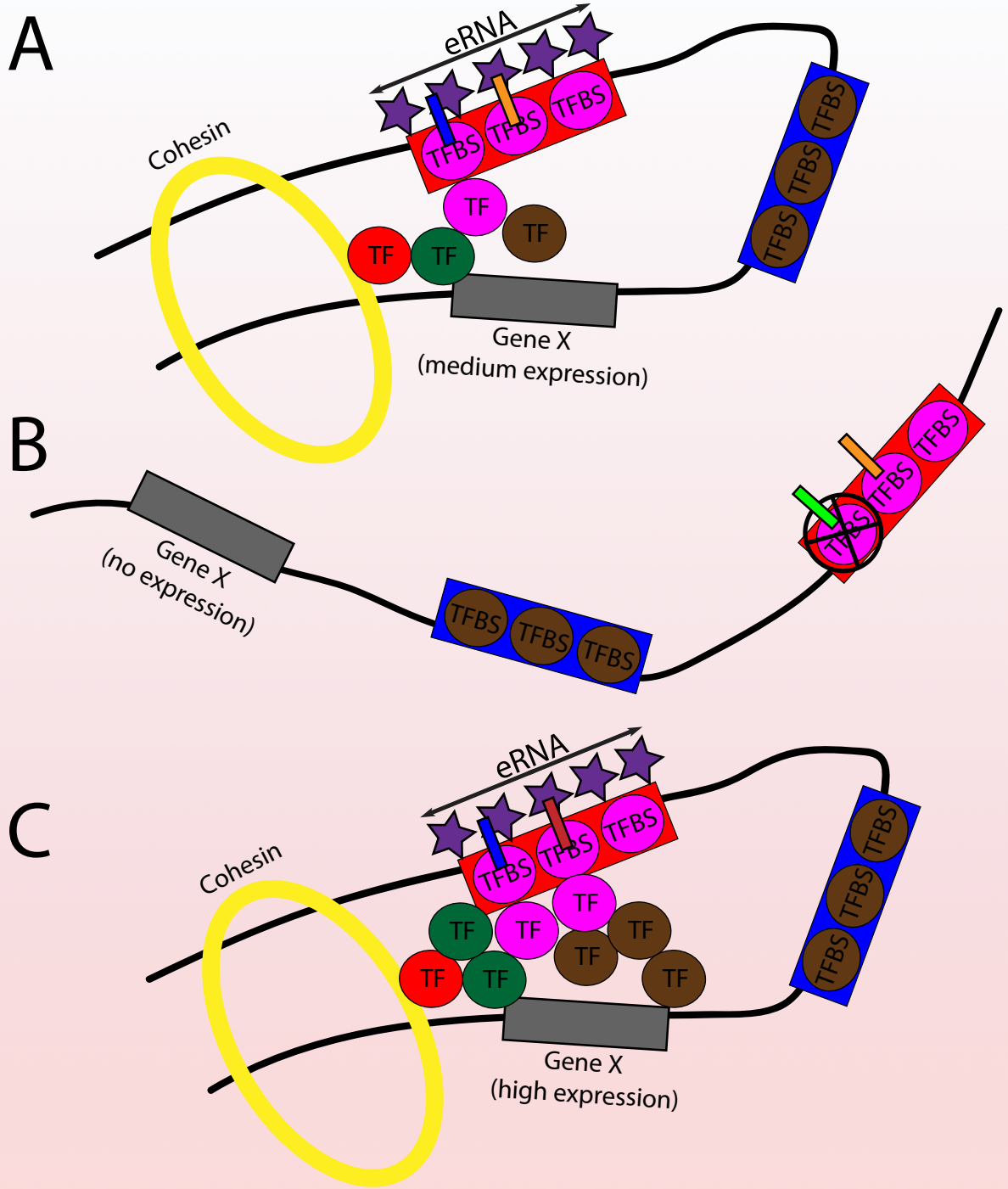
Noncoding variants may affect transcriptional enhancers



Enhancers are tissue-specific and have stereotypical properties



- TFBS-affecting variants may act as eQTLs
- Reference alleles are blue and orange rectangles
- Green variant abolishes TFBS
- Red variant increases TF strength



