Using eQTL networks to decipher the architecture of complex traits

Maud Fagny

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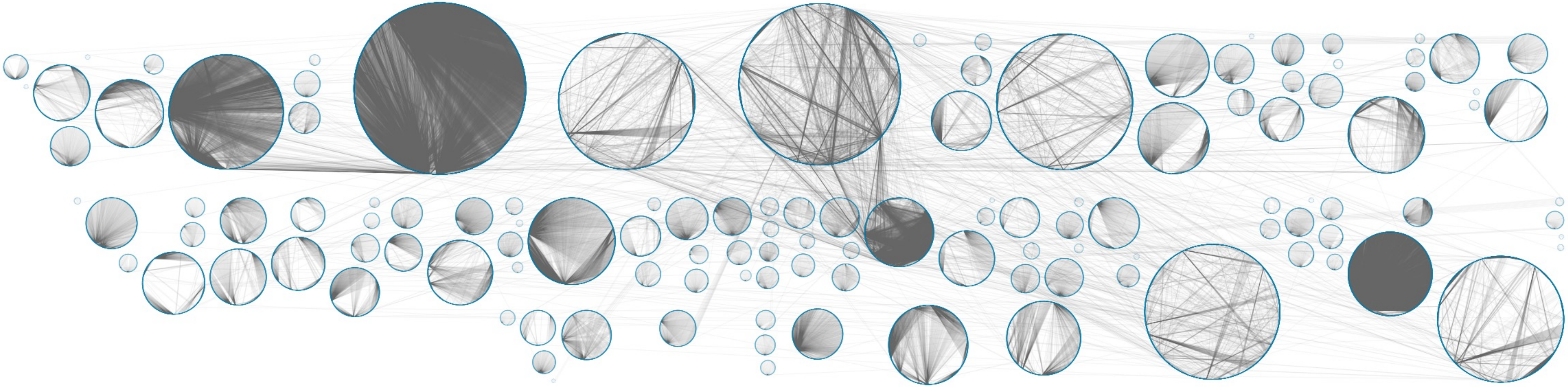


Using eQTL networks to decipher the architecture of complex traits

Maud Fagny, PhD

INRAE, Gif-sur-Yvette

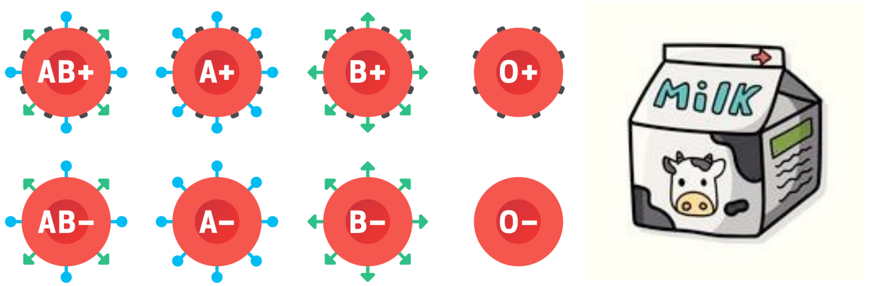
Outline

- Introduction:
    - The genetic architecture of complex traits
    - Why studying eQTL networks ?
- Biologically characterizing cancer risk SNP with eQTL networks
- Improving our understanding of complex trait heritability
- Detecting past selection events?
- Conclusion and future topics

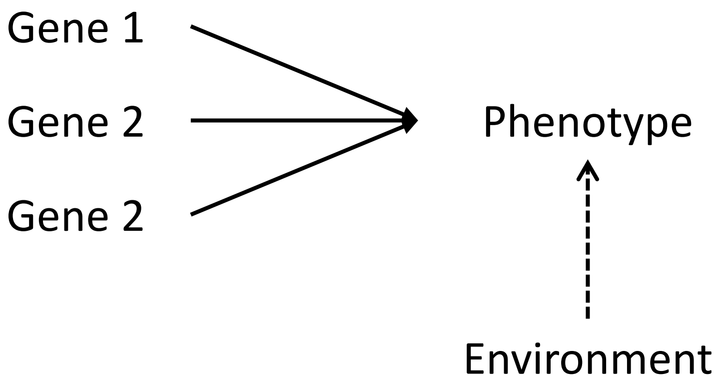
Mendelian *vs.* Polygenic traits

Mendelian traits:

Gene → Phenotype



Complex traits:

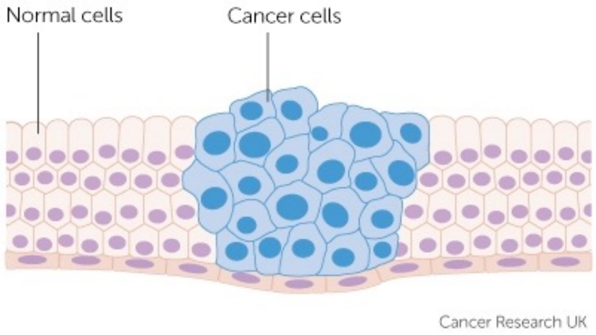

Gene 1

Gene 2

Gene 2

Phenotype

Environment



Cancer Research UK

Genetic architecture of some often-studied traits

Monogenic
Mendelian
1 trait = 1 gene

Oligogenic
1 trait = 2-10 genes

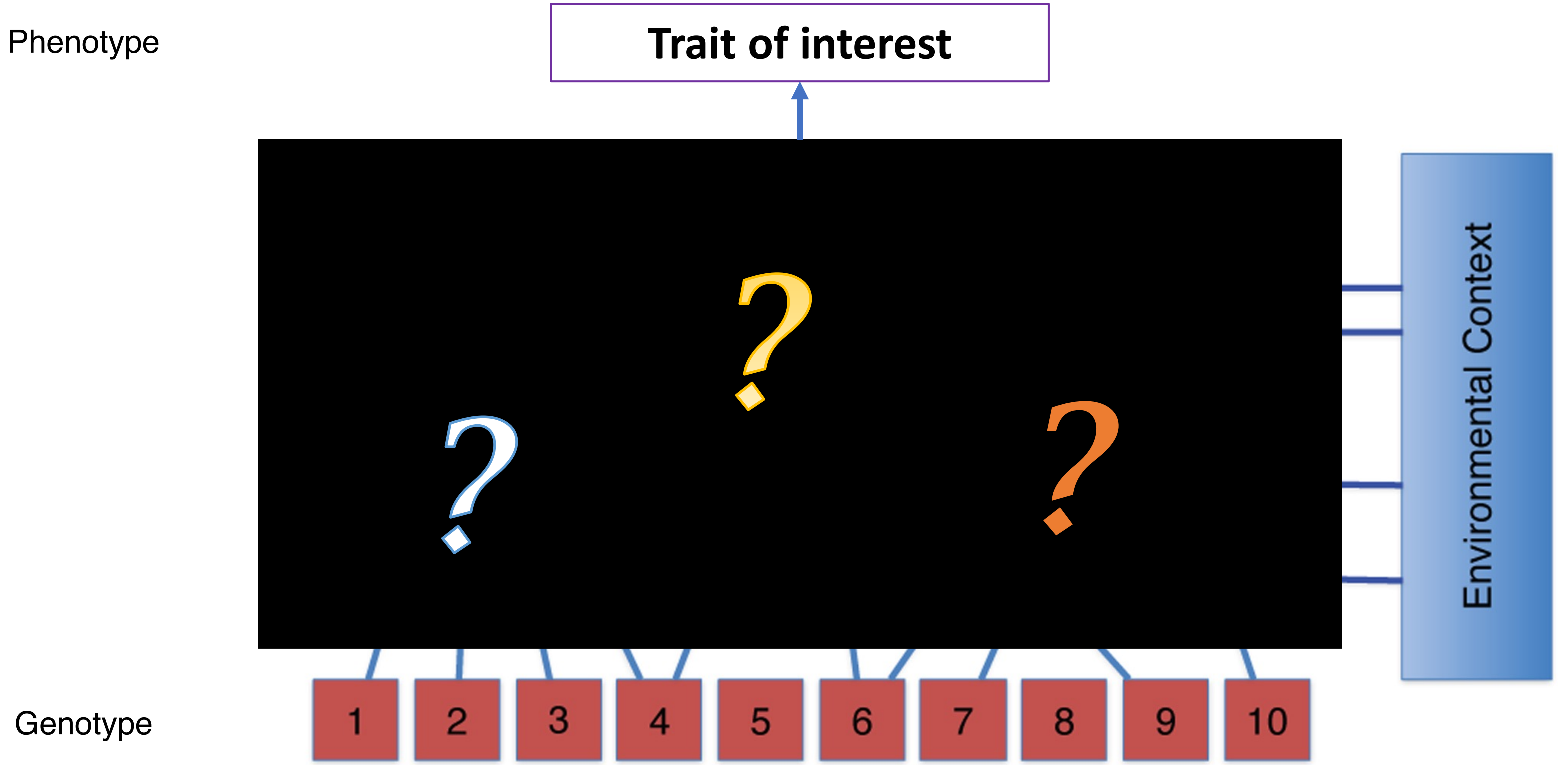
Polygenic
1 trait = many genes

Genetic architecture of some often-studied traits

Monogenic	**Oligogenic**	**Polygenic**
Mendelian		
1 trait = 1 gene	1 trait = 2-10 genes	1 trait = many genes
Lactose tolerance	Skin/eye/hairs color	Risk to develop schizophrenia
Sickle-cell disease	Risk to develop type II diabetes	Adult size

Risk to develop a cancer

Diving deeper in the architecture of complex traits



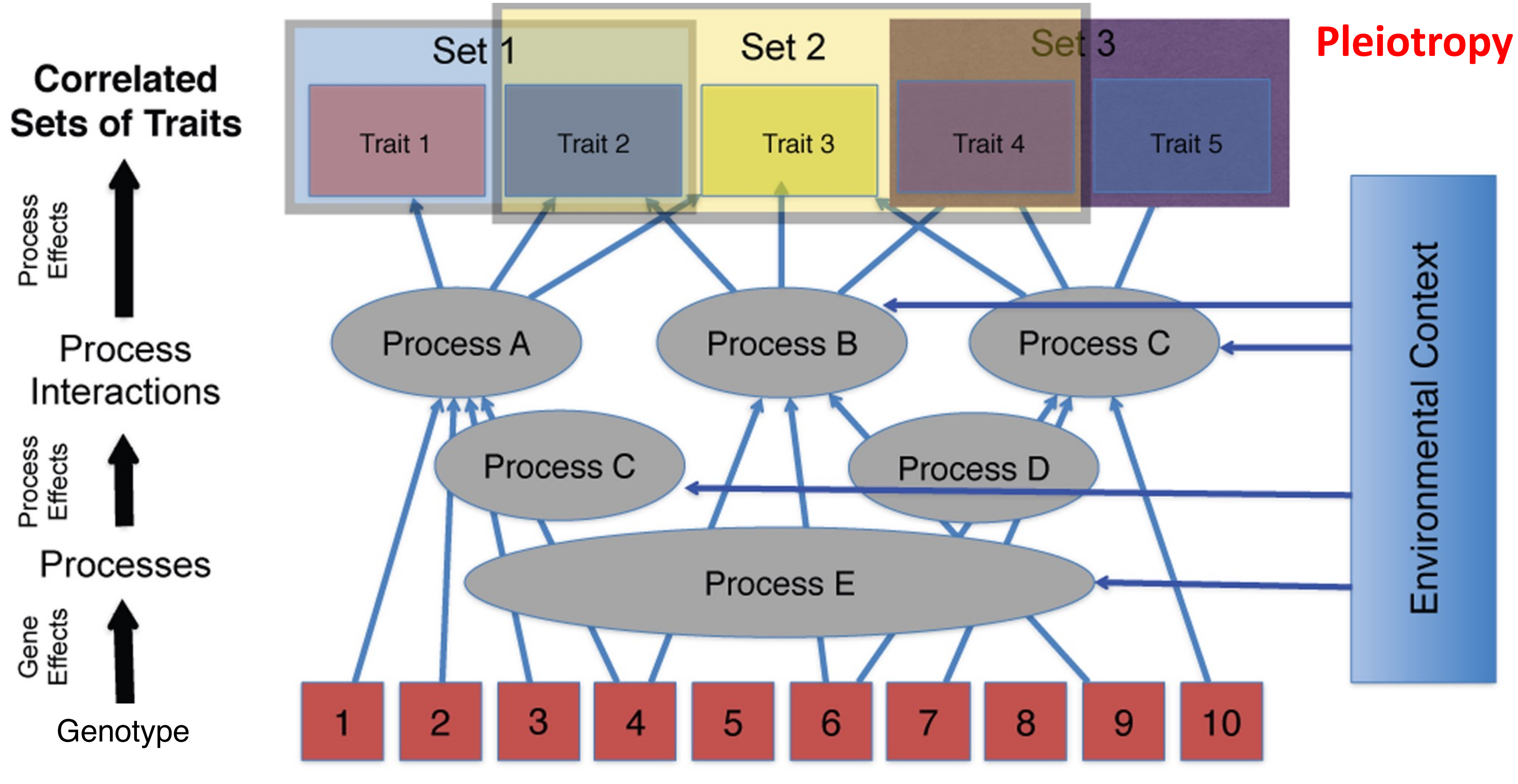
Adapted from Hallgrimsson *et al.*, *PLoS Genetics*, 2014

- The genotype-phenotype gap:

Mechanisms by which most genetic variation identified in GWAS affect the final phenotype **unknown**

Diving deeper in the architecture of complex traits

Gene Regulatory Networks



Pleiotropy

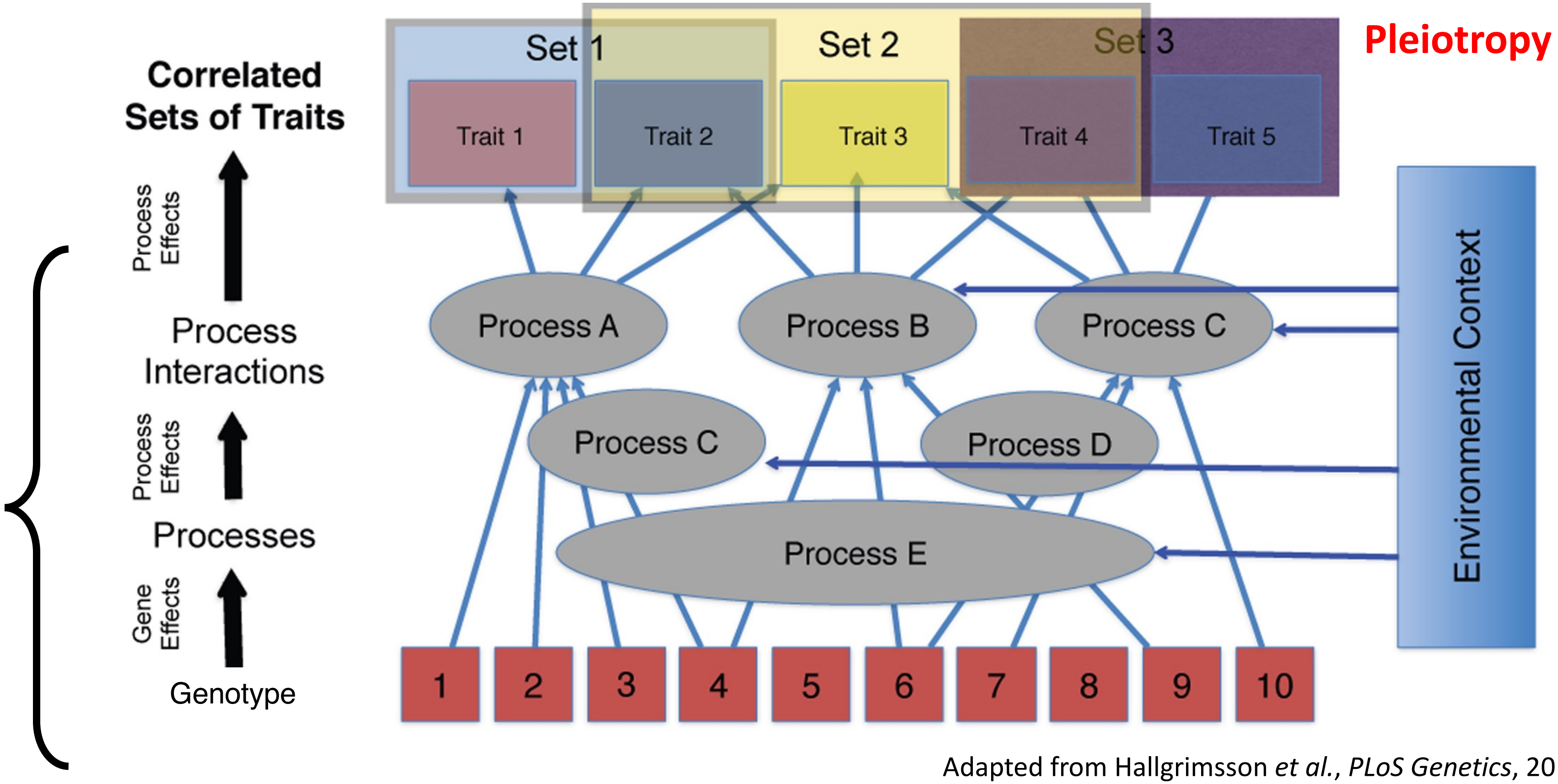
Adapted from Hallgrimsson *et al.*, *PLoS Genetics*, 2014

- ➢ The importance of gene regulatory networks

Diving deeper in the architecture of complex traits

Gene Regulatory Networks

Redundancy
Tissue-specificity



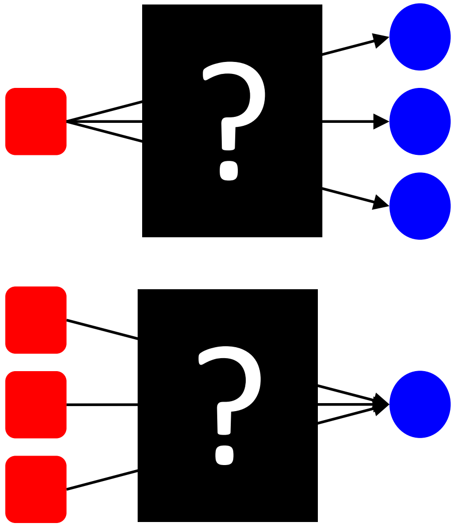
Pleiotropy

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

- Complex interactions at the basis of polygenic traits, including pleiotropy and redundancy

