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Maud Fagny

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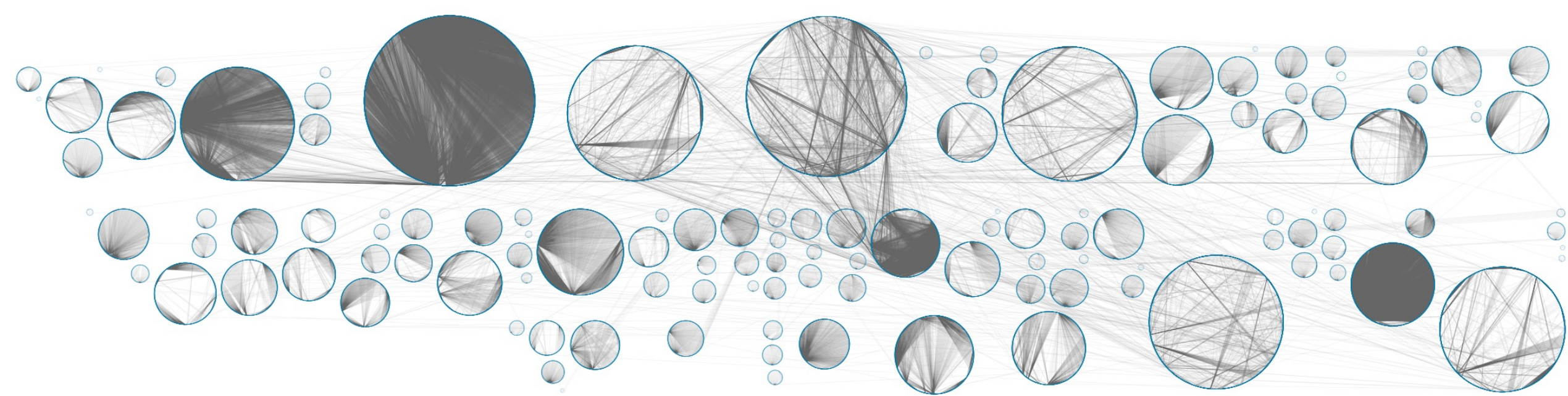
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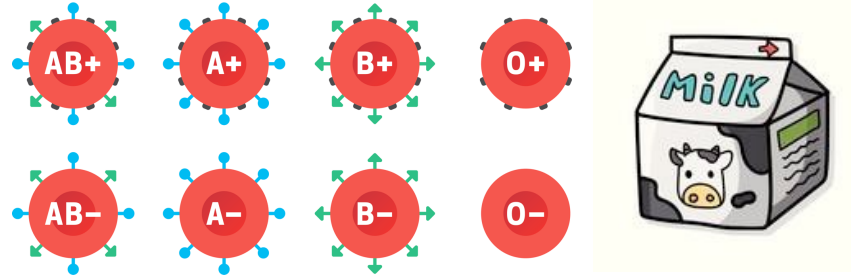
# Using eQTL networks to functionally characterize regulatory mutations

