The adaptation of polygenic traits: from genes to phenotypes, are regulatory networks the missing link?

Katherine Stone, John Platig, John Quackenbush, Maud Fagny

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Génétique Quantitative et Évolution Le Moulon

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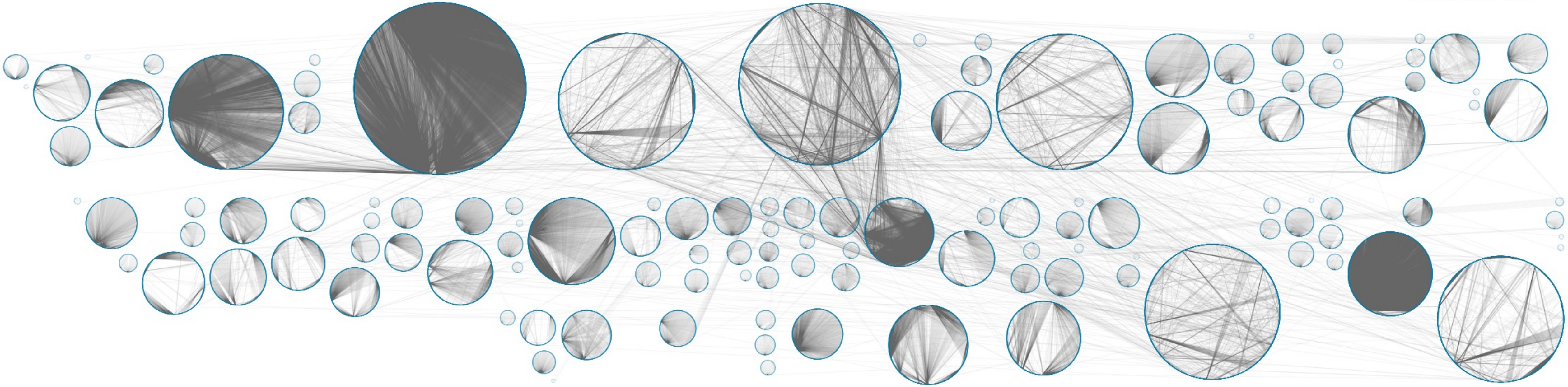
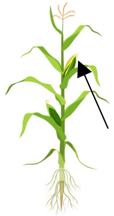


The adaptation of polygenic traits: from genes to phenotypes, are regulatory networks the missing link?

Maud Fagny, PhD

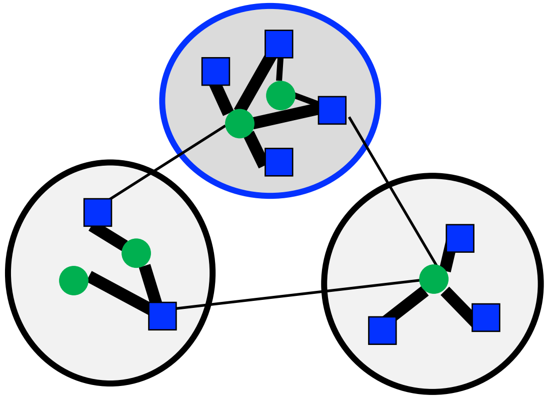


Université Paris-Saclay Faculté des Sciences d'Orsay
INRAE
CNRS
AgroParisTech Talents d'une planète soutenable

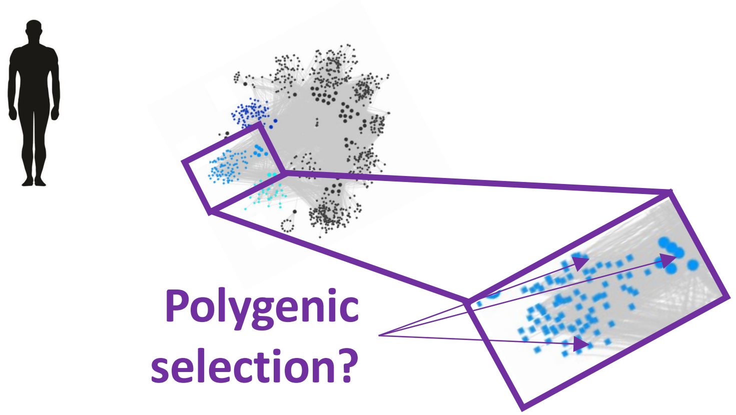
EuroEvoDevo 2024, Helsinki, 25-28/06/2024

Research questions

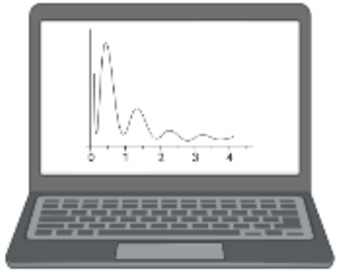
What is the role of *cis*-regulatory elements articulated GRN in crops response to the environment?



How do GRN respond to the environment?



What role do GRN play in long-term adaptation?



Can we use GRN information to improve yield prediction?

Outline

Introduction:

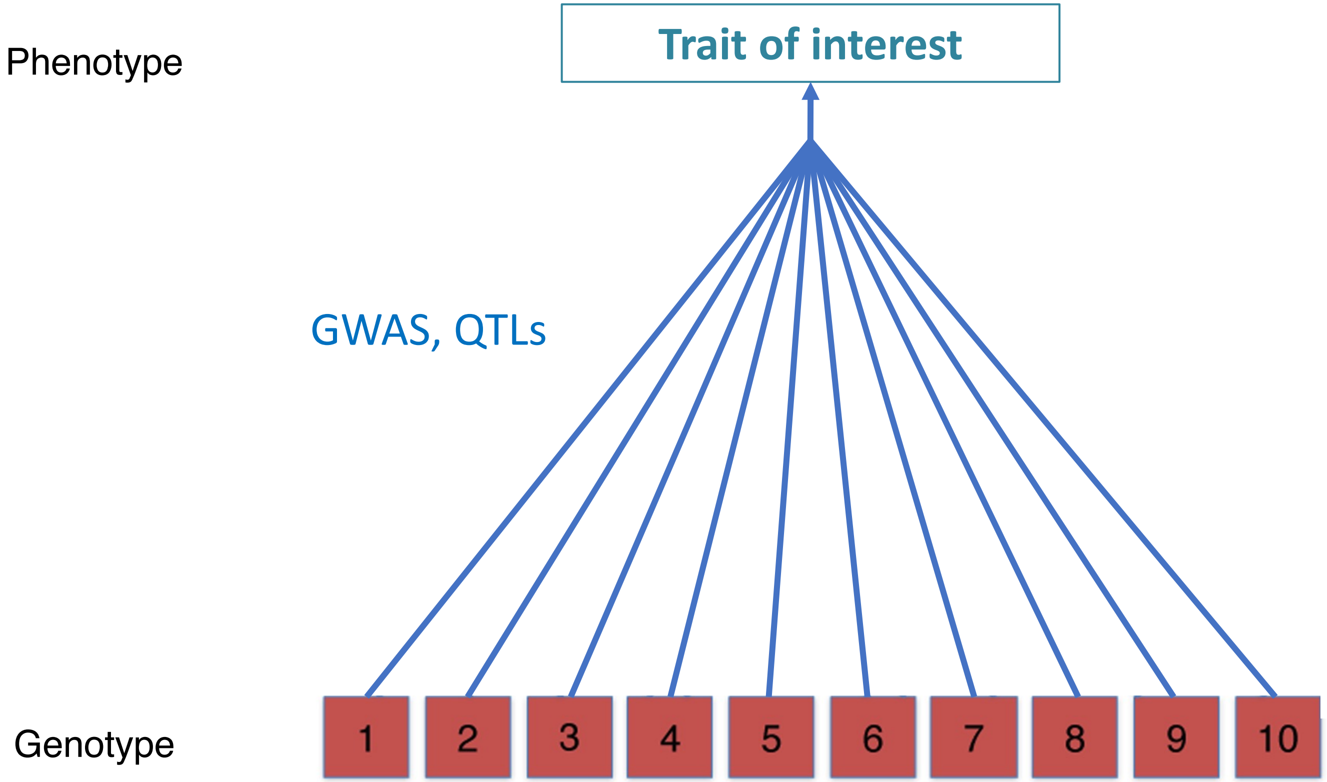
- Polygenic trait adaptation: knowledges and challenges
- The importance of regulatory regions and how to make sense of them

1) A link between network architecture and polygenic trait heritability

2) A crucial role for local hubs in adaptation

Conclusions & prospects: eQTL networks to identify polygenic adaptation?

Polygenic traits (quantitative genetics)