The different challenges

Complexity



Pleiotropy

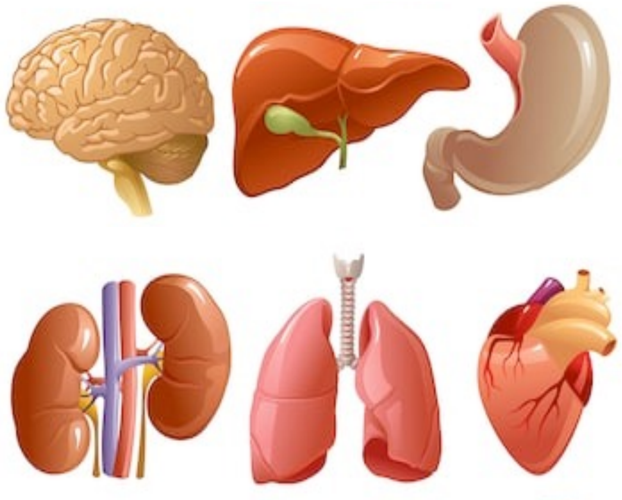
Redundancy

Mutations

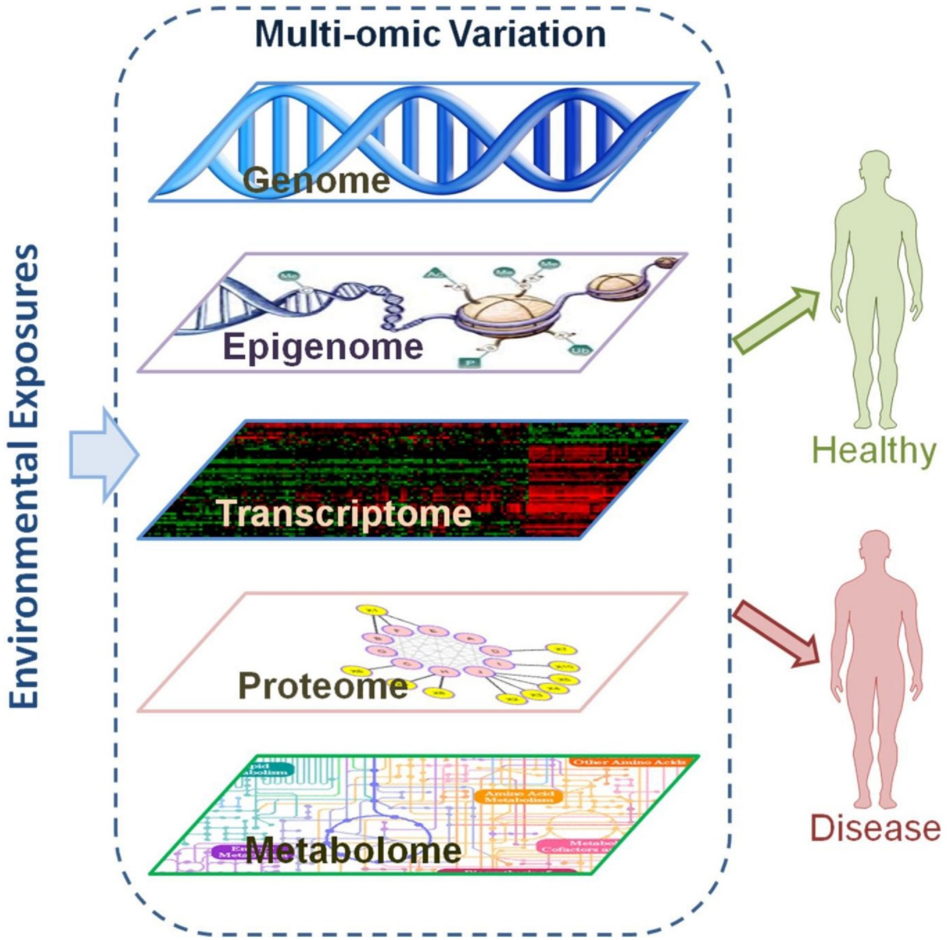
Traits

Genotype-Phenotype Gap

Tissue-Specificity



Exploring the genotype-phenotype gap



GWAS SNPs:

Intermediate frequencies

&

Small effect size on phenotype

&

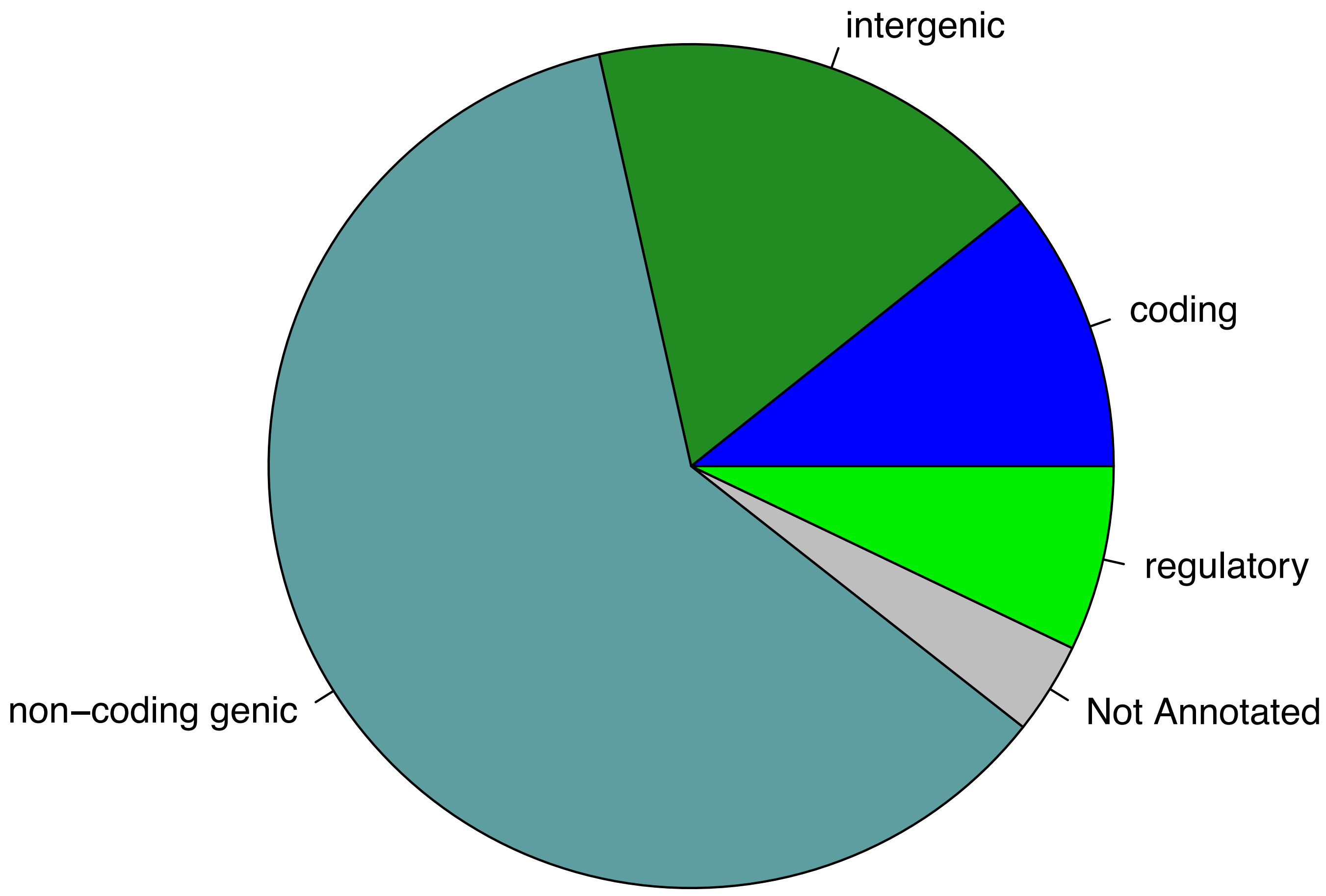
Tissue-specific effect

&

Located in regulatory regions

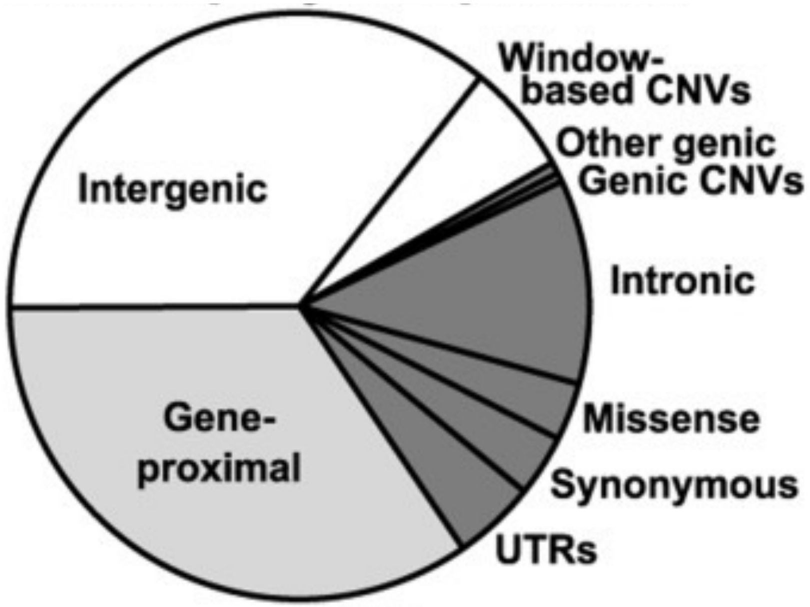
The importance of gene expression regulation in polygenic phenotypes

GWAS in humans



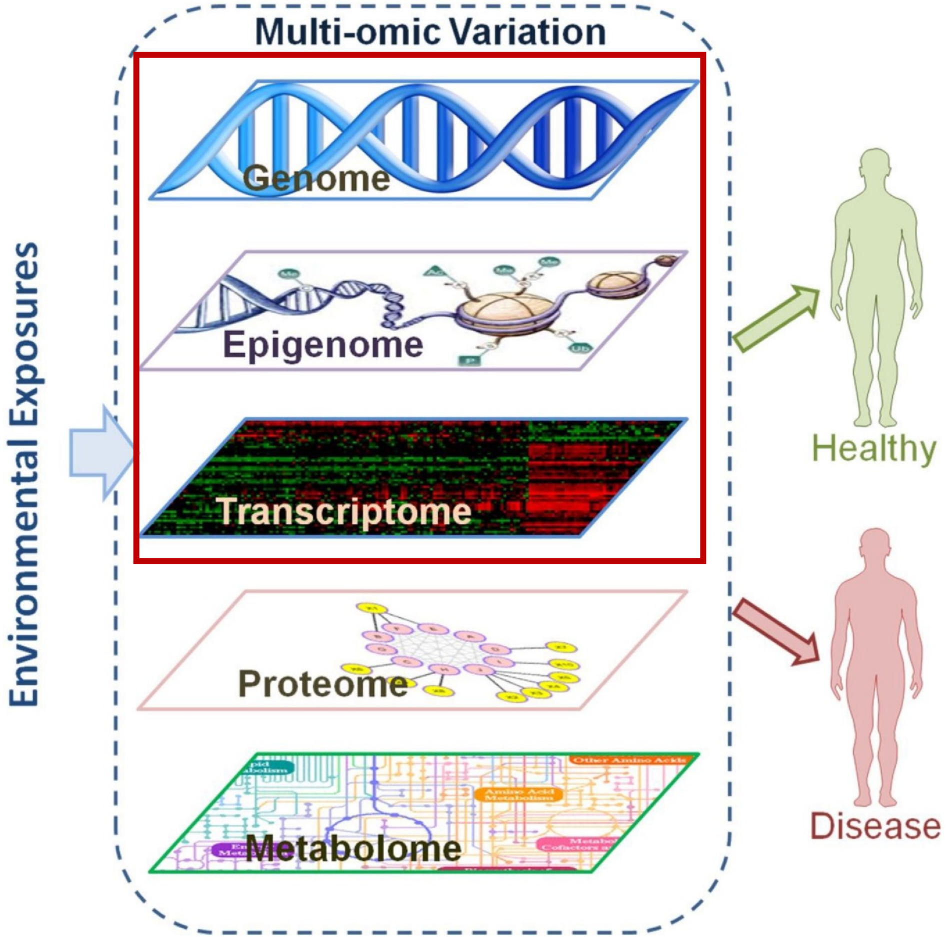
n=144,876

GWAS for developmental traits in maize



n = 4,802

Exploring the genotype-phenotype gap



GWAS SNPs:

Intermediate frequencies

&

Small effect size on phenotype

&

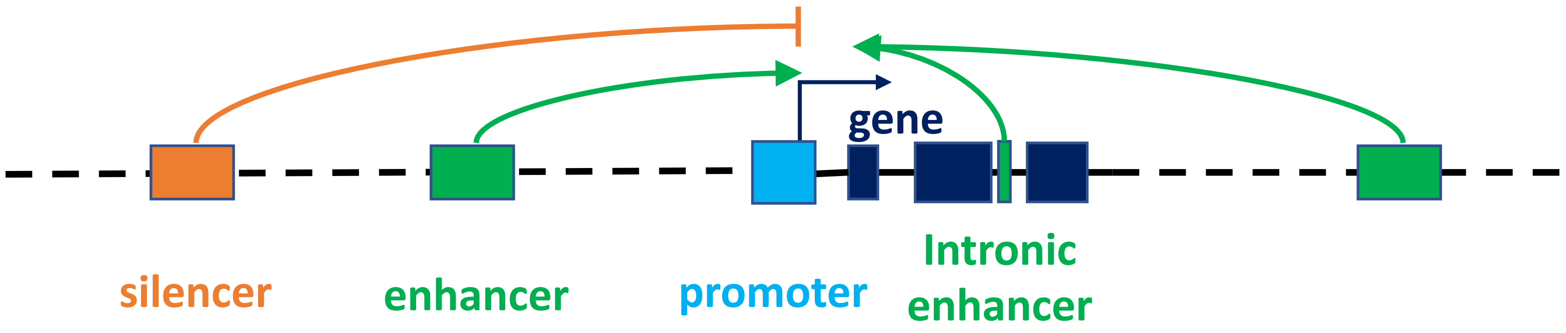
Tissue-specific effect

&

Located in regulatory regions

Gene Expression Regulation in cis and in trans

cis-acting elements



gene

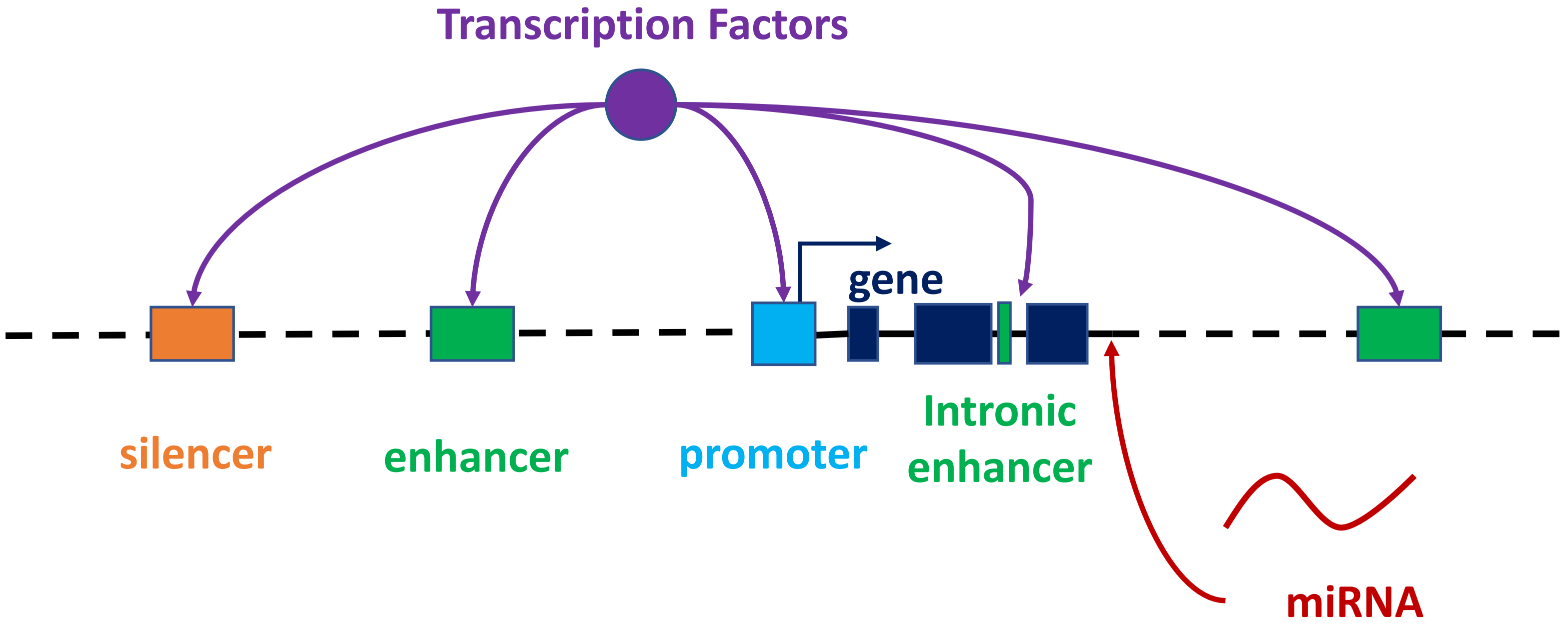
silencer

enhancer

promoter

Intronic enhancer

trans-acting elements



Transcription Factors

gene

silencer

enhancer

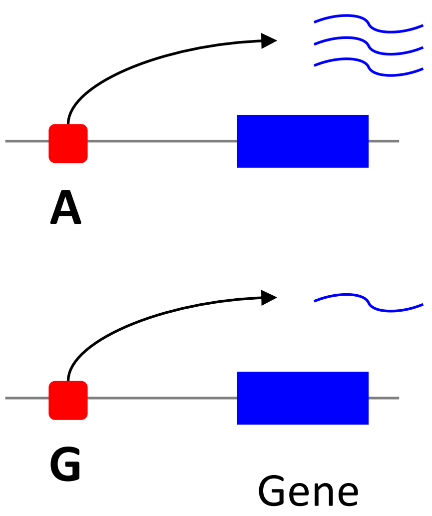
promoter

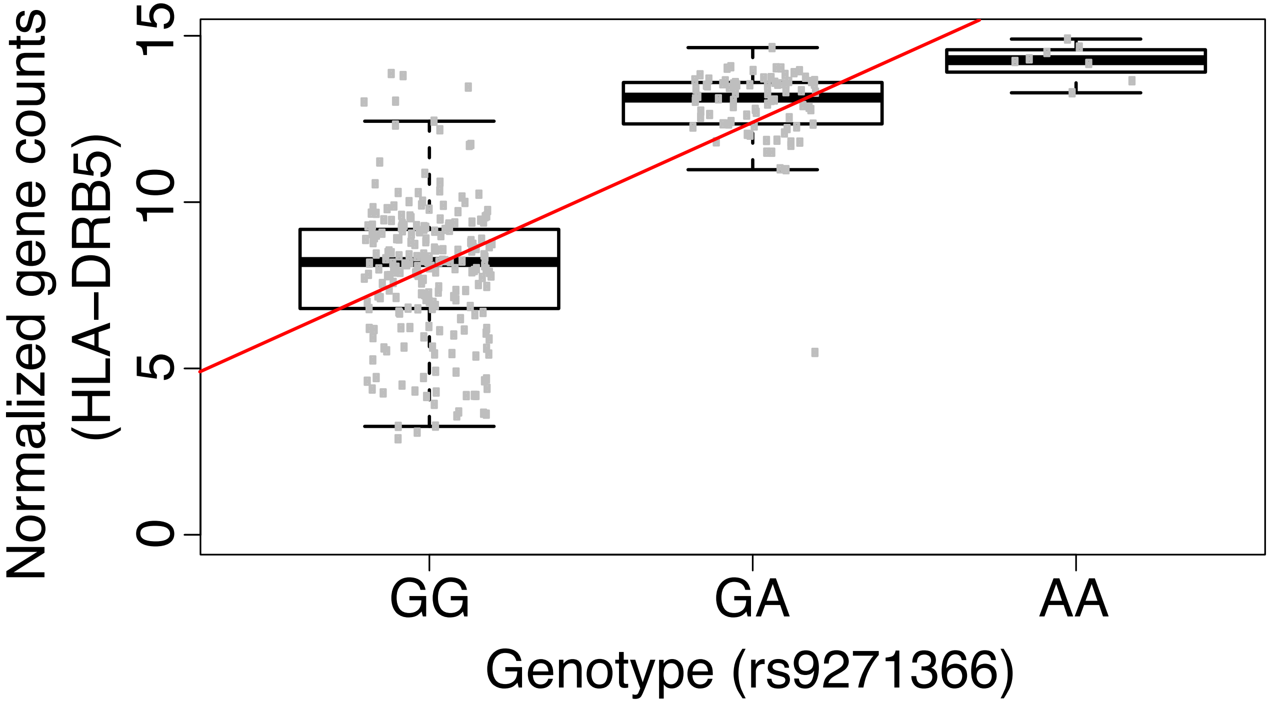
Intronic enhancer

miRNA

Building a bridge between genotype and phenotype: Step 1 – the expression Quantitative Trait Loci (eQTLs)