Maud Fagny, PhD  
INRAE, Gif-sur-Yvette

# Mendelian vs. Polygenic traits

## Mendelian traits:

Gene  $\longrightarrow$  Phenotype

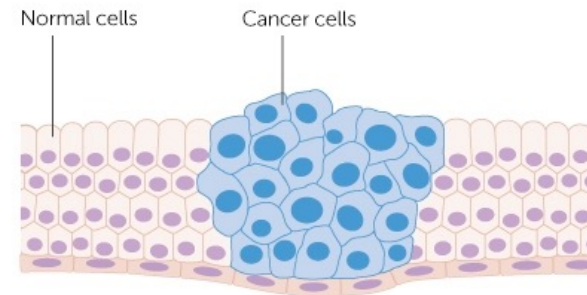


## Complex traits:

Gene 1  
Gene 2  
Gene 2

$\longrightarrow$  Phenotype

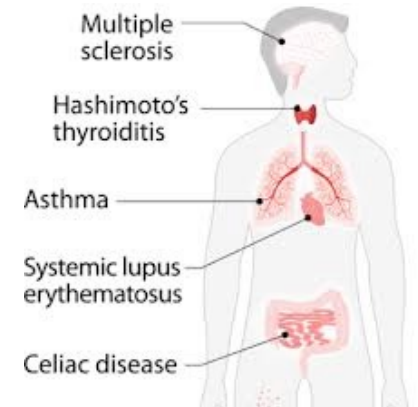
Environment  $\uparrow$



Cancer Research UK



© Comica, 2018



# Genetic architecture of some often-studied traits

## Monogenic

Mendelian

1 trait = 1 gene

Risk to develop a cancer

Adult size

Skin/eye/hairs color

## Oligogenic

1 trait = 2-10 genes

Risk to develop  
schizophrenia

Lactose tolerance

## Polygenic

1 trait = many genes

Risk to develop type II  
diabetes

Sickle-cell disease

# Genetic architecture of some often-studied traits

**Monogenic**

**Oligogenic**

**Polygenic**

Risk to develop a cancer

Risk to develop schizophrenia

Risk to develop type II diabetes

Adult size

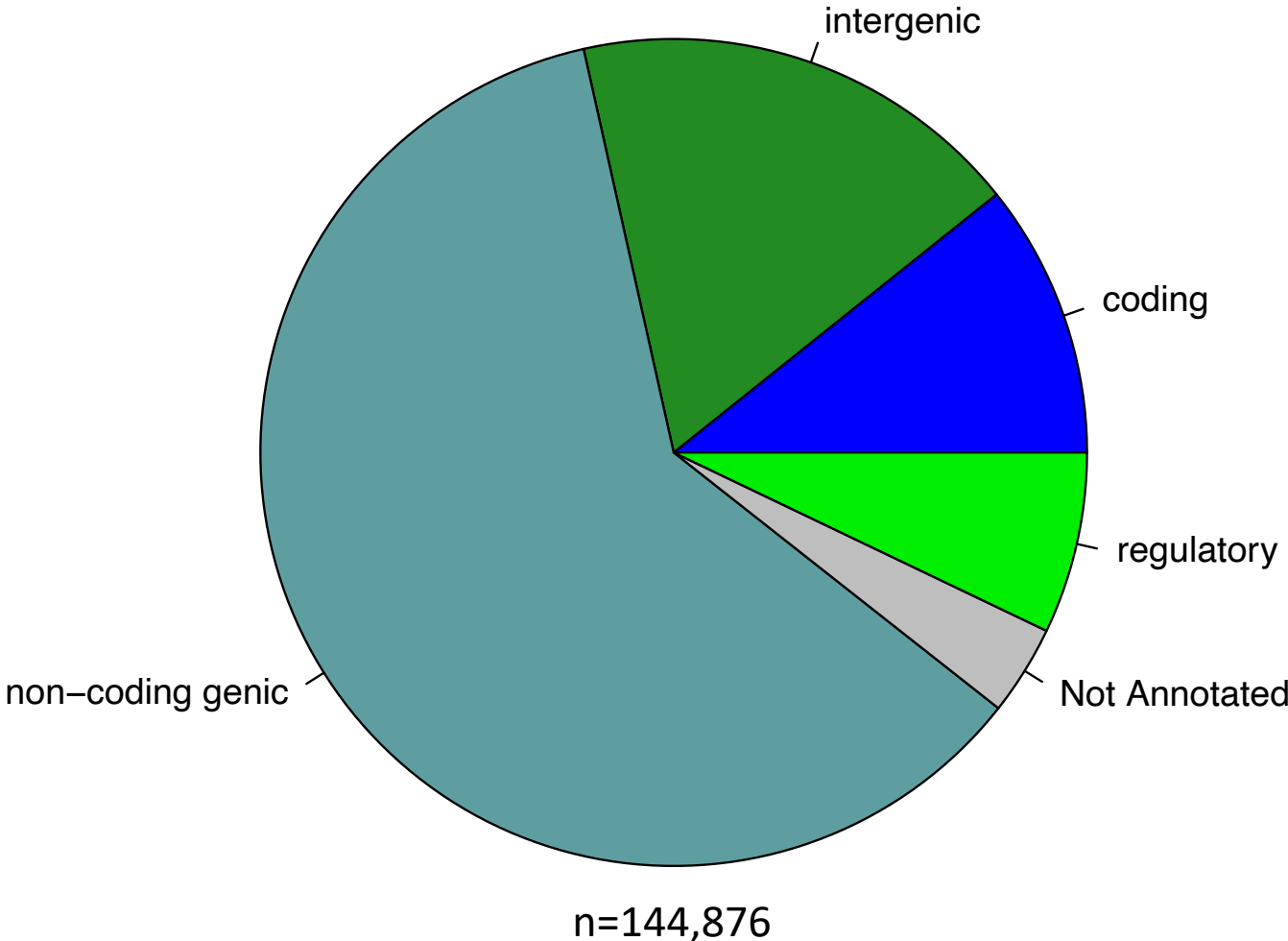
Lactose tolerance

Skin/eye/hairs color

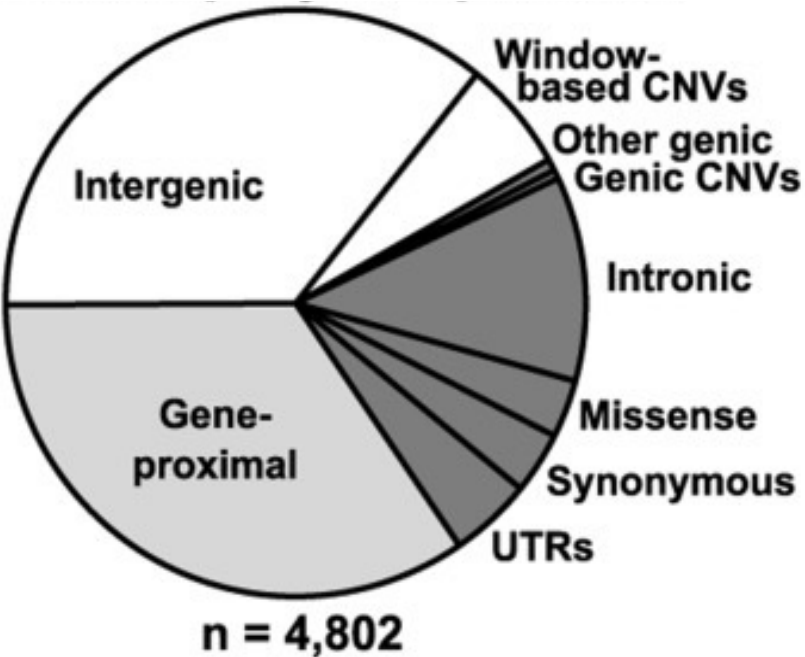
Sickle-cell disease

# The importance of gene expression regulation in polygenic phenotypes

**GWAS in humans**

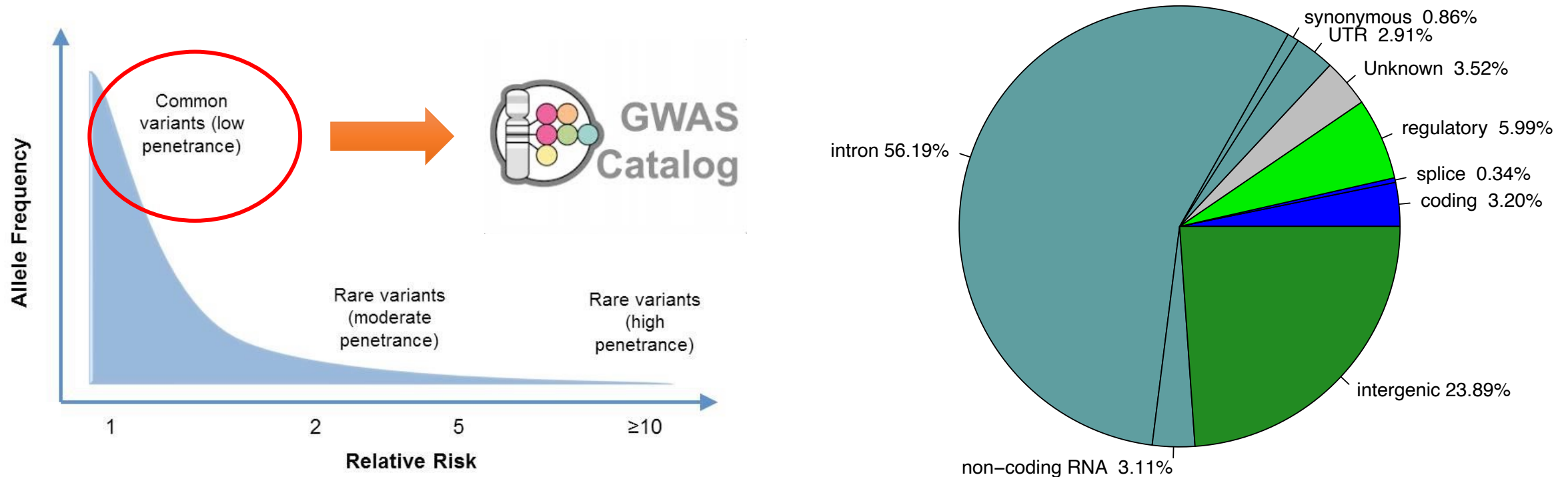


**GWAS for developmental traits in maize**



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

## Genetic Architecture of Cancer Risk



Adapted from *Cancer Genetics Overview* (PQD®)

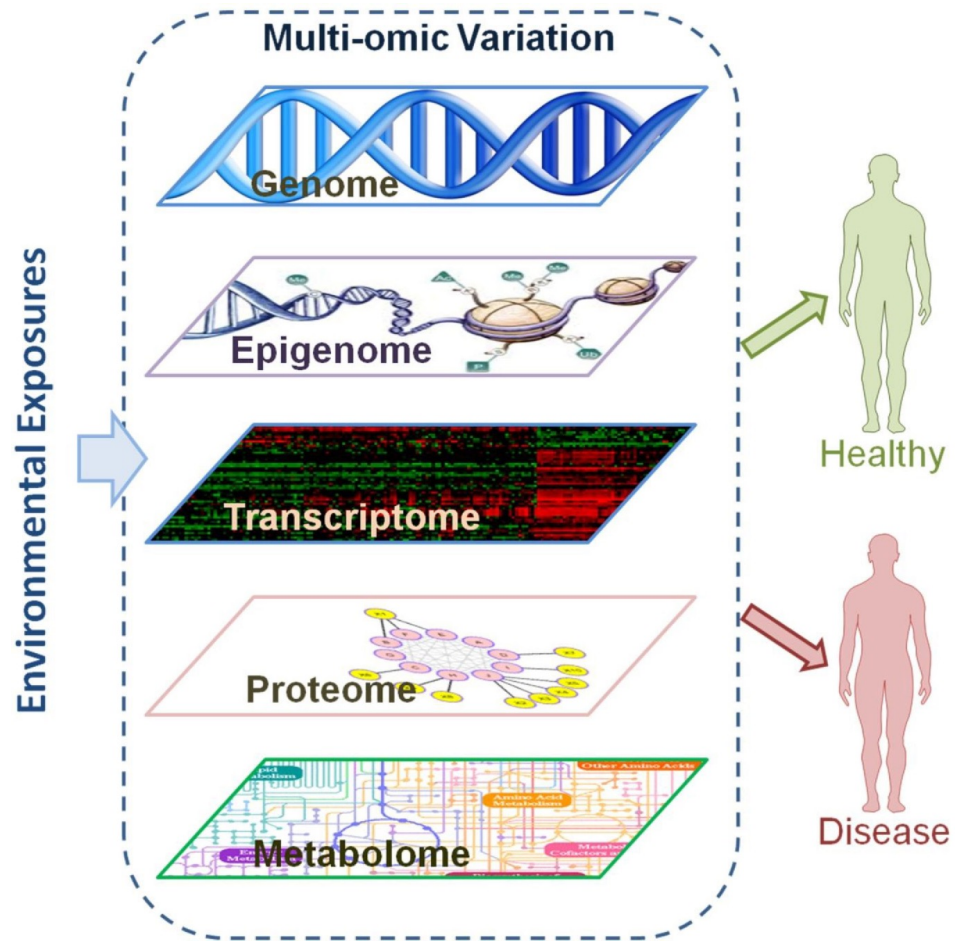
- 4,587 SNPs associated to 265 cancer-related traits
- 87% of cancer-risk SNPs with an odds ratio under 3

How can we functionally annotate regulatory SNPs associated with traits & diseases?