Phenotype

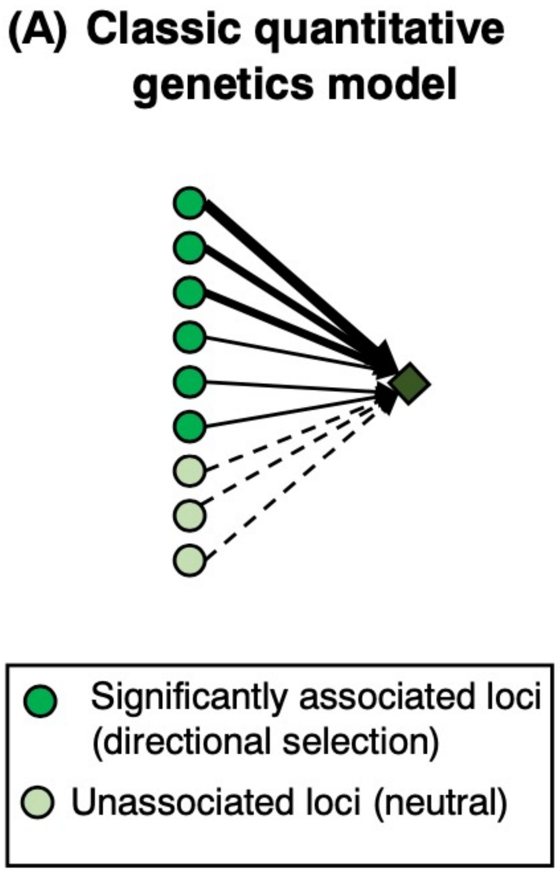
Trait of interest

GWAS, QTLs

Genotype

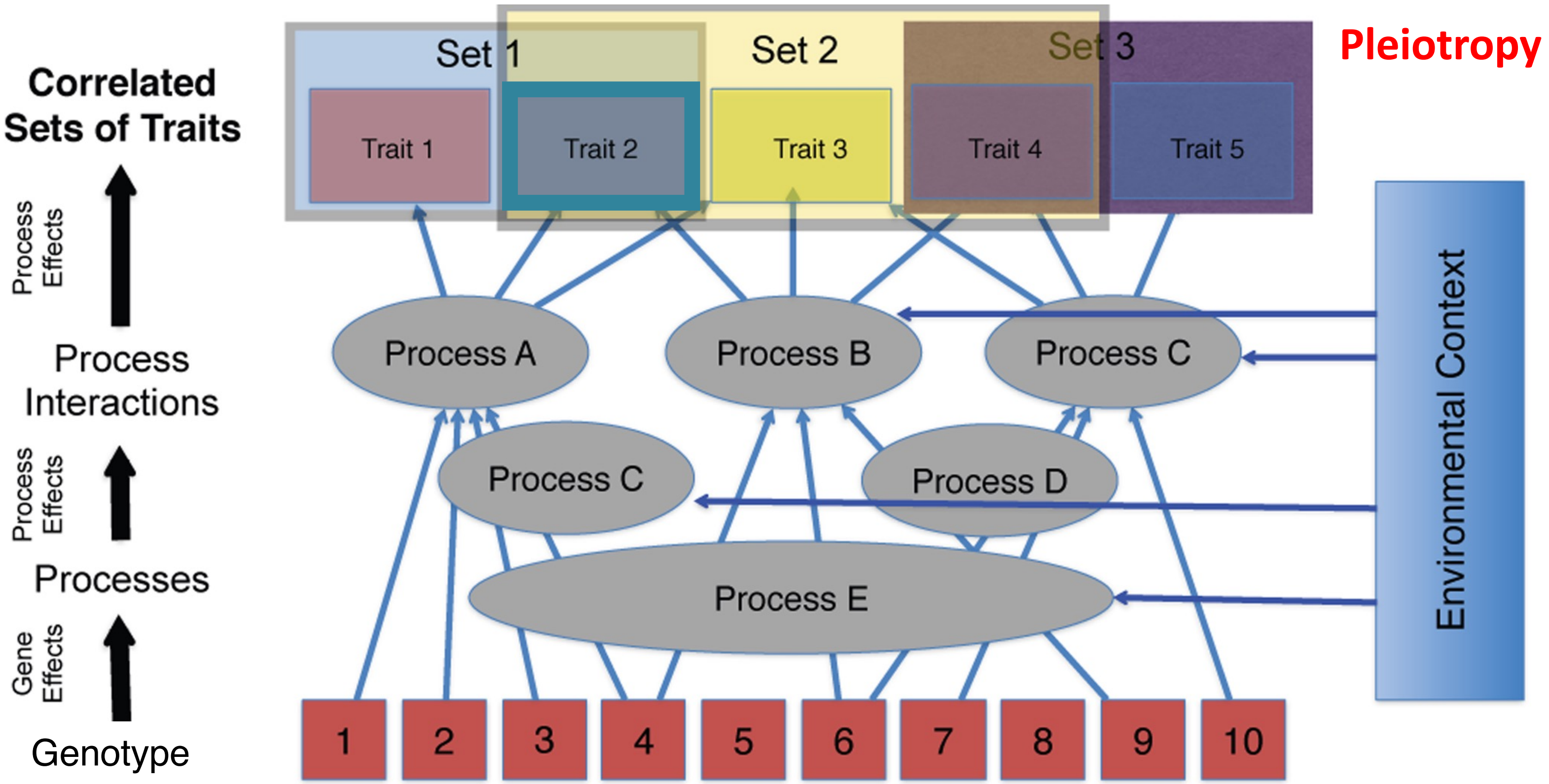
1 2 3 4 5 6 7 8 9 10

Adapted from Hallgrimsson *et al.*, *PLoS Genetics*, 2014

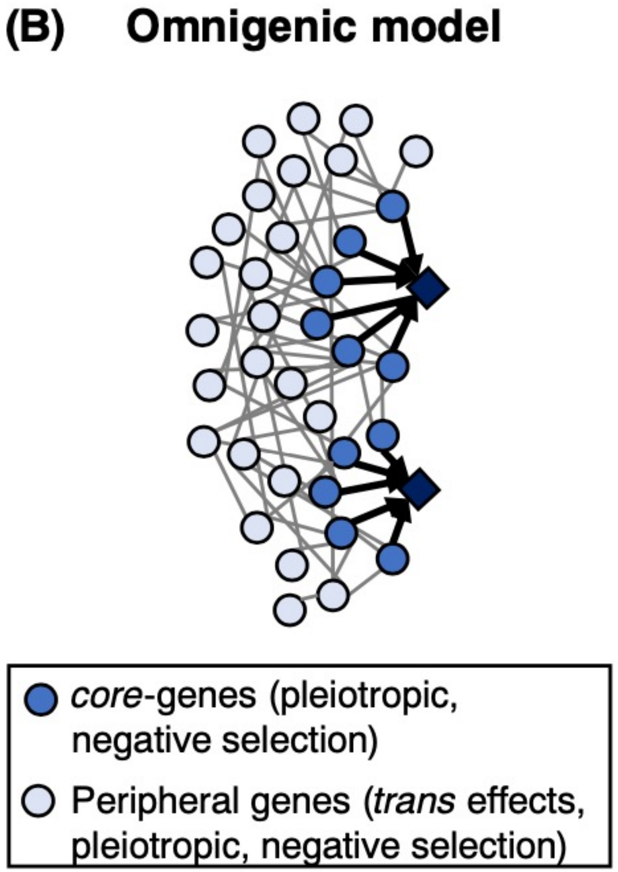


- ➢ **One trait determined by several independant loci**

Genetic architecture of polygenic traits (systems biology)

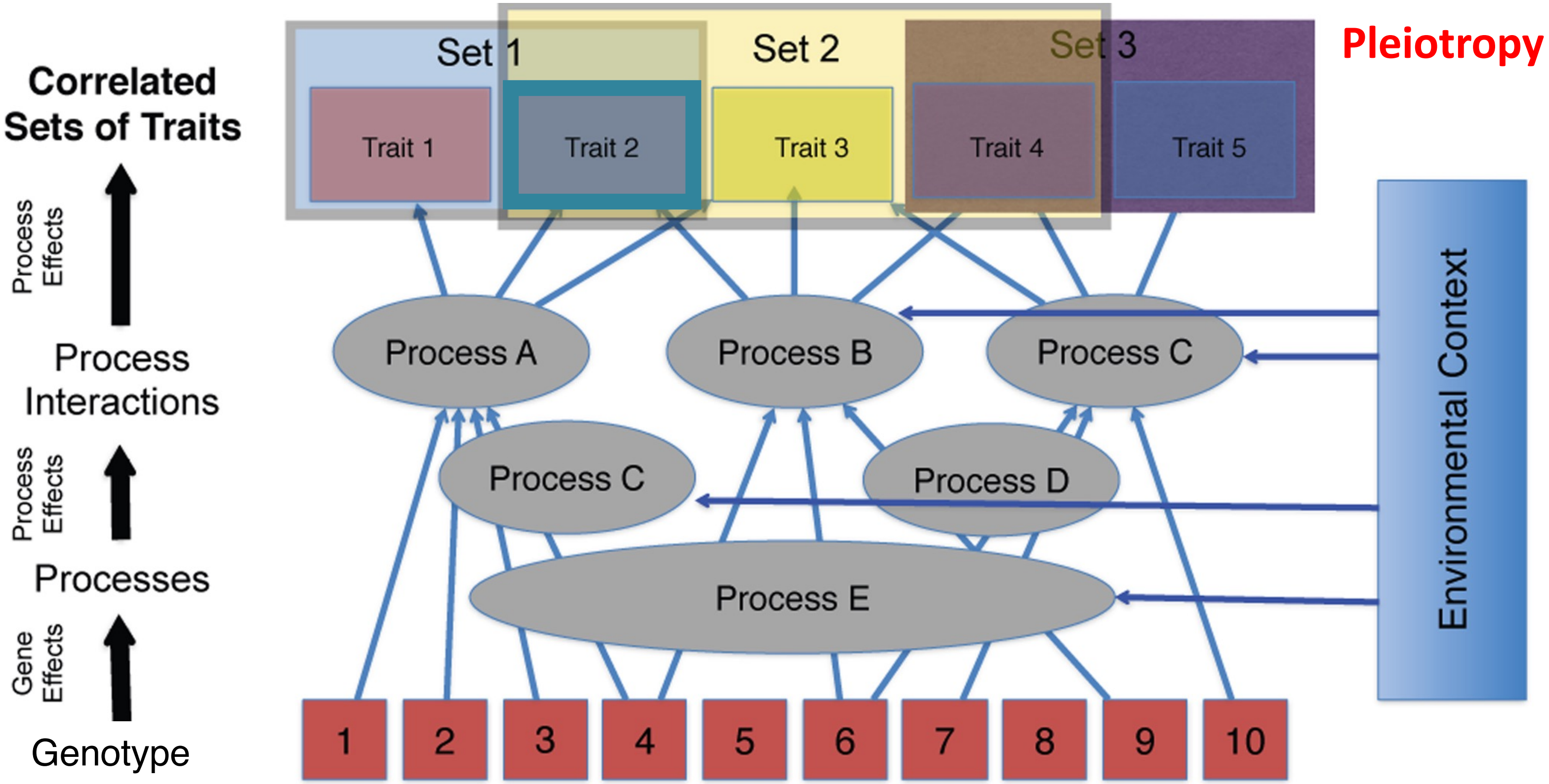


Adapted from Hallgrimsson *et al.*, *PLoS Genetics*, 2014



- **Limited possibilities for adaptation of polygenic traits?**

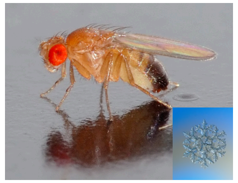
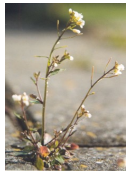
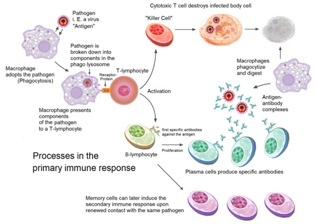
Polygenic traits are important in adaptation (population genetics)

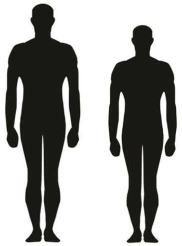


Pleiotropy

Adapted from Hallgrimsson *et al.*, *PLoS Genetics*, 2014

A role in adaptation



- **Apparent incompatibility between model & results**
- **A need to further explore molecular bases of polygenic traits**

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The importance of regulatory mutations

Location of SNP associated to polygenic traits in GWAS

30-60% Gene body
(mostly intronic)

20-30% Intergenic

distal *cis*-regulatory elements
(enhancers, silencers)