Expression quantitative trait locus (eQTL)

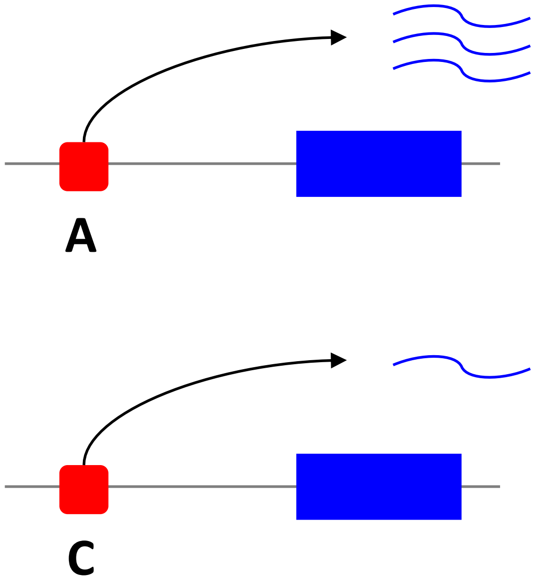




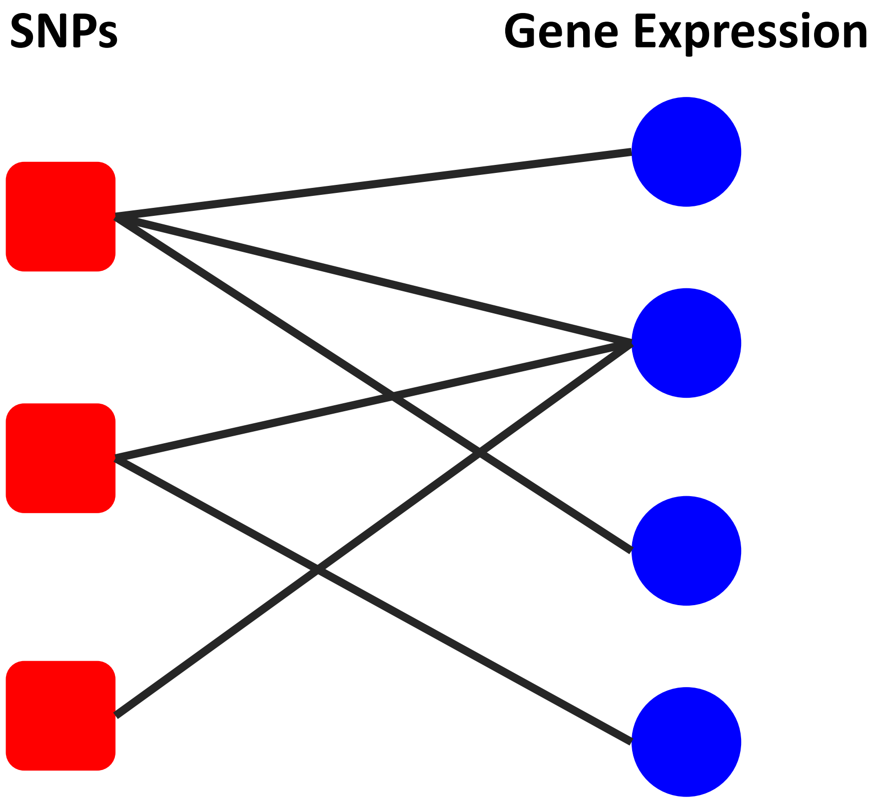
- ➢ **Expression quantitative traits loci are potential regulatory SNPs**
- ➢ **SNPs associated to traits or diseases are enriched for eQTLs**

Organising the complexity: a graph representation

Expression quantitative trait locus



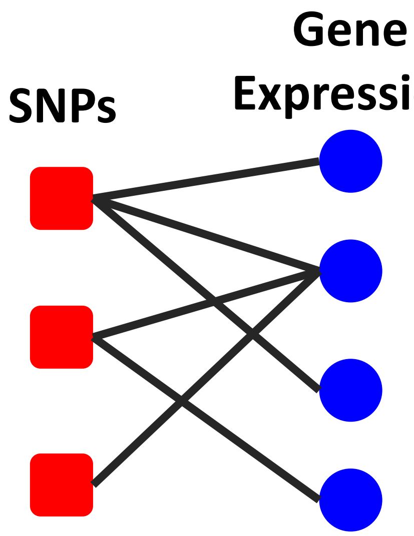
Cis- and trans-eQTL bipartite networks



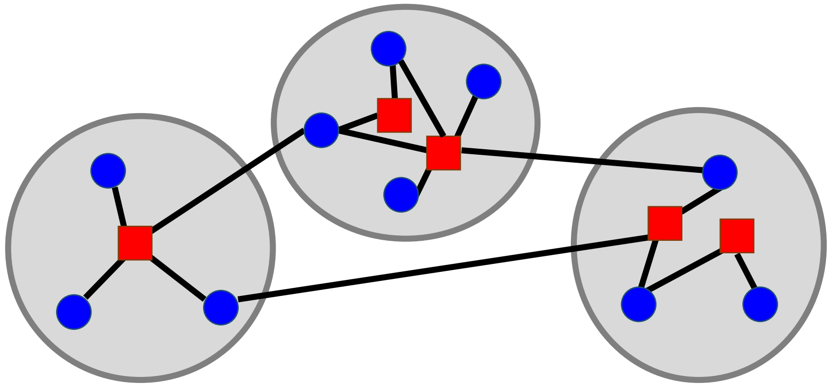
- **Using a systems biology network approach to groups SNPs influencing the expression of the same genes**

Grouping SNPs using a network property : modularity

Cis- and trans-eQTL bipartite network

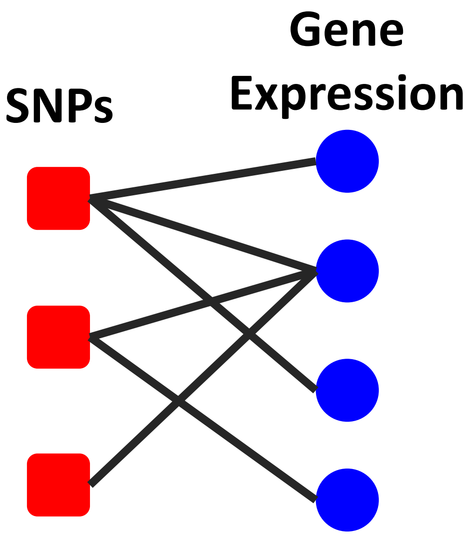


Community detection

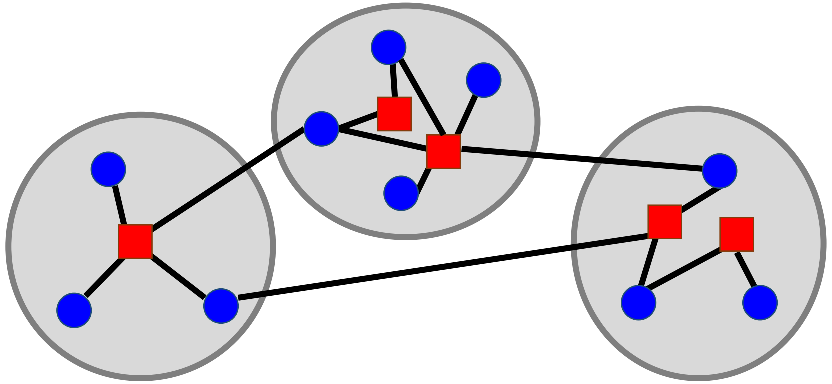


Grouping SNPs using a network property : modularity

Cis- and trans-eQTL bipartite network



Community detection



Bipartite Modularity Maximization

$$Q = \sum_i (e_{ii} - a_i^2)$$

Fraction of network links in community i

Fraction of links expected by chance

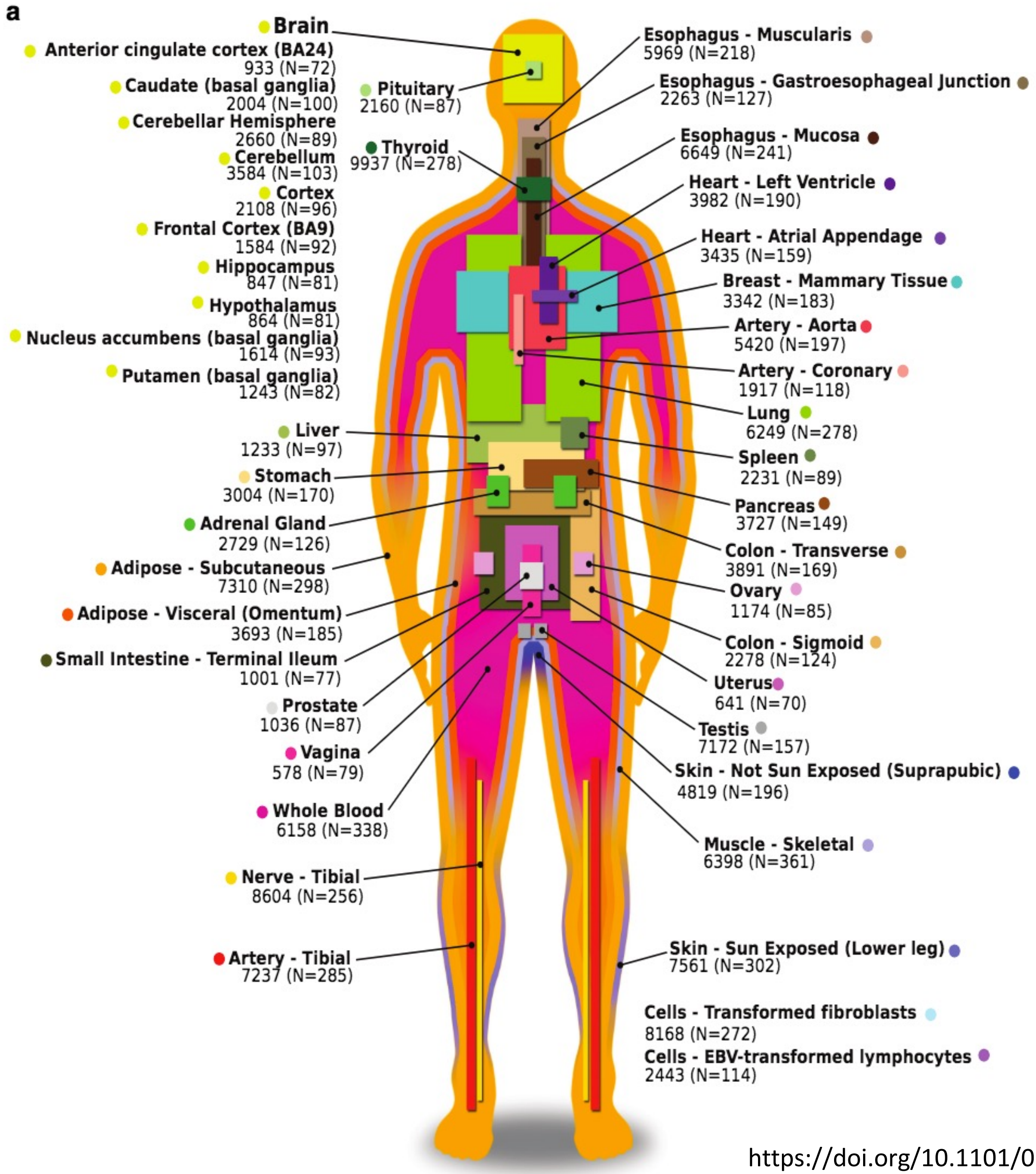
Platig et *al.* (2016) **PLoS Comp Bio**
Barber et *al.* (2007) **Phys Rev E Stat Nonlin Soft Matter Phys**

Taking into account the tissue-specificity

Get tissue-specific expression data !

GTEx

- **449 individuals.**
- **Genotyping data:**
    - 84.3% European Am.
    - 13.7% African Am.
    - 1% Asian Am.
- **RNA sequencing data:**
    - 13 tissues.



https://doi.org/10.1101/074450

Approach summary: building tissue-specific eQTL networks

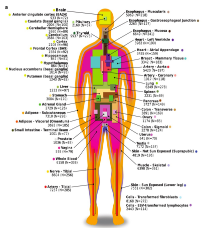
Data

13 tissues, 450 individuals, 4904 samples

Imputed Genotypes (5,640,985 SNPs)

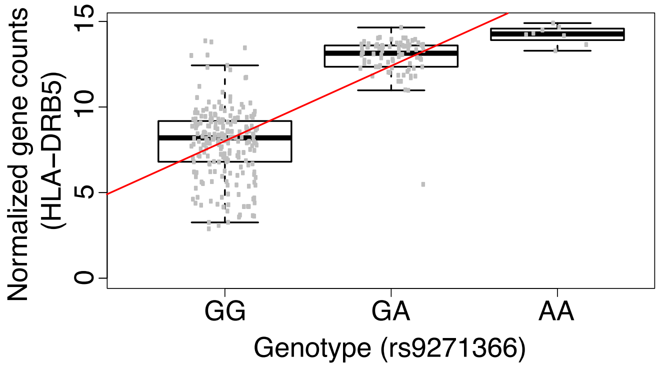
RNA-Seq data (29,242 genes)

GTEx

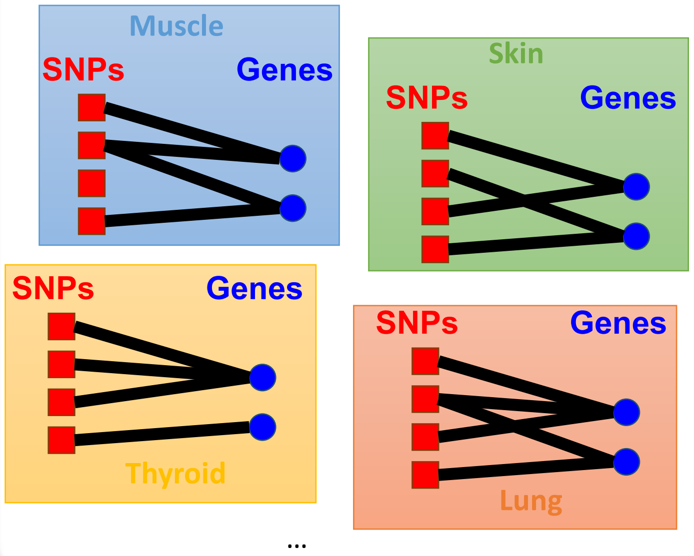


eQTL mapping in each tissue

cis- and trans-eQTLs mapping (*MatrixEQTL*)

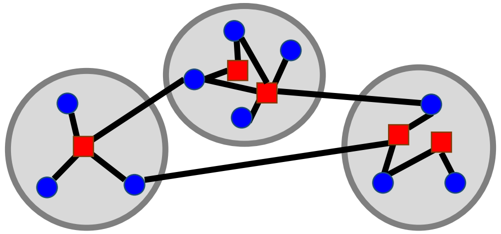


Bipartite Networks

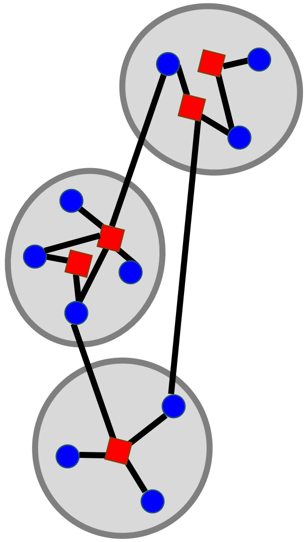


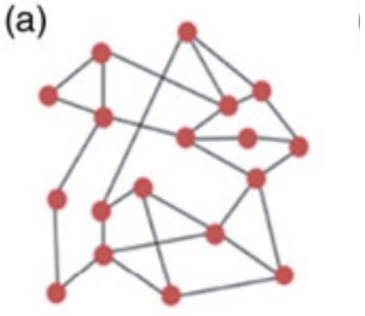
Modules detection

Bipartite Modularity Maximization (*condor*)