# Exploring the genotype-phenotype gap



## Cancer-risk SNPs:

Intermediate frequencies

&

Small effect size on phenotype

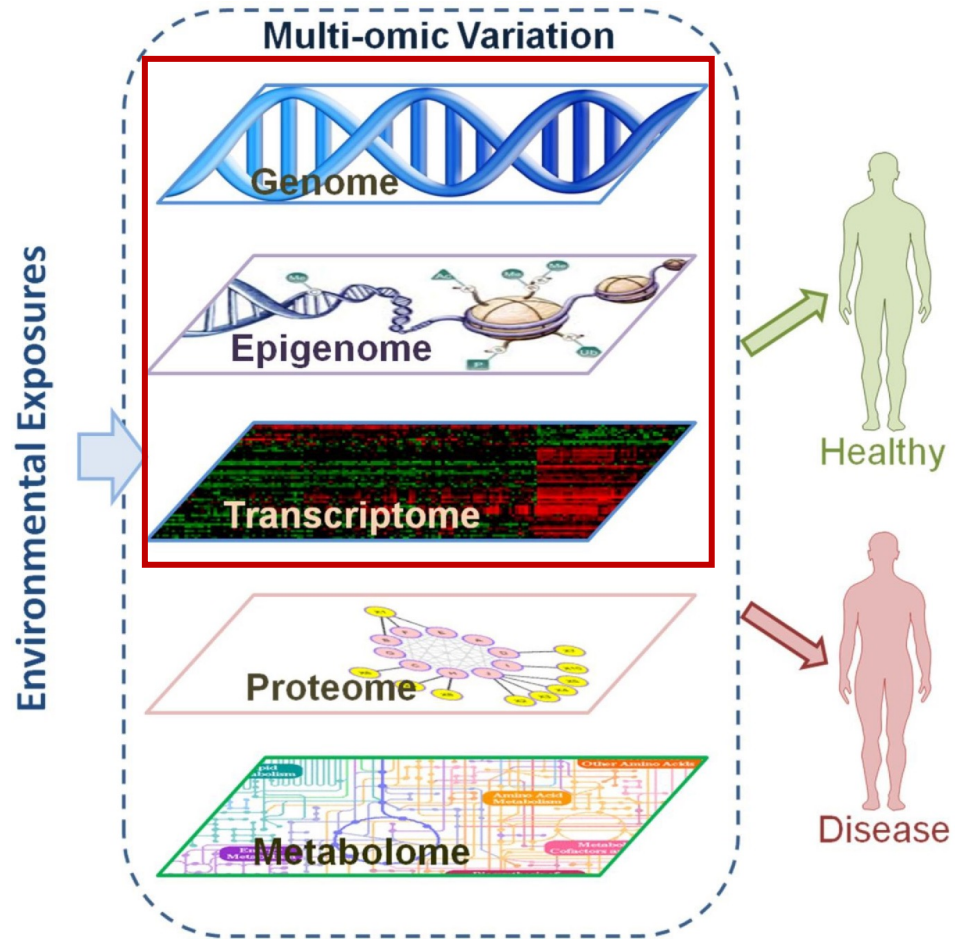
&

Tissue-specific effect

&

Located in regulatory regions

# Exploring the genotype-phenotype gap



## Cancer-risk SNPs:

Intermediate frequencies

&

Small effect size on phenotype

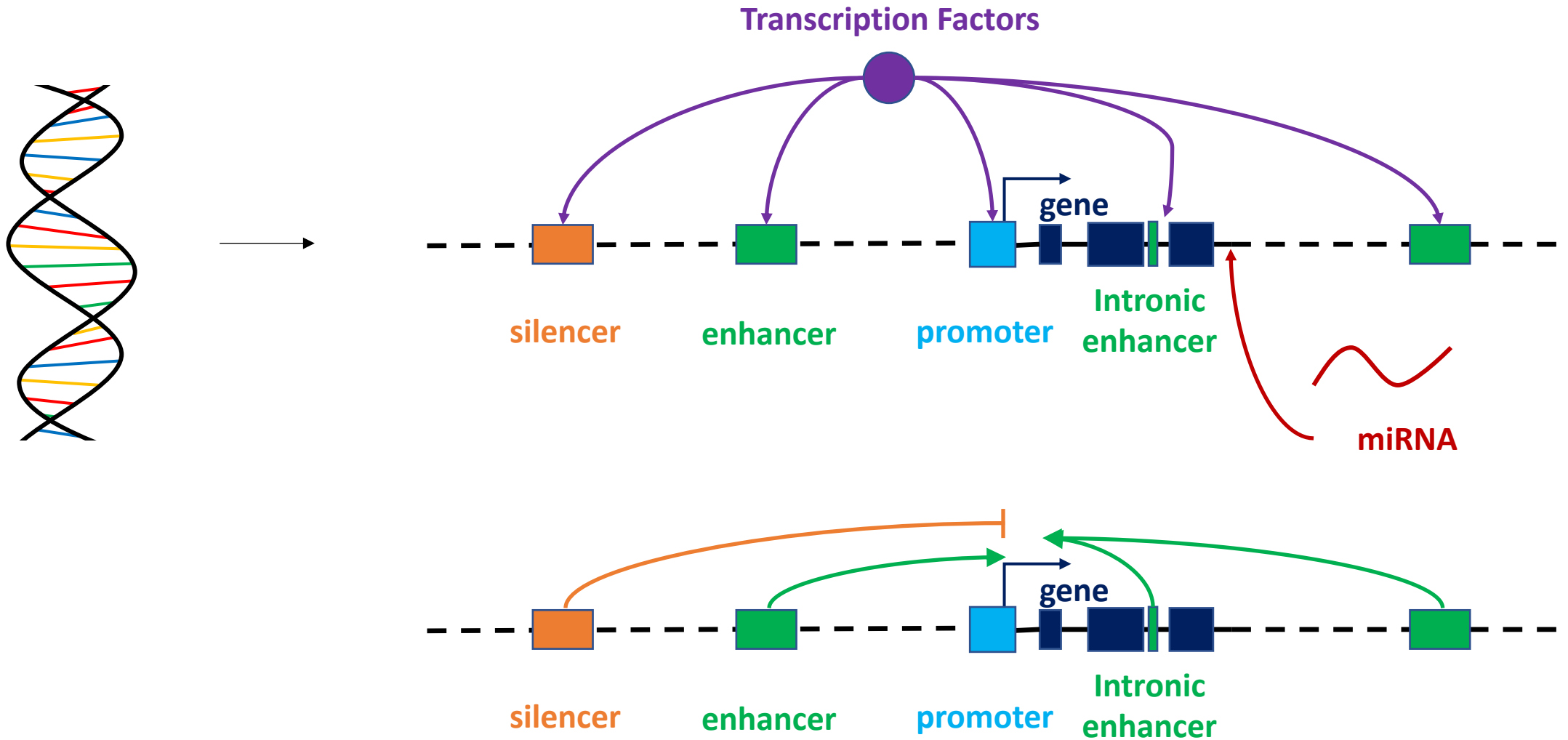
&

Tissue-specific effect

&

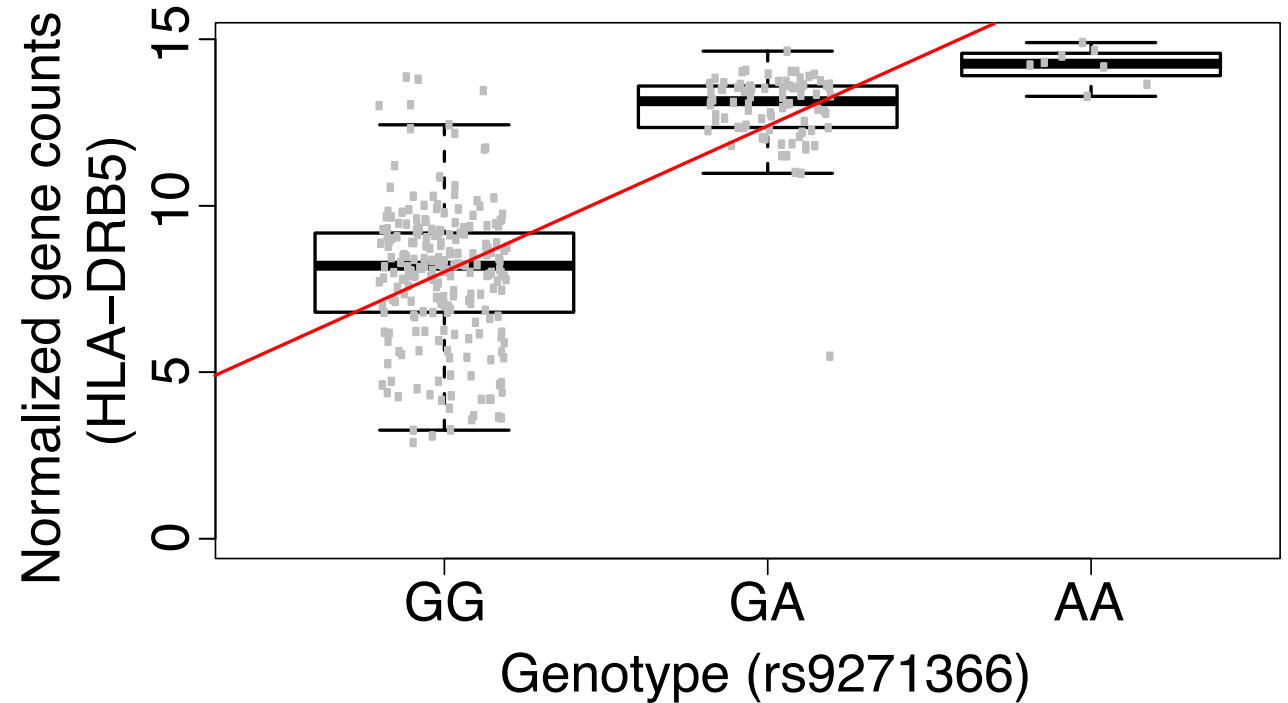
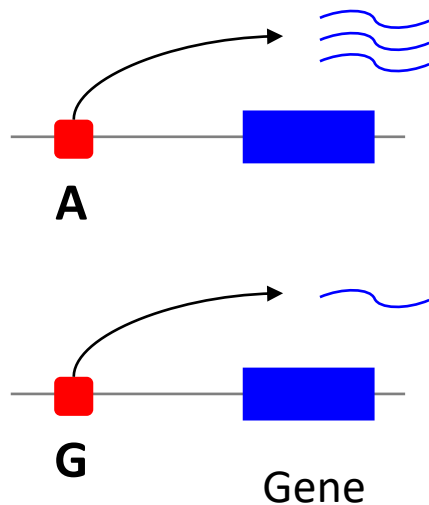
**Located in regulatory regions**

# Intergenic and non-coding genic regions regulate gene expression



# Identifying the gene targeted by regulatory SNPs: eQTLs

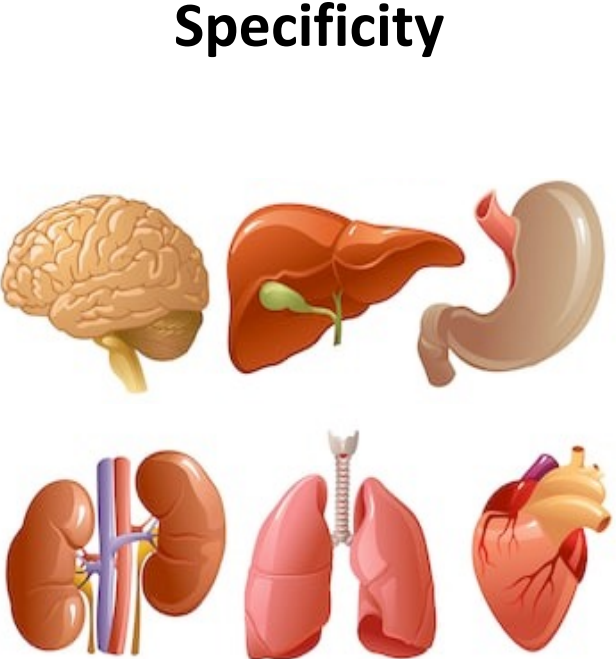
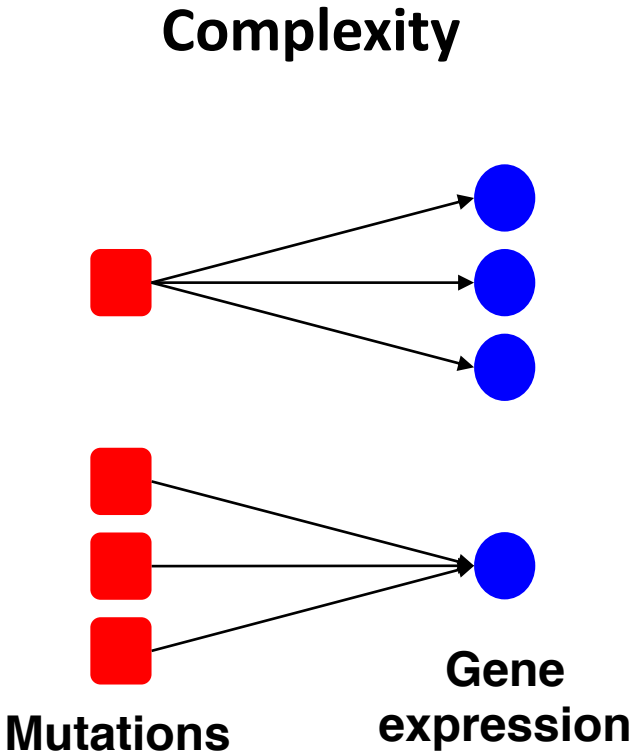
## Expression quantitative trait locus (eQTL)



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

A complex relationship between mutations and gene expression

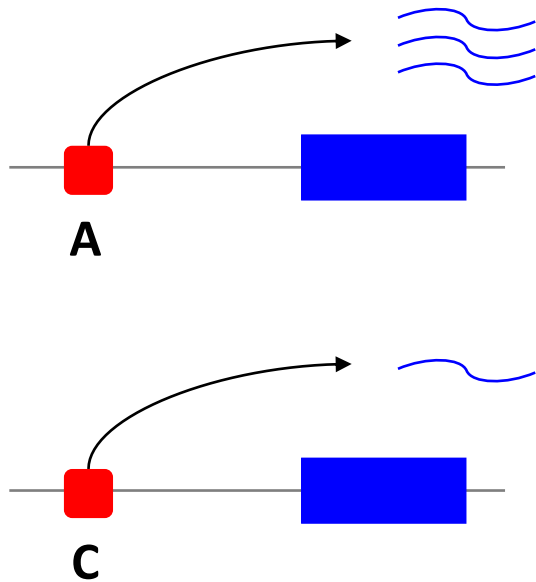
# A complex relationship between mutations and gene expression



How to handle the complexity?