10-30% promoters

- ***Cis*-regulatory elements contain most of the trait associated SNPs**

Getting eQTLs for different tissues

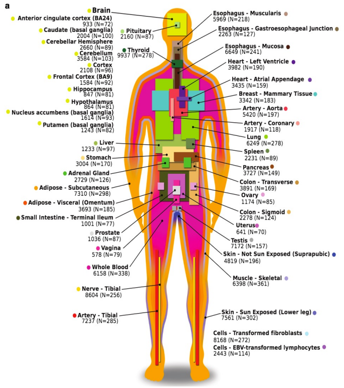
Data

29 tissues, up to 706 individuals

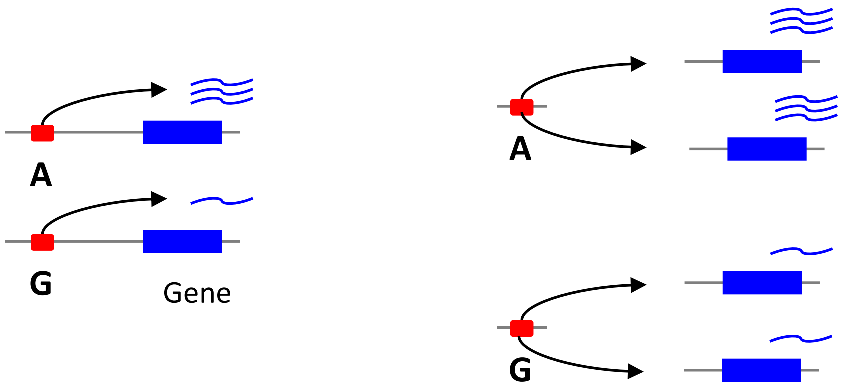
Genotypes

RNA-Seq data

GTEx



cis- and *trans-*eQTL mapping



Organizing the complexity with eQTL networks

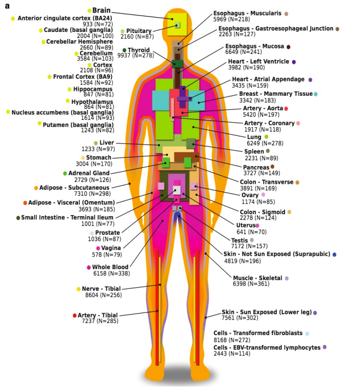
Data

29 tissues, up to 706 individuals

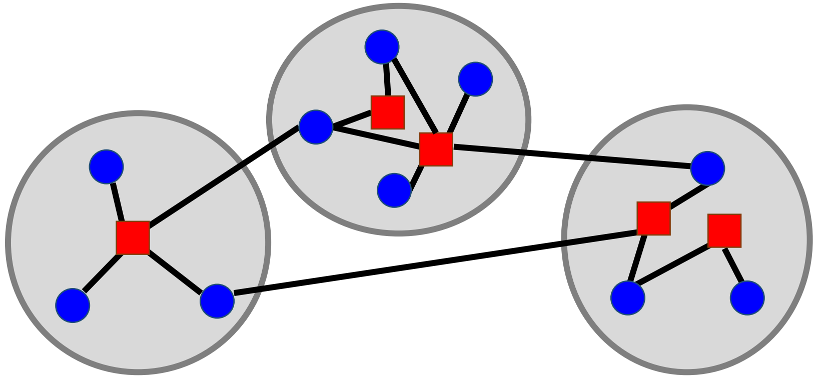
Genotypes

RNA-Seq data

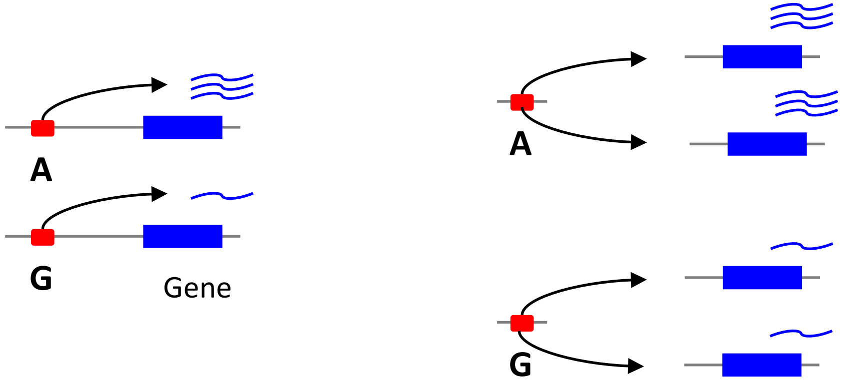
GTEx



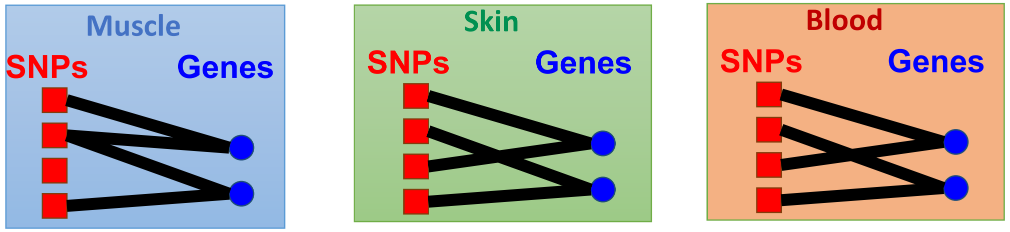
Network modules detection



cis- and *trans*-eQTL mapping

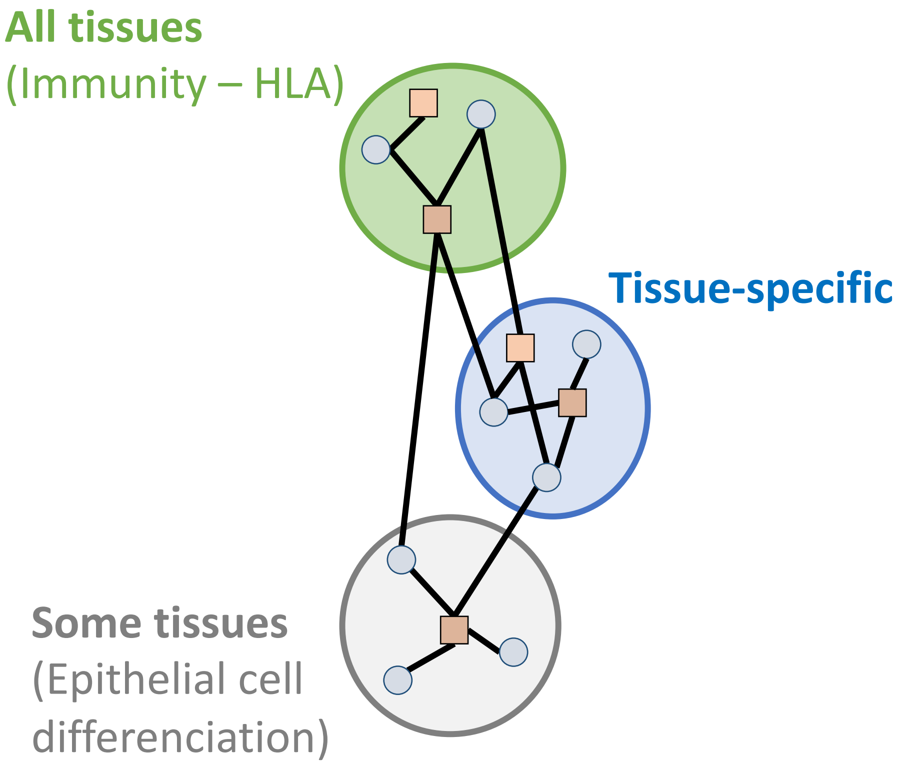


Bipartite Networks representation



29 tissues

eQTL networks are structured by biological functions

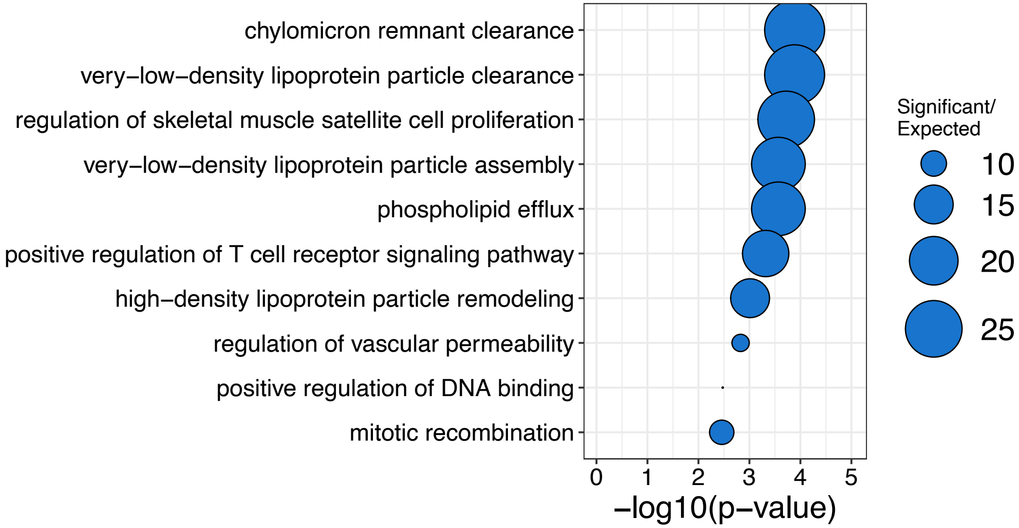


All tissues
(Immunity – HLA)

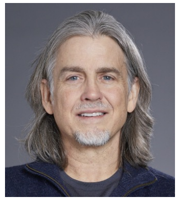
Tissue-specific

Some tissues
(Epithelial cell differenciation)

Lipoprotein particles turn-over
(Visceral Adipose Tissue)



John Platig

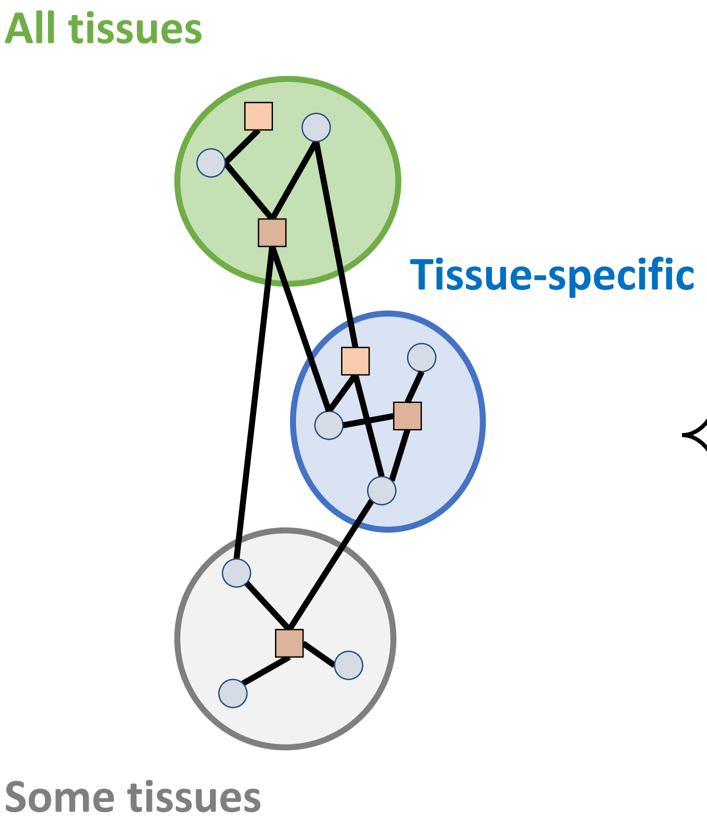


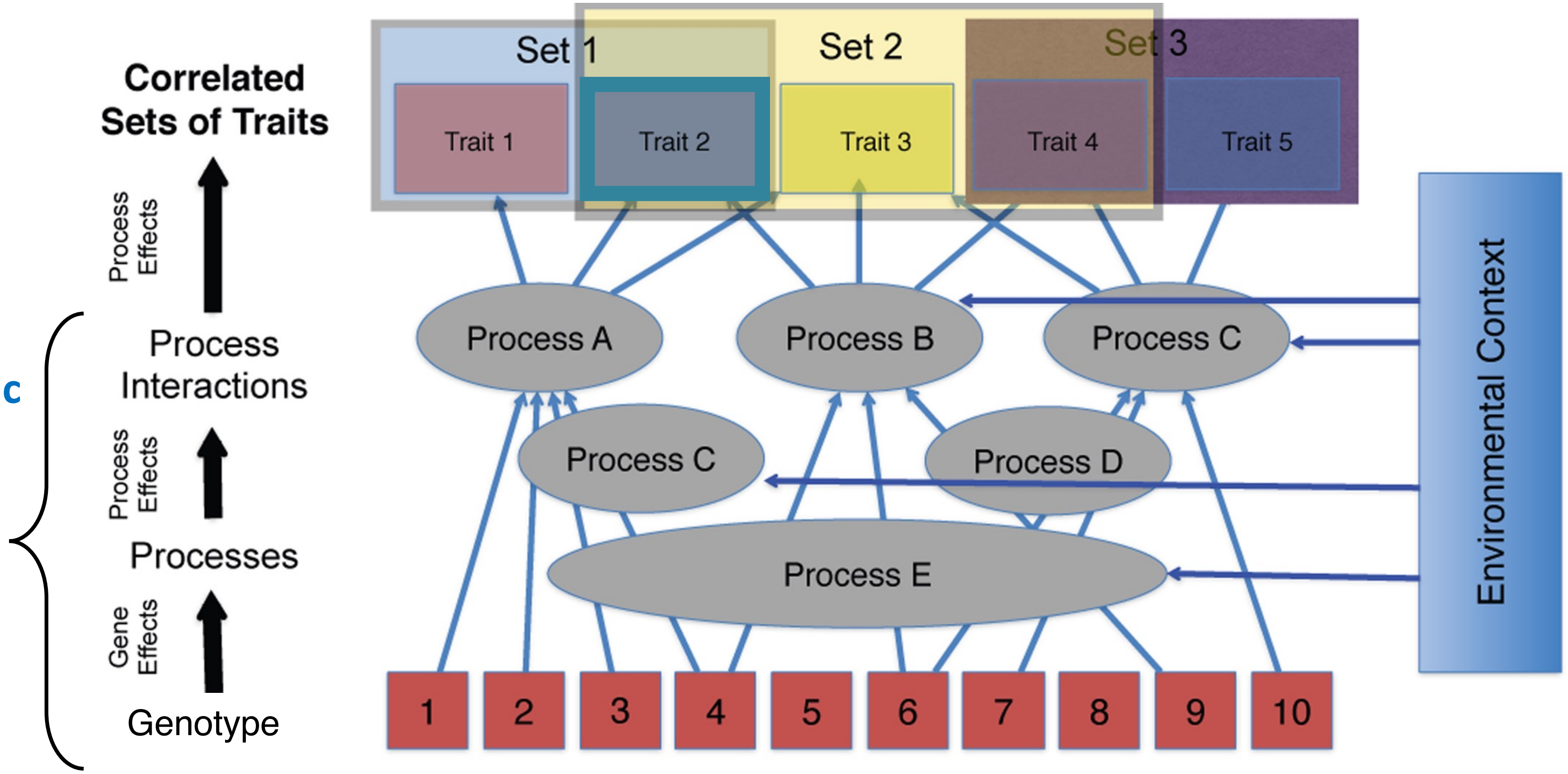
John Quackenbush

- **By enclosing SNPs effect into one module-function, network structure could open up a space for polygenic trait adaptation**

Fagny *et al.*, *PNAS*, 2017
Fagny *et al.*, *BJC*, 2019
Gaynor et al., *Cell Rep. Met.*, 2022

Gene regulatory networks as the missing link?

