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## Gene regulatory network structure help us understand how polygenic phenotypes adapt

Katherine Stone, John Platig, Frederic Austerlitz, John Quackenbush, Maud Fagny

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**HAL Id: hal-04646291**

**<https://hal.inrae.fr/hal-04646291v1>**

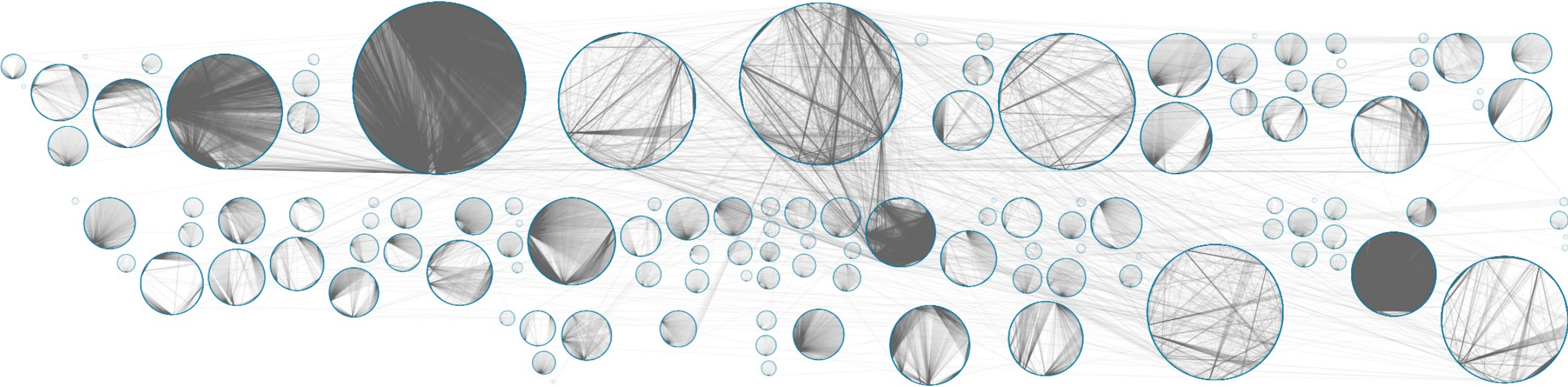
Submitted on 12 Jul 2024

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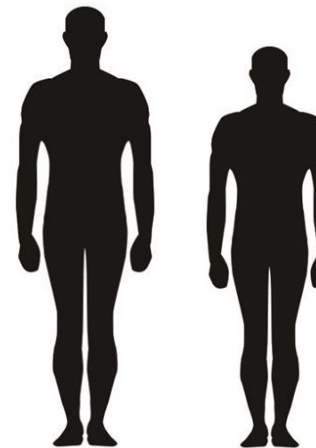
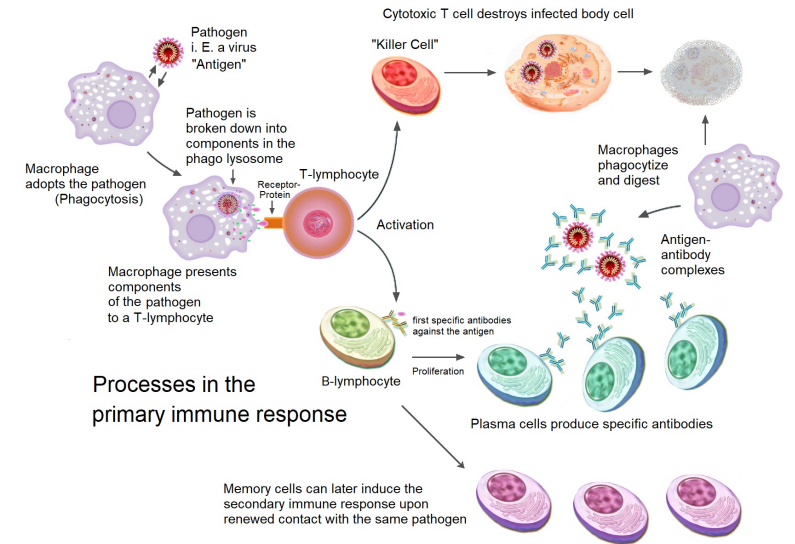
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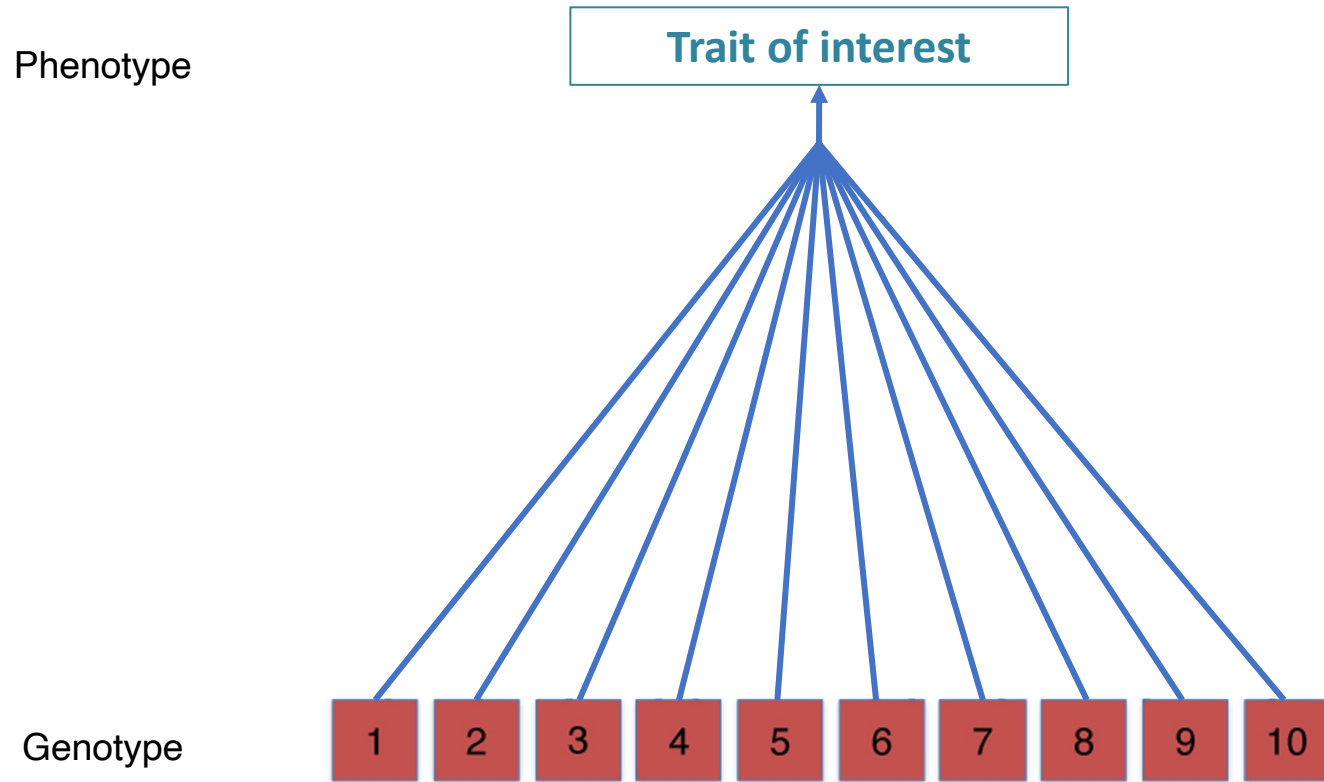
# Gene regulatory network structure help us understand how polygenic phenotypes adapt