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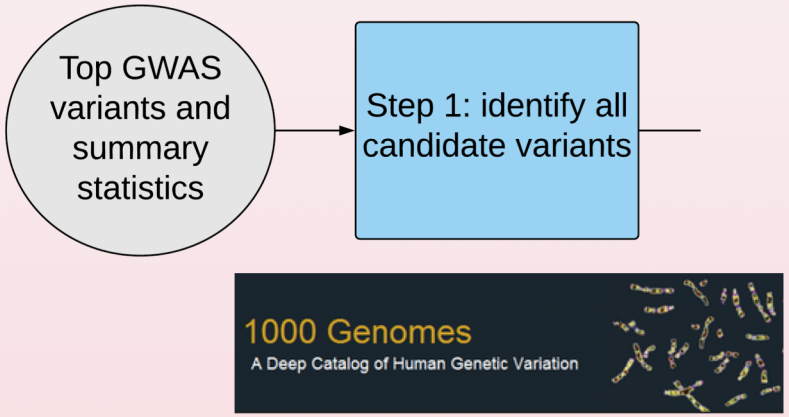
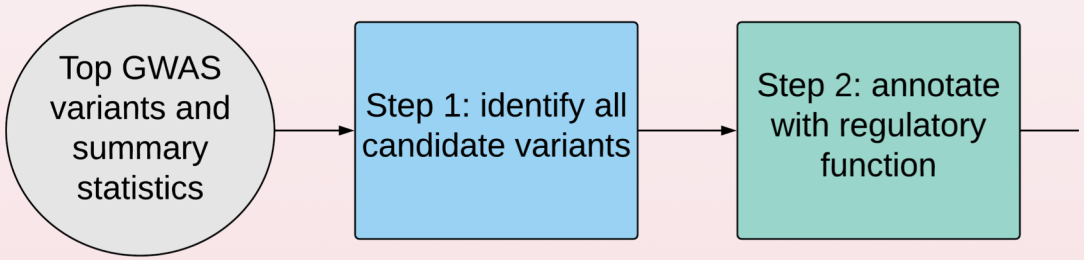
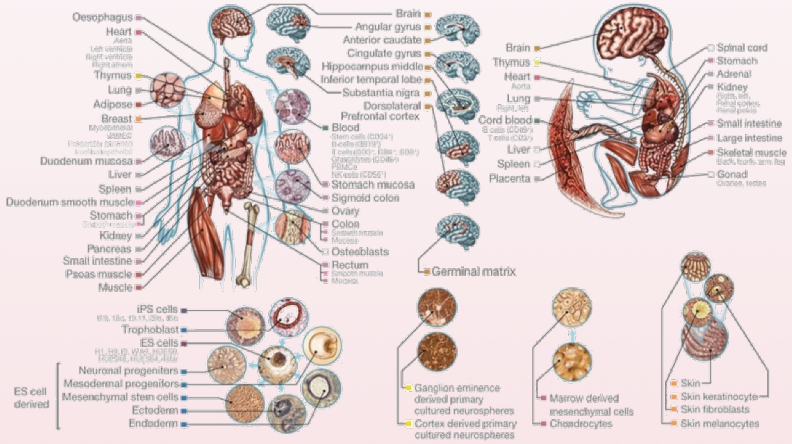
INFERNO: INFERring the molecular mechanisms of NOncoding genetic variants



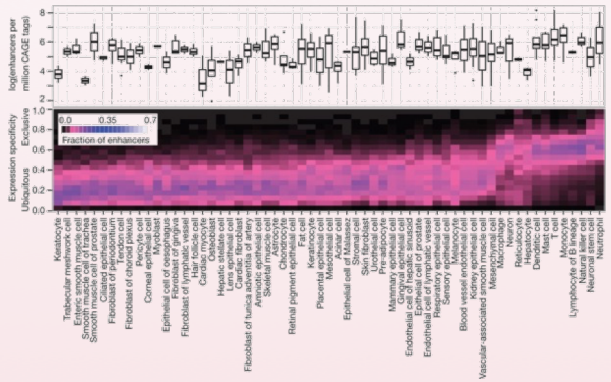
Amlie-Wolf et al., NAR 2018

INFERNO: INFERring the molecular mechanisms of NOncoding genetic variants





Roadmap ChromHMM enhancers
(127 tissues + cell types)



FANTOM5 eRNA enhancers
(112 tissues + cell types)

Leung, Y. Y., Kuksa, P. P., **Amlie-Wolf, A.**, Valladares, O., Ungar, L. H., Kannan, S., Gregory B.D., & Wang, L. S. (2016). DASHR: database of small human noncoding RNAs. *Nucleic acids research*, *44*(D1), D216-D222.