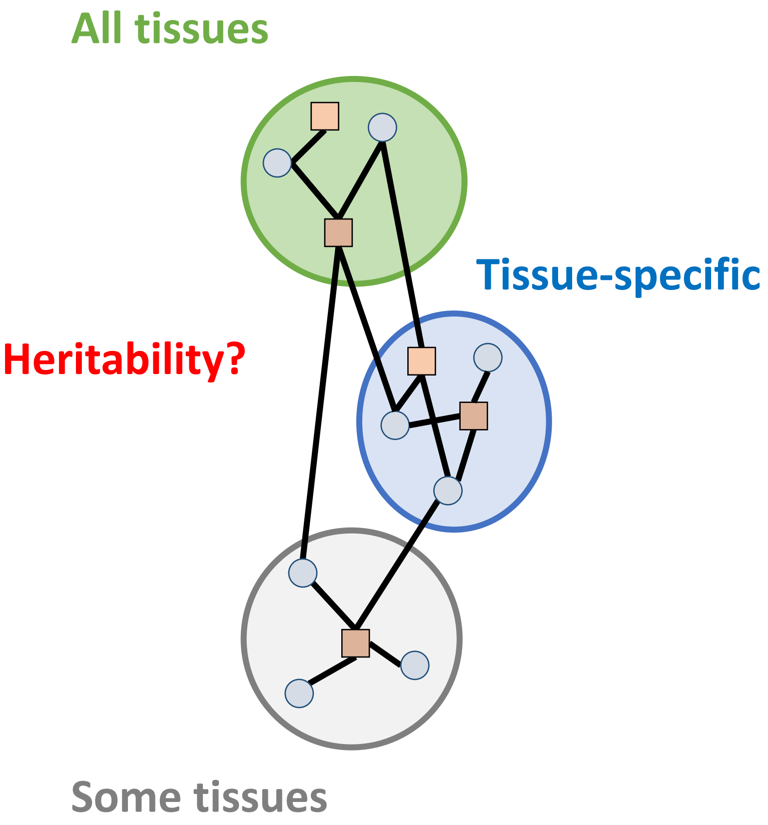




Adapted from Hallgrimsson *et al.*, *PLoS Genetics*, 2014

- **Can the exploration of gene regulatory network structure help us better understand polygenic trait adaptation?**

Questions



- **How is trait heritability spread in eQTL networks ?**
- **Is there a link between network topology and signature of selection ?**

Katherine L. Stone
(Bachelor student)

Sheila Gaynor
(PhD Student)

Gaynor *et al.*, *Cell Rep. Met.*, 2022
Stone *et al. (In Prep)*

Outline

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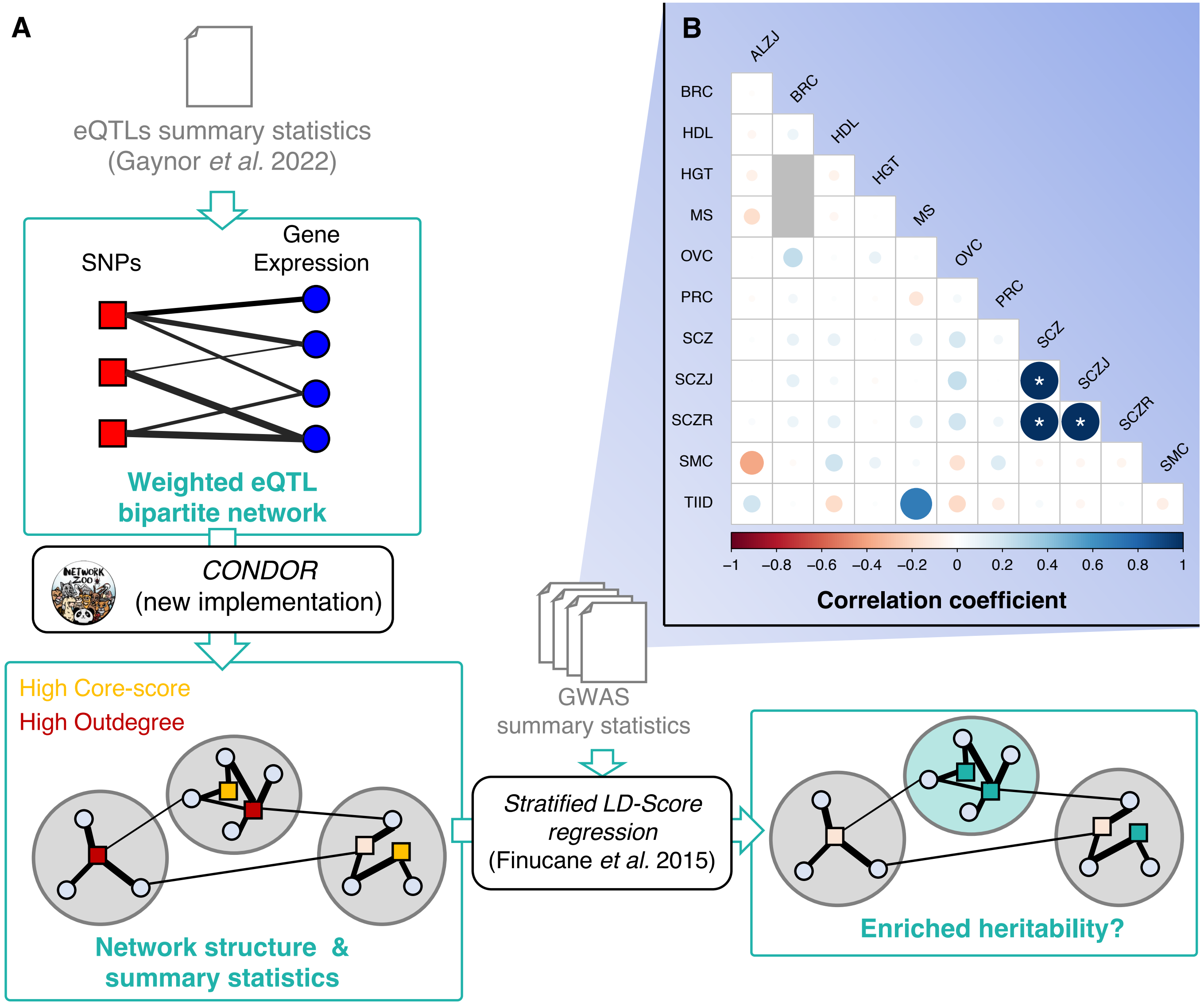
10 traits and a wide range of genetic architecture

Trait or disease	Abbreviation	Genetic structure	Estimated genetic heritability
Alzheimer's disease	ALZJ	Oligogenic	58-90%
Breast Cancer	BRC	Polygenic	31%
HDL	HDL	Polygenic	40-60%
Height	HGT	Omnigenic	50%
Multiple Sclerosis	MS	Polygenic	64%
Ovarian Cancer	OVC	Polygenic	39%
Prostate Cancer	PRC	Polygenic	57%
Schizophrenia	SCZP	Polygenic	79%
Schizophrenia	SCZR	Polygenic	79%
Schizophrenia	SCZ	Polygenic	79%
Smoking Cessation	SMC	Polygenic	75%
Type 2 diabetes	TIID	Oligogenic	25-72%

Where is most of the heritability located?



eQTLs summary statistics (Gaynor *et al.* 2022)

SNPs

Gene Expression

Weighted eQTL bipartite network

CONDOR (new implementation)

High Core-score

High Outdegree

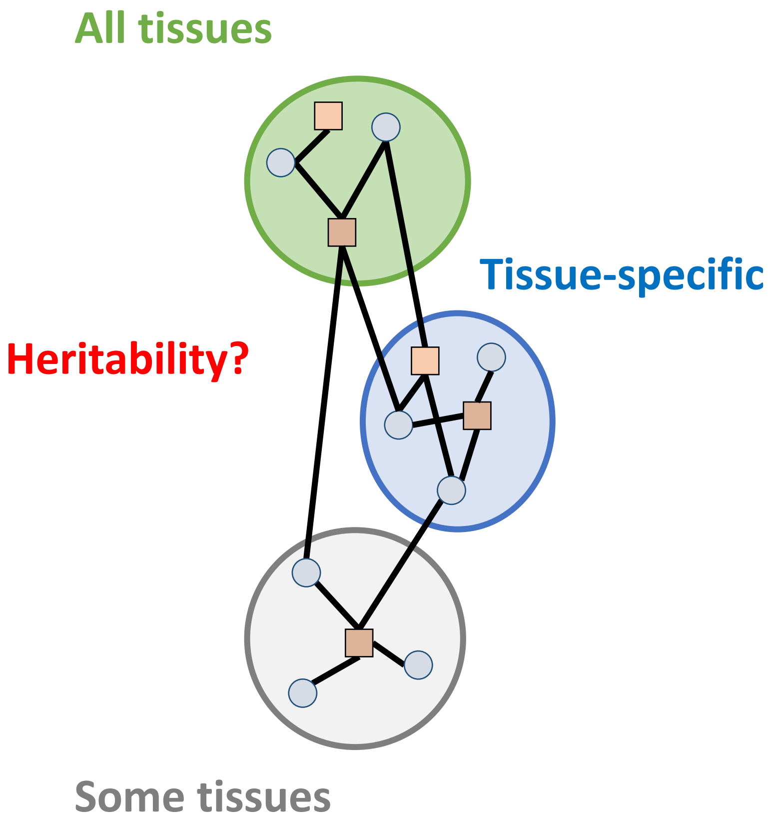
Network structure & summary statistics

GWAS summary statistics

Stratified LD-Score regression (Finucane *et al.* 2015)

Enriched heritability?

In which modules is most of the heritability located?



All tissues

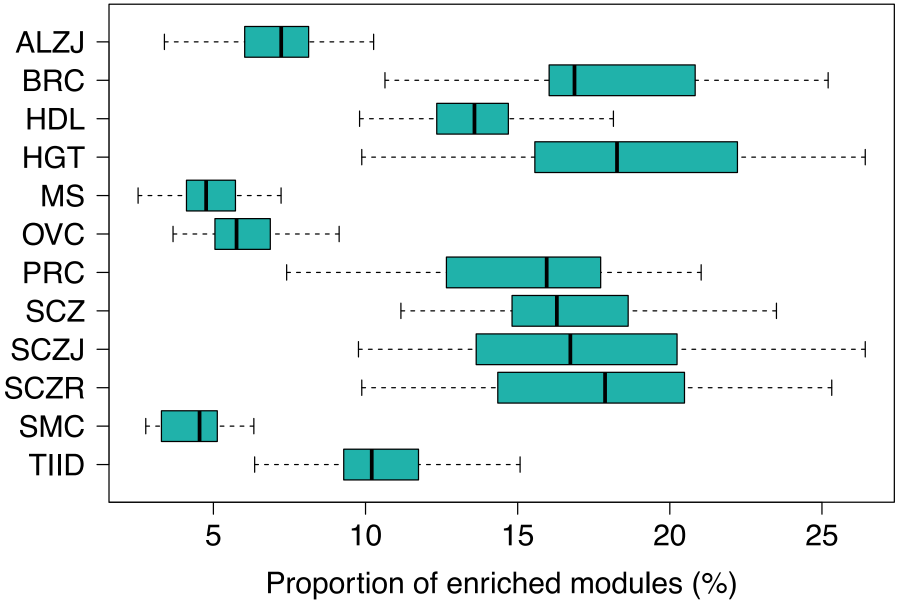
Tissue-specific

Heritability?