Maud Fagny, PhD

# A role for polygenic phenotypes in adaptation



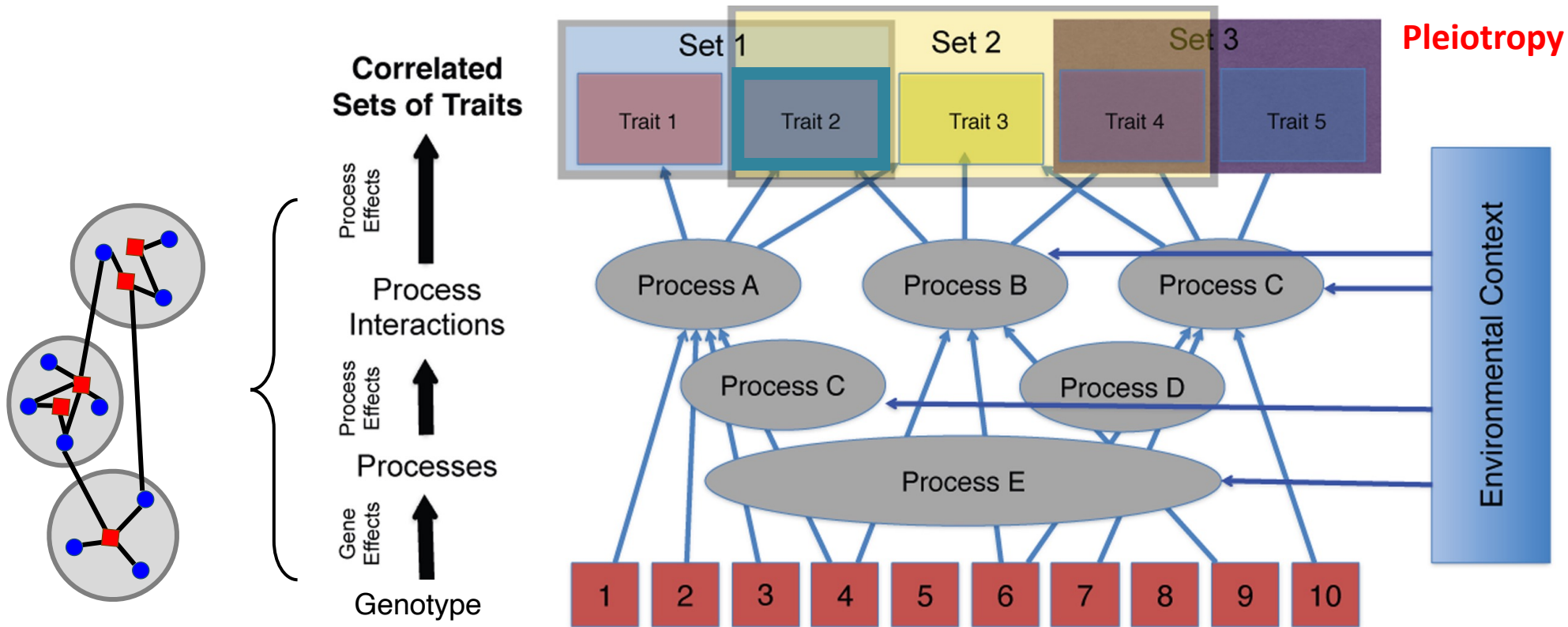
# Genetic architecture of polygenic traits



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

- One trait determined by several independent loci

# Genetic architecture of polygenic traits



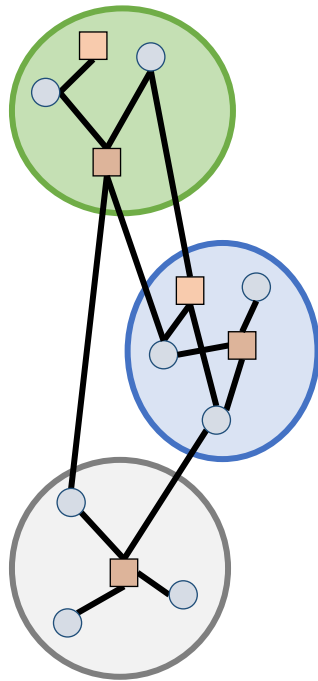
Adapted from Hallgrímsson *et al.*, *PLoS Genetics*, 2014

- A complex picture with high pleiotropy
- Dig deeper in the molecular structure to understand how polygenic traits can adapt

# Questions

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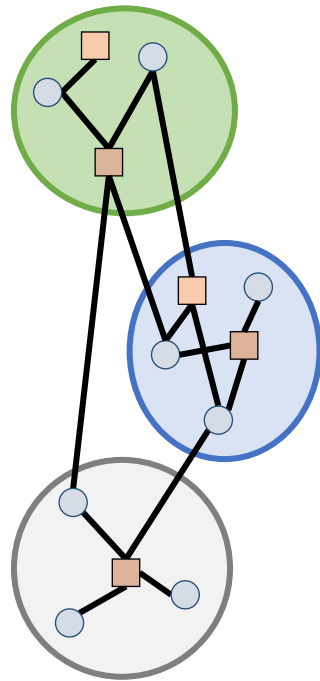
Heritability?



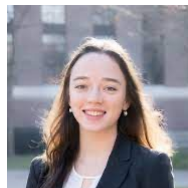
- **How is polygenic trait heritability spread in regulatory networks ?**
- **Is there a link between network topology and signature of selection ?**

# Questions

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



Katherine L. Stone  
(Bachelor student)



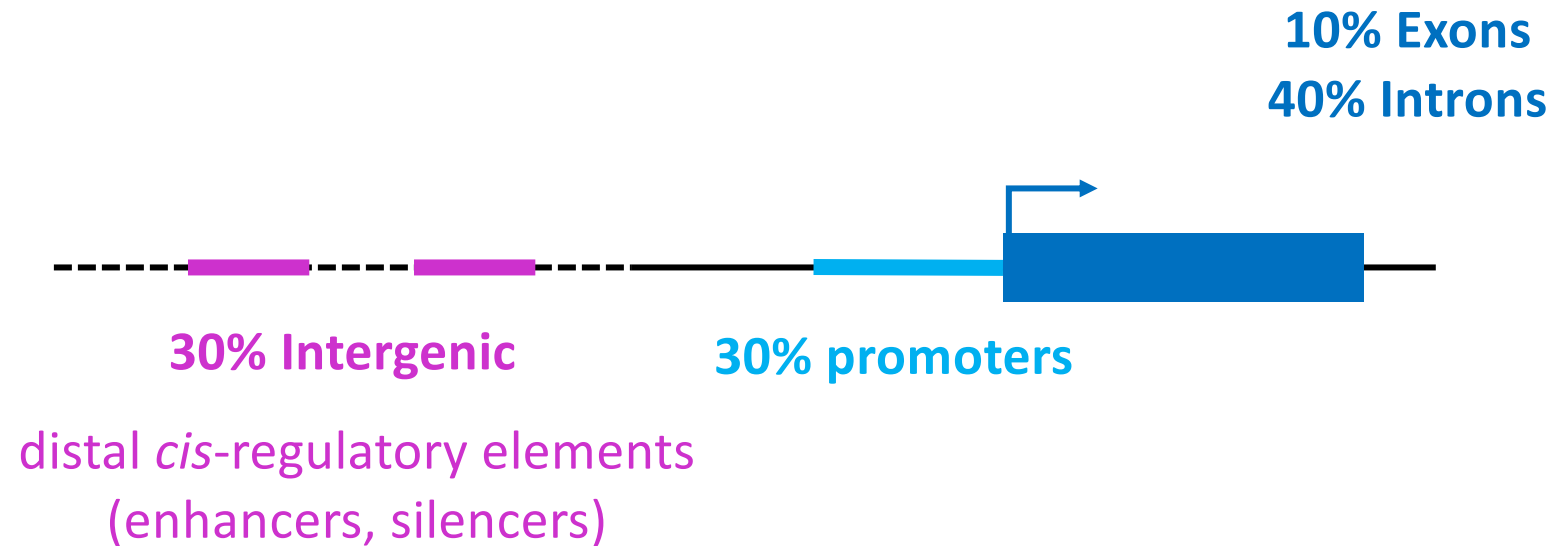
Sheila Gaynor  
(PhD Student)