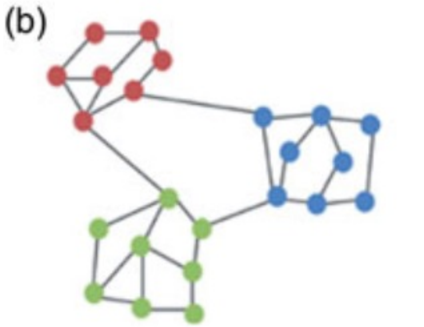
eQTL networks have high modularity





A random network

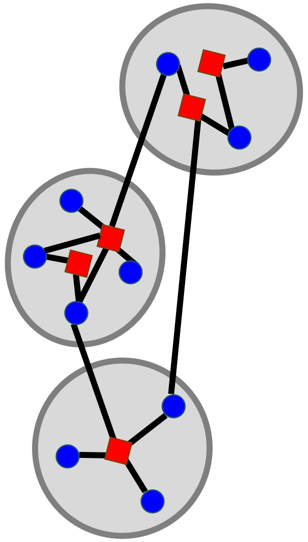
Modularity $\sim$ 0

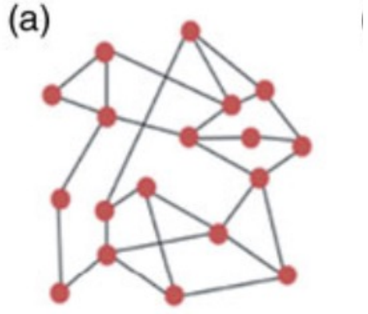


A modular network

Modularity >> 0

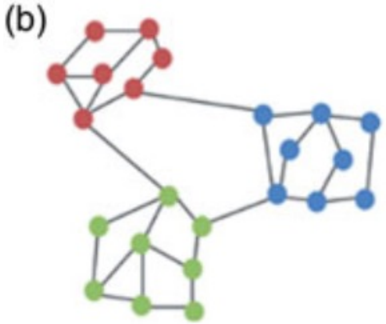
eQTL networks have high modularity





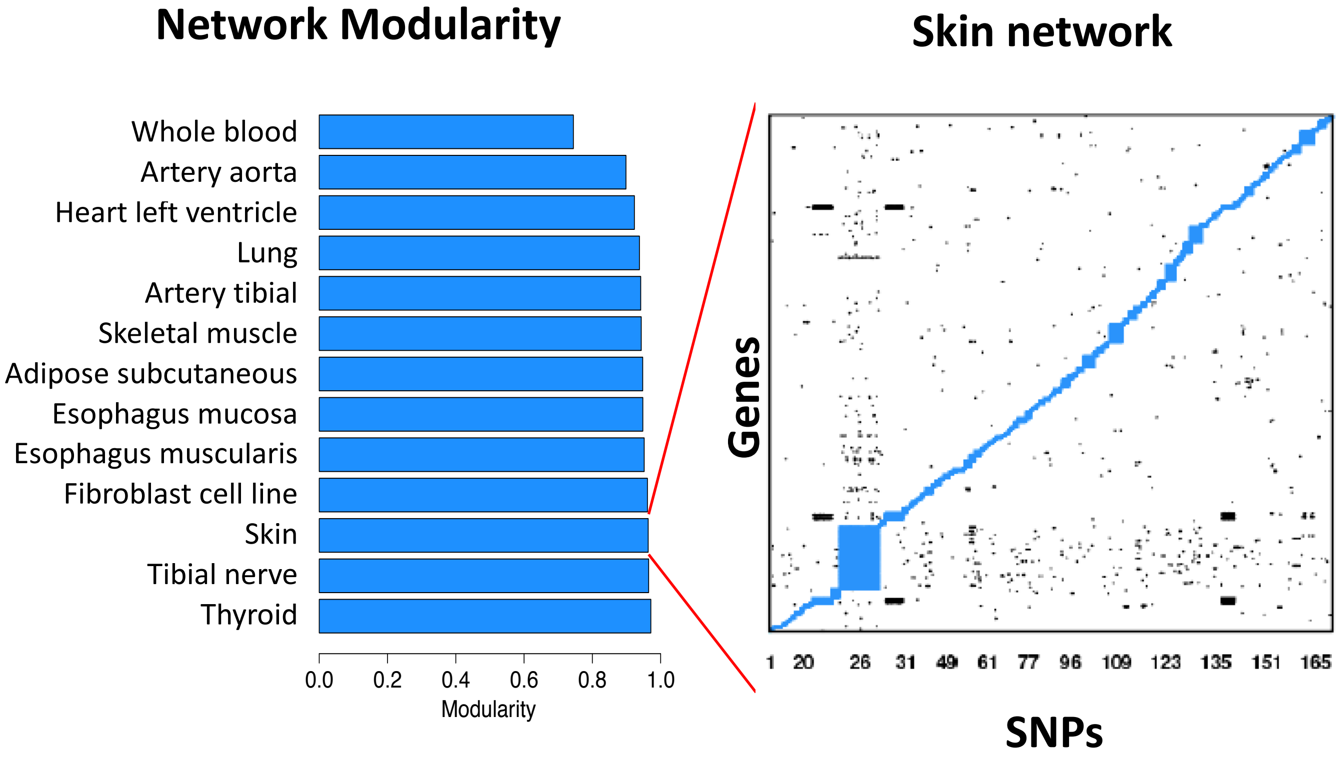
A random network

Modularity ~ 0



A modular network

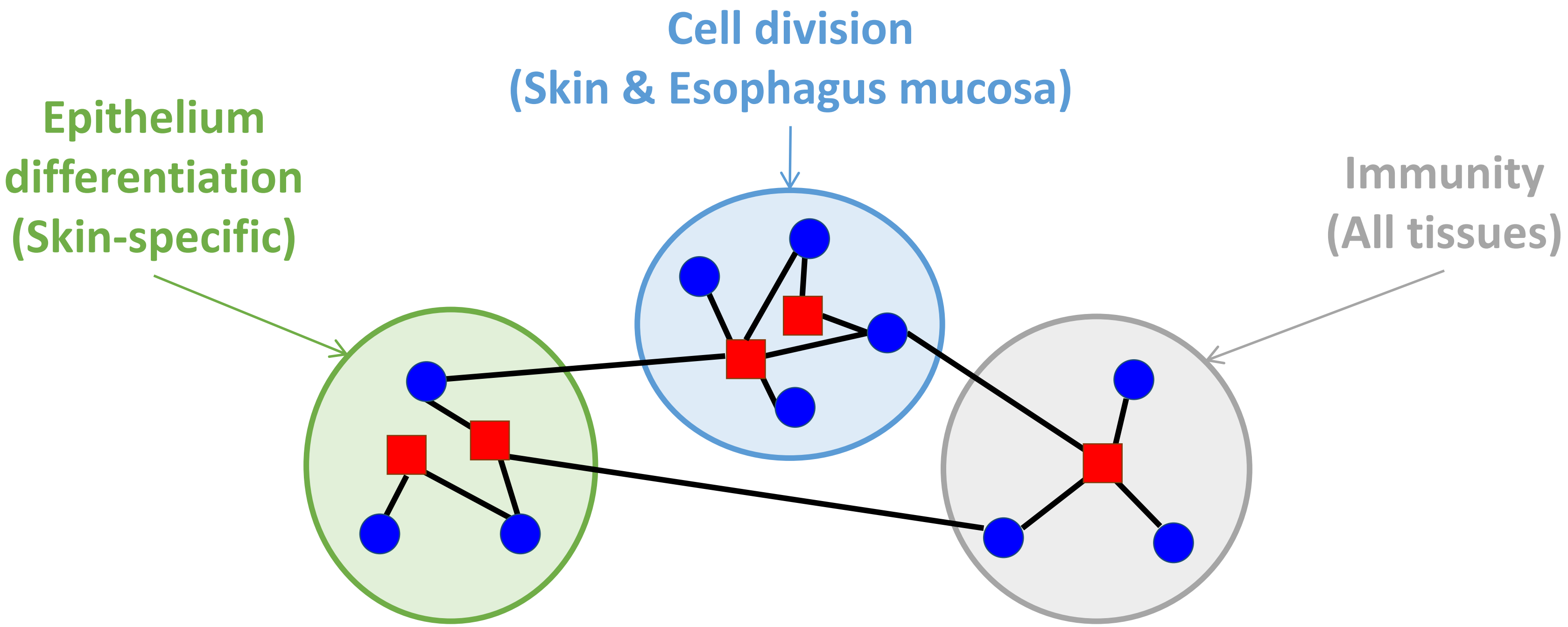
Modularity >> 0



Fagny et *al.* (2017) **PNAS**

Communities correspond to biological functions of tissues

Example of communities identified in skin eQTL network



- **Groups of SNPs regulate groups of genes involved in similar functions.**
- **Communities can be tissue-specific or shared across tissues**

Fagny et *al.* (2017) **PNAS**

Research question:
Understanding the genetic architecture of complex traits

- **Biological characterization of SNPs identified by GWAS: How do genetic variation influence a trait ? Which biological pathways are involved?**
- **Heritability: Which mutations most affect the trait? Where are they located in the regulatory network**
- **Natural Selection: How do such a complex trait evolve?**

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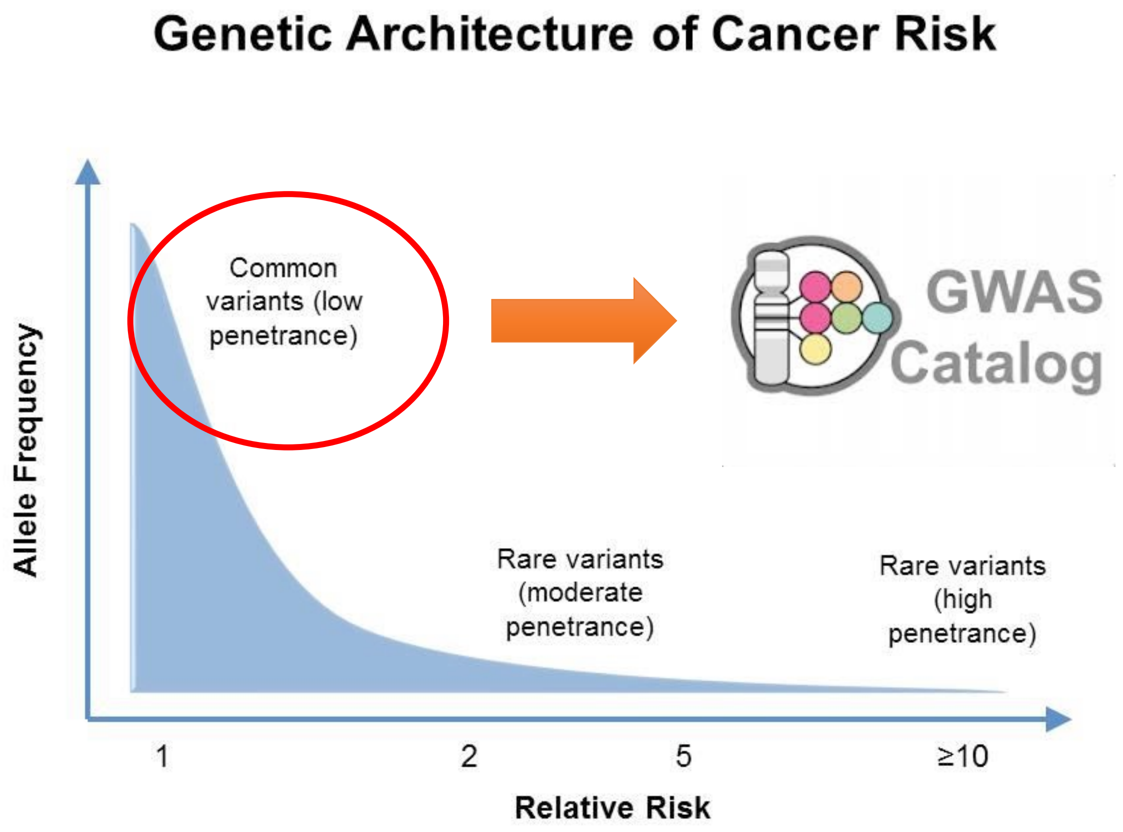
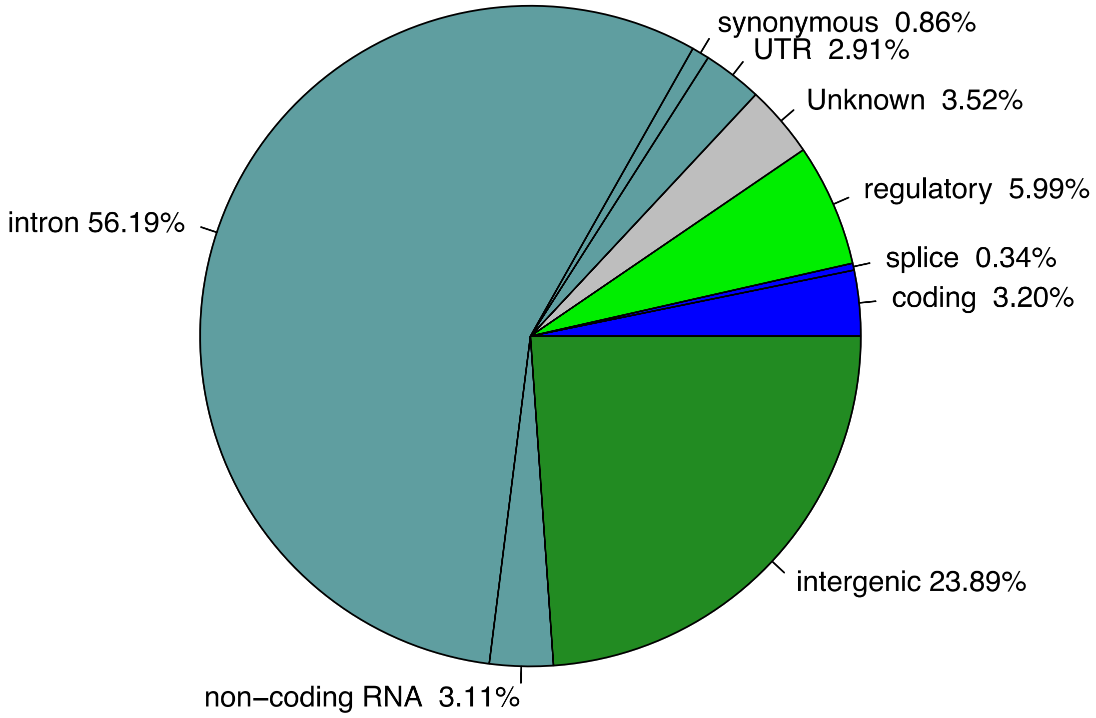
John Platig,
Assistant Professor,
Univ. Of Virginia

A particularly complex trait: the risk to develop cancer(s)

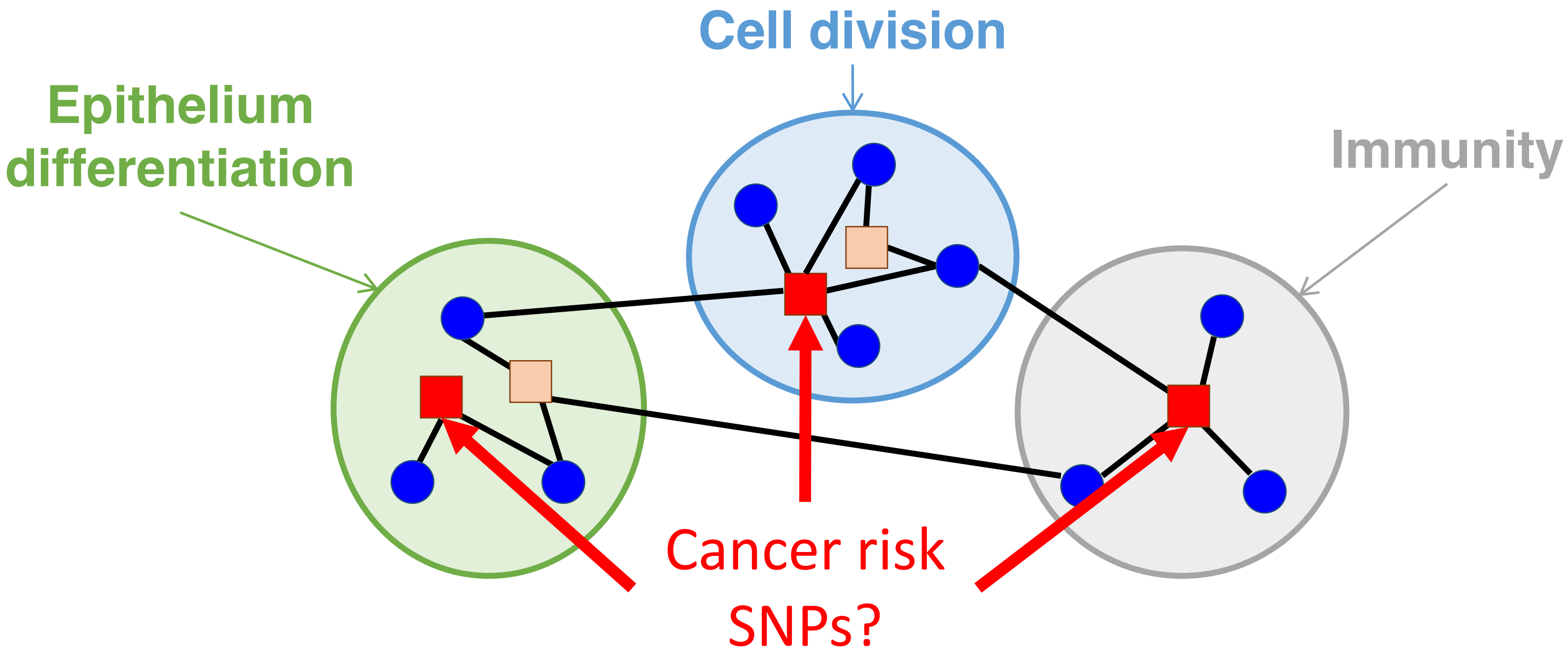




Adapted from *Cancer Genetics Overview (PQD®)*

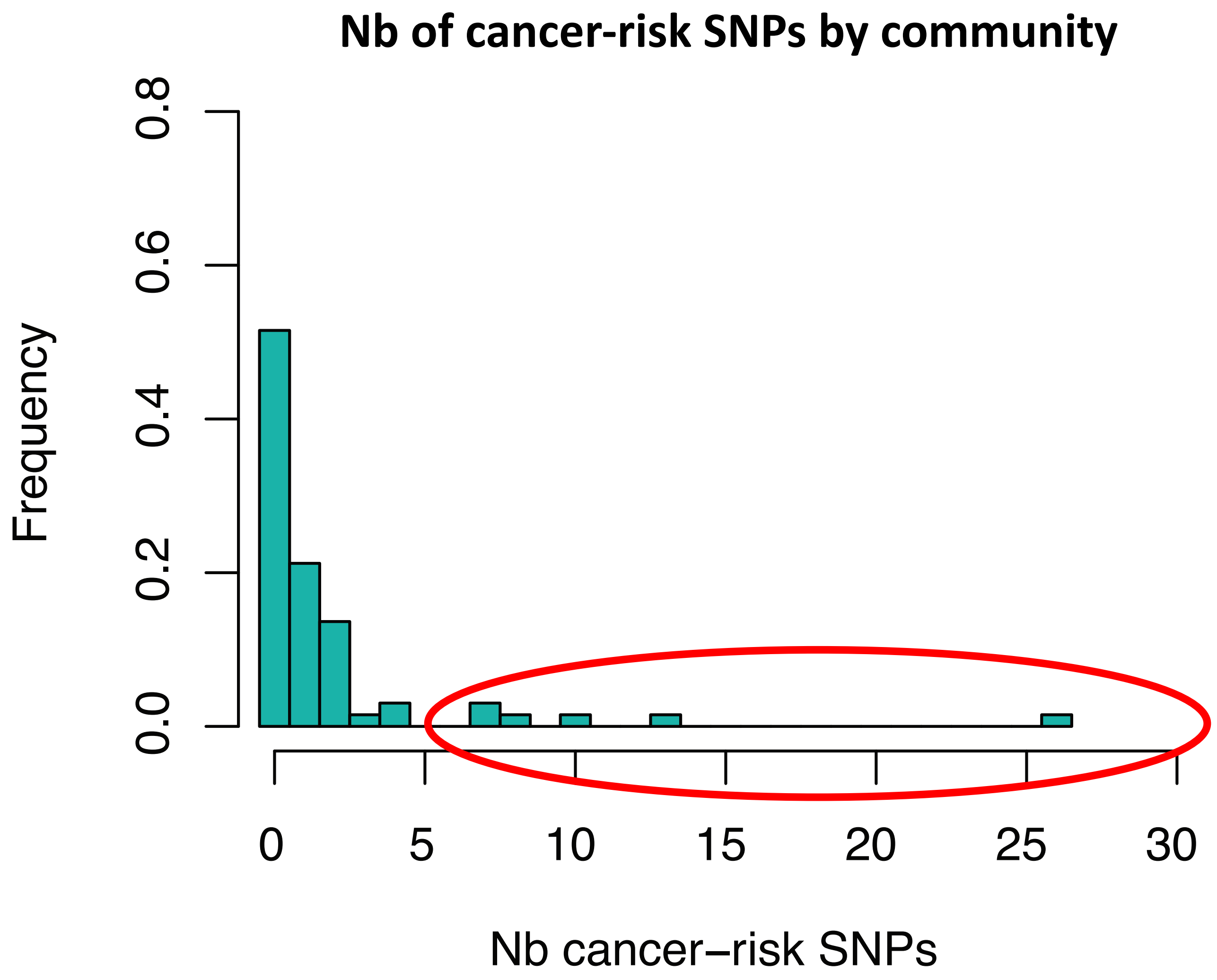
- 4,587 SNPs associated to 265 cancer-related traits
- 87% of cancer-risk SNPs with an odds ratio under 3