Some tissues

Heritability is clustered in a few biologically-relevant modules

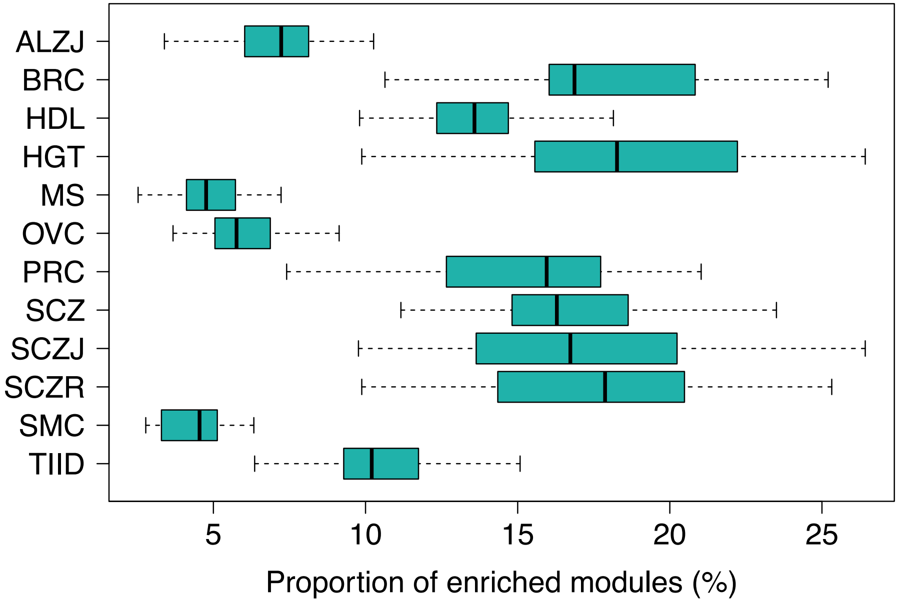
Proportion of modules enriched for SNPs carrying a high heritability



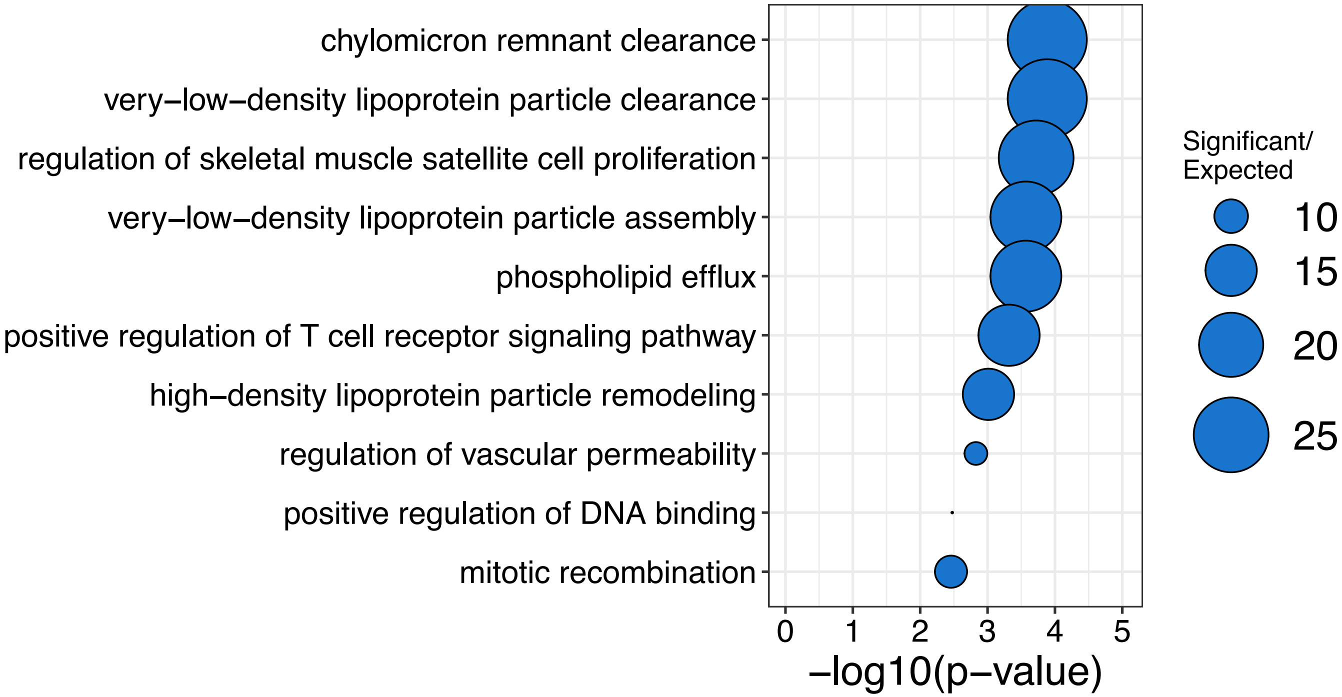
- ➢ **Most of the heritability is clustered in a few modules**

Heritability is clustered in a few biologically-relevant modules

Proportion of modules enriched for SNPs carrying a high heritability

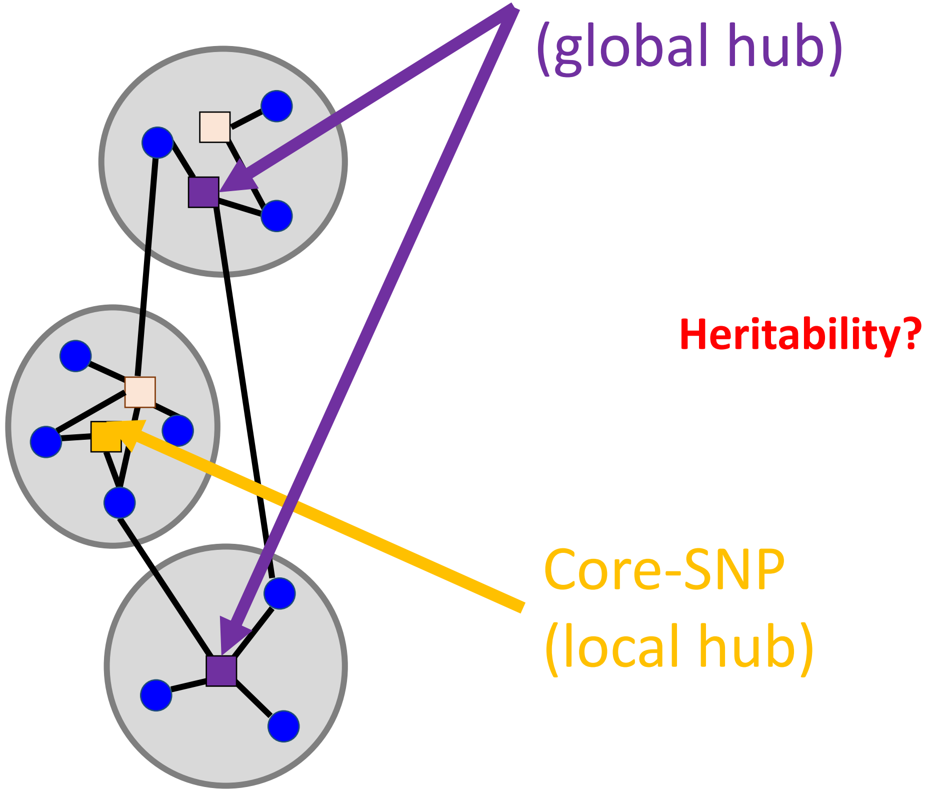


HDL levels heritability
Lipoprotein turn-over module (Adipose Visceral)



- ➢ **Most of the heritability is clustered in a few modules**
- ➢ **Heritability is clustered in tissue-specific, biologically relevant modules**

In which SNP classes is heritability located?

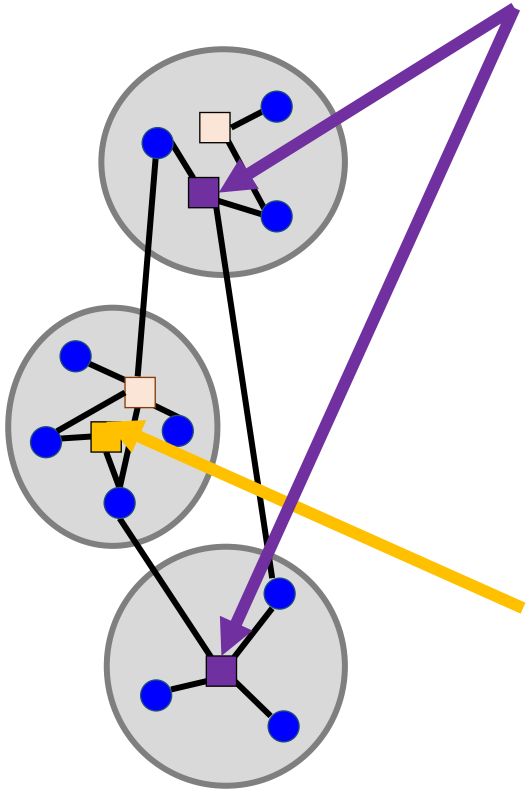


High-degree SNP
(global hub)

Heritability?

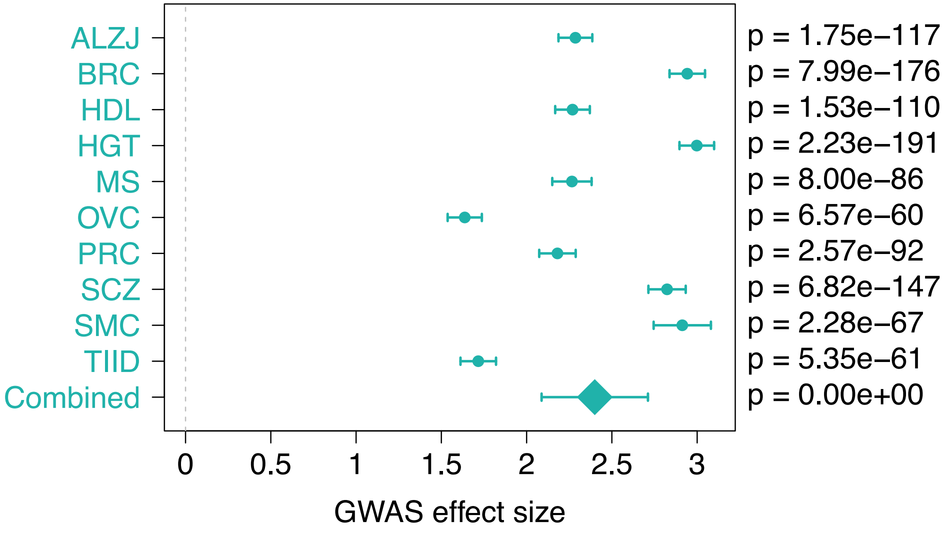
Core-SNP
(local hub)

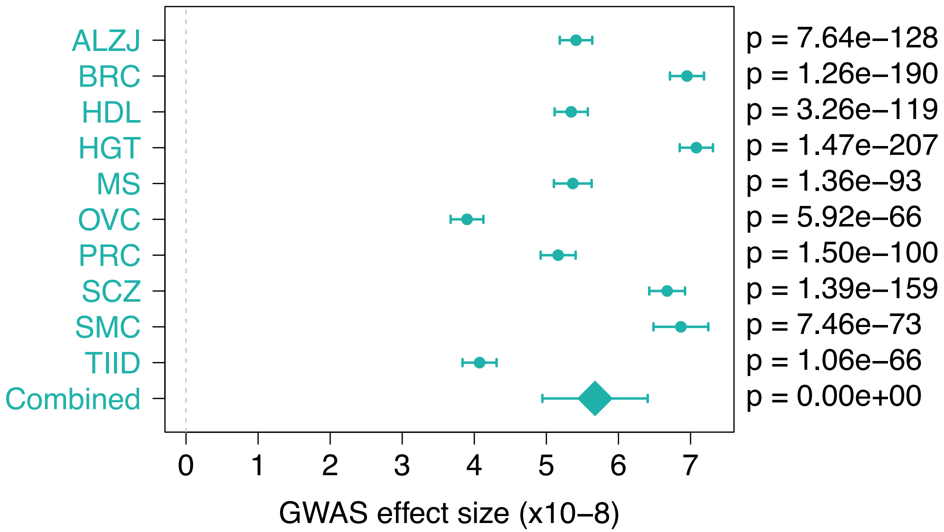
Heritability is clustered in global and local hubs



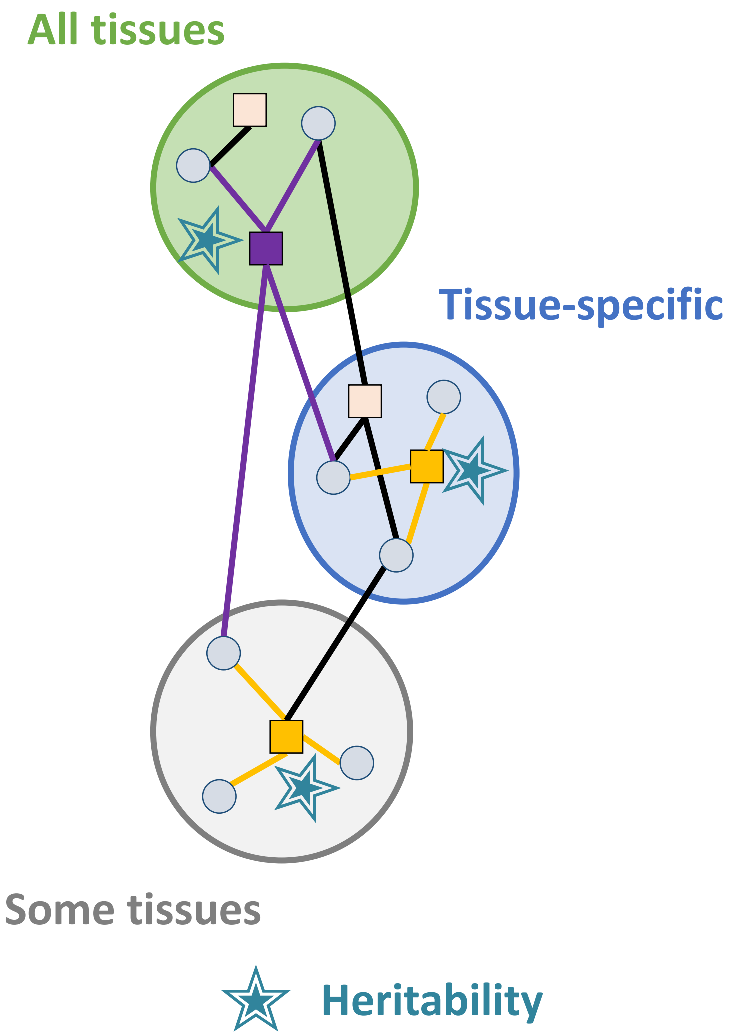
High-degree SNP
(global hub)

Core-SNP
(local hub)





Conclusion: polygenic trait heritability in eQTL networks



Heritability is clustered in

- Tissue-specific modules (Limit the propagation of mutation effect?)
- Local and global hubs (higher-than-average impact on function?)