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

# The importance of regulatory mutations

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## Location of SNP associated to polygenic traits in GWAS



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

# Summarizing regulatory interactions with eQTL networks

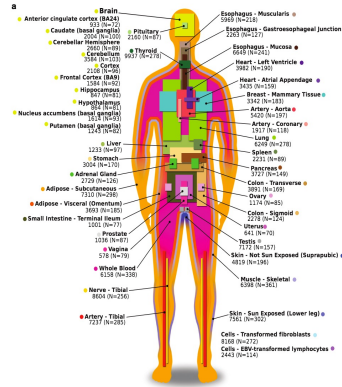


29 tissues

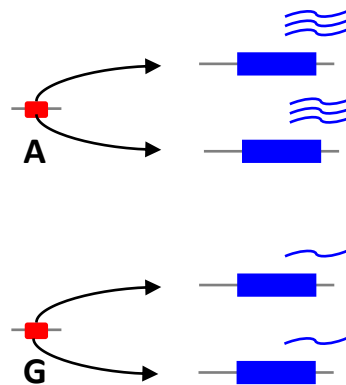
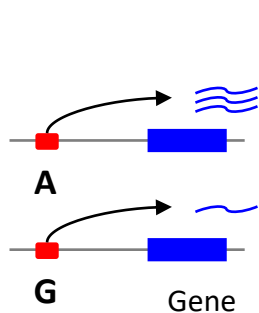
Up to 706 individuals

Genotypes

RNA-Seq data



GTEx data



eQTL summary statistics

# Making sense of eQTL networks

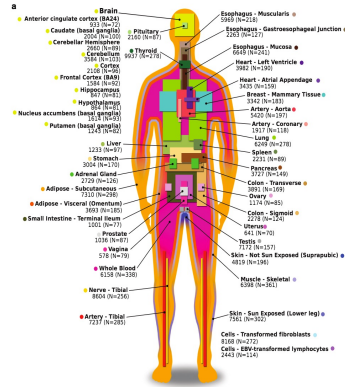


29 tissues

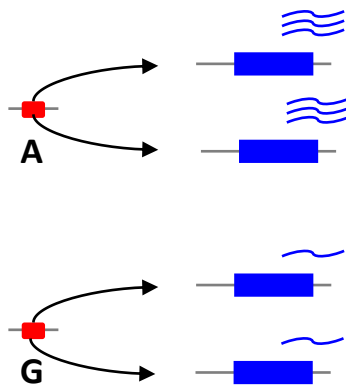
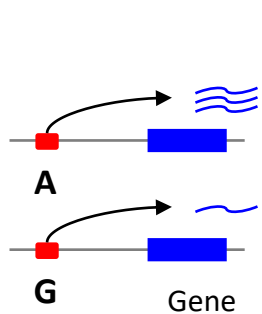
Up to 706 individuals

Genotypes

RNA-Seq data



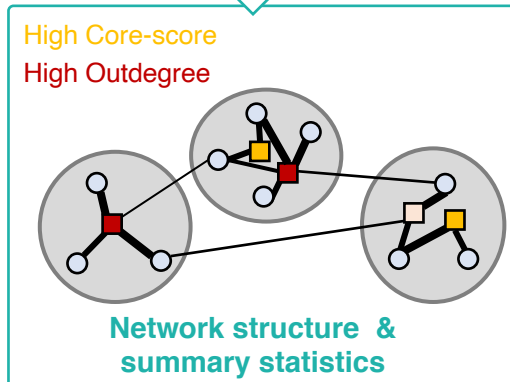
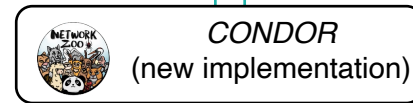
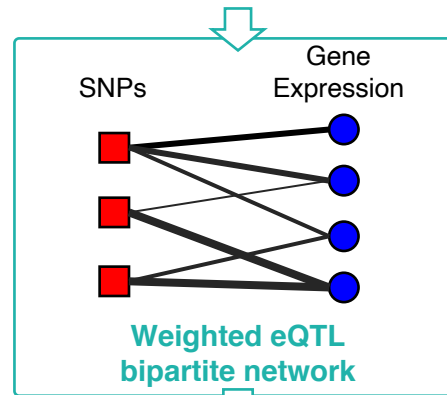
GTEx data



eQTL summary statistics

A

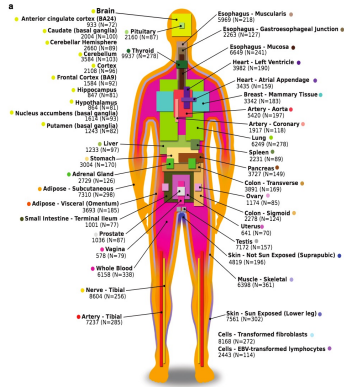
eQTLs summary statistics  
(Gaynor *et al.* 2022)



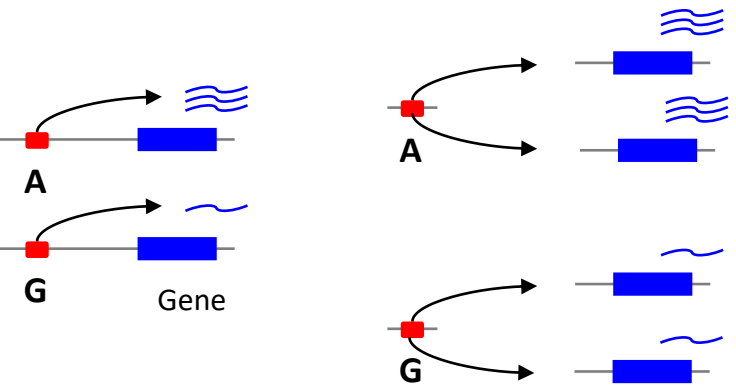
# GWAS summary statistics



29 tissues  
Up to 706 individuals  
Genotypes  
RNA-Seq data

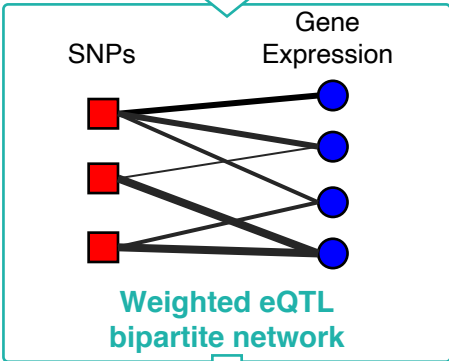


GTEx data

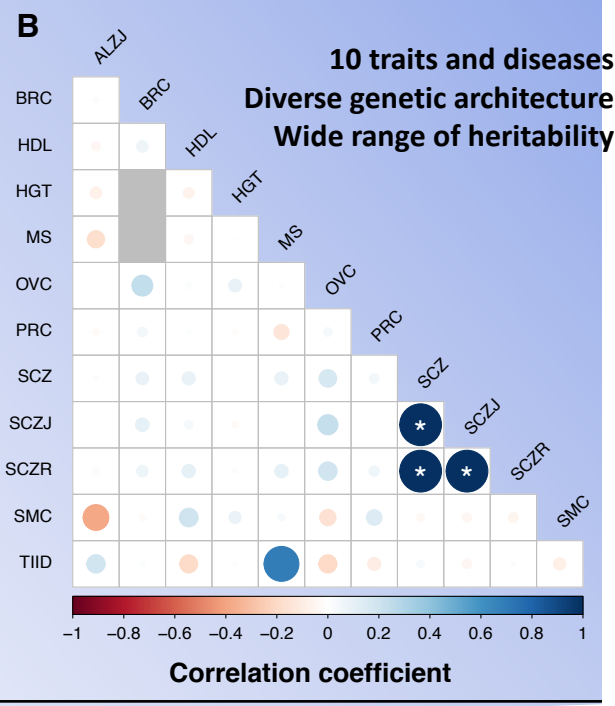
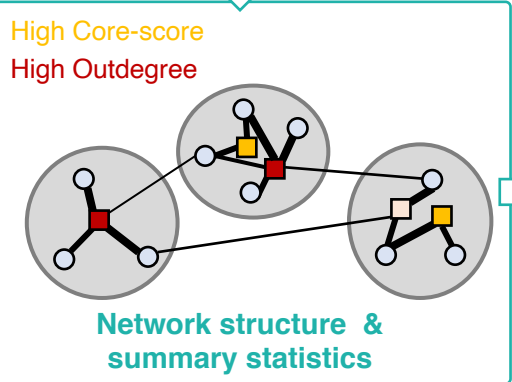


eQTL summary statistics

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



CONDOR  
(new implementation)