Mapping cancer-risk SNPs to eQTL networks



- ➢ **Where do the cancer-risk SNPs map in these networks?**
- ➢ **In which community are they located?**
- ➢ **What are their properties?**

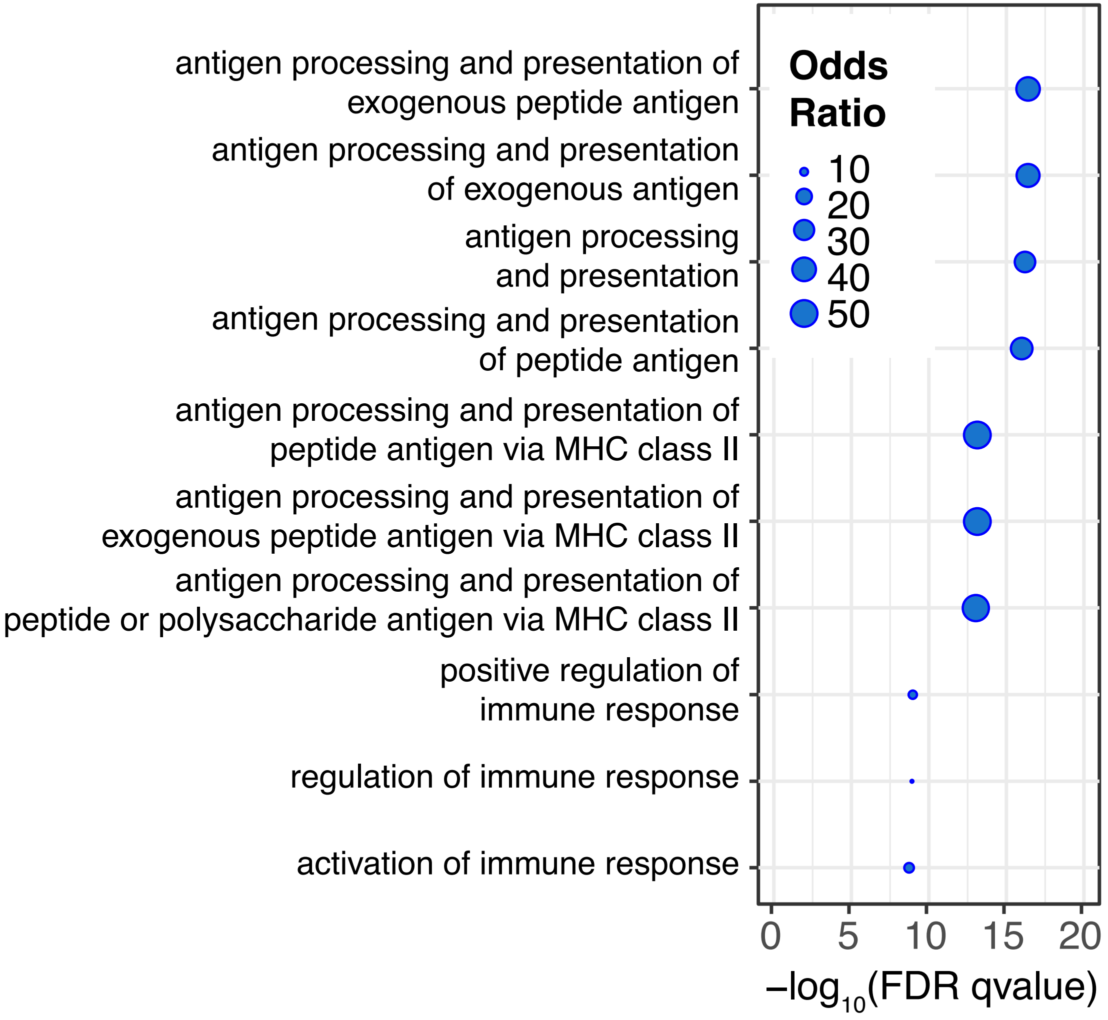
Mapping cancer-risk SNPs to eQTL networks



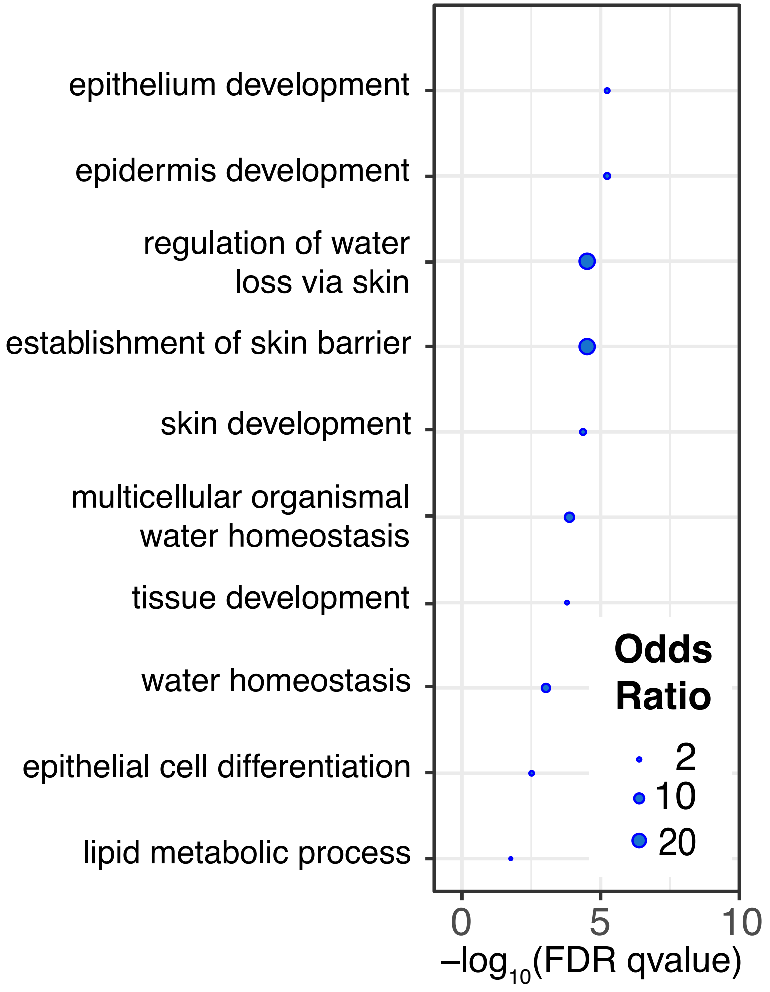
- **2-6 communities enriched in cancer risk SNPs by tissue**

Biological function of cancer-risk SNPs-enriched communities

Enriched in multiple cancer risk SNPs (all tissues)

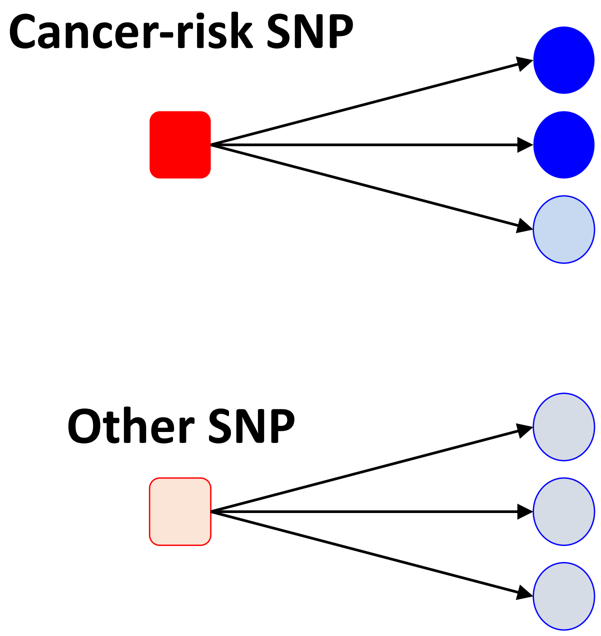


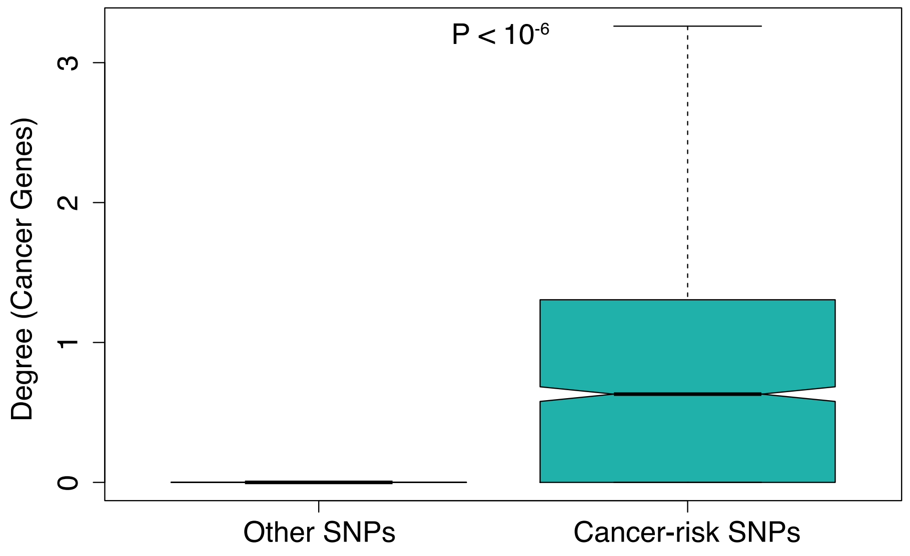
Enriched in breast cancer risk SNPs (skin)



Cancer-risk SNPs preferentially target oncogenes

Genes targeted by cancer risk SNPs?

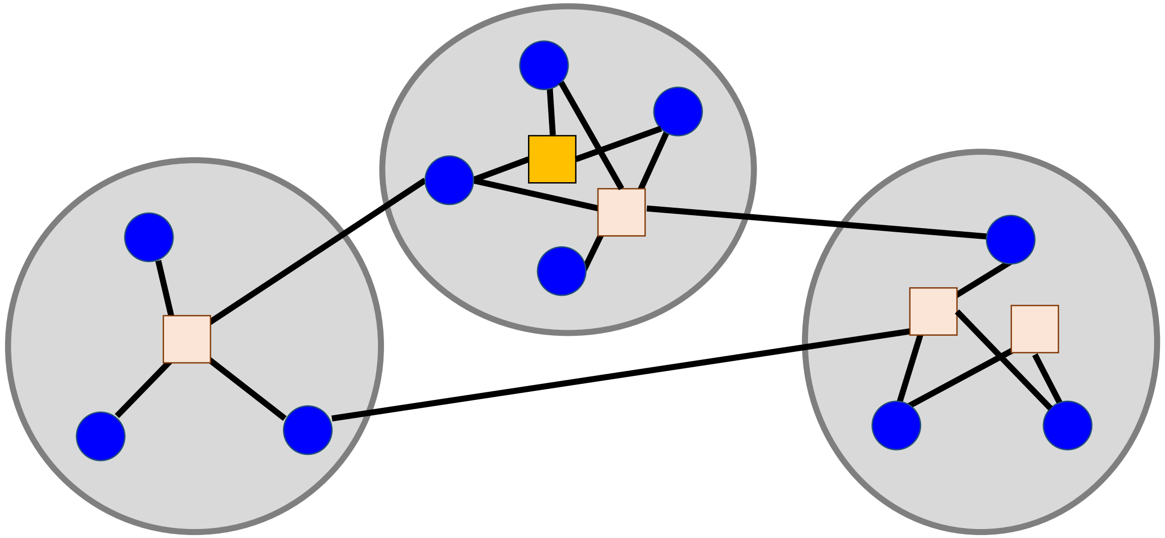




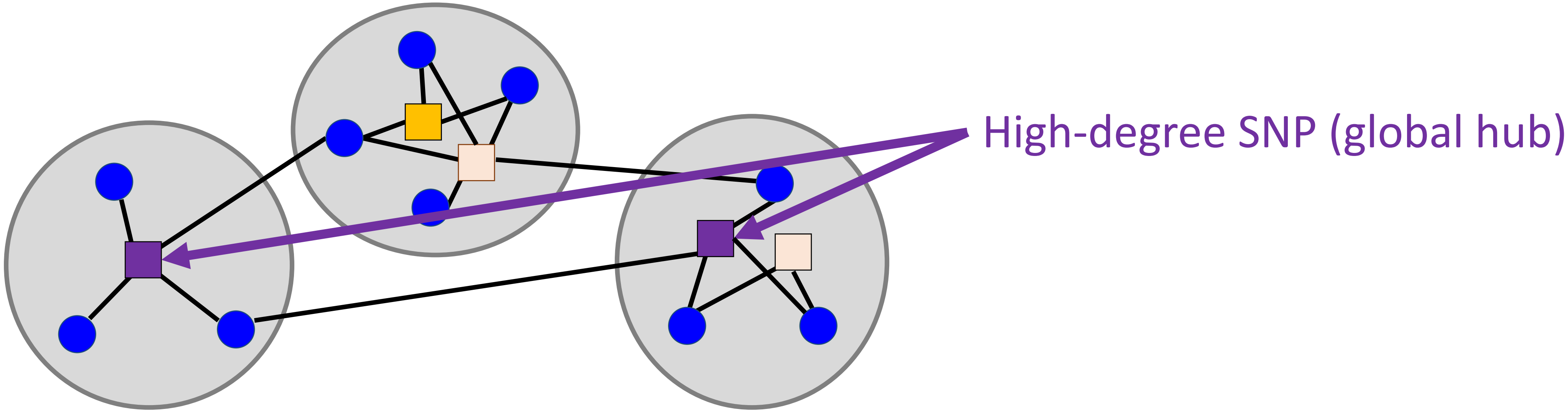
○ **Others**

● **Oncogenes**
Tumor suppressors

What are the properties of cancer-risk SNPs in the eQTL networks?

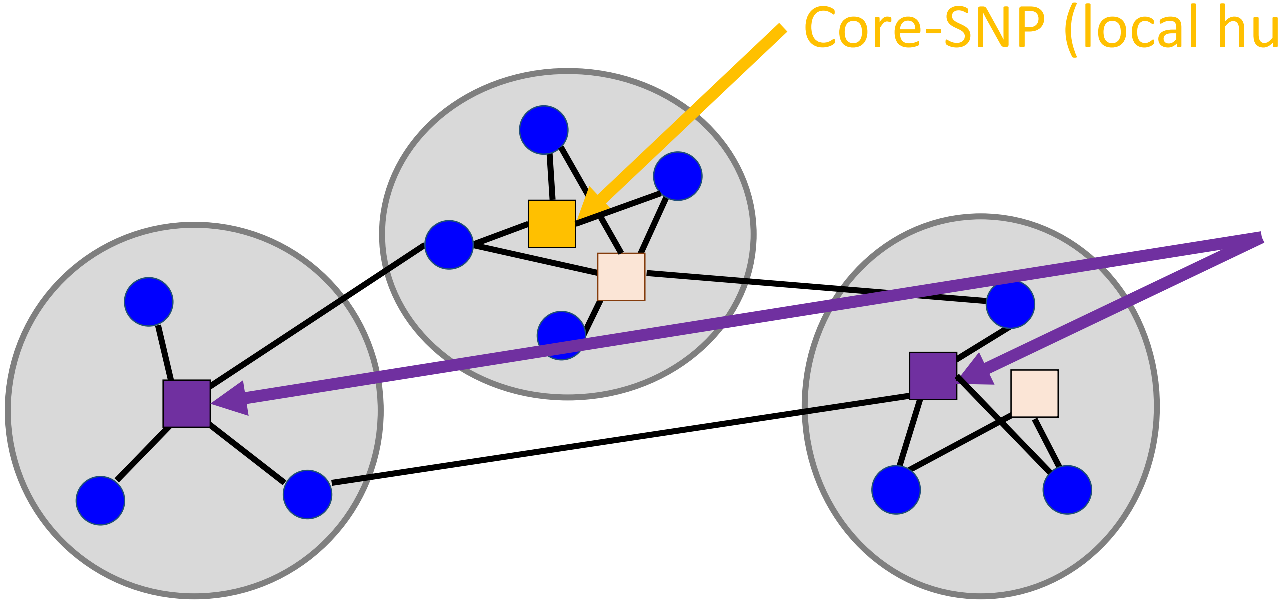


2 hypotheses: high-degree?



High-degree SNP (global hub)

Or high core-score?