Kuksa PP, **Amlie-Wolf A**, Katanić Ž, Valladares O, Wang L-S, Leung YY. DASHR 2.0: integrated database of human small non-coding RNA genes and mature products. *Bioinformatics*. 2018.

dashr

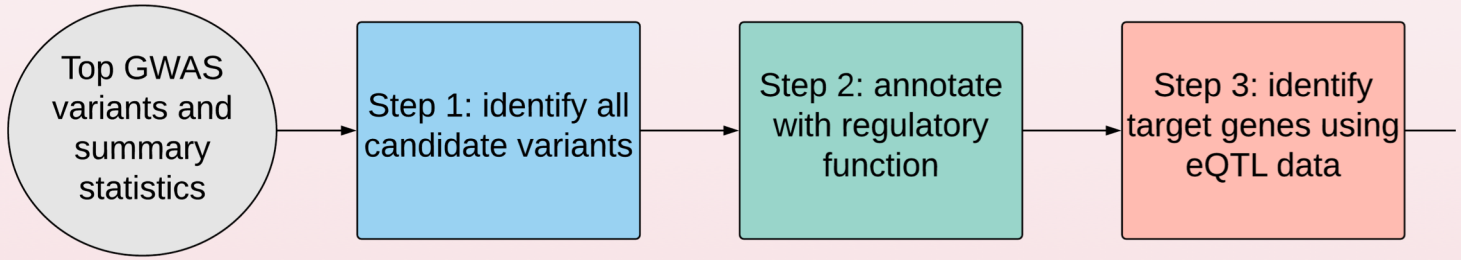
Database of Small Human Noncoding RNAs

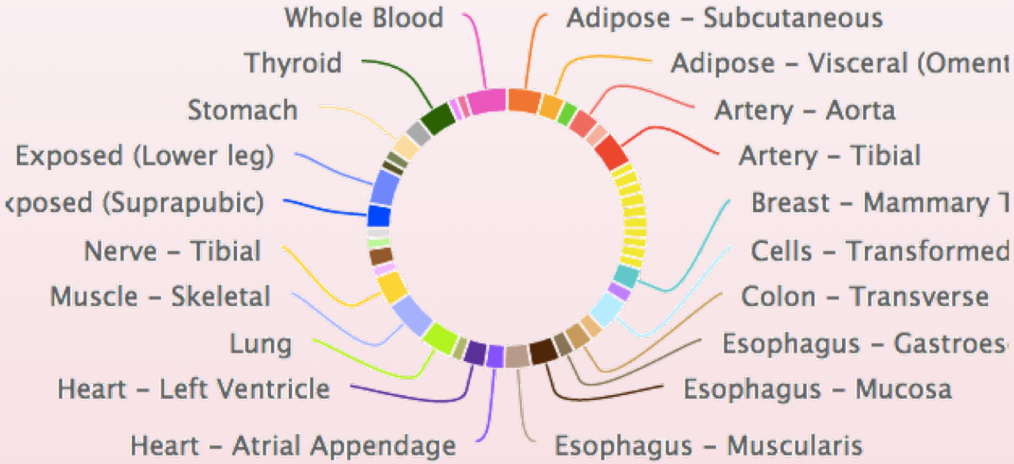
185 tissues + cell type

HOMER TFBSs

Amlie-Wolf et al., NAR 2018

INFERNO: INFERring the molecular mechanisms of NOncoding genetic variants





GTEx eQTLs (44 tissues + cell types)