# How to handle the complexity?

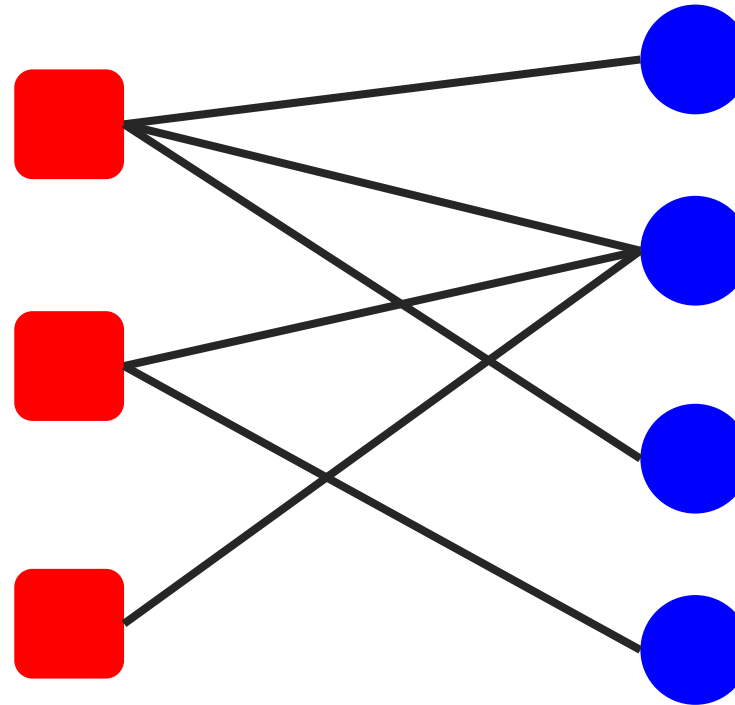
## Expression quantitative trait locus



## Cis- and trans-eQTL bipartite networks

SNPs

Gene Expression

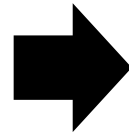
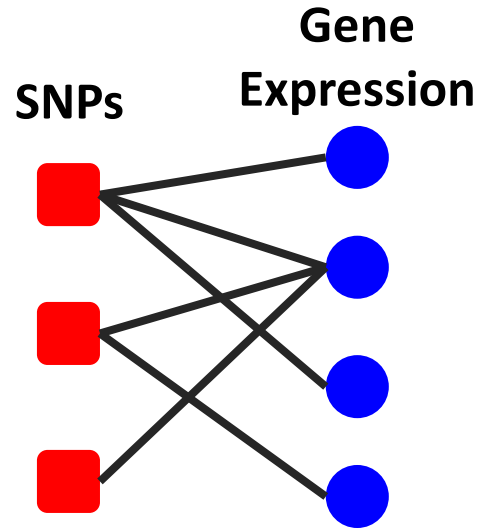


- Using a systems biology network approach to groups SNPs influencing the expression of the same genes

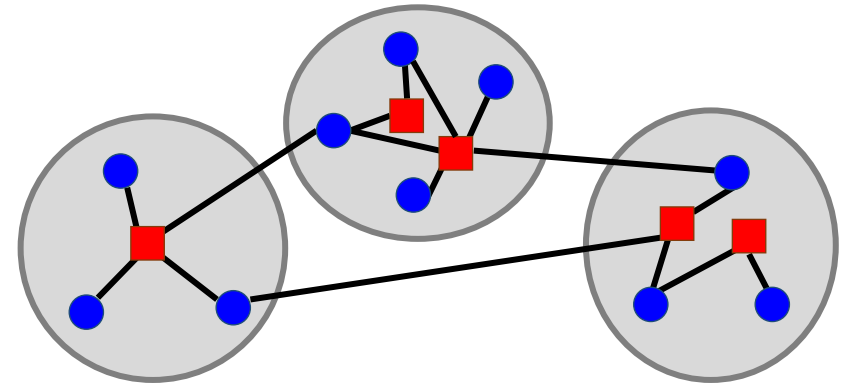


# Grouping SNPs using a network property : modularity

Cis- and trans-eQTL bipartite network

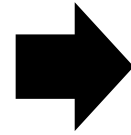
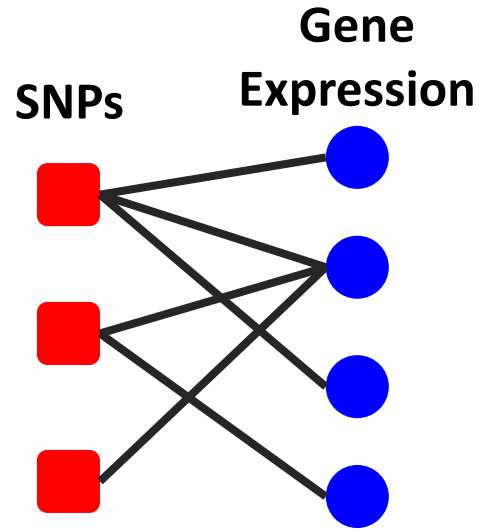


Community detection

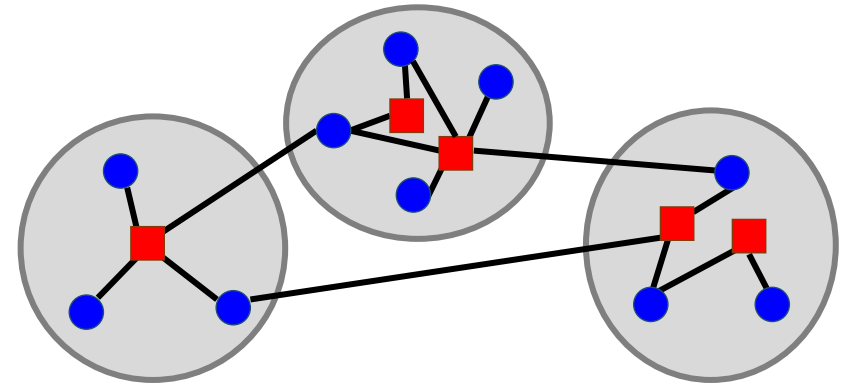


# Grouping SNPs using a network property : modularity

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



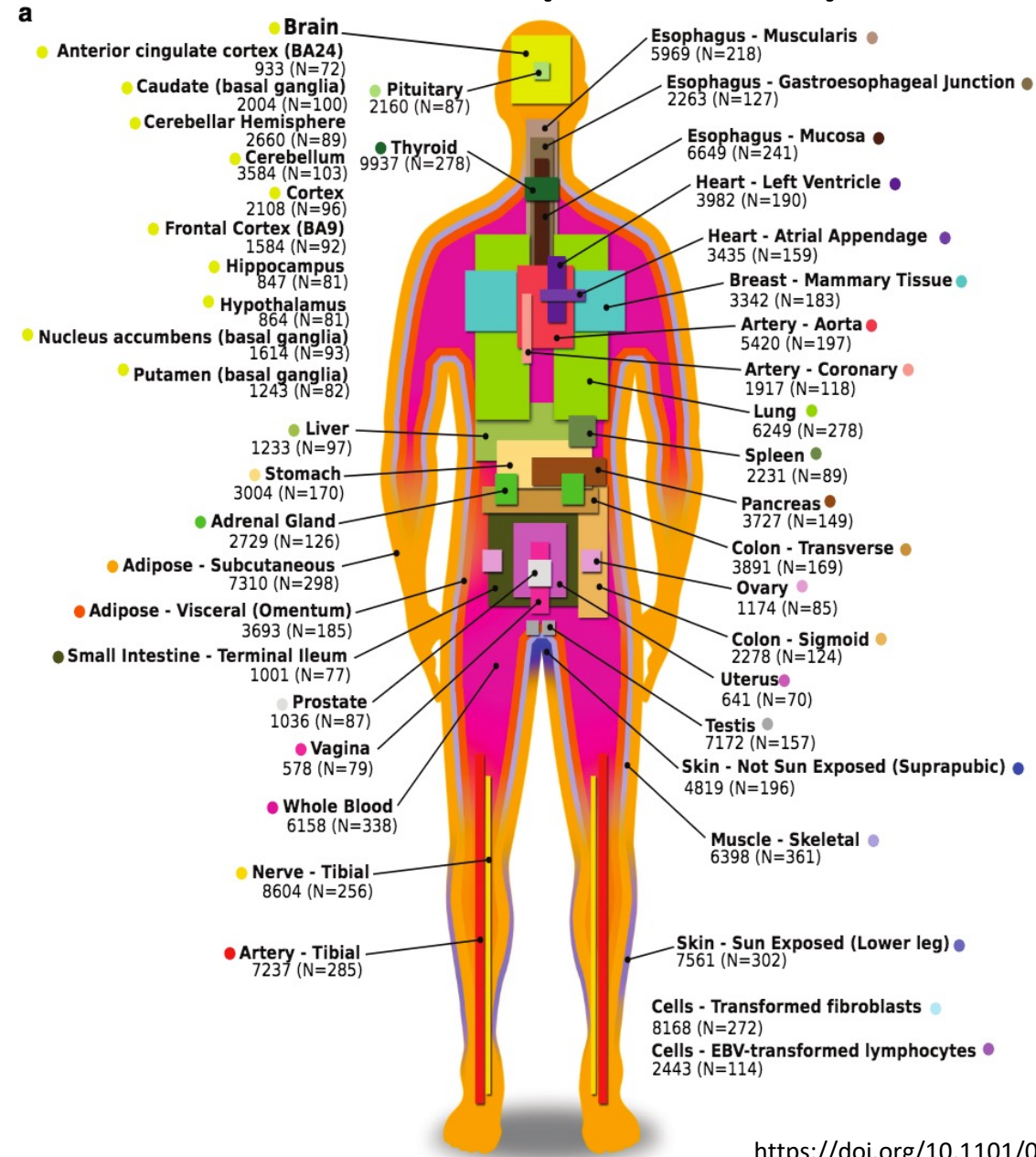
How to handle the tissue-specificity?