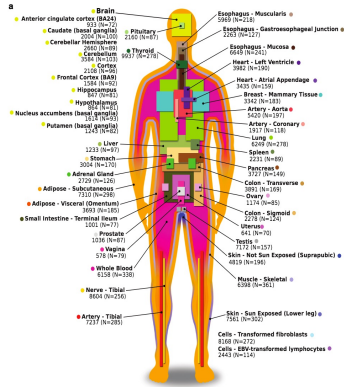


GWAS  
summary statistics

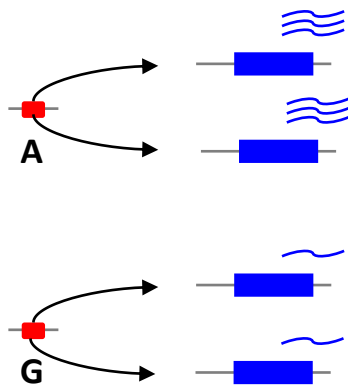
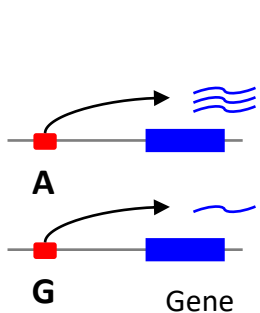
# Where is most of the heritability located?



29 tissues  
Up to 706 individuals  
Genotypes  
RNA-Seq data



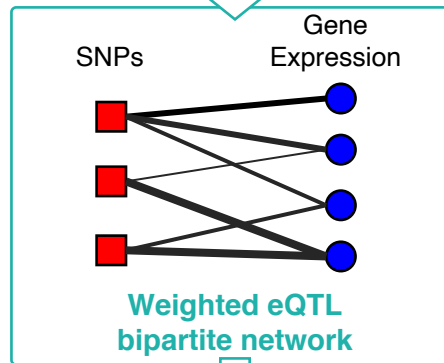
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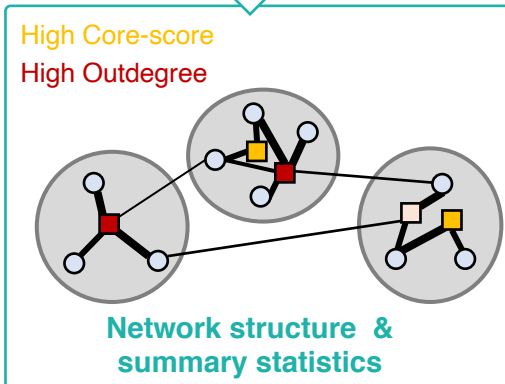
eQTL summary statistics

A

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

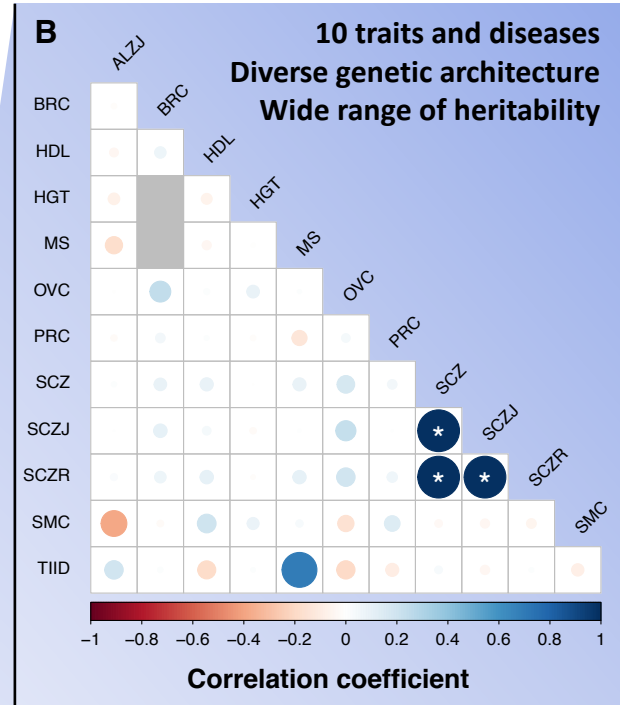
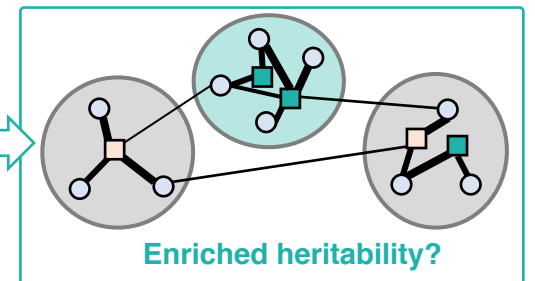


CONDOR  
(new implementation)