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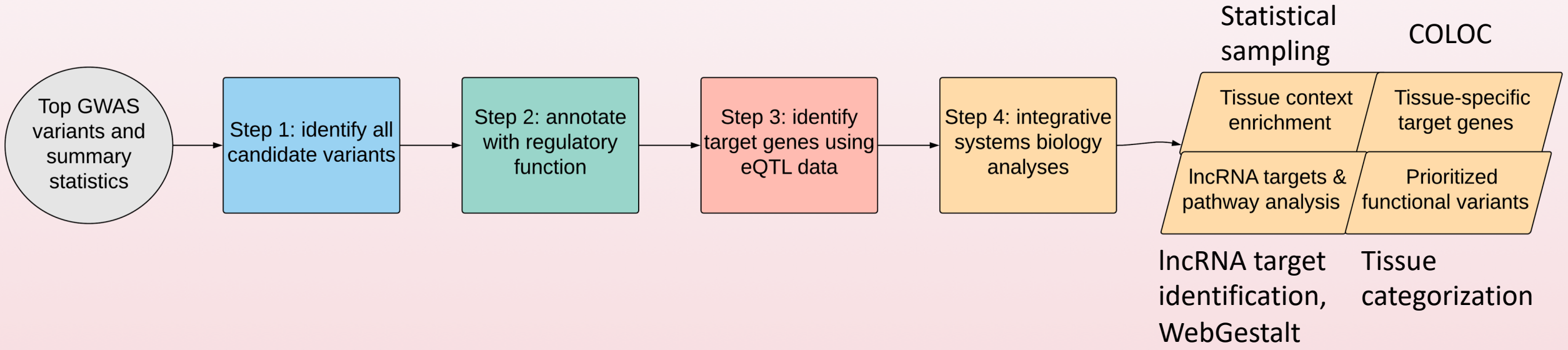
INFERNO: INFERring the molecular mechanisms of NOncoding genetic variants



- Open source pipeline implemented in R, Python, and bash
- **Amlie-Wolf A**, Tang M, Mlynarski EE, Kuksa PP, Valladares O, Katanic Z, Tsuang D, Brown CD, Schellenberg GD, Wang LS. INFERNO: inferring the molecular mechanisms of noncoding genetic variants. Nucleic Acids Research 2018:211599. doi:10.1093/nar/gky686.

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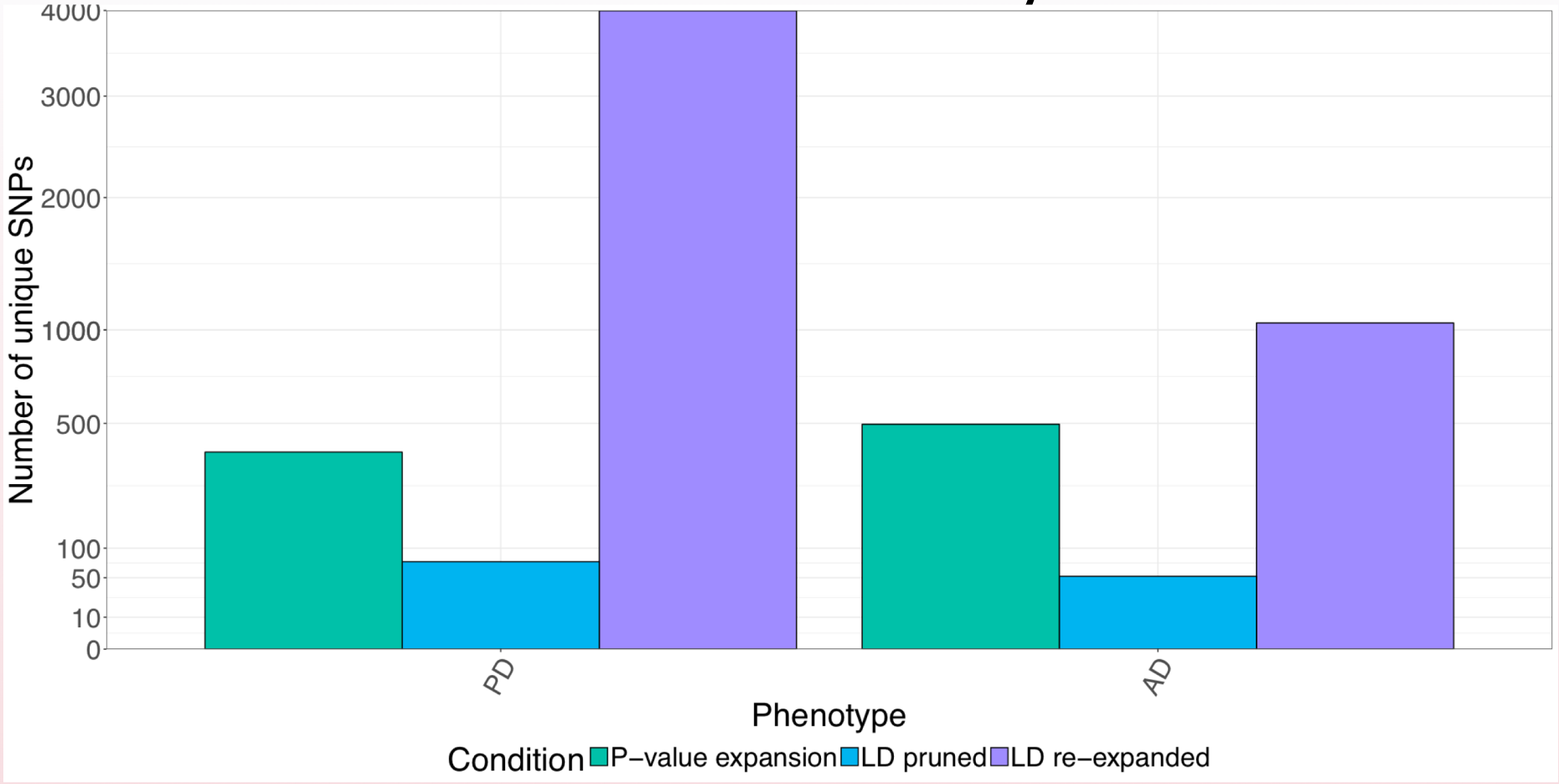
Data: GWAS summary statistics