# How to handle the tissue-specificity?

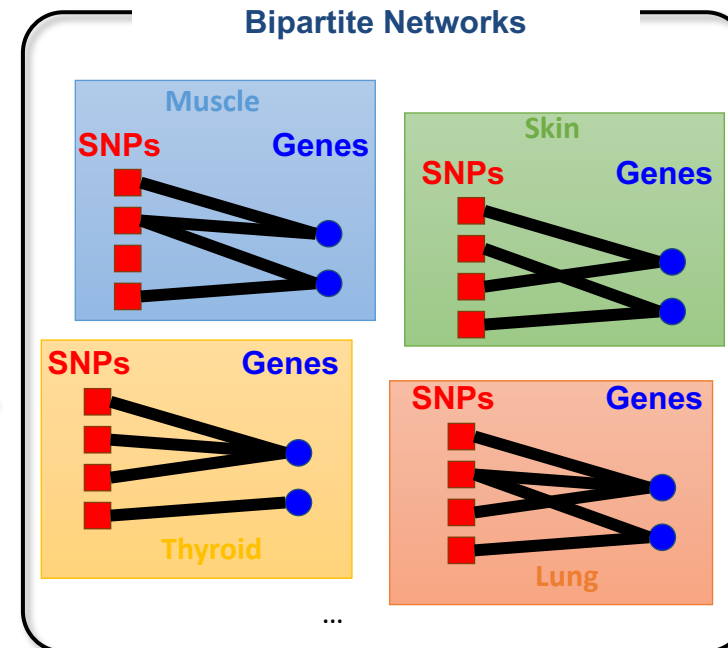
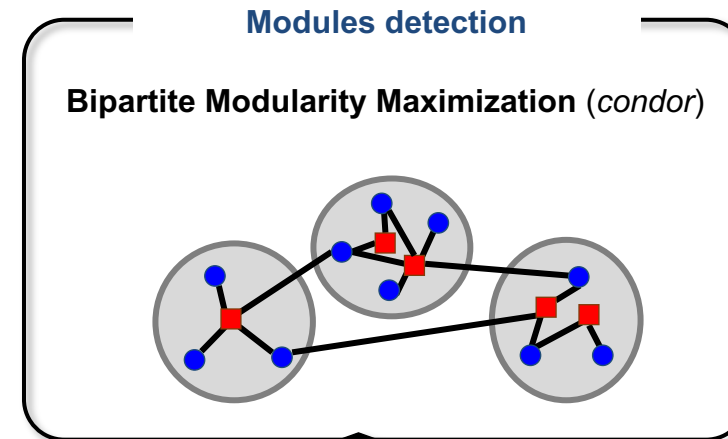
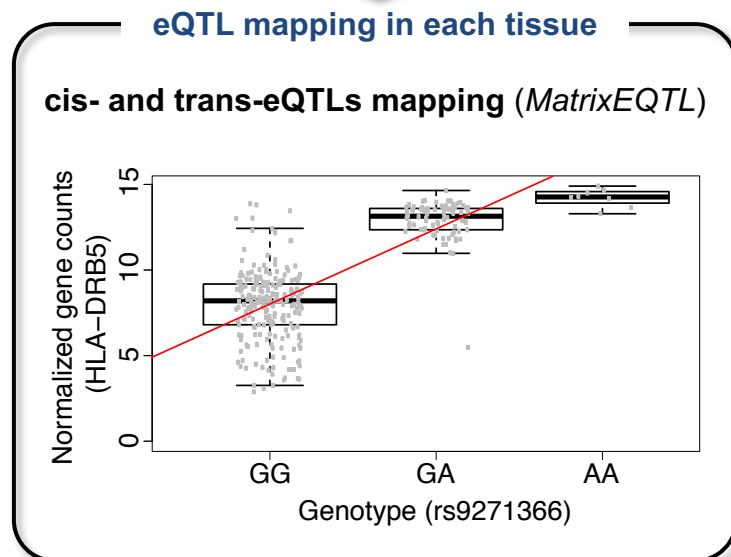
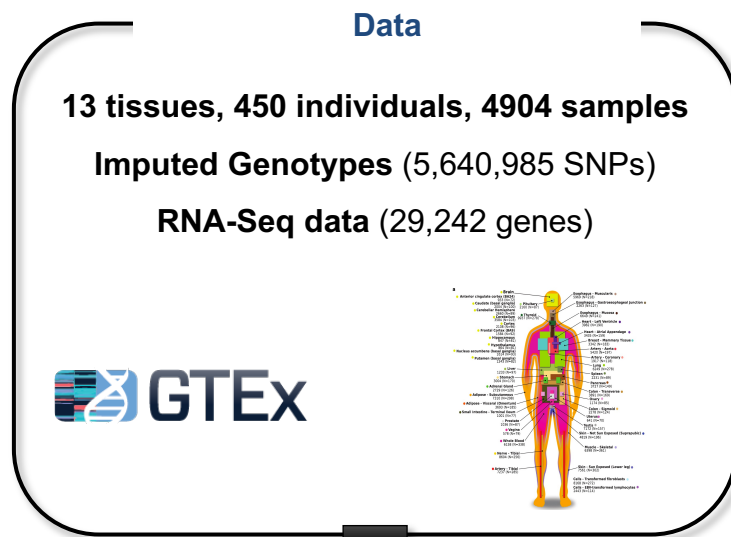
Get tissue-specific expression data !



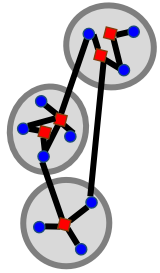
- 449 individuals.
- Genotyping data:
  - 84.3% European Am.
  - 13.7% African Am.
  - 1% Asian Am.
- RNA sequencing data:
  - 13 tissues.



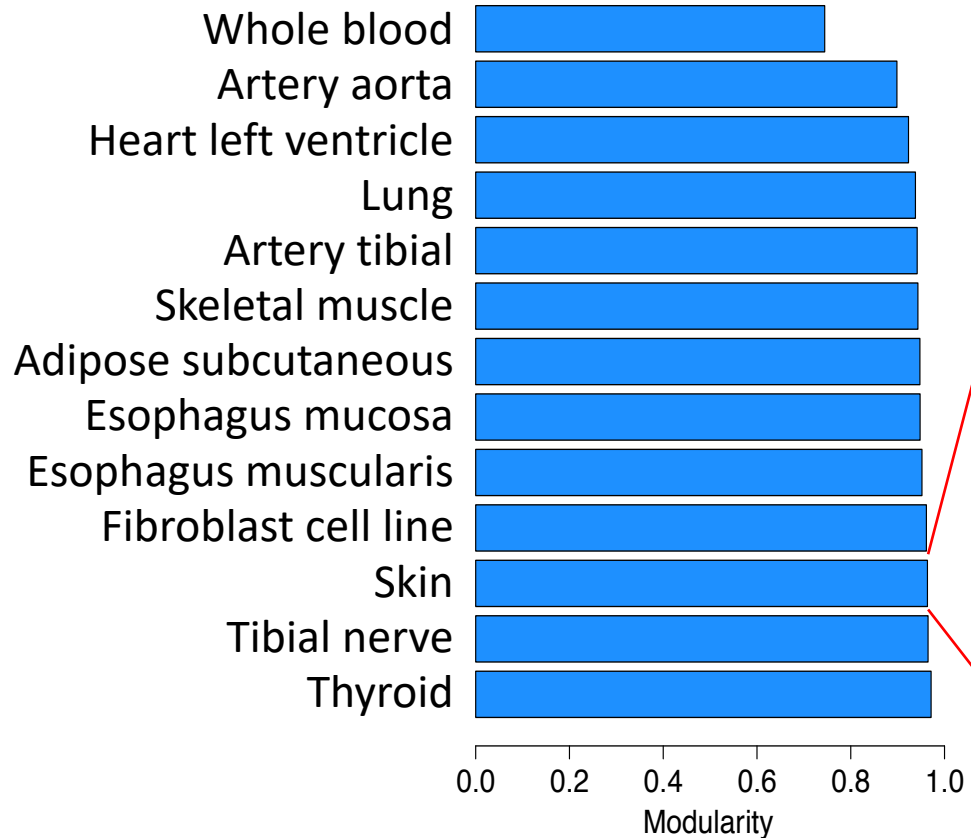
# Approach summary: building tissue-specific eQTL networks