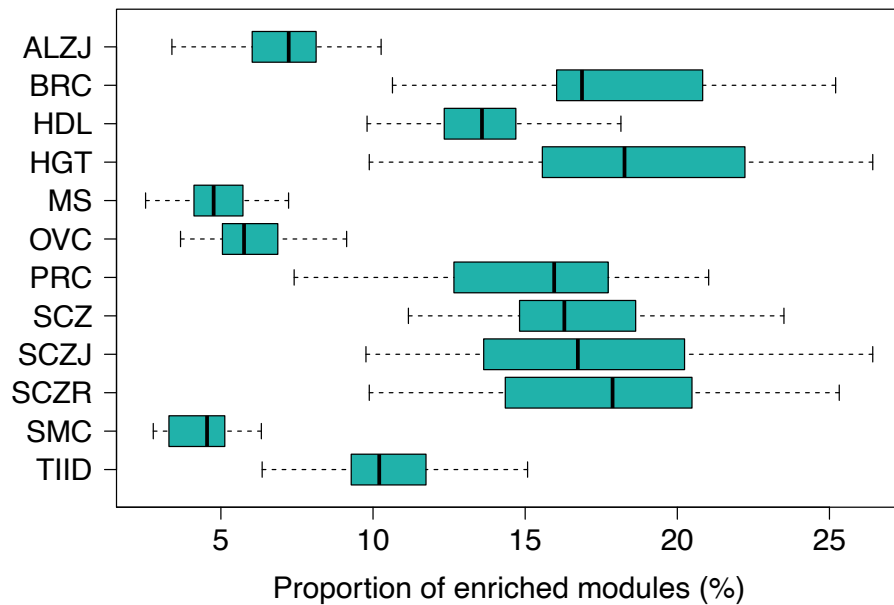
GWAS  
summary statistics

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



# Heritability is clustered in a few biologically-relevant modules

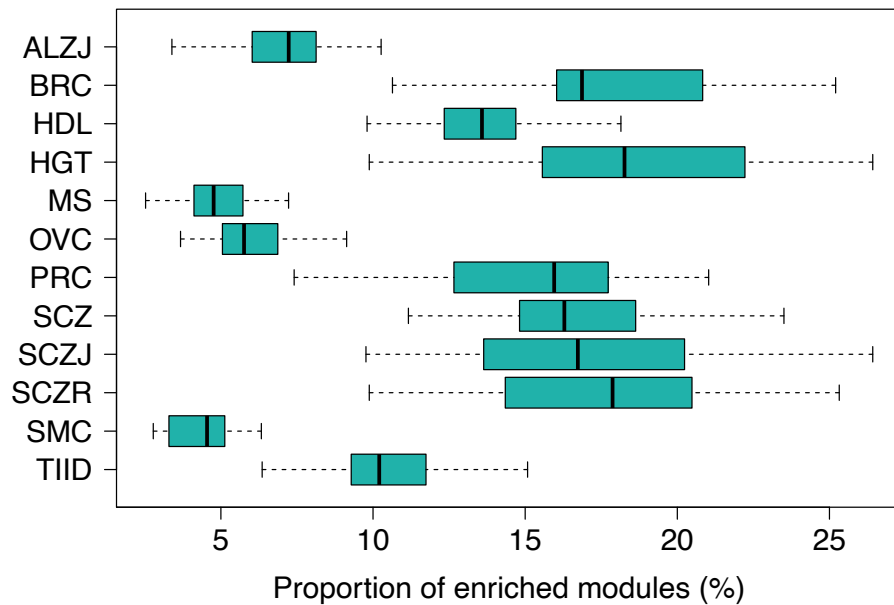
Proportion of modules enriched for SNPs carrying a high heritability



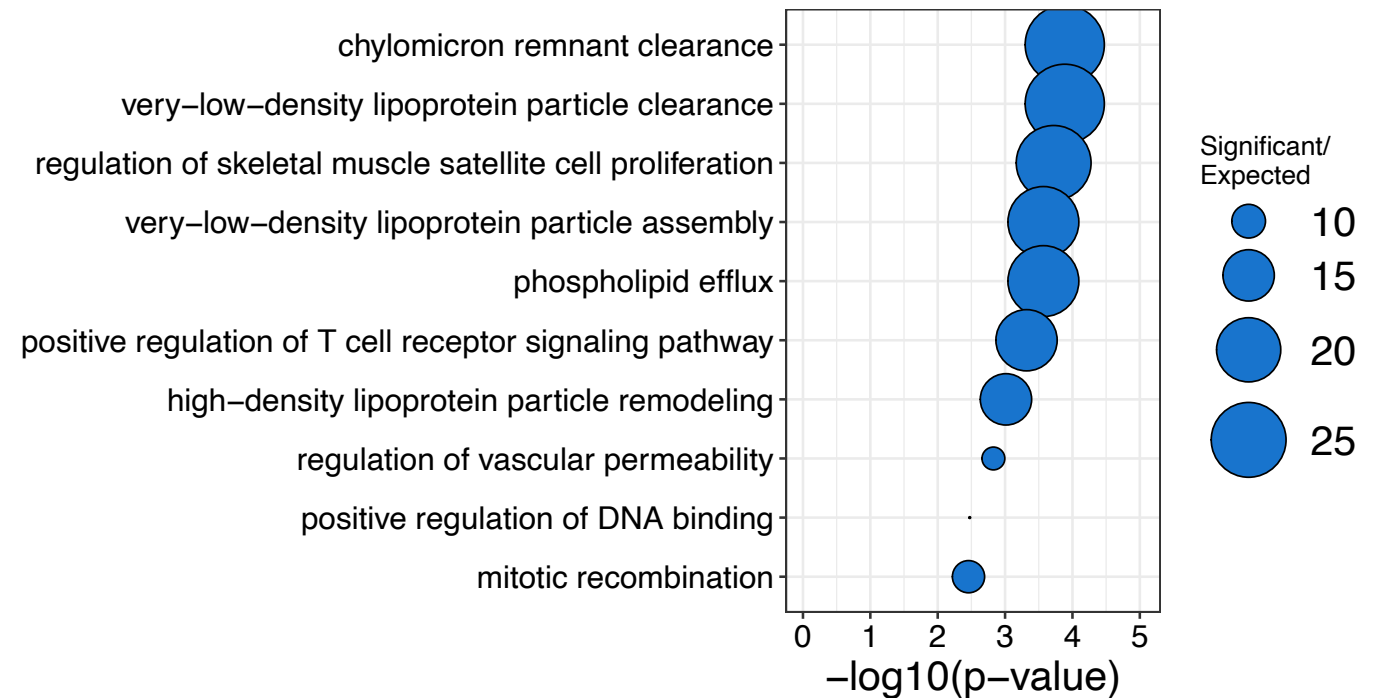
➤ Most of the heritability is clustered in a few modules

# Heritability is clustered in a few biologically-relevant modules

Proportion of modules enriched for SNPs carrying a high heritability



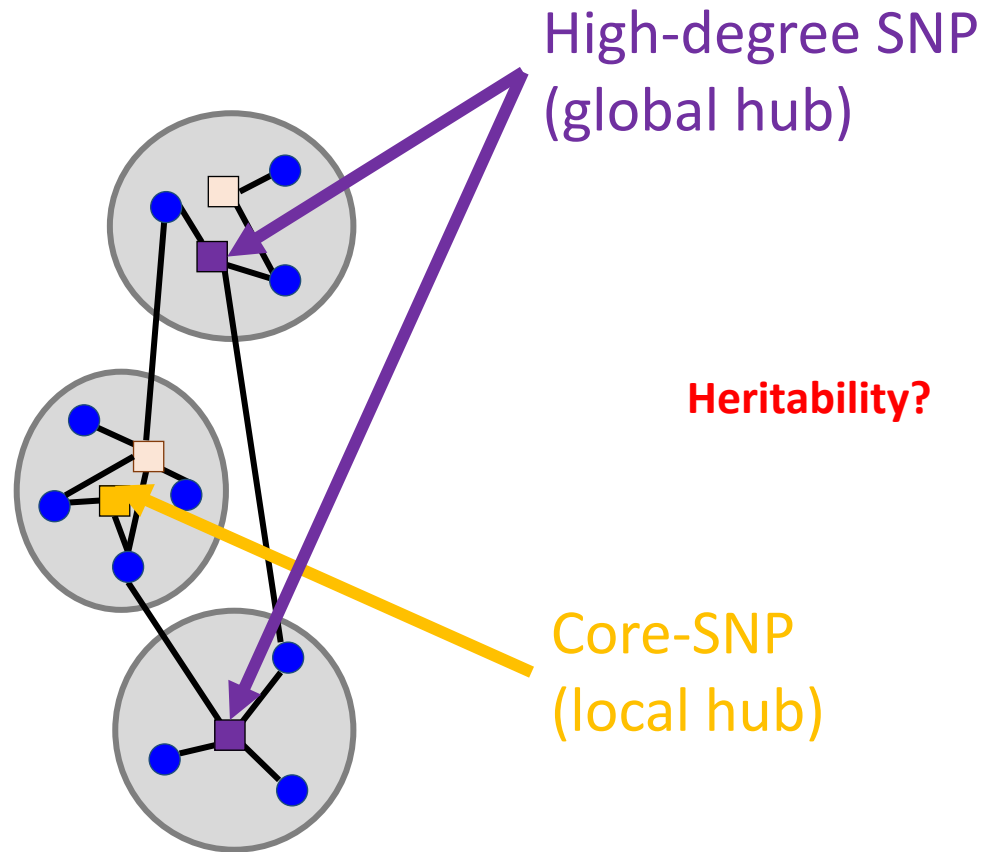
HDL levels heritability  
Lipoprotein turn-over module (Adipose Visceral)