➢ **Structuration & Tissue-specificity open up paths for polygenic traits to evolve!**

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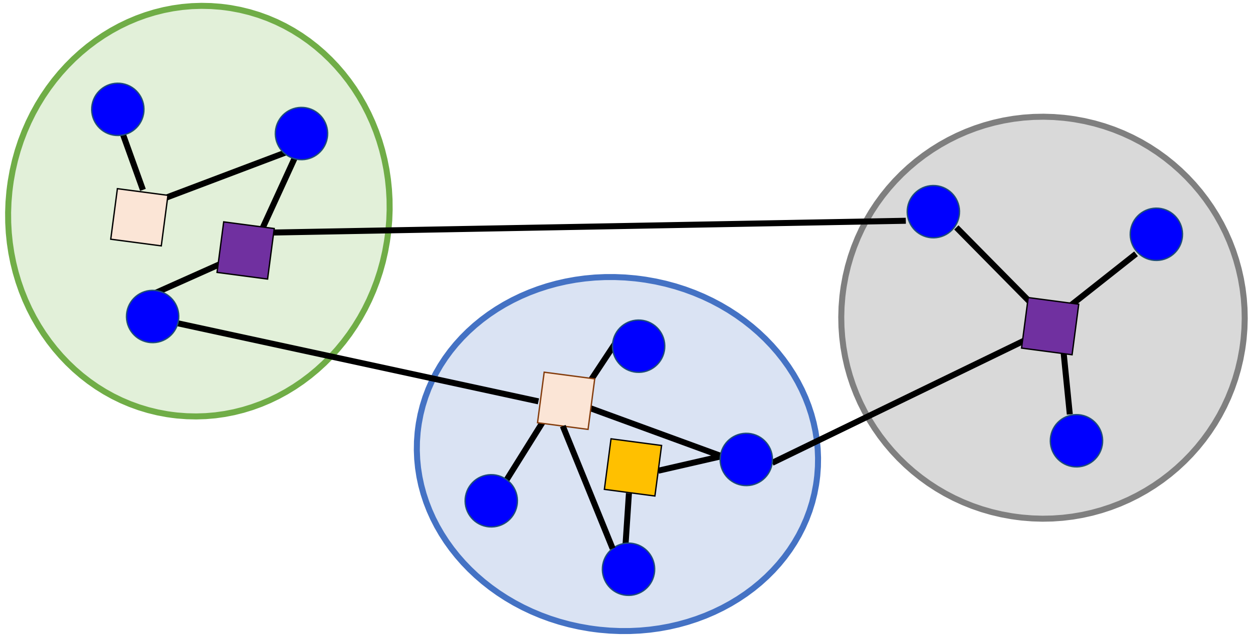
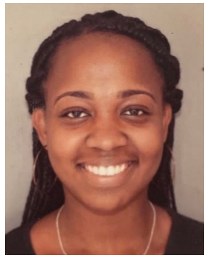
Where is selection located?



Fanny Pouyet

Frédéric Austerlitz

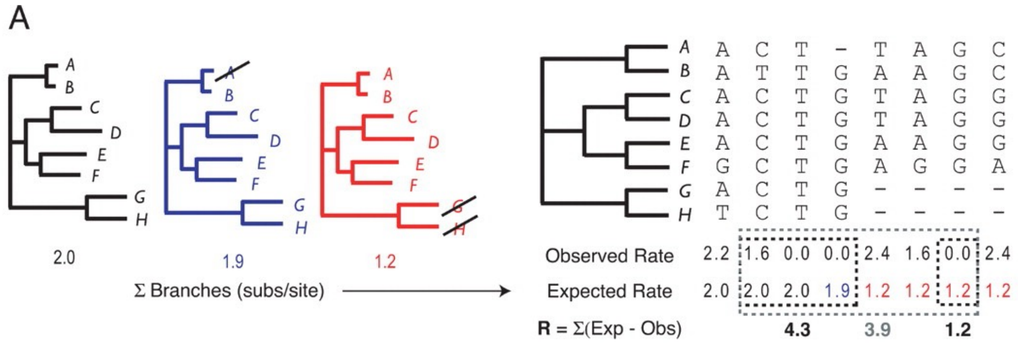


Rosanne Phebe
(M1 Student)

Themis Lemarchand
(M2 Student)

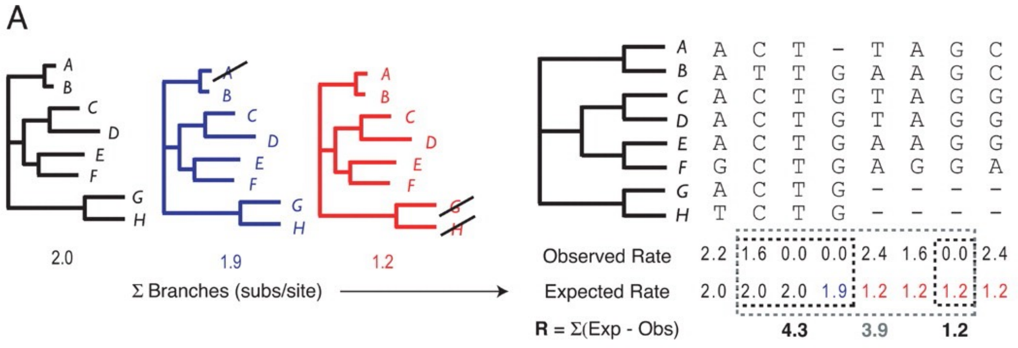
- **Negative selection?**
- **Positive selection?**
- **Polygenic selection?**