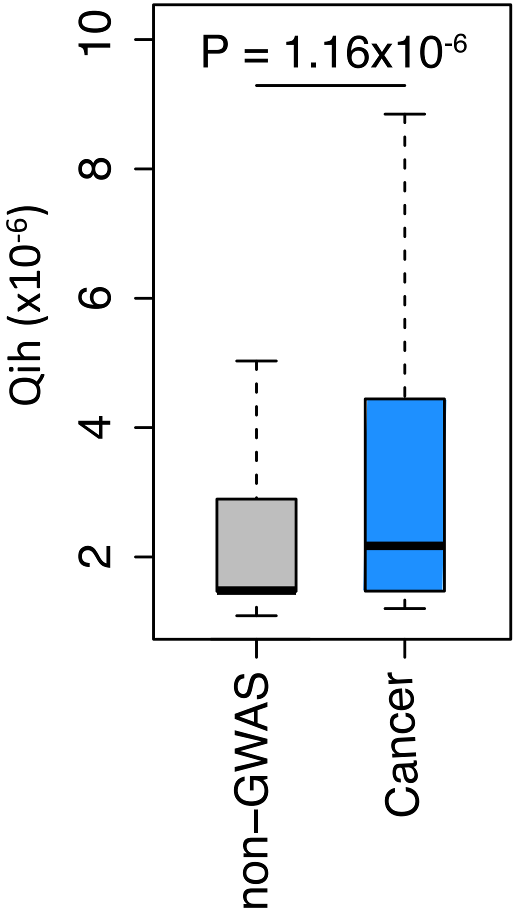
Core-SNP (local hub)

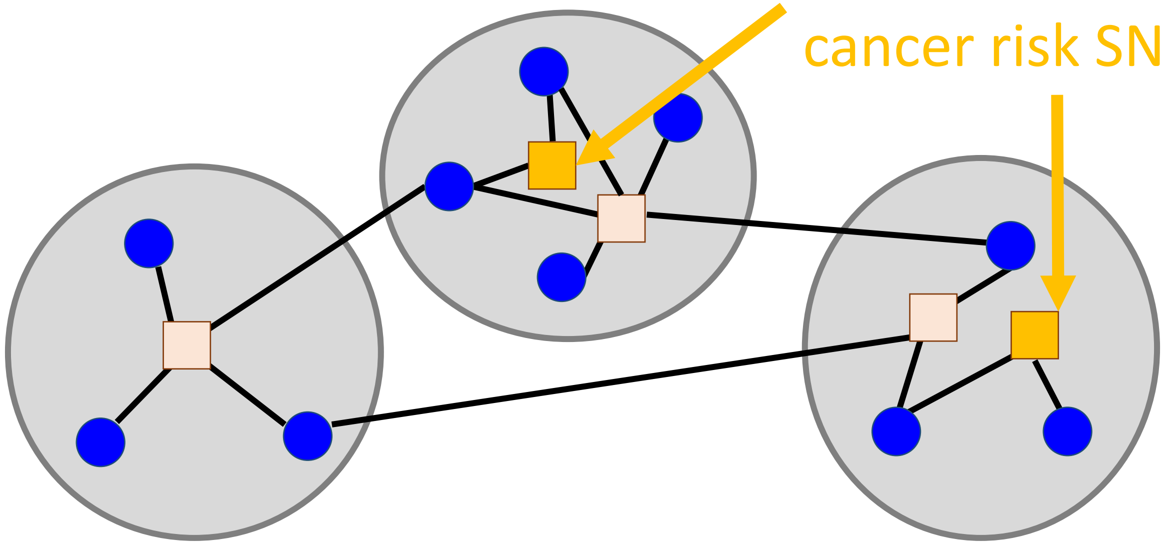
High-degree SNP (global hub)

Core-score for SNP i in community h

$$Q_{ih} = \frac{1}{m}\sum_{j} \underbrace{\left(\widetilde{A}_{ij} - \frac{k_i d_j}{m}\right)}_{\text{Observed – expected edge between SNP I and gene j}} \delta(C_i, h)\underbrace{\delta(C_j, h)}_{\text{Is gene j in community h?}}$$

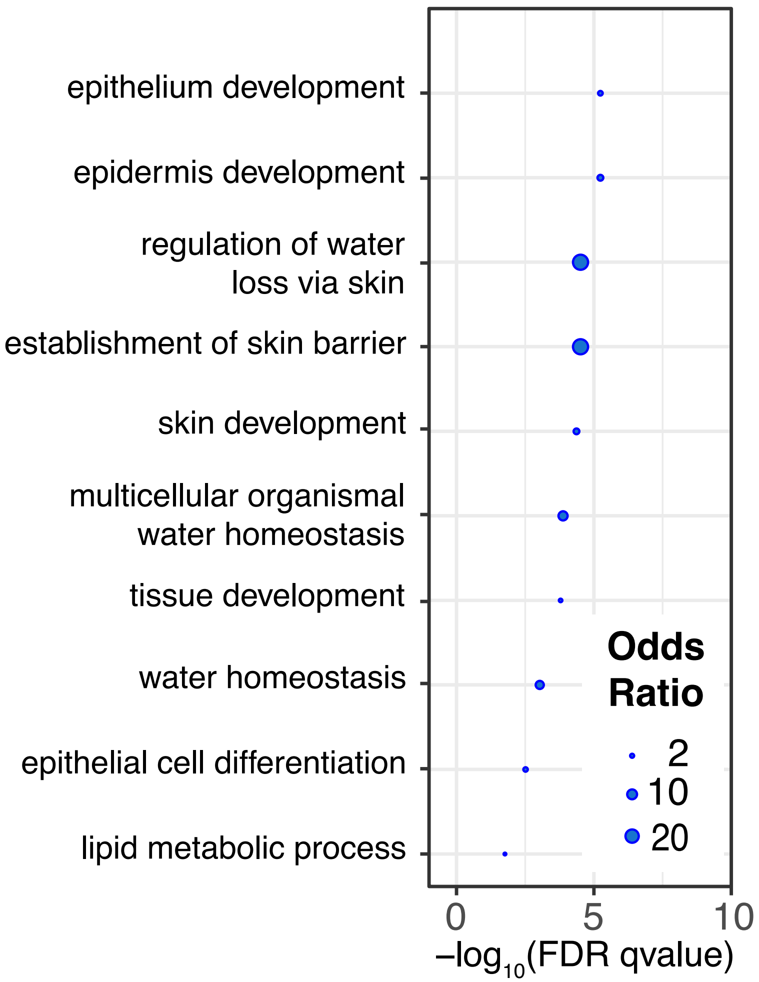
Cancer-risk SNPs are local hubs

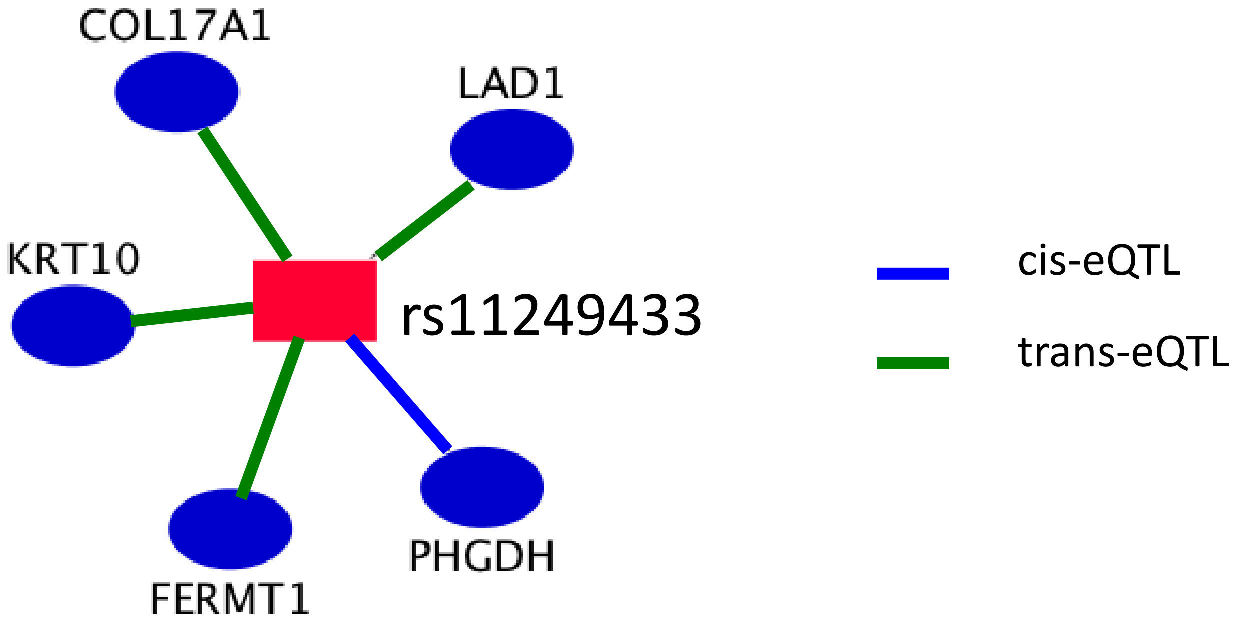




Core-SNPs/
cancer risk SNPs

An example of breast cancer risk SNP





- ➢ rs11249433 is associated to breast cancer
- ➢ It targets genes that are deregulated in epithelium cancers (EMS).

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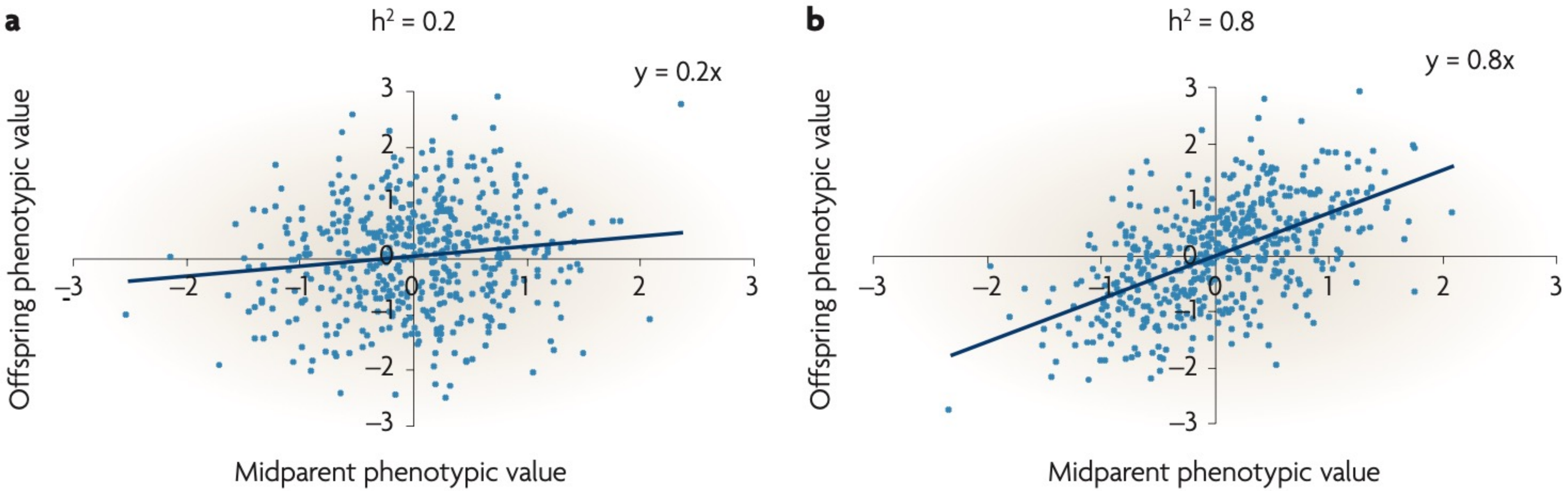
Katherine Stone
(Bachelor student)

Genetic heritability

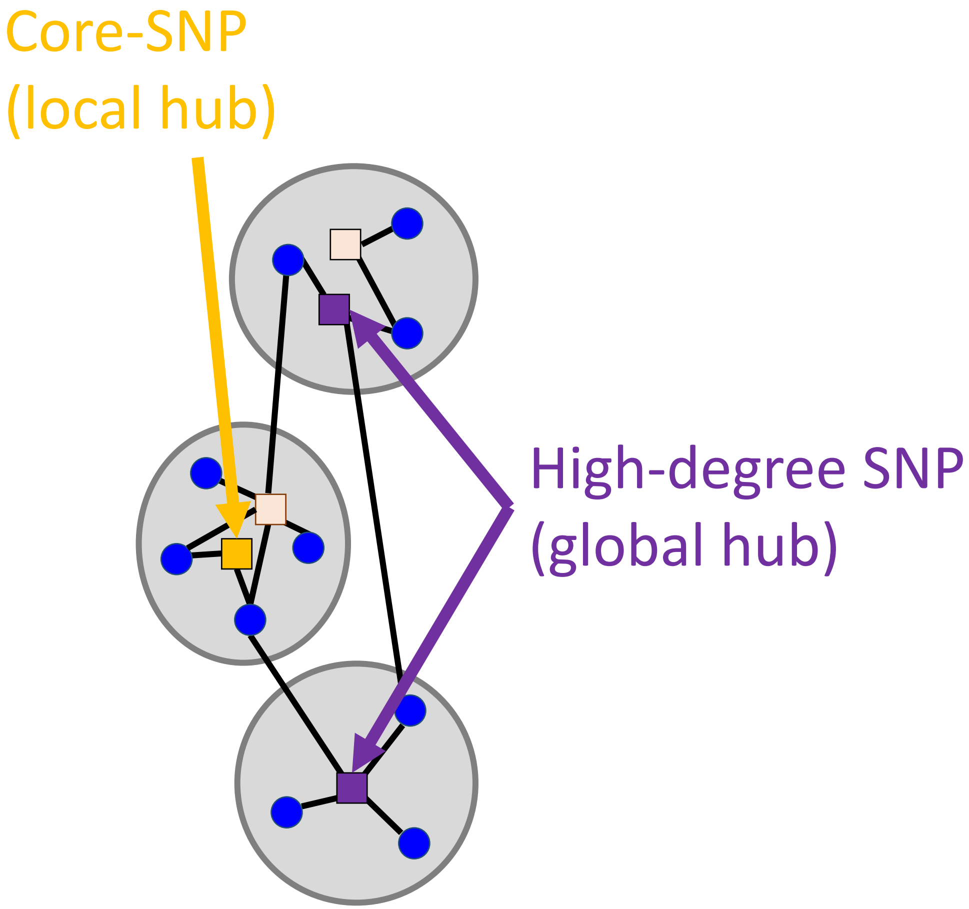


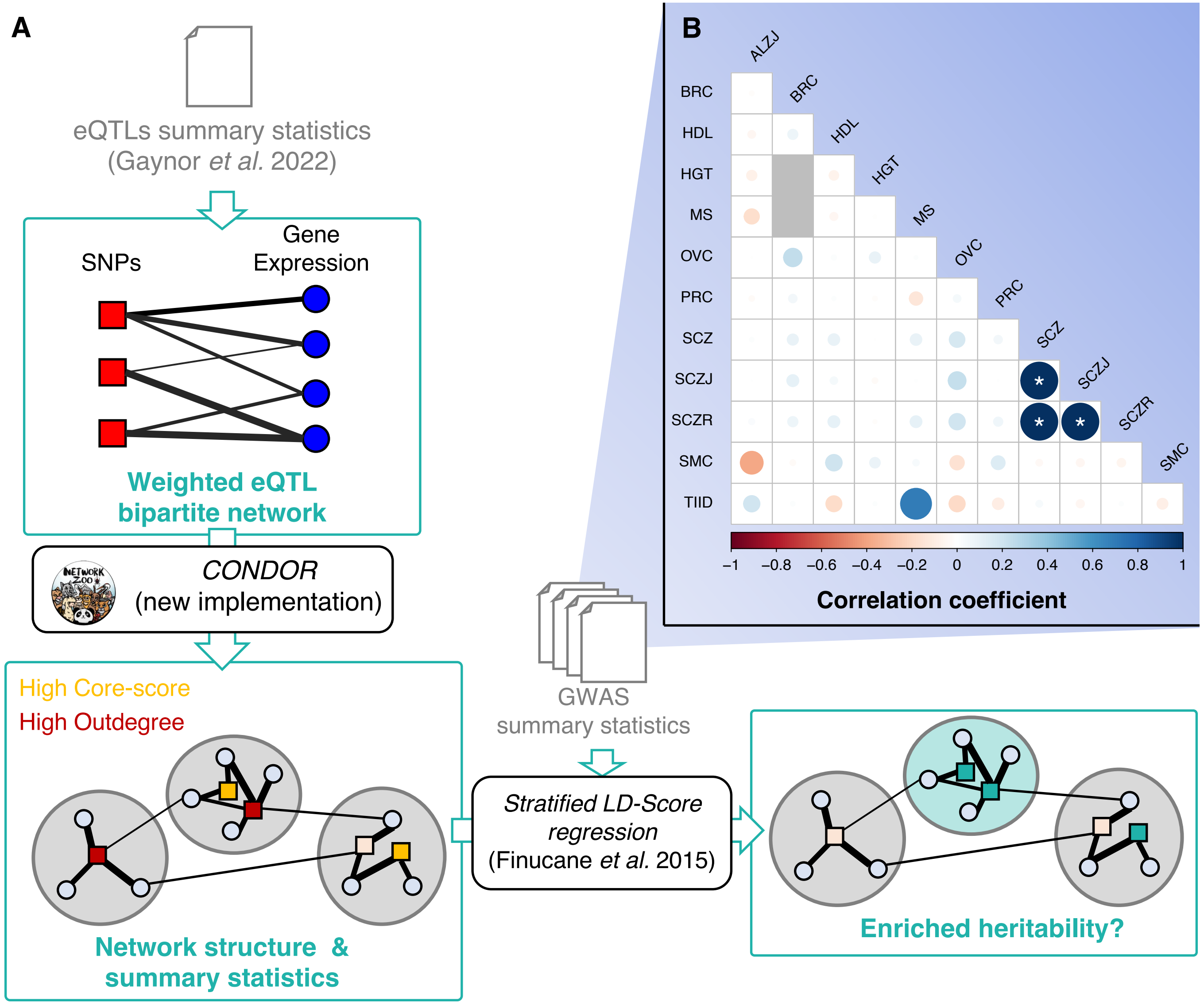
h^2 = heritability, proportion of variance explained by additive genetic value

Visscher *et al.* (2008) *Nature Review Genetics*

Genetic heritability in a network

Where is most of the heritability located?



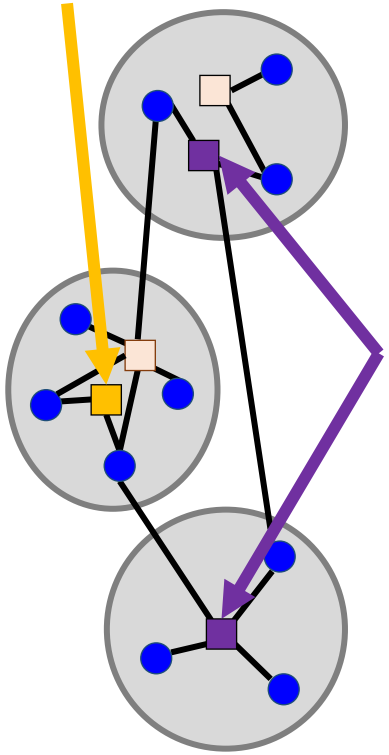


Traits

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%

Genetic heritability in a network

Is there a link between the amount of heritability explained and the network topology?