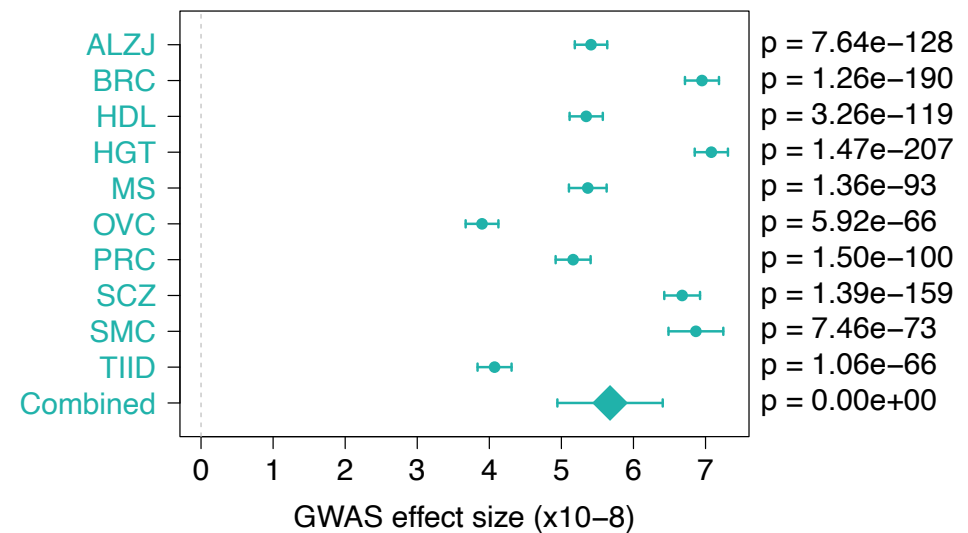
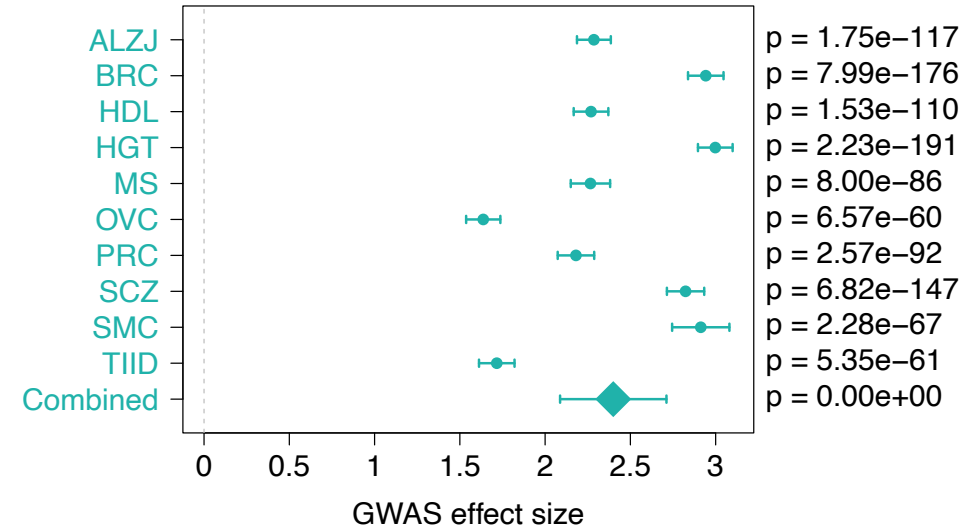
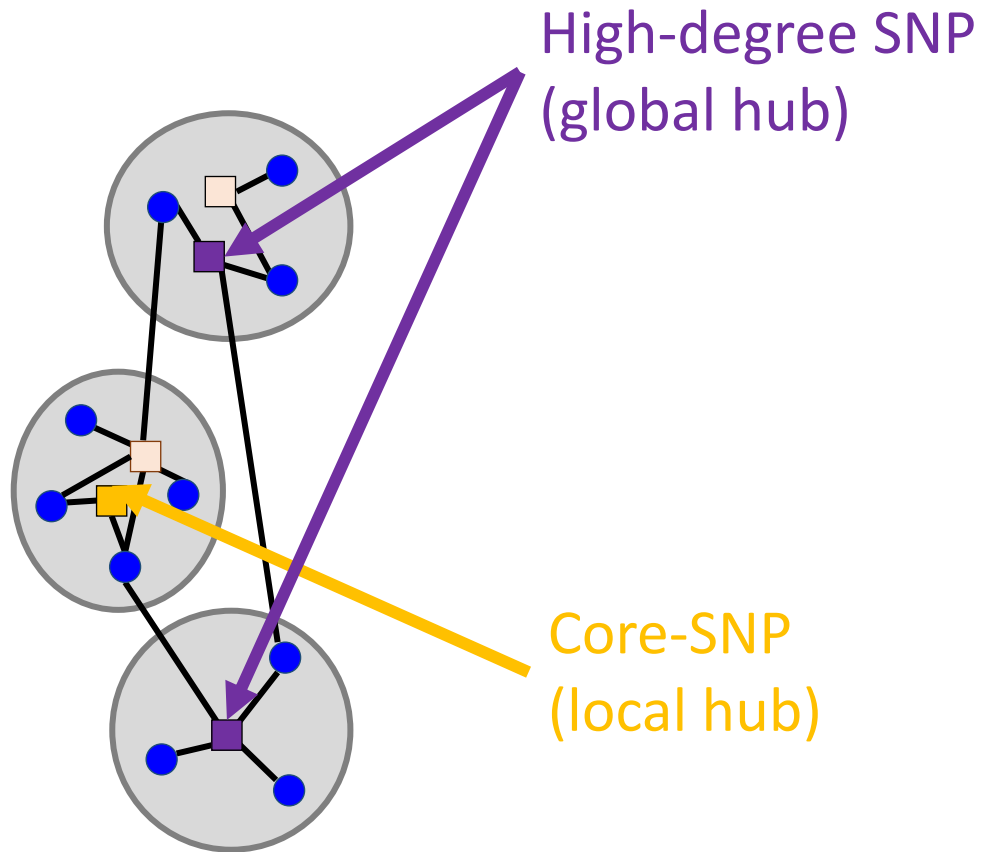
- Most of the heritability is clustered in a few modules
- Heritability is clustered in tissue-specific, biologically relevant modules

# In which SNP classes is heritability located?

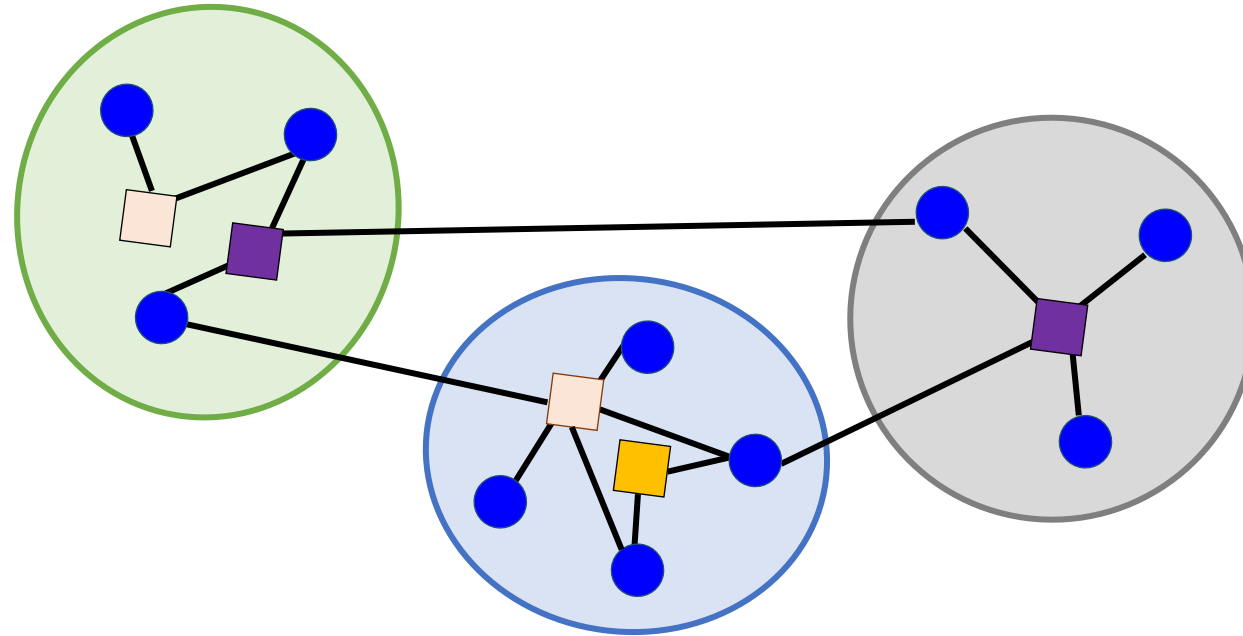
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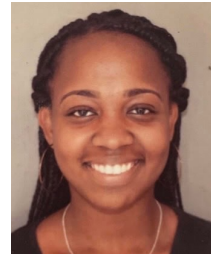
# Heritability is clustered in global and local hubs