Global and local hubs are generally constrained



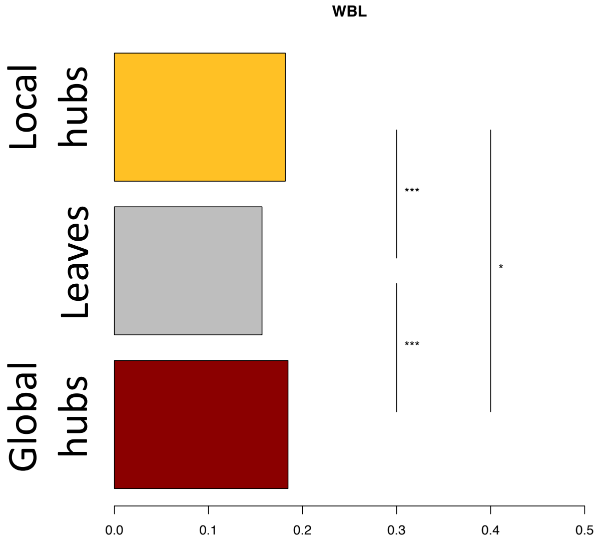
Principle of GERP score

Global and local hubs are generally constrained



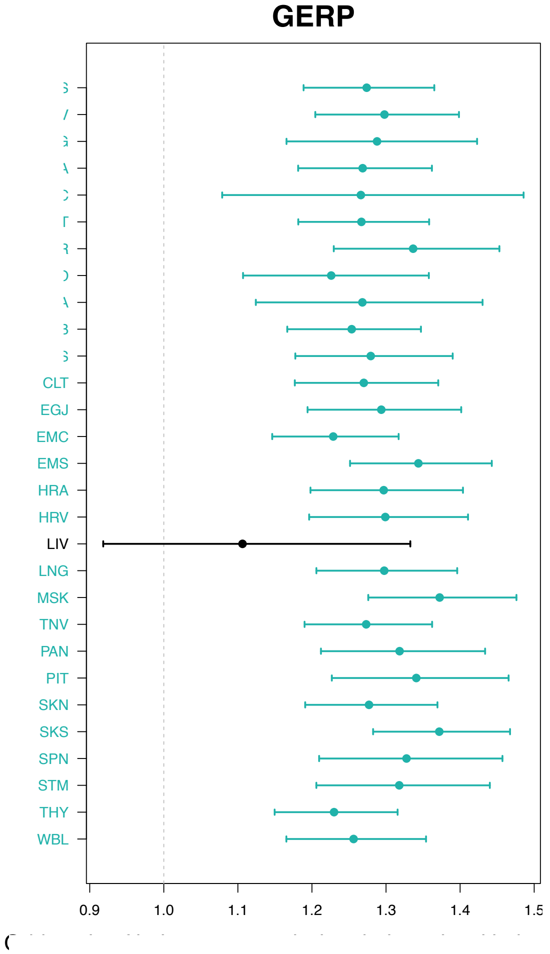
Principle of GERP score

In whole blood network

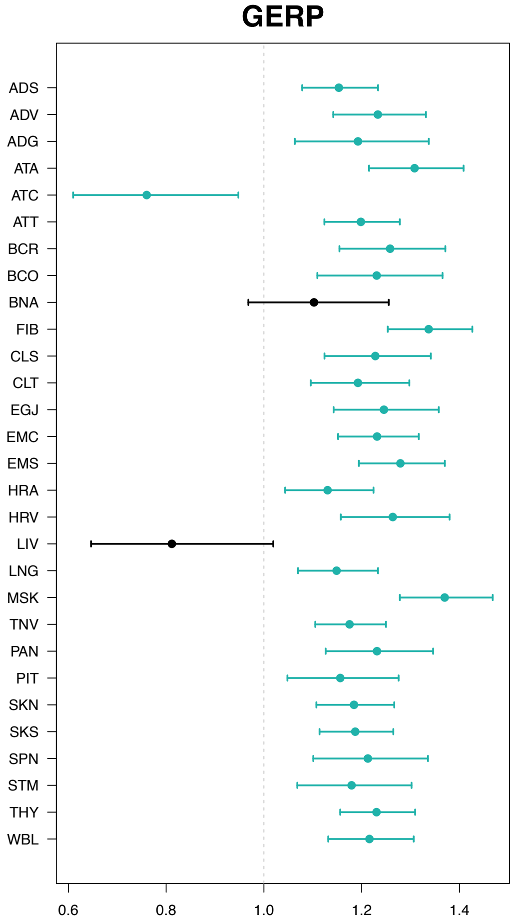


Proportion of conserved sites

Tissues



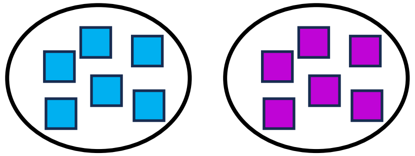
Odds Ratios for local hubs



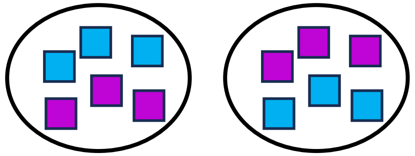
Odds Ratios for global hubs

- **Hubs are generally more constrained than leaves**

Local hubs are enriched for high population differentiation

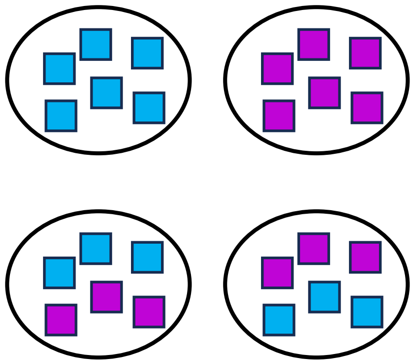


$F_{ST} = 1$



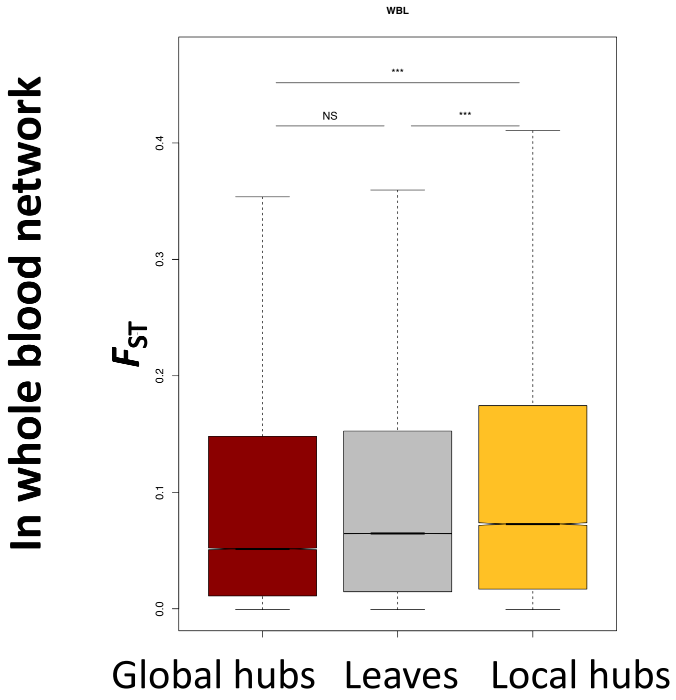
$F_{ST} = 0$

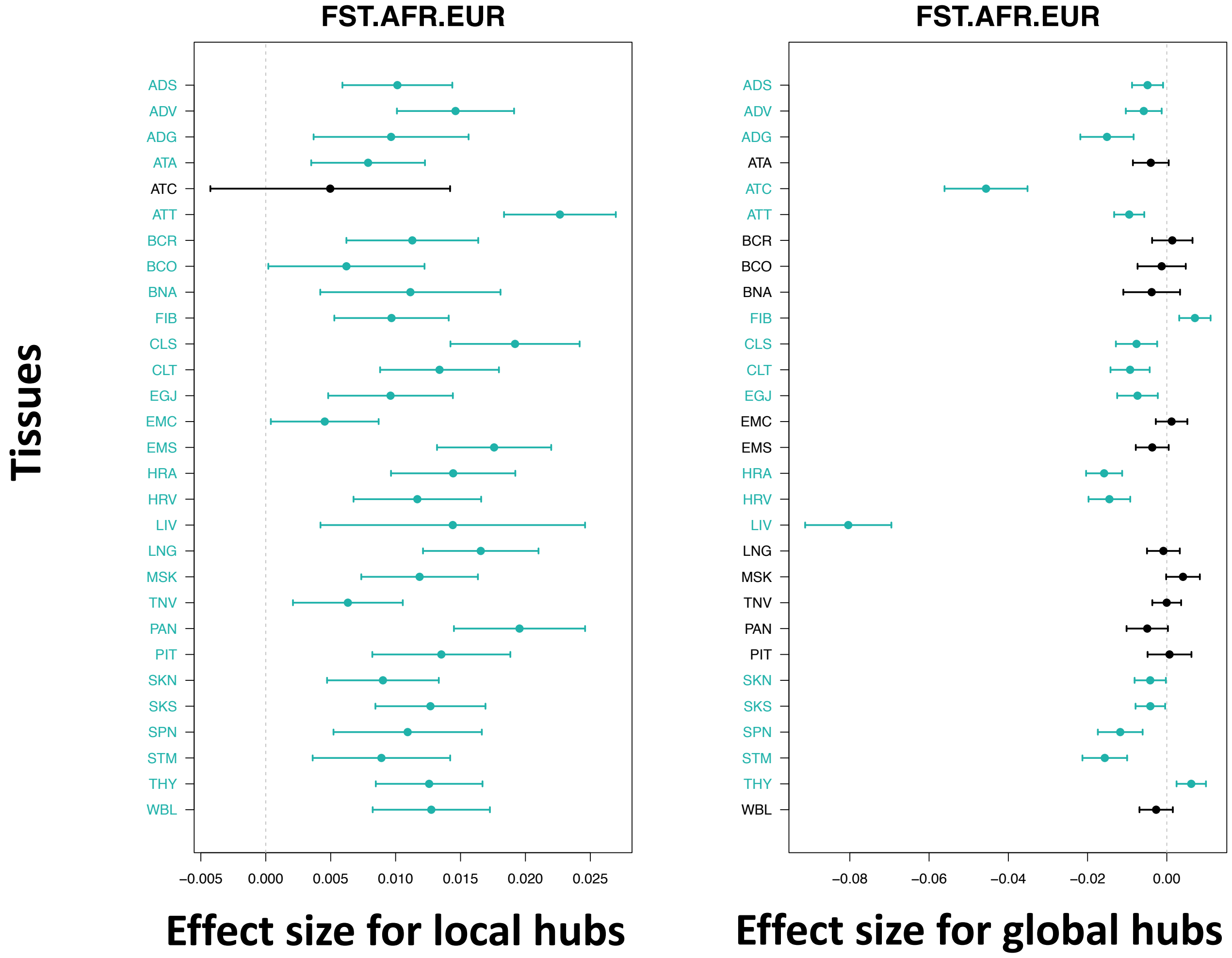
Local hubs are enriched for high population differentiation



$F_{ST} = 1$

$F_{ST} = 0$





- **Local hubs are enriched for frequency shifts (polygenic selection)?**

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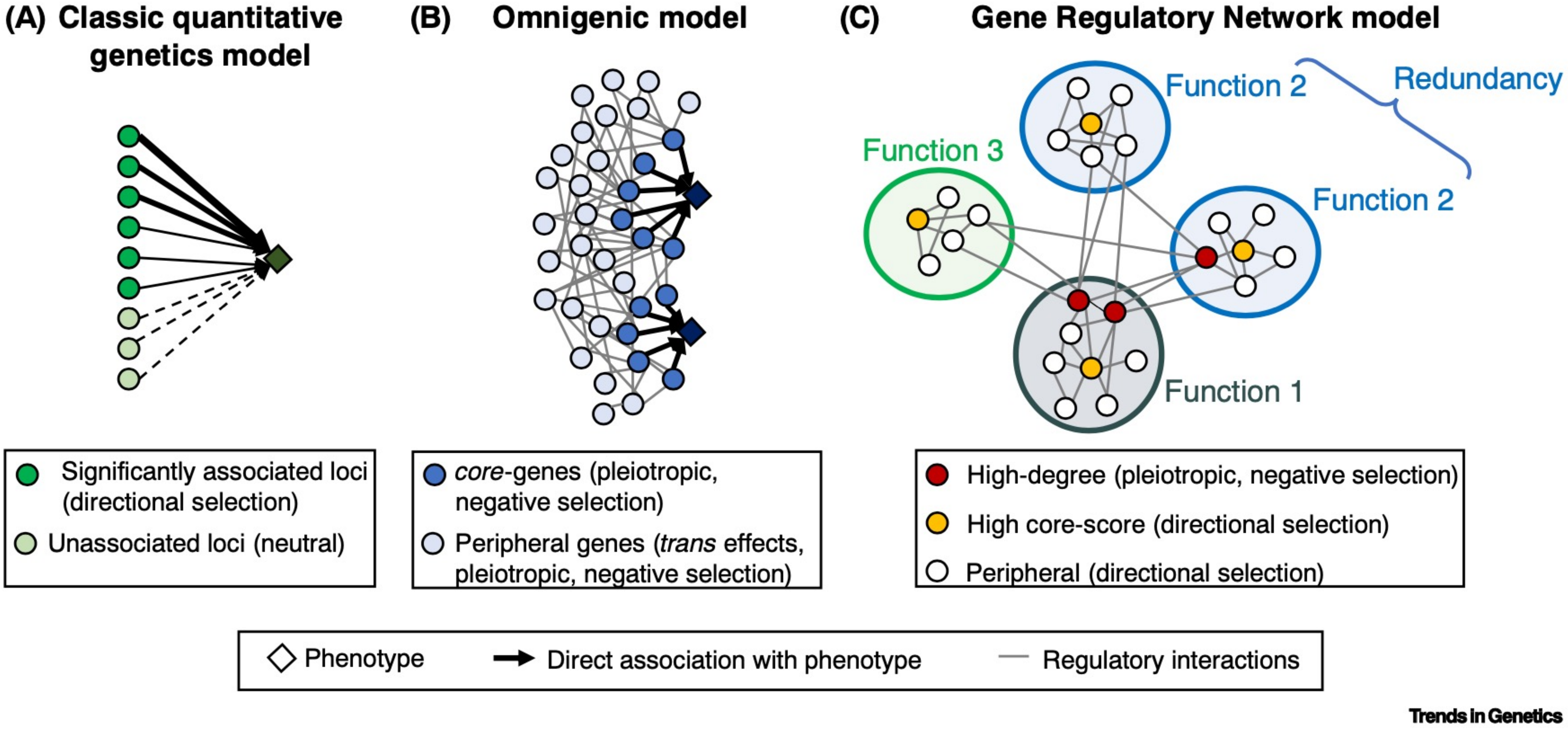
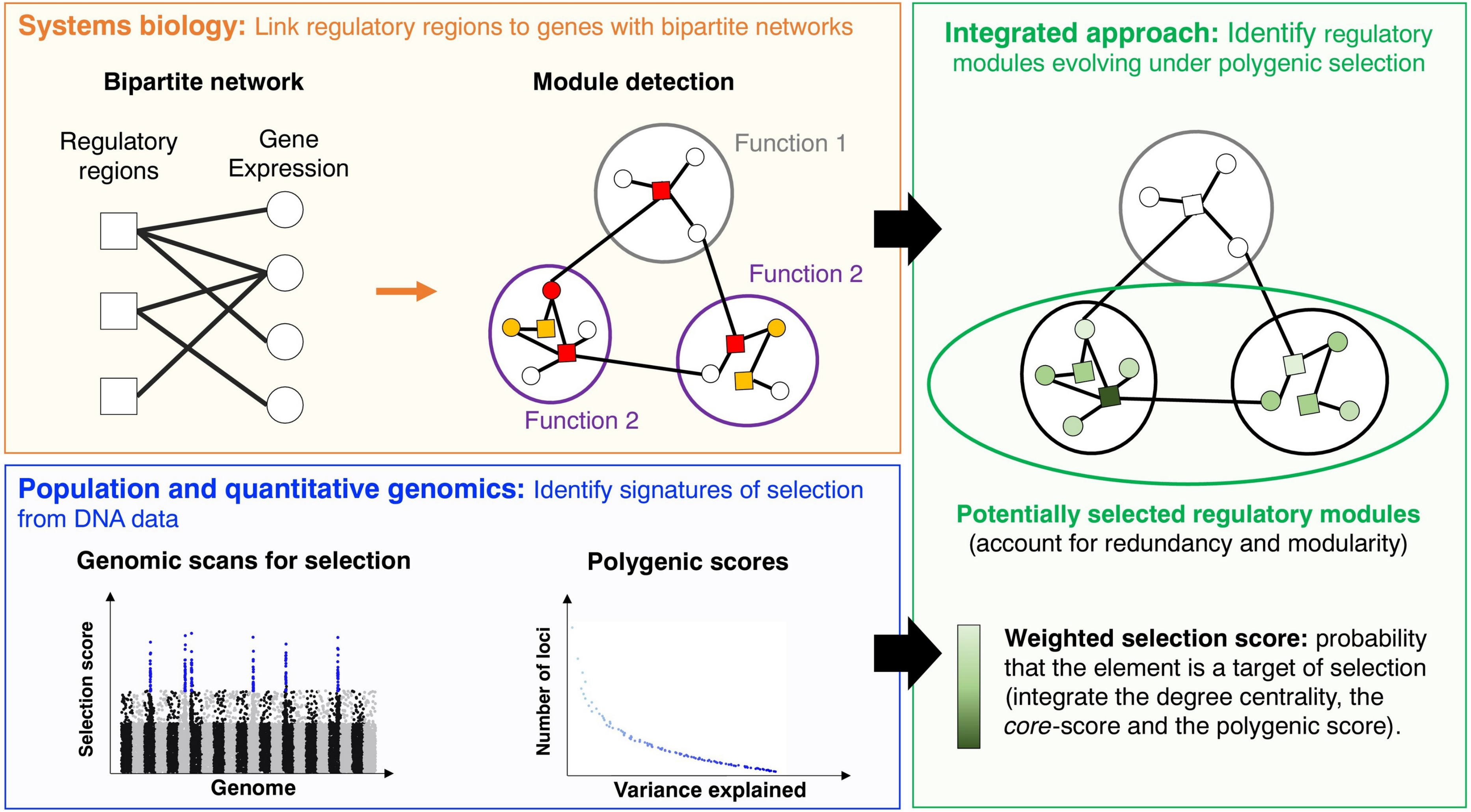
Summary: Consequences of model on adaptation



Proposed approach



Systems biology: Link regulatory regions to genes with bipartite networks

Bipartite network

Module detection

Population and quantitative genomics: Identify signatures of selection from DNA data

Genomic scans for selection

Polygenic scores

Integrated approach: Identify regulatory modules evolving under polygenic selection

Potentially selected regulatory modules
(account for redundancy and modularity)

Weighted selection score: probability that the element is a target of selection (integrate the degree centrality, the *core*-score and the polygenic score).