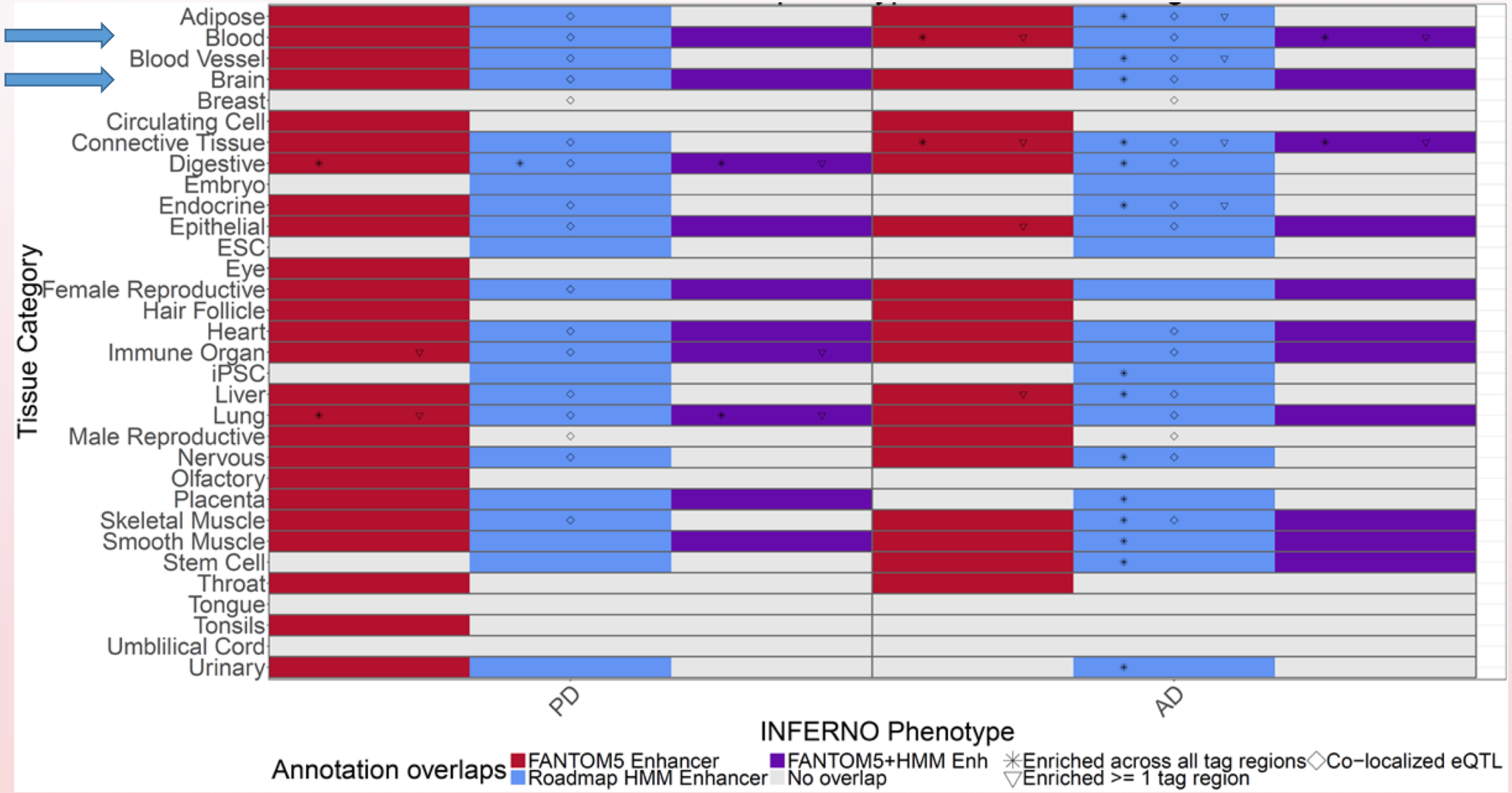
1. AD: IGAP top 19 loci

   Lambert JC *et al., Nat Genet. 2013 Dec;45(12):1452-8.*

2. PD: top 22 loci from international PD genomics consortium

   Nalls MA *et al.*, Nat Genet. 2014 Sep;46(9):989-93