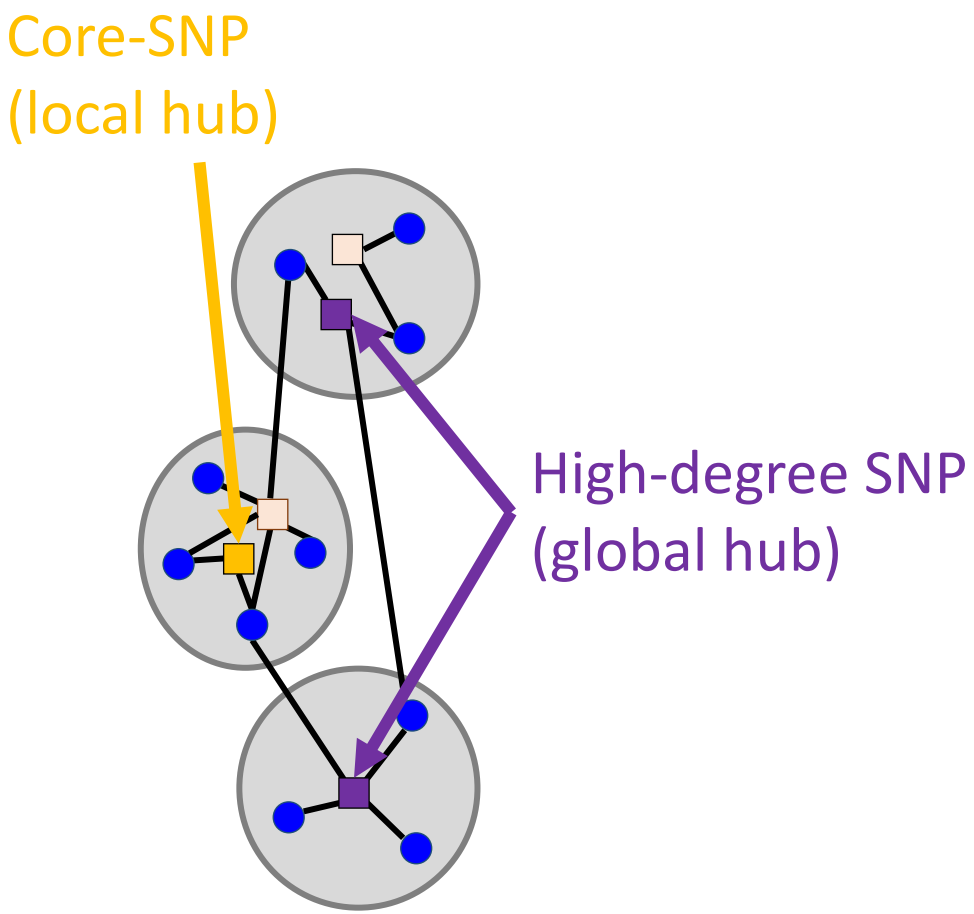


Core-SNP
(local hub)

High-degree SNP
(global hub)

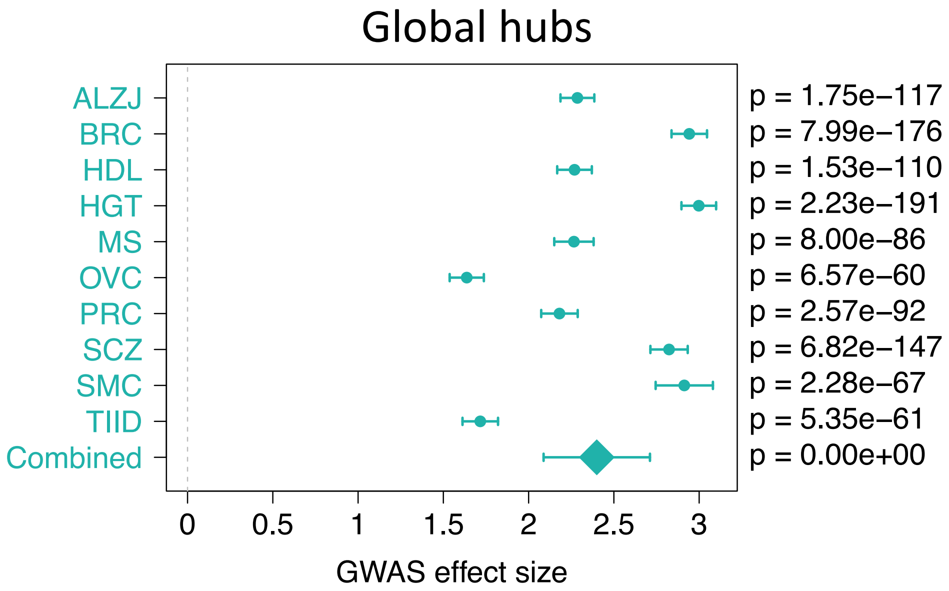
Genetic heritability in a network

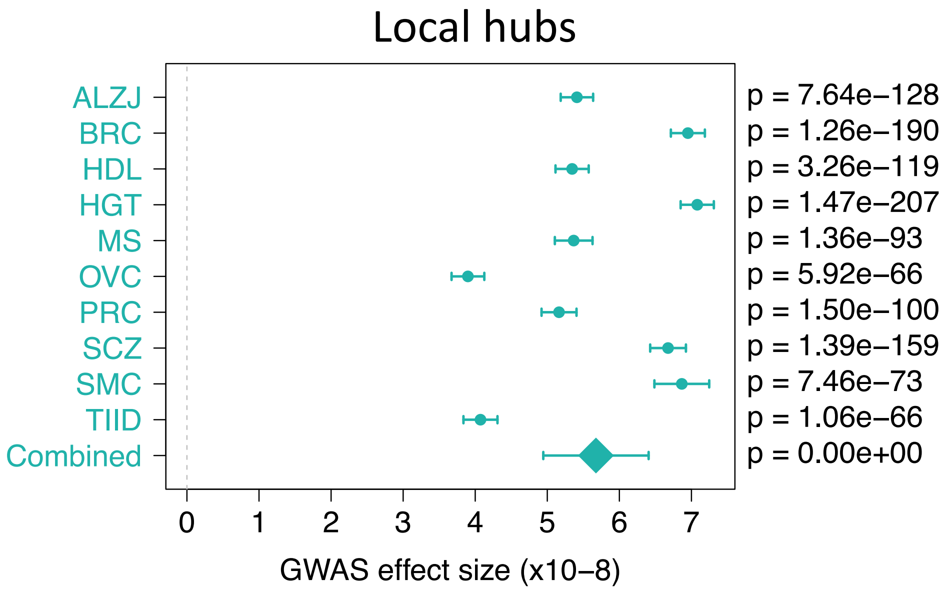
Is there a link between the amount of heritability explained and the network topology?



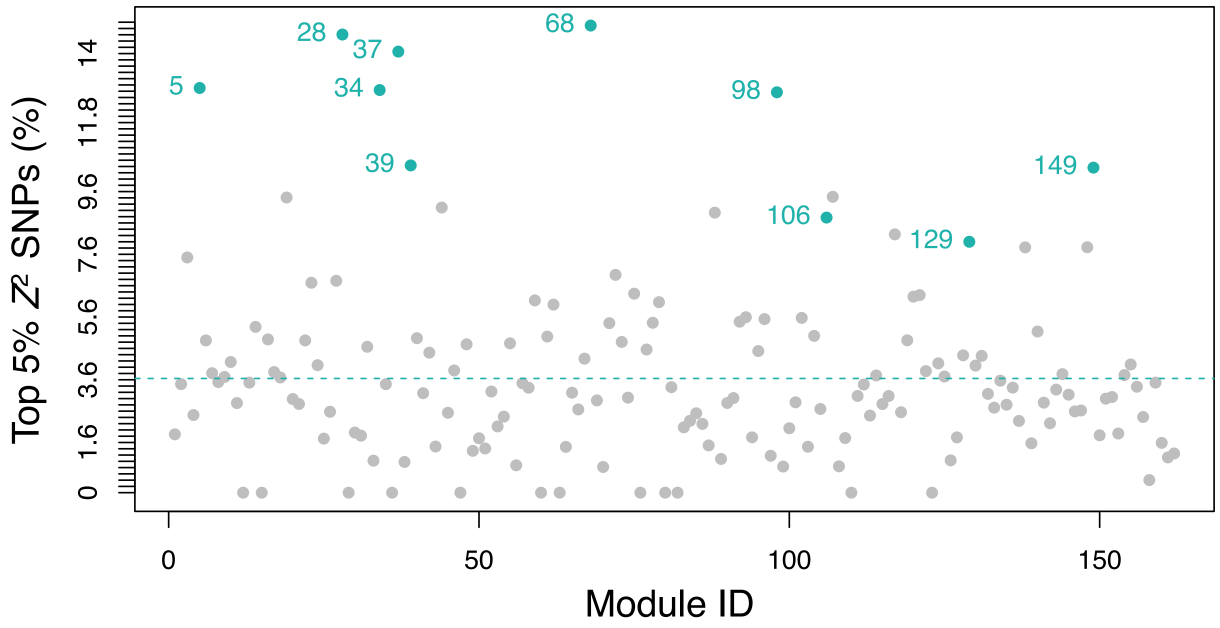
Core-SNP (local hub)

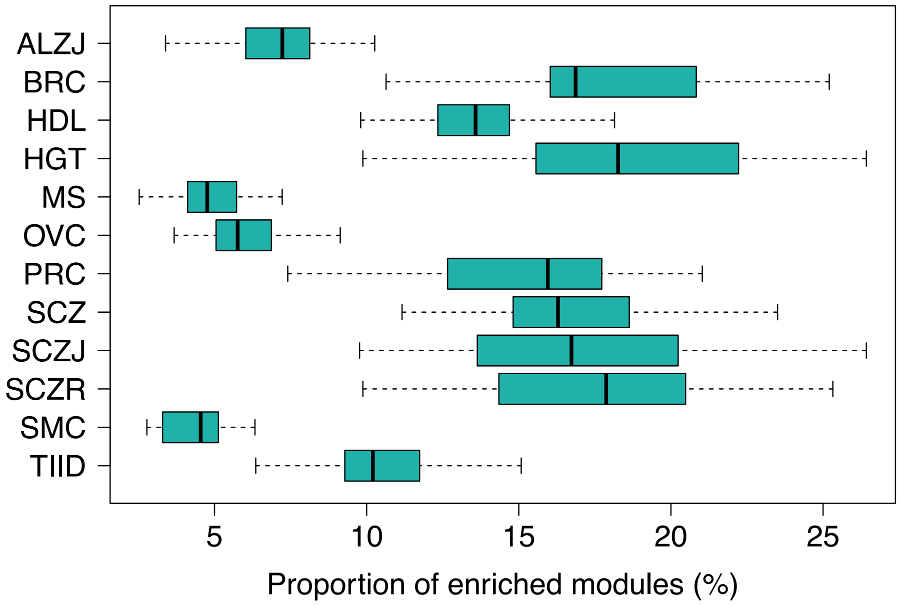
High-degree SNP (global hub)





Genetic heritability among communities

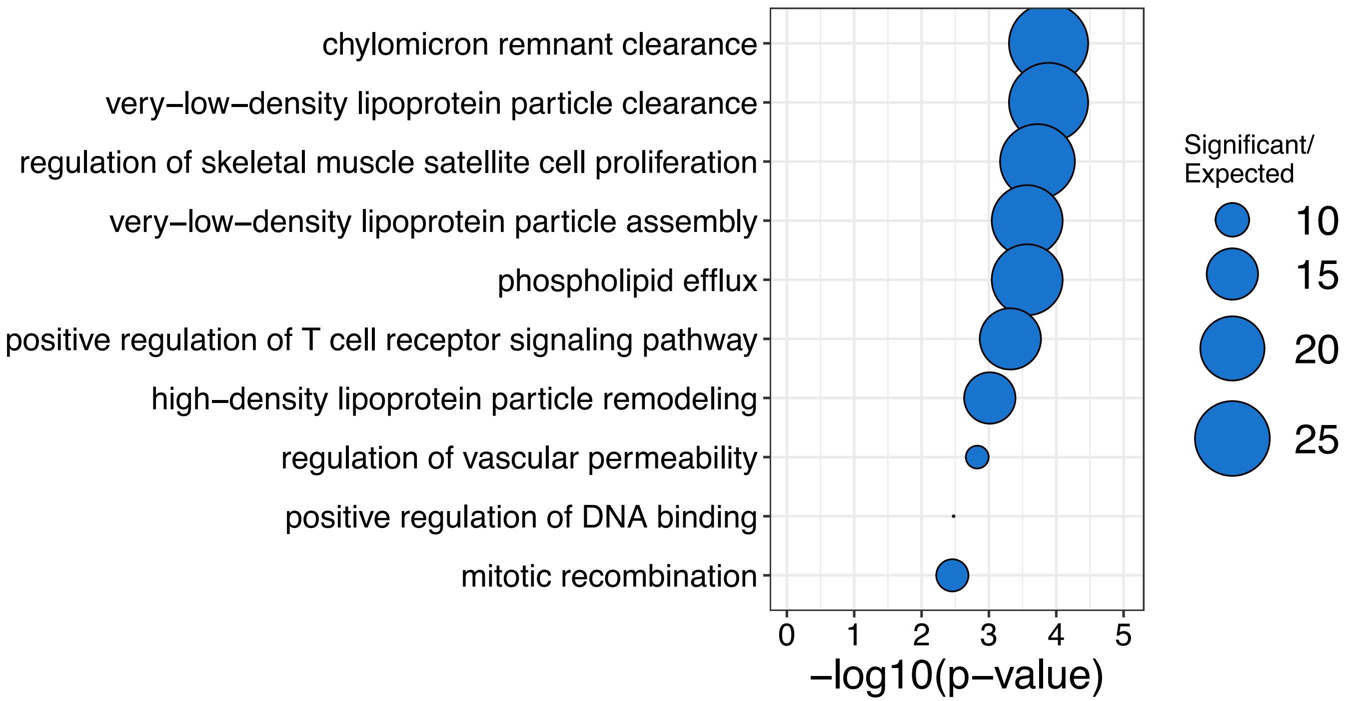




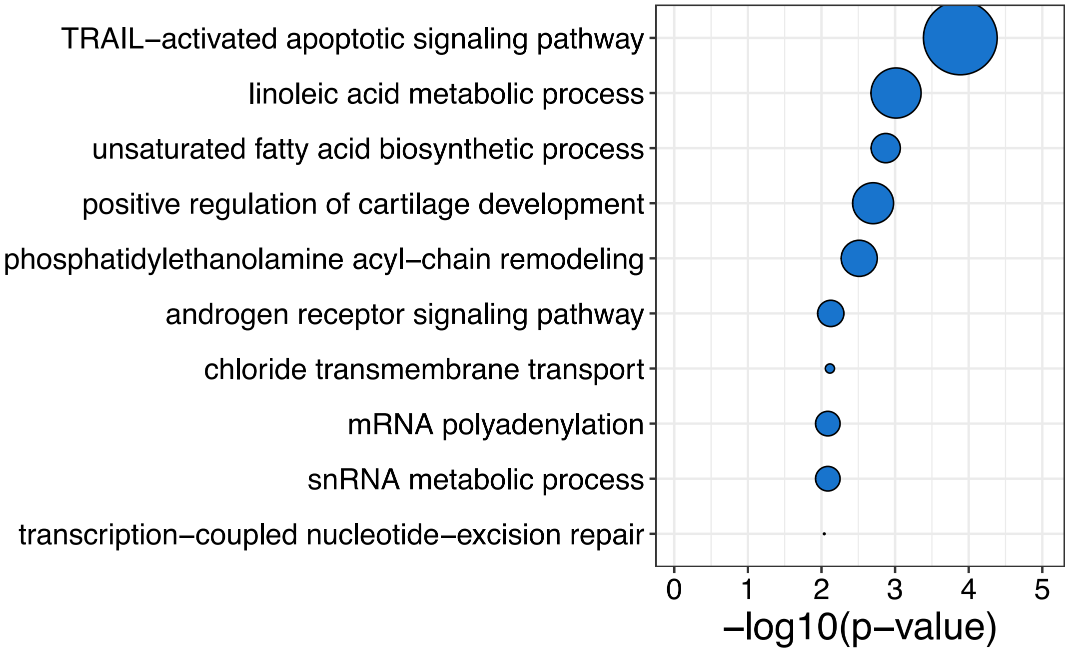
- Most of the heritability is concentrated in a few communities

Genetic heritability and biological functions

Adipose Visceral Omentum community
HDL levels



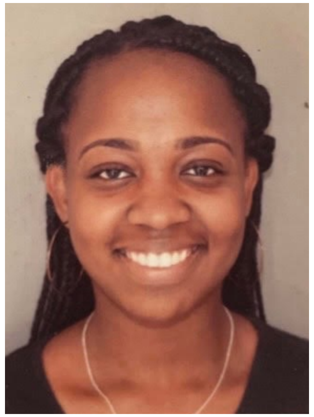
Colon sigmoid community
prostate cancer



- Genetic heritability is concentrated in tissue-specific, biologically relevant communities

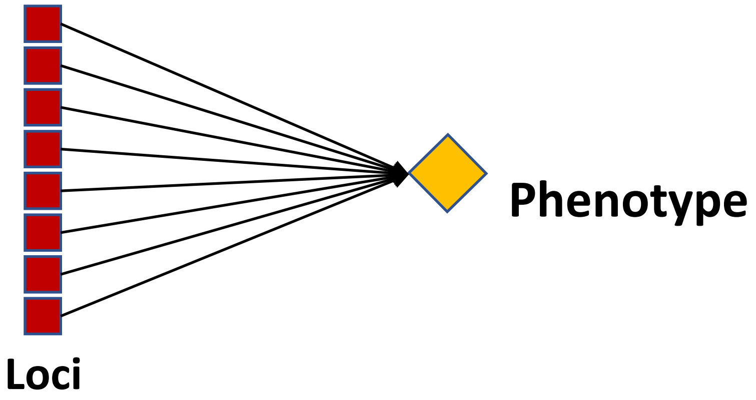
Research question:
Understanding the genetic architecture of complex traits

- **Biological characterization of SNPs identified by GWAS: How do genetic variation influence a trait ? Which biological pathways are involved?**
- **Heritability: Which mutations most affect the trait? Where are they located in the regulatory network**
- **Natural Selection: How do such a complex trait evolve?**



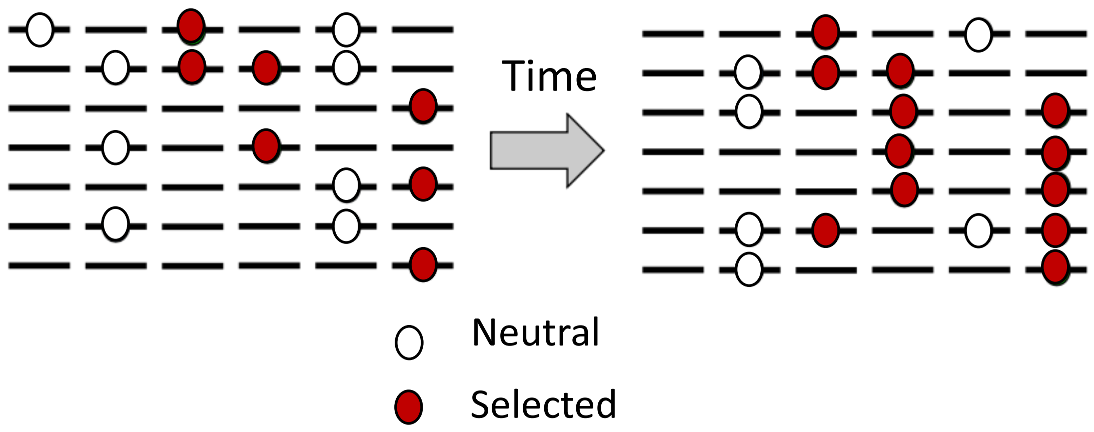
Rosanne Phebe (M1)