Trends in Genetics

Acknowledgments

GEvAD

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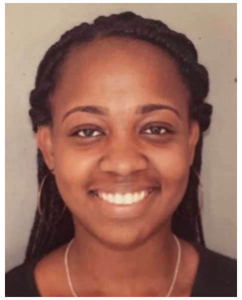
Fanny Pouyet



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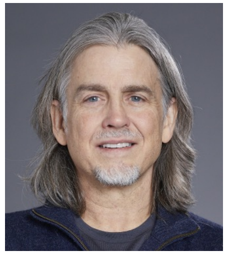
Harvard School of Public Health

Katherine L. Stone



John Quackenbush

Sheila Gaynor

University of Virginia

John Platig

Fundings

INRAE

université PARIS-SACLAY FACULTÉ DES SCIENCES D'ORSAY

MARIE CURIE ACTIONS

Agence Nationale de la Recherche ANR

To go further

Trends in Genetics

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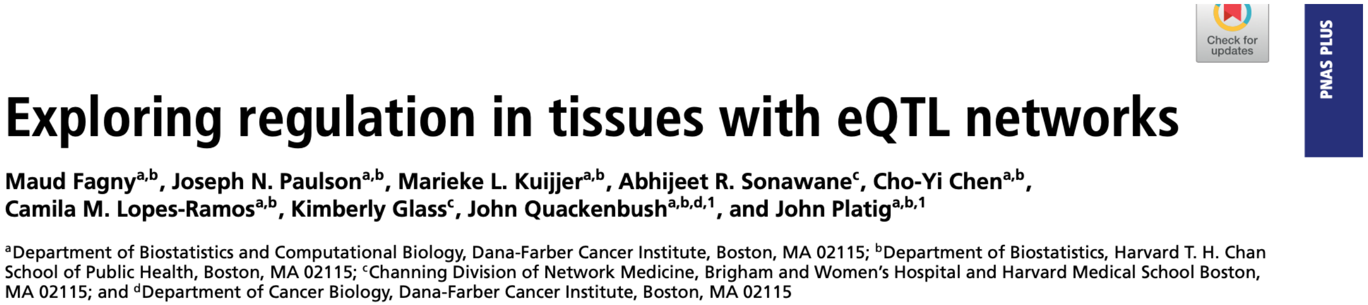
CellPress

Opinion

Polygenic Adaptation: Integrating Population Genetics and Gene Regulatory Networks

Maud Fagny[1], Frédéric Austerlitz[1]



PNAS PLUS

Check for updates

Exploring regulation in tissues with eQTL networks

Maud Fagny[a,b], Joseph N. Paulson[a,b], Marieke L. Kuijjer[a,b], Abhijeet R. Sonawane[c], Cho-Yi Chen[a,b], Camila M. Lopes-Ramos[a,b], Kimberly Glass[c], John Quackenbush[a,b,d,1], and John Platig[a,b,1]

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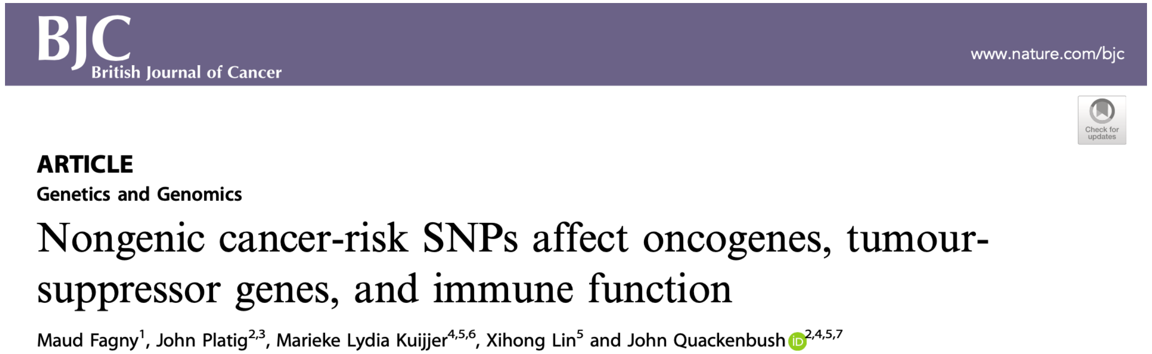

BJC British Journal of Cancer

www.nature.com/bjc

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ARTICLE

Genetics and Genomics

Nongenic cancer-risk SNPs affect oncogenes, tumour-suppressor genes, and immune function

Maud Fagny[1], John Platig[2,3], Marieke Lydia Kuijjer[4,5,6], Xihong Lin[5] and John Quackenbush[2,4,5,7]

CSH Cold Spring Harbor Laboratory

bioRχiv

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Complex Traits Heritability is Highly Clustered in the eQTL Bipartite Network

Katherine Stone[1,2], John Platig[3,4,5], John Quackenbush[1,2,6], and Maud Fagny[1,2,7]

Advertisement: Postdoc 24 months

Polygenic selection in gene regulatory networks

From September 2024

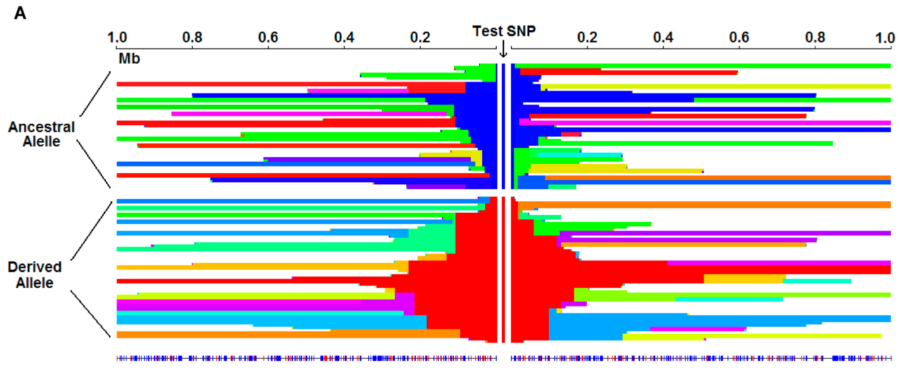
GQE – Le Moulon – IDEEV – Université Paris-Saclay

GEvAD team

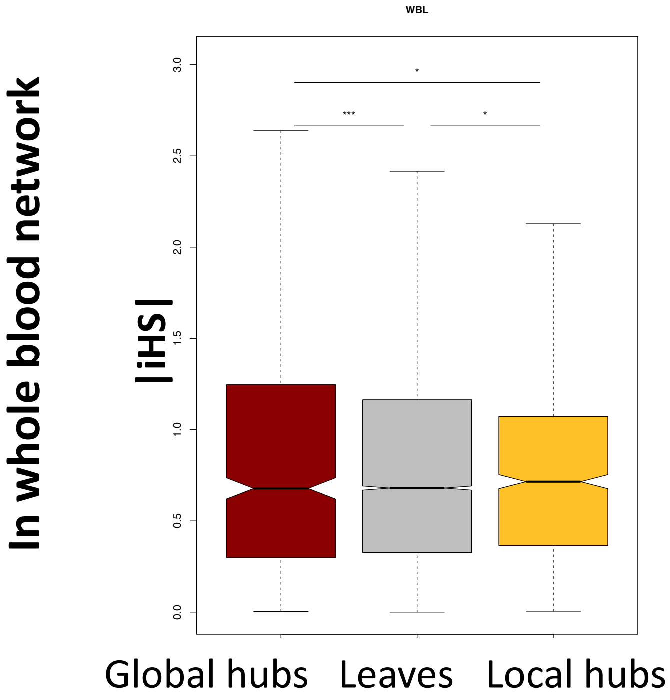
Funded by ANR NETWITS

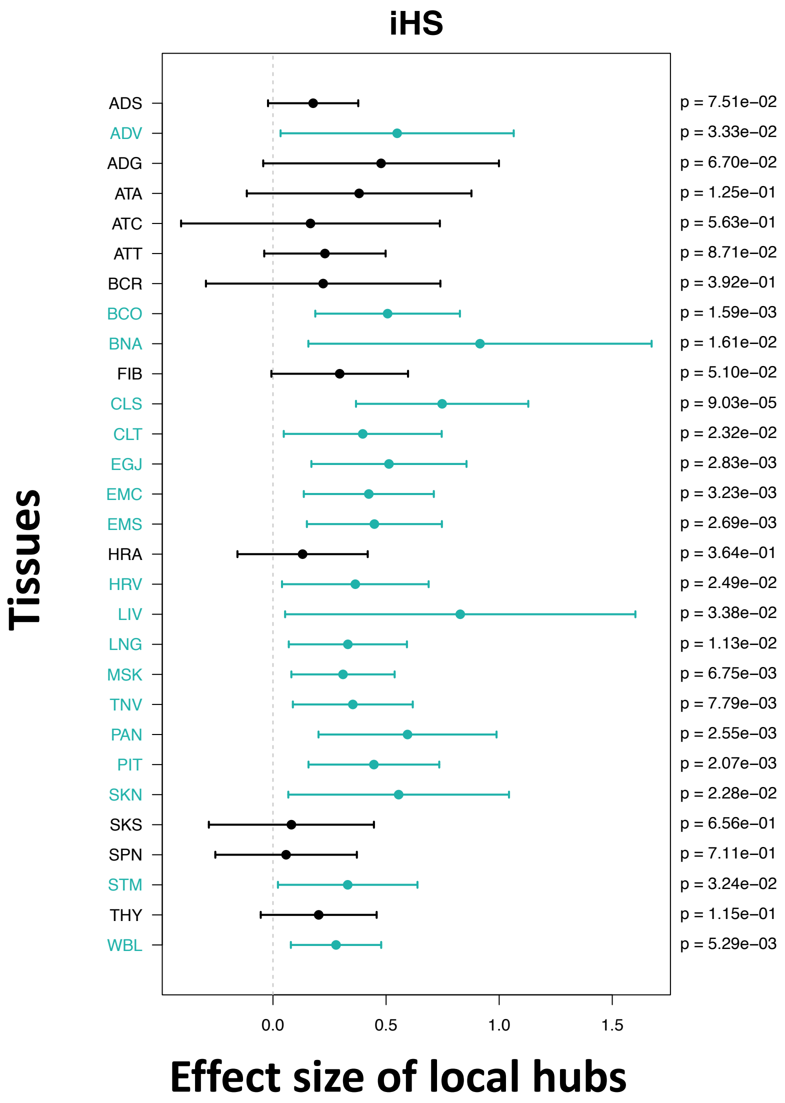
https://moulon.inrae.fr/en/news/2023/11/research-engineer-position-24-months/

No clear pattern for recent sweep signatures



Haplotype length





Possible scenario of gene expression changes caused by SNPs