AD and PD genetic regulatory signals are enriched in several tissue contexts



8/22 loci (36%) in PD **10/19 loci (53%) in AD**

AD results: https://www.biorxiv.org/content/10.1101/401471v1

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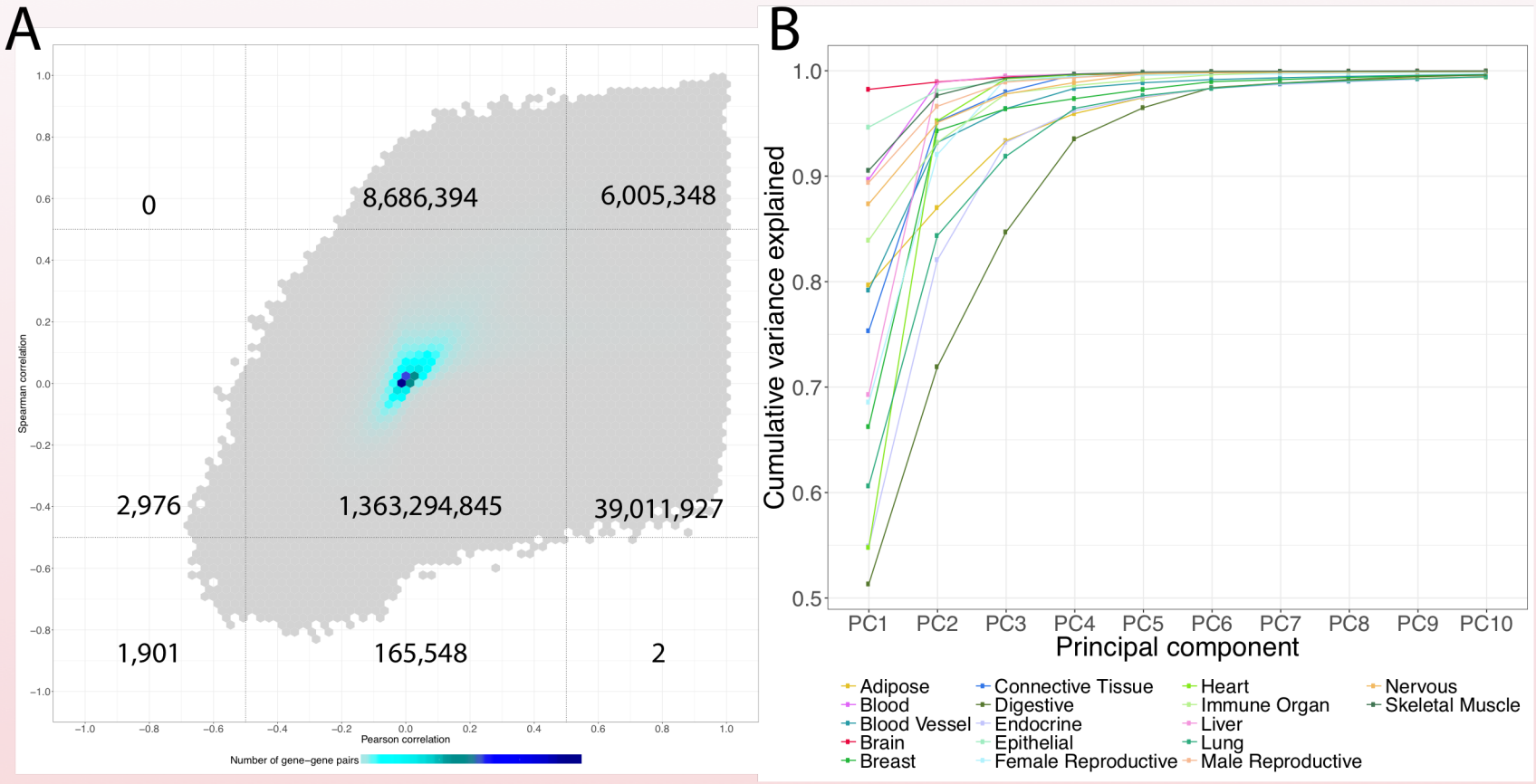
lncRNA post-eQTL analysis