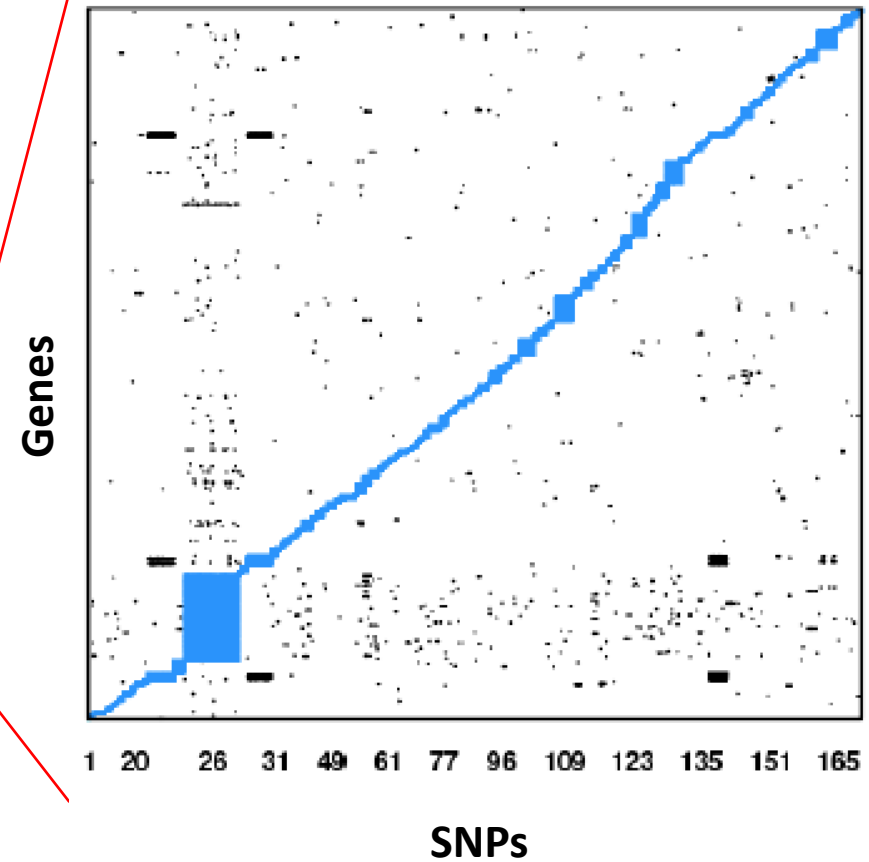
# eQTL networks have high modularity



## Network Modularity

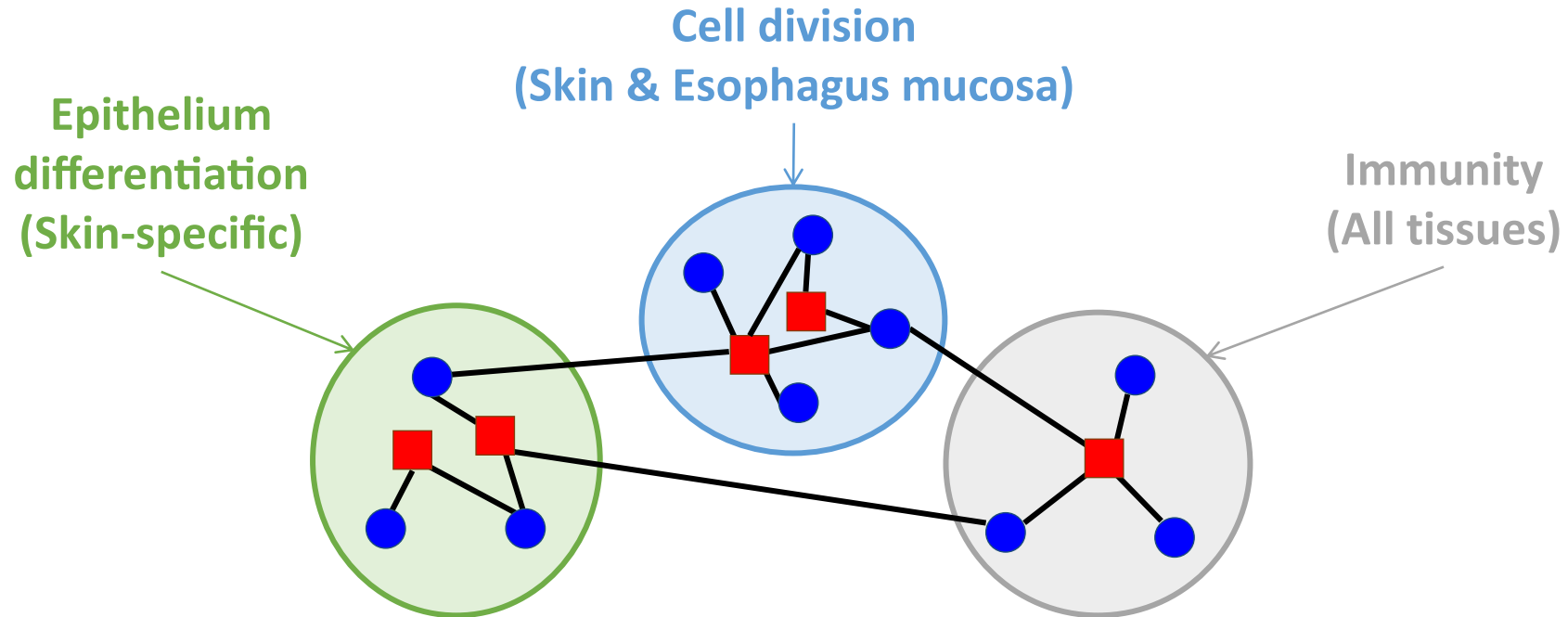


## Skin network



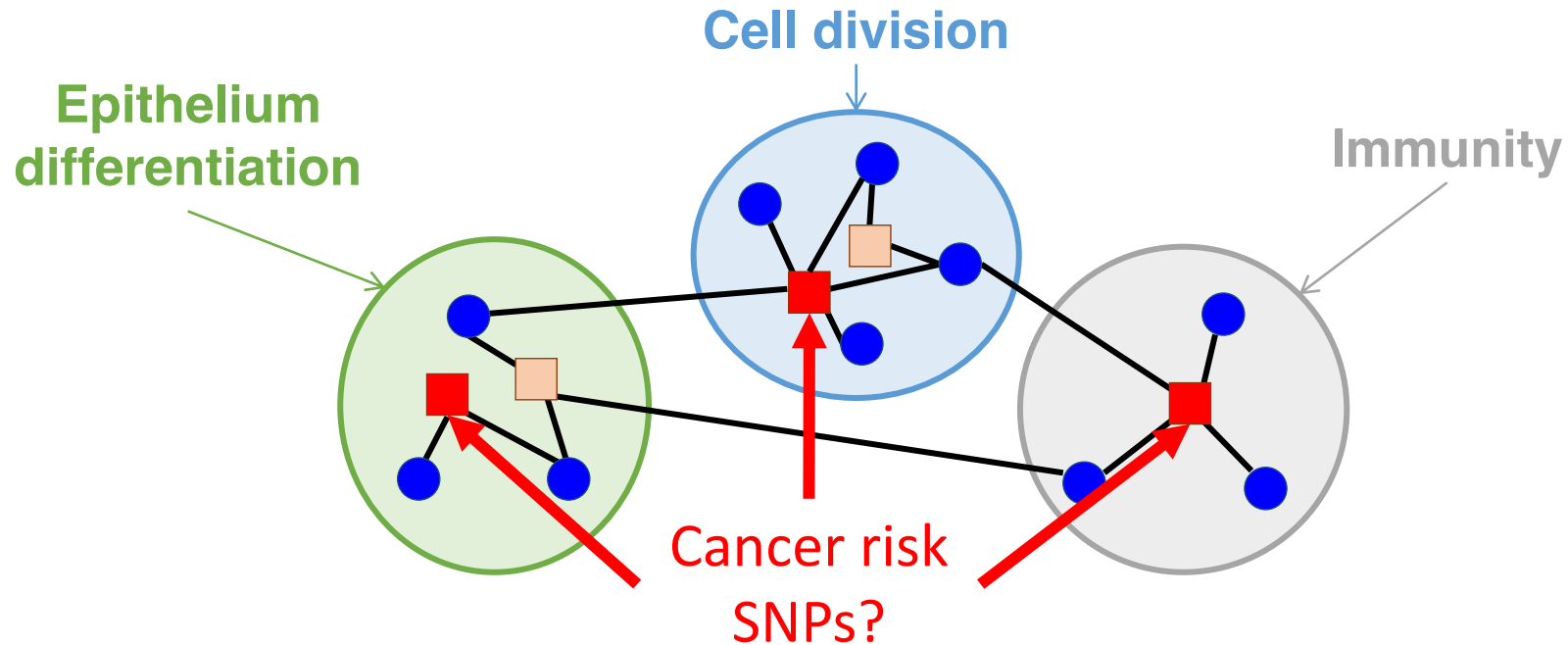
# Communities correspond to biological functions of tissues

## 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**

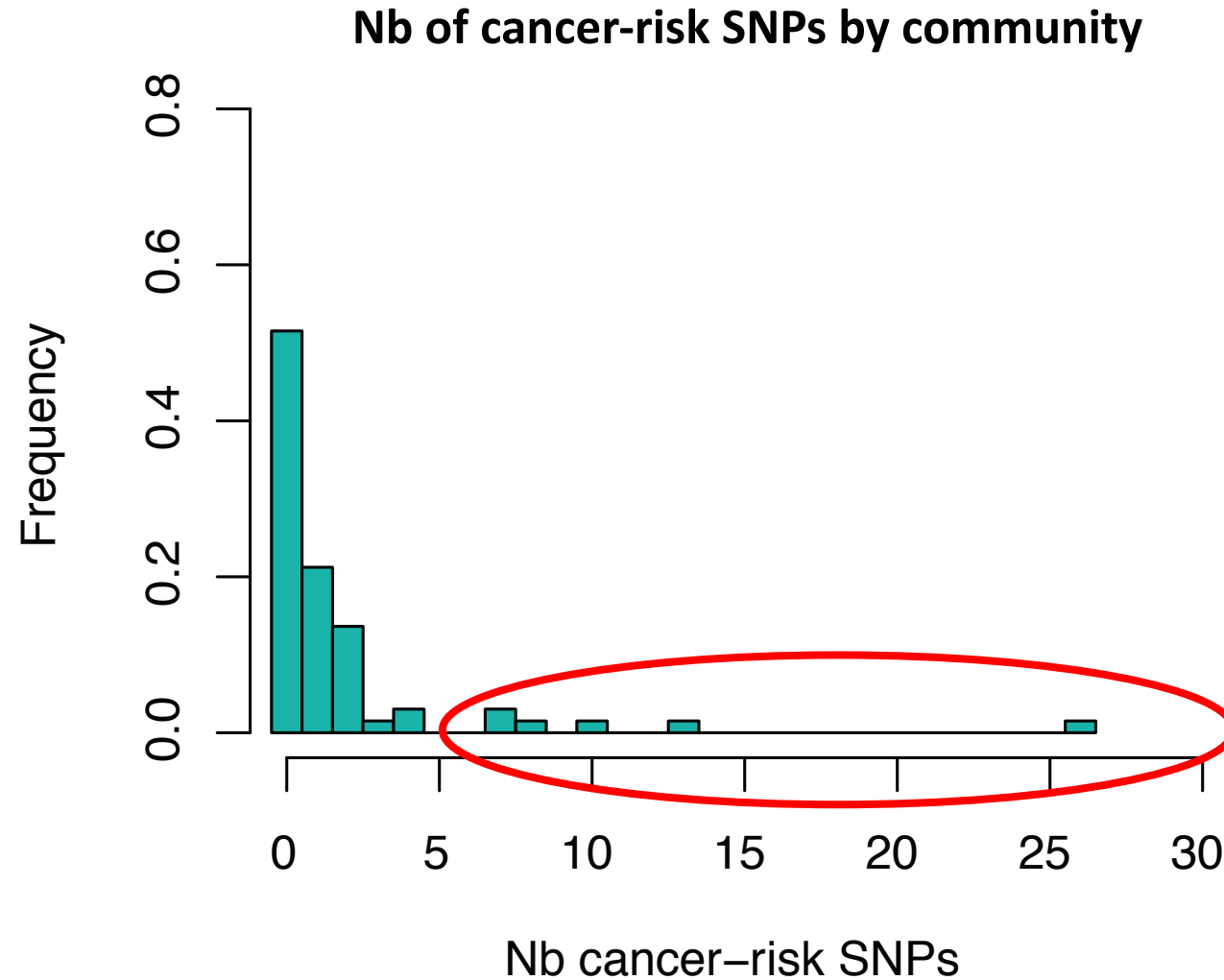
# Mapping cancer-risk SNPs to eQTL networks



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



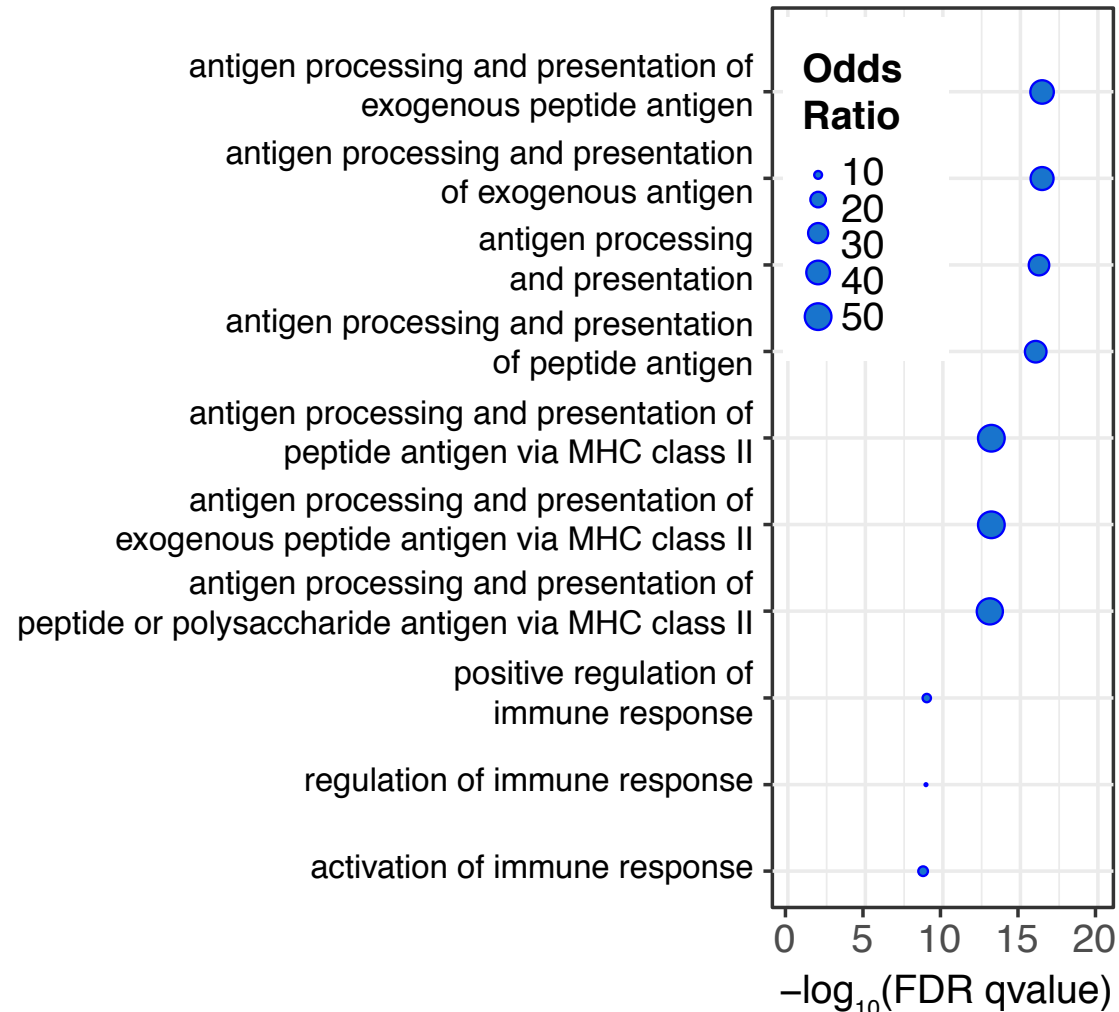
# Mapping cancer-risk SNPs to eQTL networks