# Where is selection located?



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

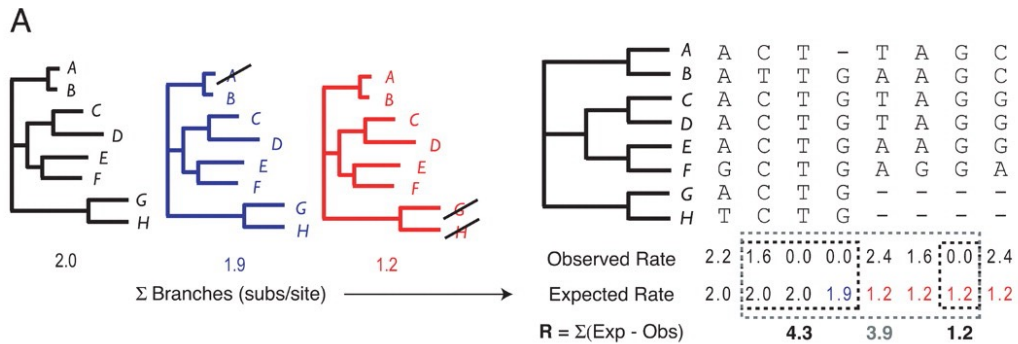


Rosanne Phebe  
(M1 Student)



Themis Lemarchand  
(M2 Student)

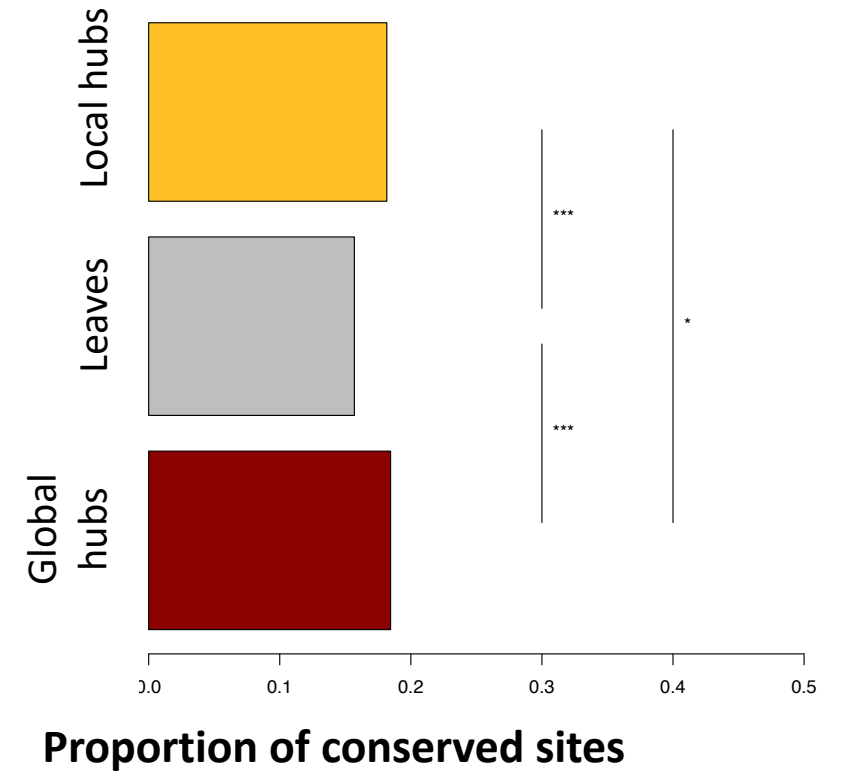
# Global and local hubs are generally constrained



**Principle of GERP score**

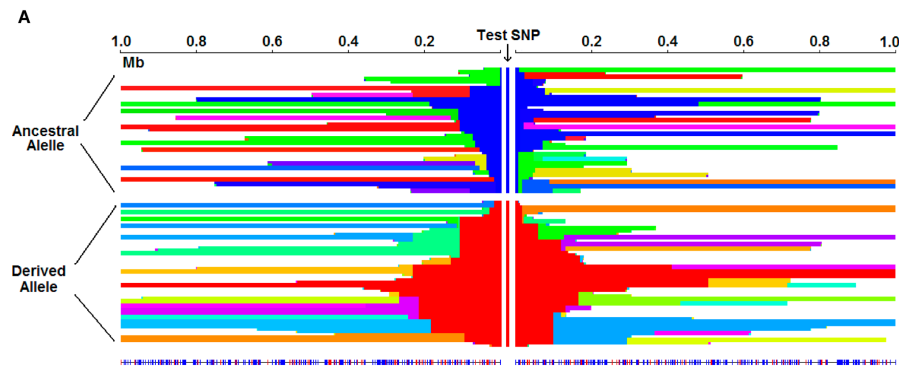
**Comparison of Expected-Observed substitution rate**

**In whole blood network**



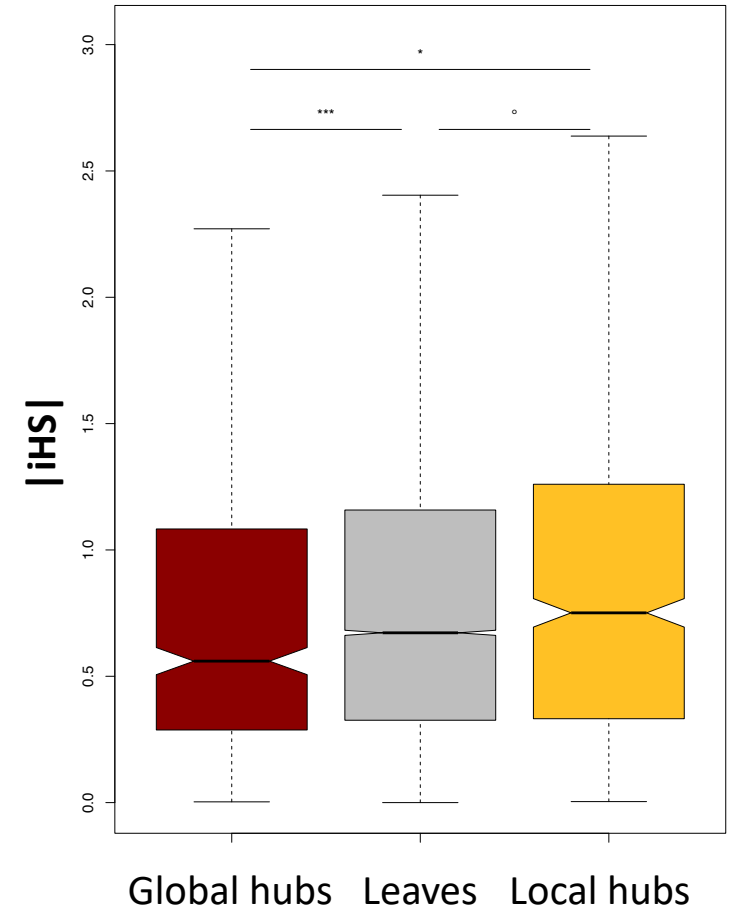
➤ **Hubs are generally more constrained than leaves**