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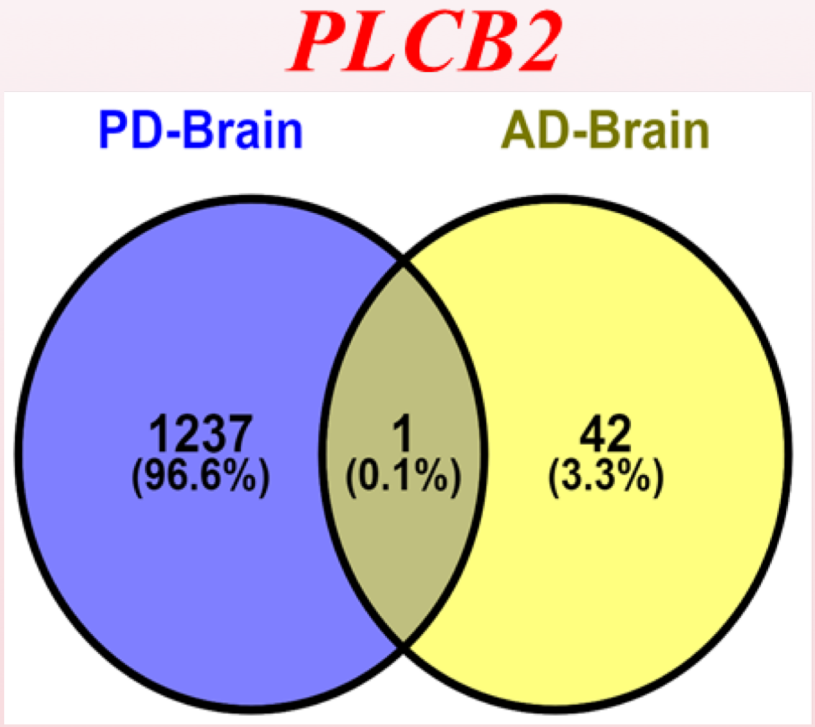
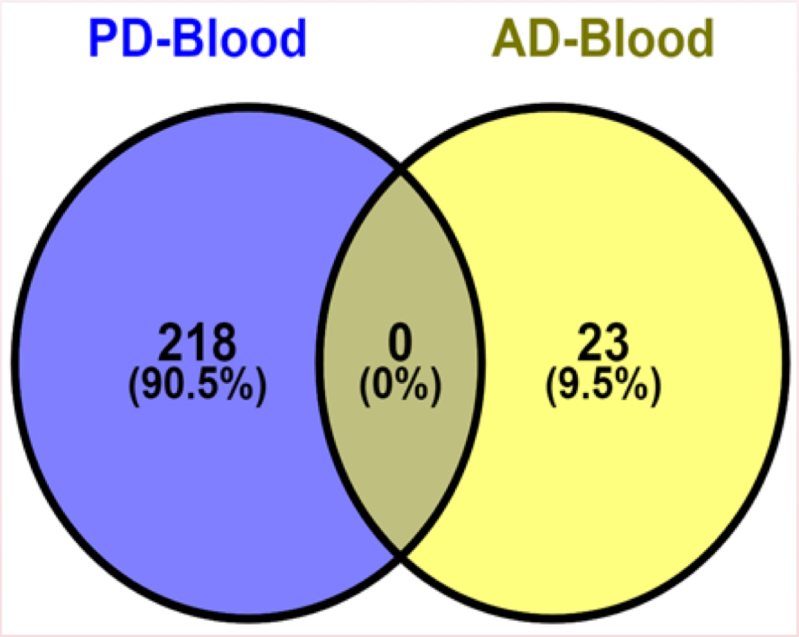
- Correlation across GTEx RNA-seq datasets to identify co-regulated networks with lncRNAs
- Tissue class-specific analysis using principal components correction