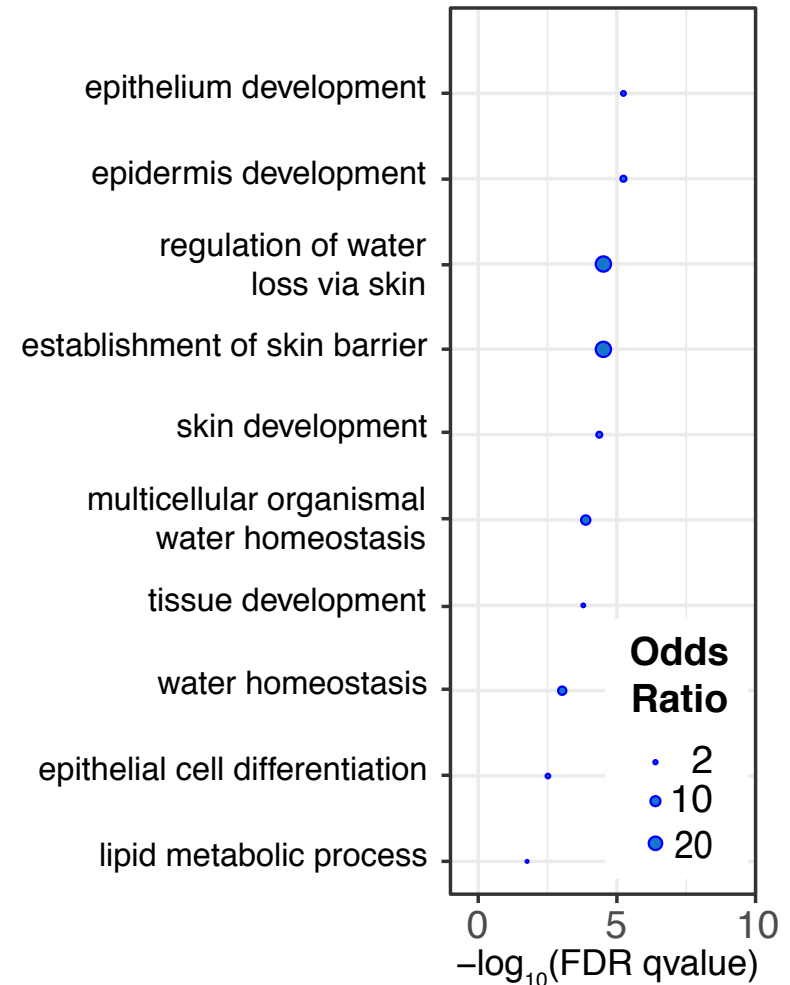
➤ **2-6 communities enriched in cancer risk SNPs by tissue**

# Biological function of cancer-risk SNPs-enriched communities

## Enriched in multiple cancer risk SNPs (all tissues)

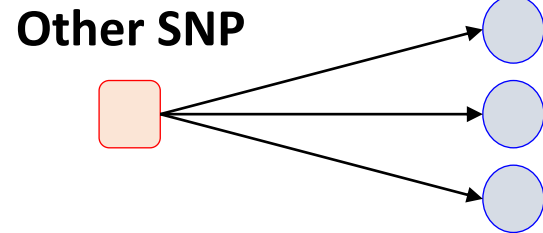
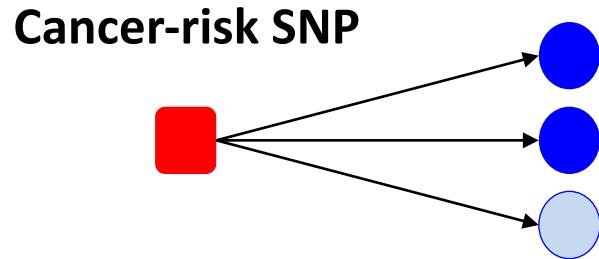