Polygenic adaptation: from phenotype to molecules



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

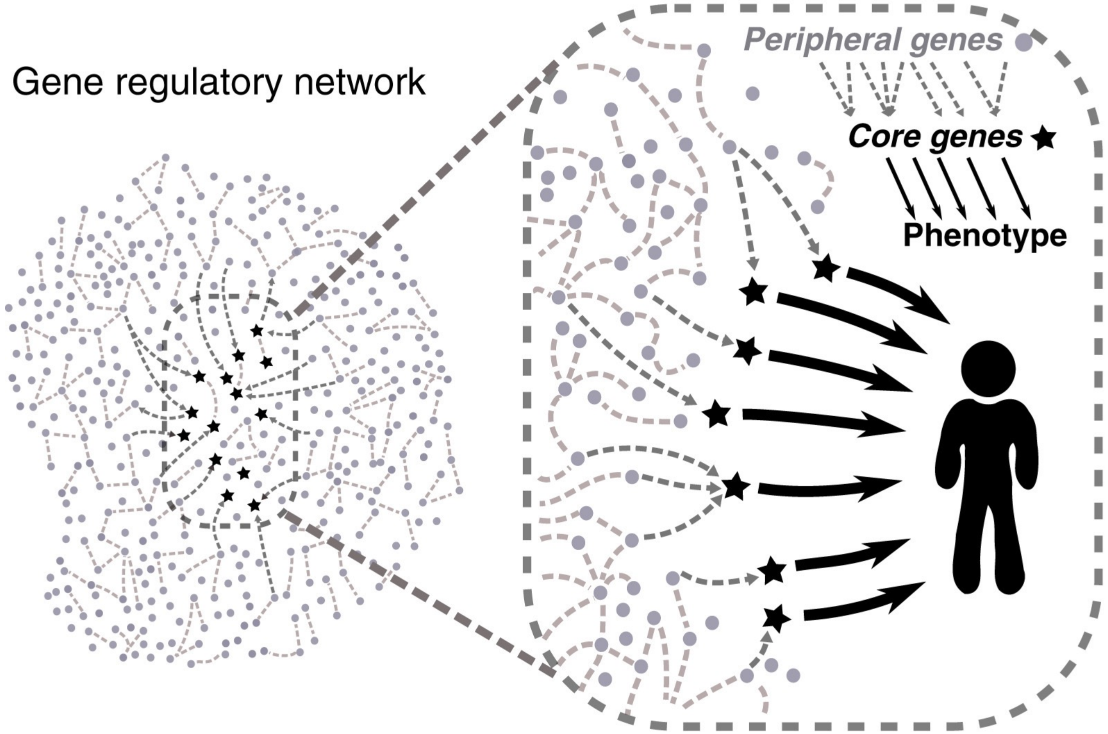
Polygenic adaptation at the molecular level



- The omnigenic model
- Pleiotropic loci

The genetic architecture of complex traits may limit adaptation

The omnigenic model

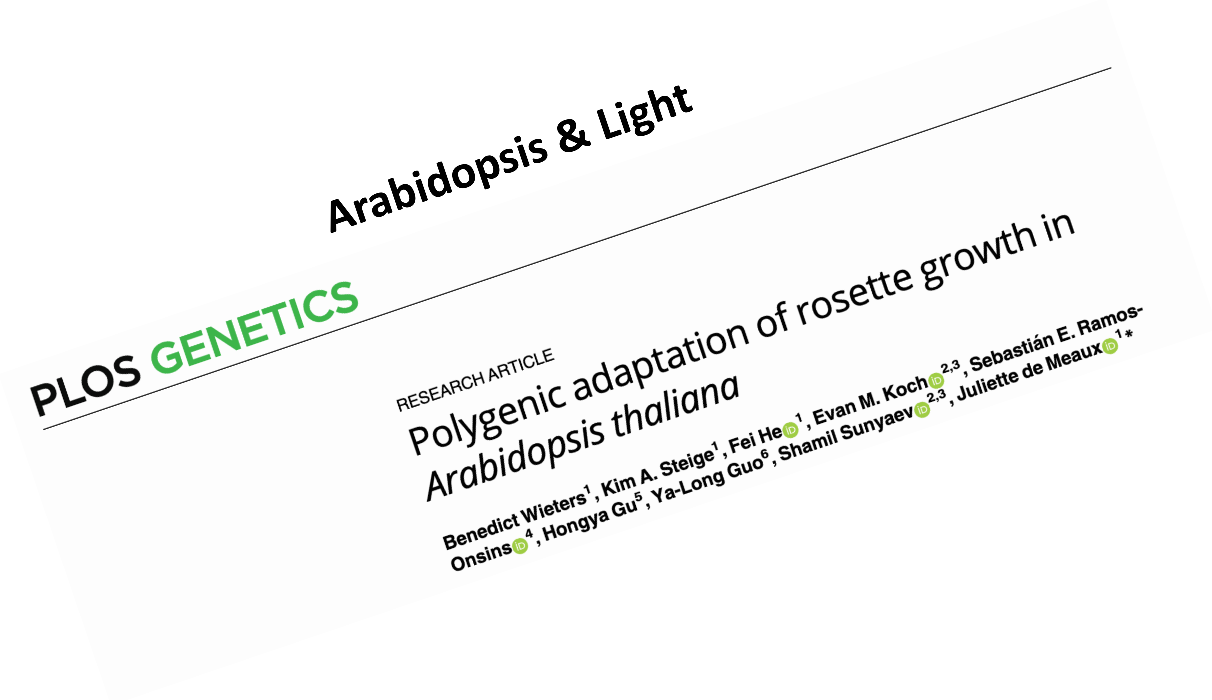


Boyle *et al.*, *Cell*, 2017
Liu *et al.*, *Cell*, 2019

- **High pleiotropy**

But… Many examples of polygenic adaptation

Arabidopsis & Light



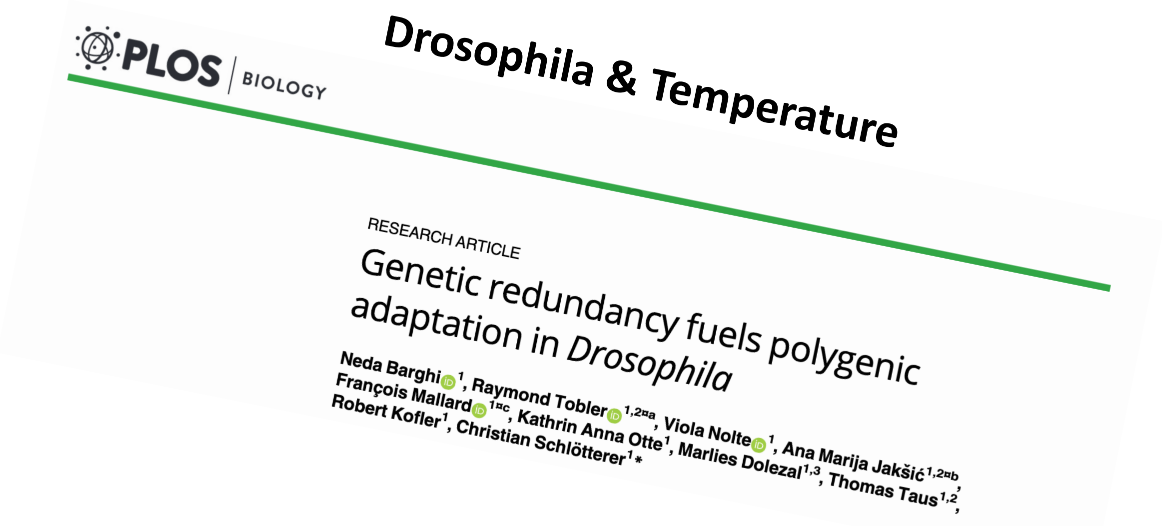
PLOS GENETICS

RESEARCH ARTICLE

Polygenic adaptation of rosette growth in *Arabidopsis thaliana*

Benedict Wieters[1], Kim A. Steige[1], Fei He[1], Evan M. Koch[2,3], Sebastián E. Ramos-Onsins[4], Hongya Gu[5], Ya-Long Guo[6], Shamil Sunyaev[2,3], Juliette de Meaux[1]*

Drosophila & Temperature



PLOS | BIOLOGY

RESEARCH ARTICLE

Genetic redundancy fuels polygenic adaptation in *Drosophila*

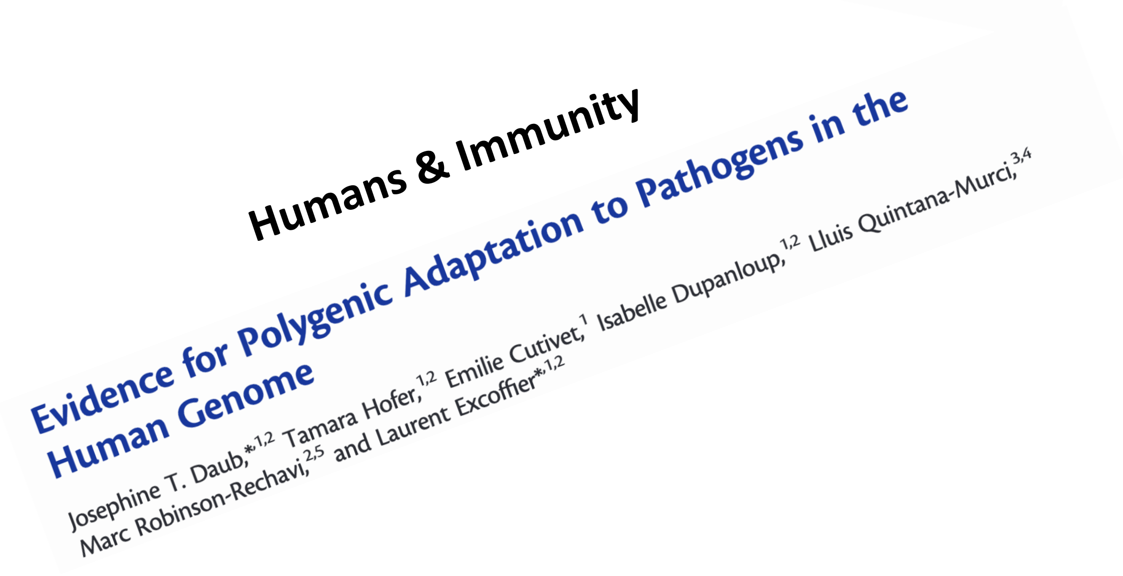
Neda Barghi[1], Raymond Tobler[1,2¤a], Viola Nolte[1], Ana Marija Jakšić[1,2¤b], François Mallard[1¤c], Kathrin Anna Otte[1], Marlies Dolezal[1,3], Thomas Taus[1,2], Robert Kofler[1], Christian Schlötterer[1]*

Maize & Altitude

Molecular Parallelism Underlies Convergent Highland Adaptation of Maize Landraces

Li Wang,*[1,2,3] Emily B. Josephs,[4,5] Kristin M. Lee,[3] Lucas M. Roberts,[2] Rubén Rellán-Álvarez,[6,7] Jeffrey Ross-Ibarra,*[3,8] and Matthew B. Hufford*[2]

Humans & Immunity

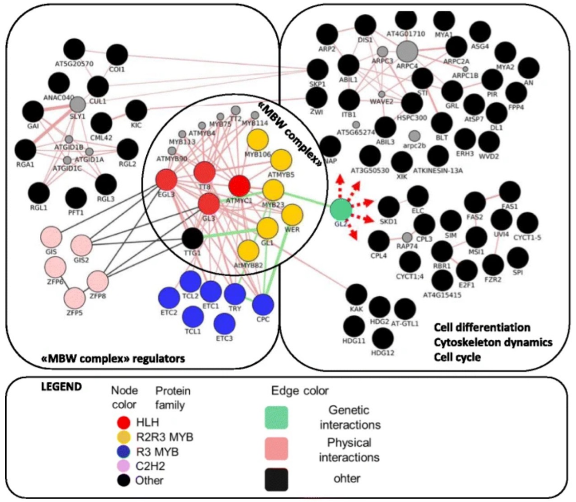


Evidence for Polygenic Adaptation to Pathogens in the Human Genome

Josephine T. Daub,*[1,2] Tamara Hofer,[1,2] Emilie Cutivet,[1] Isabelle Dupanloup,[1,2] Lluis Quintana-Murci,[3,4] Marc Robinson-Rechavi,[2,5] and Laurent Excoffier*[1,2]

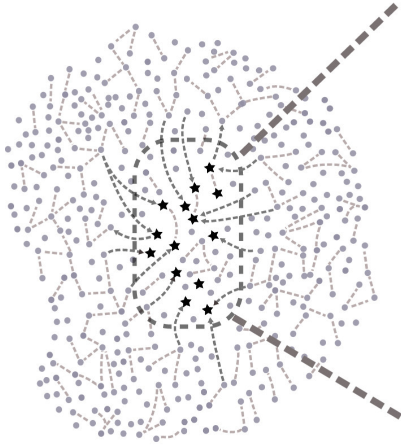
Structuration & Tissue-specificity & Redundancy

Structured GRN (Arabidopsis)

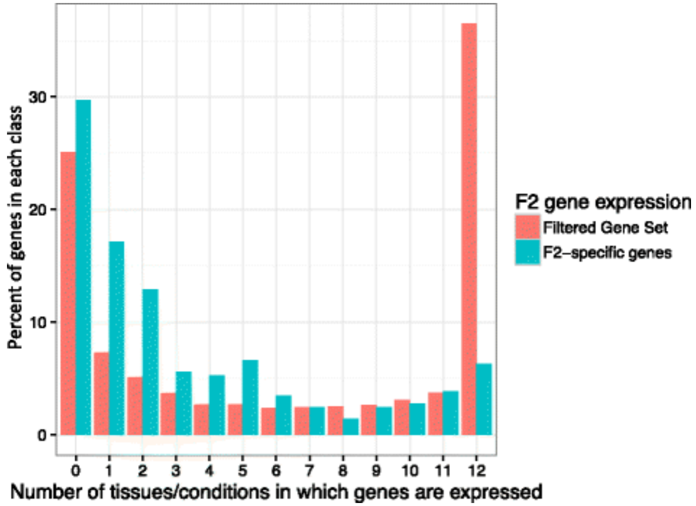


Doroshkov *et al.*, *BMC Plant Biology*, 2019

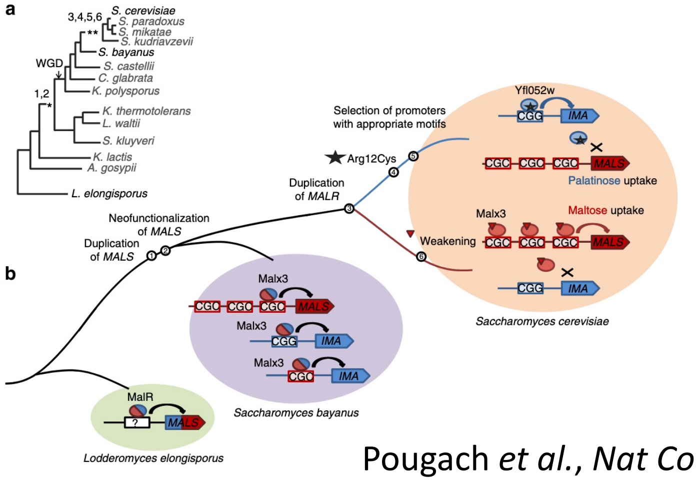
The omnigenic model



Tissue-specific gene expression (maize)



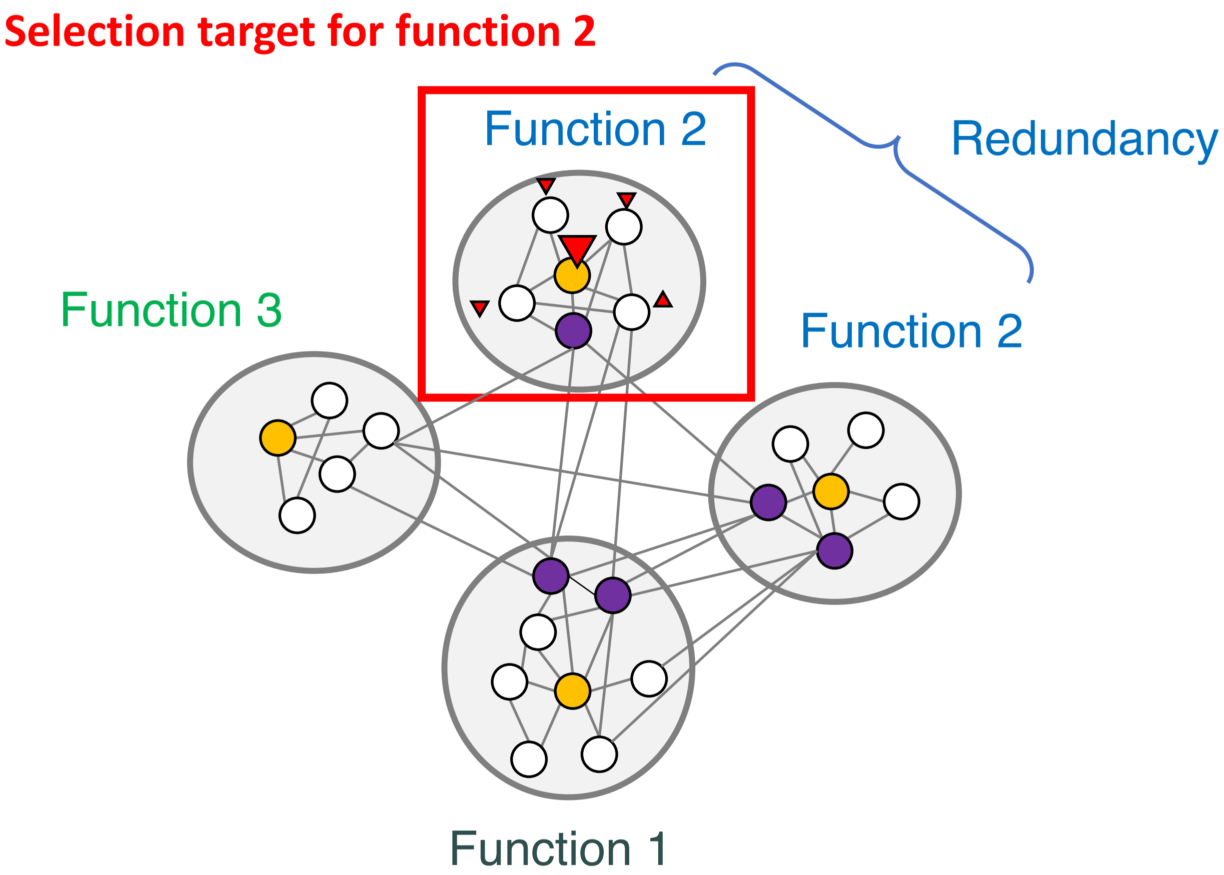
Darracq *et al.*, *BMC Genomics*, 2018



Pougach *et al.*, *Nat Comm*, 2014

Redundancy and neofunctionalization (yeast)

Proposed model: a major role for redundancy and node topology in evolvability



Take-home message

- Expression quantitative trait loci (eQTL) bipartite networks can help functionally annotating SNPs associated with complex traits
- Cancer-risk SNPs are :
  - located preferentially in local hubs and communities related to immune (several cancers), or tissue-specific (cancer-specific) functions.
  - impacting the expression of oncogenes and tumor suppressor genes
- Most of complex trait heritability is :
  - Located in local and global hubs,
  - Concentrated in a few, tissue-specific and biologically relevant communities.
- To go further:
  - eQTL network structure may help us understand how complex trait evolve despites a high level of pleiotropy