PLCB2 (Alpha-synuclein signaling) is a **lncRNA eQTL target gene** found in both AD and PD

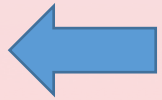




PLCB2 belongs to the Alpha-synuclein signaling in the BioSystems pathways database

Common **pathways** affected by **eQTL lncRNA target genes**: splicing, signaling and immune

Pathway type	Geneset	Description	PD	AD
GO_BP	GO:0006397	mRNA processing	***	***
	GO:0008380	RNA splicing	***	***
	GO:0016570	histone modification	***	***
	GO:0002764	immune response-regulating signaling pathway	***	***
	GO:0006281	DNA repair	***	**
	GO:0006353	DNA-templated transcription, termination	**	***
KEGG	hsa04666	Fc gamma R-mediated phagocytosis	***	***
	hsa03040	Spliceosome	***	**
	hsa03015	mRNA surveillance pathway	**	**
	hsa04670	Leukocyte transendothelial migration	***	**
	hsa04650	Natural killer cell mediated cytotoxicity	**	



AD/PD **miRNA biomarkers** bind to the 3'UTRs of target genes affected by both AD & PD variants

Disease	rsID	chr	Target gene	miRNA	Literature (Biomarker)
PD	rs5850	7	*GPNMB*	let-7c-3p	Reported[36]
AD	rs12539172	7	*NYAP1*		-
PD	rs117305991	17	*MAPT*	miR-1275/4665-5p	-
AD	rs3816605	11	*NUP160*		Reported[37]
PD	rs117305991	17	*MAPT*	miR-5010-5p	-
AD	rs3816605	11	*NUP160*		-
PD	rs11076	16	*SETD1A*	miR-542-3p	Reported[38]
AD	rs7143400	14	*FERMT2*		Reported[39]
PD	rs117305991	17	*MAPT*	miR-625-5p	-
AD	rs3816605	11	*NUP160*		-
PD	rs750952	16	*ZNF646*	miR-6825-5p	-
AD	rs74486166	11	*ARHGAP1*		-
PD	rs13708	16	*STX1B*	miR-874-5p	-
AD	rs1628077	7	*GATS*		-

Pathways affected by miRNA target genes are disease specific (validated in external database)

Genetics can imply shared tissue-specific effects of regulatory dysregulation between AD and PD

AD GWAS loci	AD Target Genes	AD lncRNA targets	AD Mechanisms
PD GWAS loci	PD Target Genes	PD lncRNA targets	PD Mechanisms
Shared? Nothing	***Shared? Not directly***	***Shared? Yes! PLCB2***	***Shared? YES!*** lncRNAs → Downstream functional effects

Conclusions

- INFERNO provides a useful tool for integrating functional genomics data to generate post-GWAS hypotheses
- INFERNO identified enhancer dysregulation and affected target genes in AD and PD
- Cross-phenotype analysis identified one gene, PLCB2, shared between AD and PD, as well as several common pathways with downstream effects

http://inferno.lisanwanglab.org/

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- Barbara Engelhardt

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