## Enriched in breast cancer risk SNPs (skin)



# Cancer-risk SNPs preferentially target oncogenes

## Genes targeted by cancer risk SNPs?

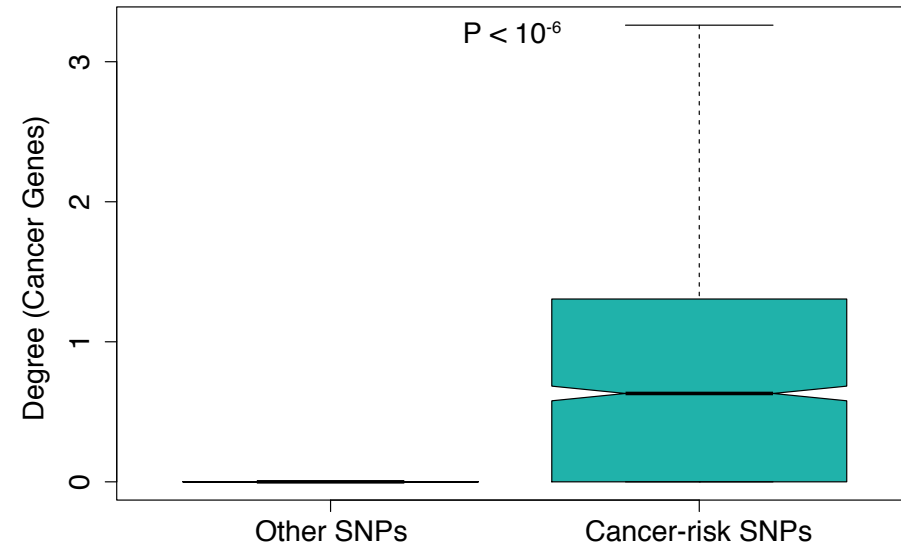


Others

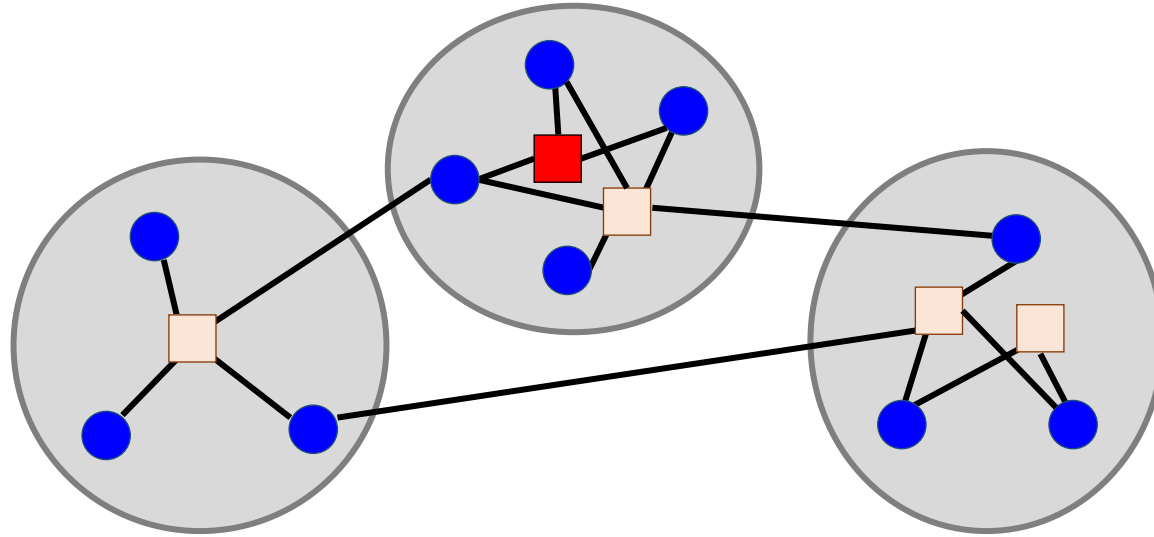


Oncogenes

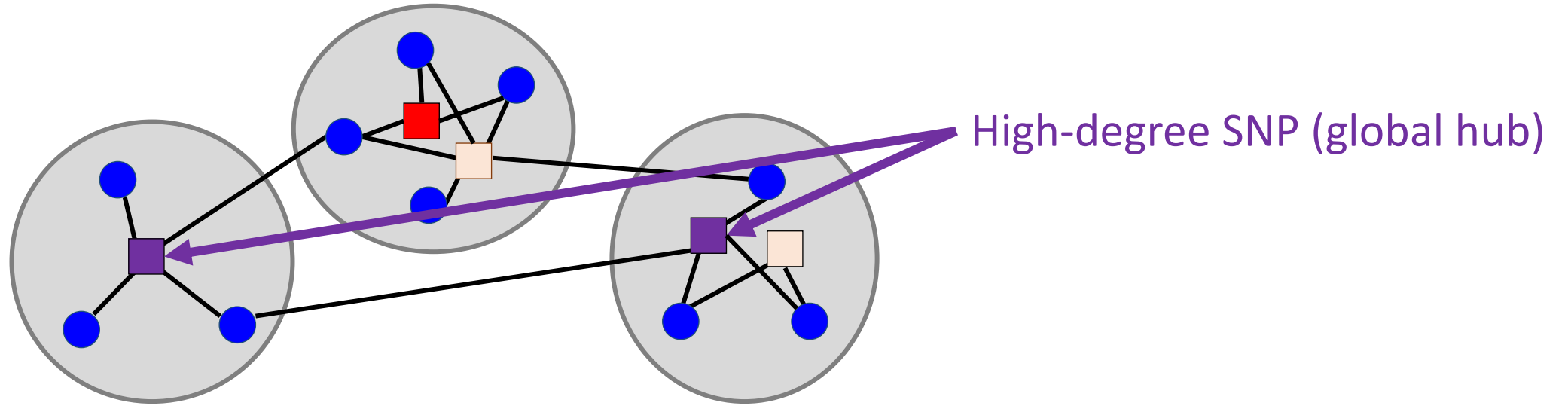
Tumor suppressors



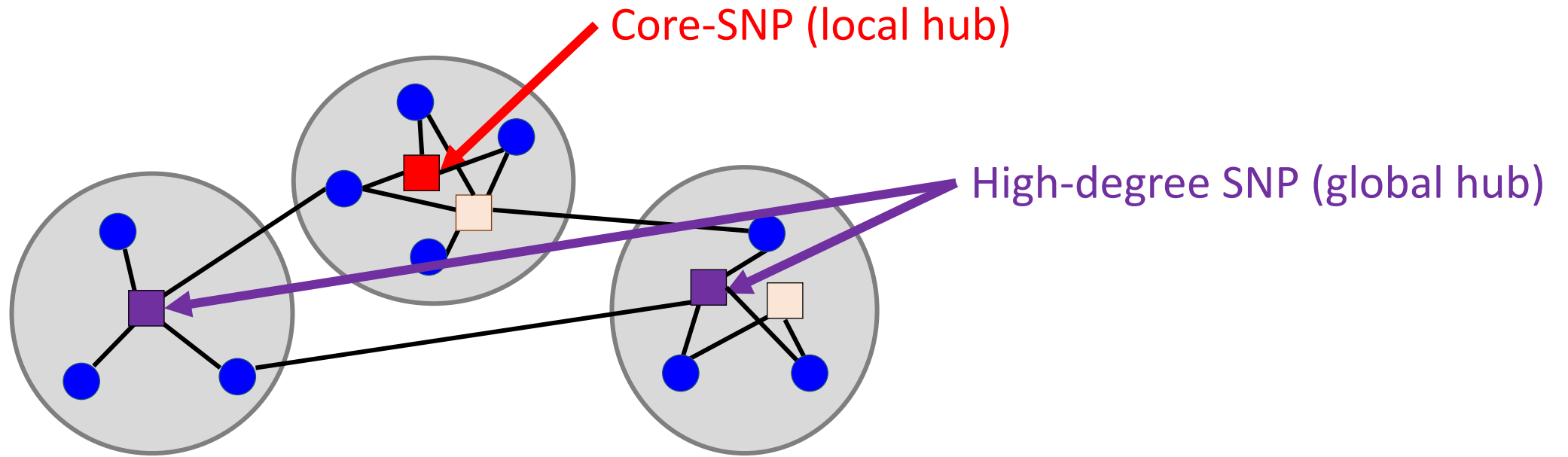
What are the properties of cancer-risk SNPs in the eQTL networks?



## 2 hypotheses: high-degree?



# Or high core-score?

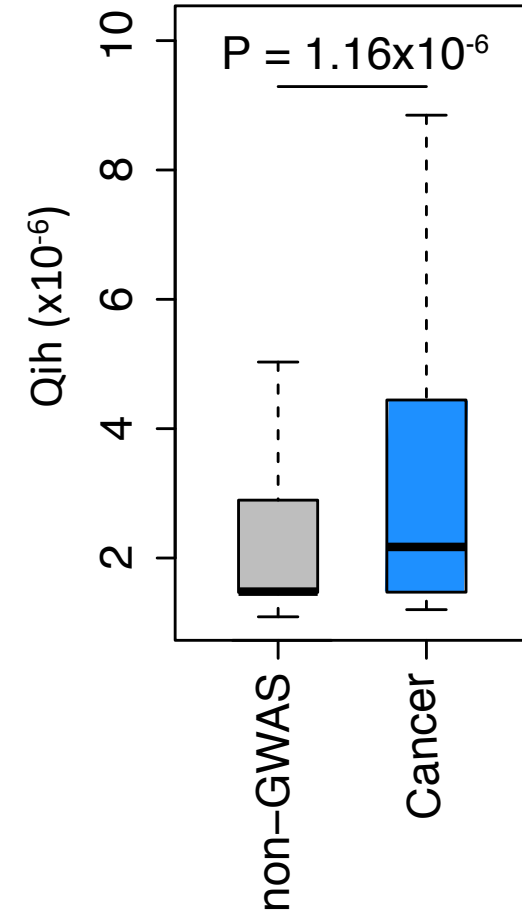
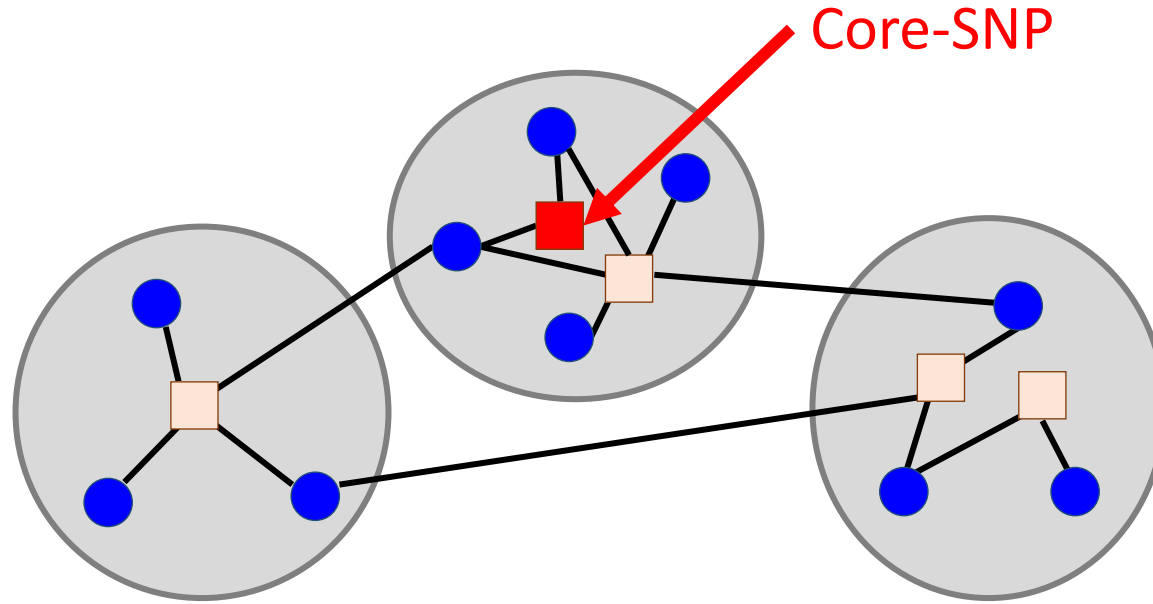


Core-score for SNP  $i$  in community  $h$

$$Q_{ih} = \frac{1}{m} \sum_j \left( \tilde{A}_{ij} - \frac{k_i d_j}{m} \right) \delta(C_i, h) \underbrace{\delta(C_j, h)}_{\text{Is gene } j \text{ in community } h?}$$

Observed – expected edge  
between SNP  $i$  and gene  $j$

# Cancer-risk SNPs are local hubs

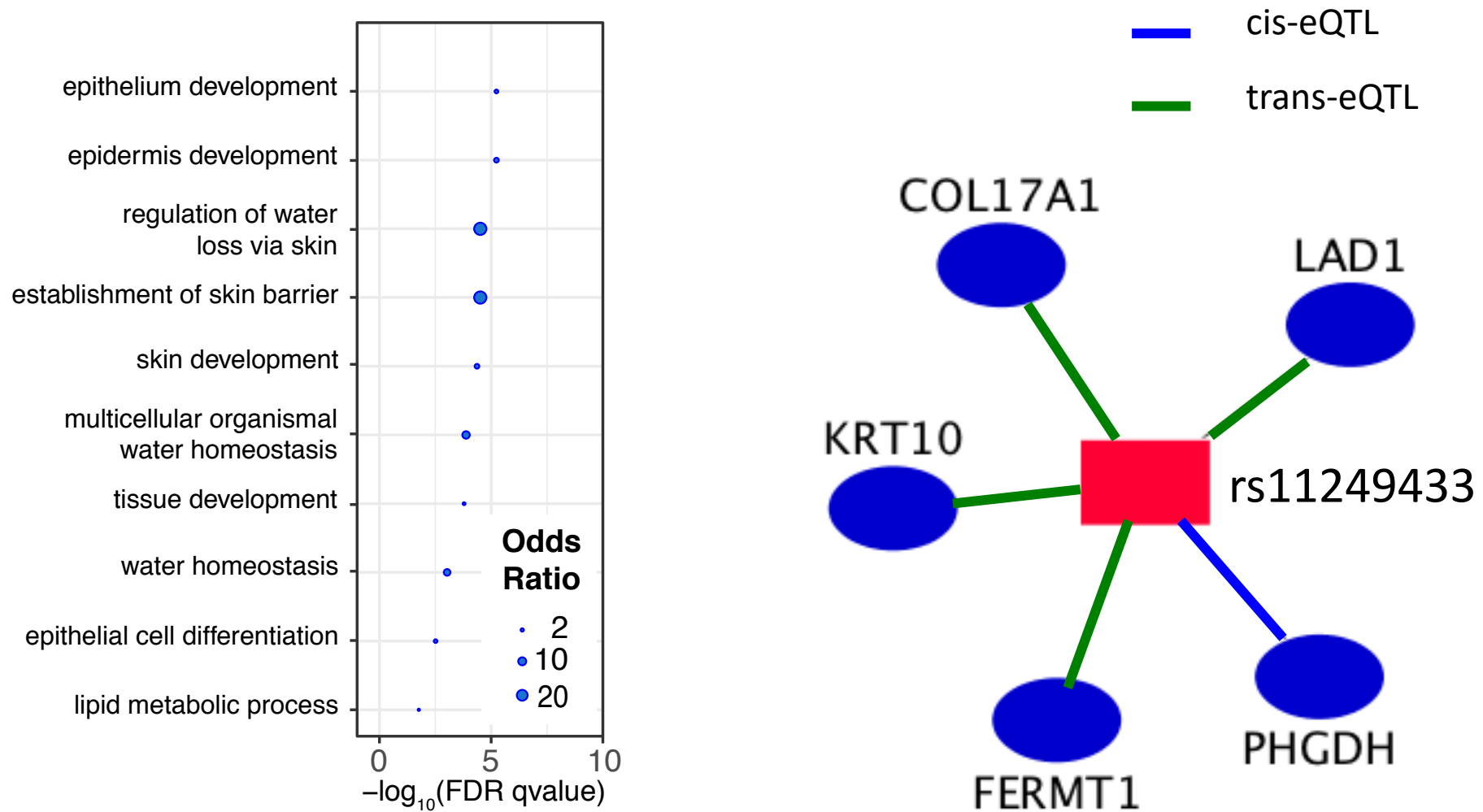


Core-score for SNP  $i$  in community  $h$

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

Observed – expected edge  
between SNP  $i$  and gene  $j$

# Example of a core, cancer-risk SNP



➤ **rs11249433 is associated to breast cancer**

➤ **Target genes deregulated in epithelium cancers (extra-cellular matrix secretion).**



# Take-home message

- Most disease-associated SNPs are located outside of coding regions, and likely impact regulatory functions.
- Expression quantitative trait loci (eQTL) bipartite networks can help functionally annotating them
- Cancer risk SNPs:
  - Impact the expression of oncogenes and tumor suppressor genes
  - Collectively deregulates groups of genes involved in recognition of damaged cells and immune response.
  - Are more likely to be “core-SNPs” impacting the expression of many genes involved in the same biological process.