# No clear pattern for recent sweep signatures



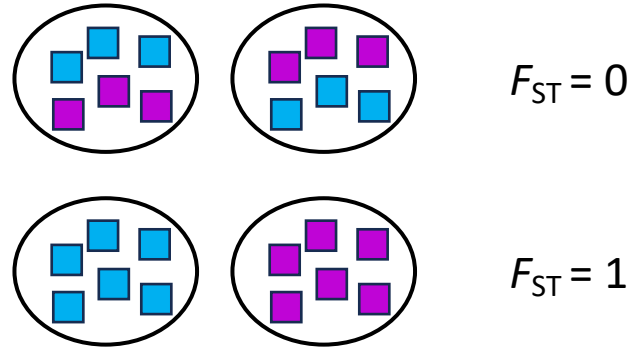
**Principle of *iHS*:**  
**comparison of haplotype length**

**In adipose subcutaneous**

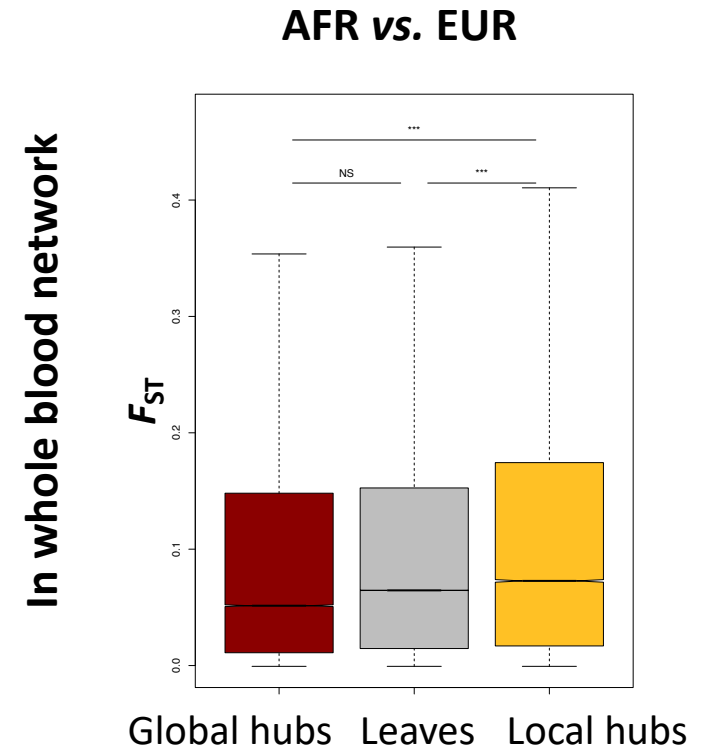


➤ No clear pattern for selection signatures

# Local hubs are enriched for high population differentiation



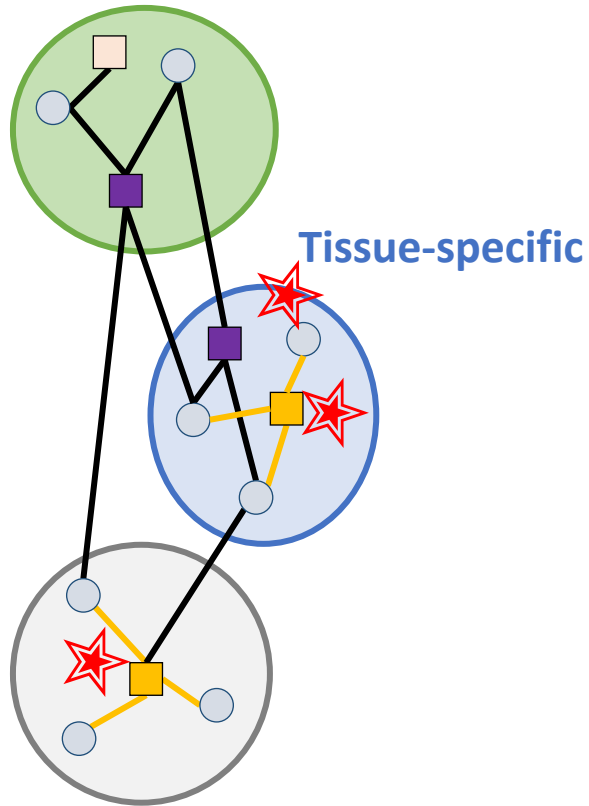
Principle of  $F_{ST}$ :  
Population differentiation



- Local hubs are enriched for polygenic selection signatures

# Conclusion

All tissues



Some tissues

 Heritability

- Heritability is clustered in tissue-specific modules
- Heritability is enriched in local and global hubs
- Hubs are in constrained regions
- Local hubs are preferential targets of polygenic selection

**Structuration & Tissue-specificity:**

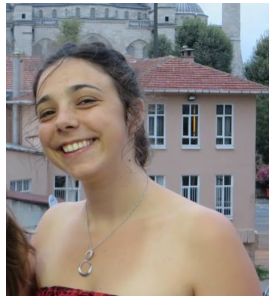
- Limit the propagation of mutation effect
- Open up paths for polygenic traits to evolve!

# Acknowledgments

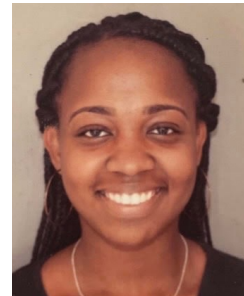
## GEvAD



## LISN, Université Paris-Saclay



Fanny Pouyet



Rosanne Phebe

## Eco-Anthropologie Musée de l'Homme, MNHN

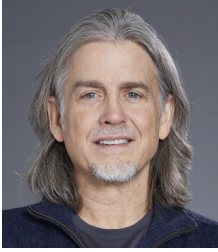


Frédéric Austerlitz

## Harvard School of Public Health



Katherine L. Stone



John Quackenbush



Sheila Gaynor

## University of Virginia



John Platig

## Fundings



# To go further

## Trends in Genetics

Volume 37, Issue 7, July 2021, Pages 631-638



Opinion

### Polygenic Adaptation: Integrating Population Genetics and Gene Regulatory Networks

Maud Fagny<sup>1</sup>  , Frédéric Austerlitz<sup>1</sup>



PNAS PLUS

BJC  
British Journal of Cancer

www.nature.com/bjc



ARTICLE

Genetics and Genomics

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

Maud Fagny<sup>1</sup>, John Platig<sup>2,3</sup>, Marieke Lydia Kuijjer<sup>4,5,6</sup>, Xihong Lin<sup>5</sup> and John Quackenbush<sup>1,2,4,5,7</sup> 

## Exploring regulation in tissues with eQTL networks

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

<sup>a</sup>Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02115; <sup>b</sup>Department of Biostatistics, Harvard T. H. Chan School of Public Health, Boston, MA 02115; <sup>c</sup>Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School Boston, MA 02115; and <sup>d</sup>Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02115



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## Complex Traits Heritability is Highly Clustered in the eQTL Bipartite Network

Katherine Stone<sup>1,2</sup>, John Platig<sup>3,4,5</sup>, John Quackenbush<sup>1,2,6</sup>, and Maud Fagny<sup>1,2,7</sup>

# 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

# Possible scenario of gene expression changes caused by SNPs

