Gene regulatory network structure help us understand how complex phenotypes adapt

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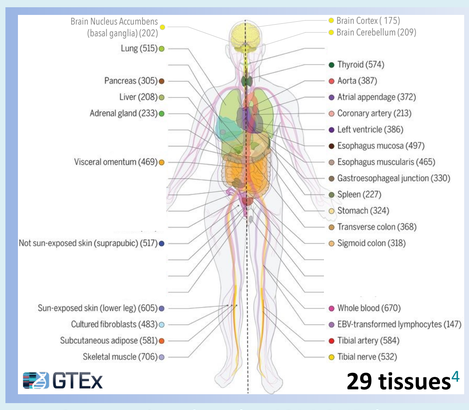
1 Background

The adaptation of populations to local environments often relies on the selection of optimal values for one or several complex traits, determined by various independent loci. GWAS studies have shown that most of these loci are located in regulatory regions[1].

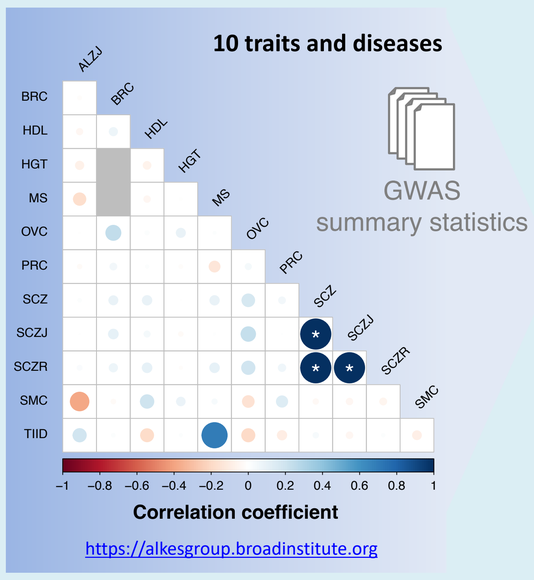
Systems biology studies model complex traits as the result of molecular interactions within the gene regulatory network[2]. Given the density of most networks, the omnigenic theory postulates that a complex trait is determined by almost all genes. While this should limit its capacity to evolve[3], many examples of complex adaptive traits exist (plant flowering time, mammal immunity, fly cold tolerance).

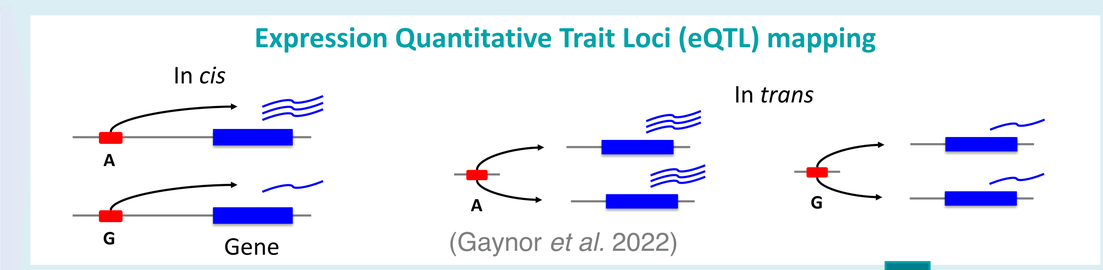
To reconciliate both views, we investigated the link between a complex trait heritability, the structure of the gene regulatory networks, and directional selection.

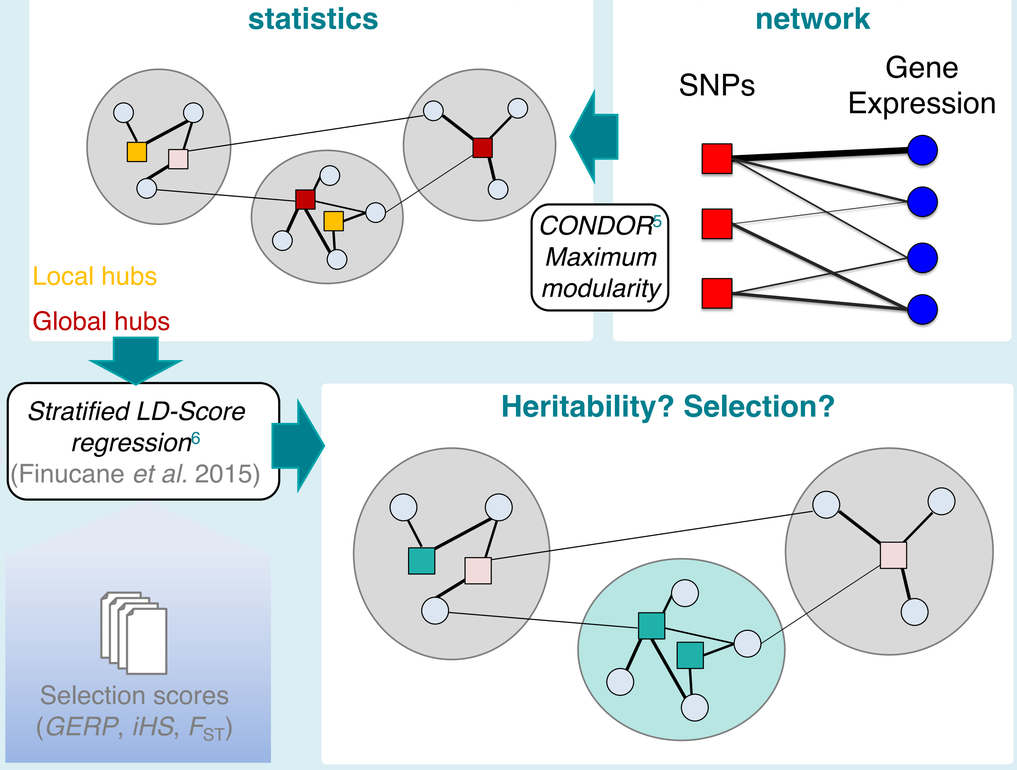
2 Methods



- Genotyping data (~43M SNPs)
- RNA-Seq data (~20k genes)
- 200 – 706 samples / tissue

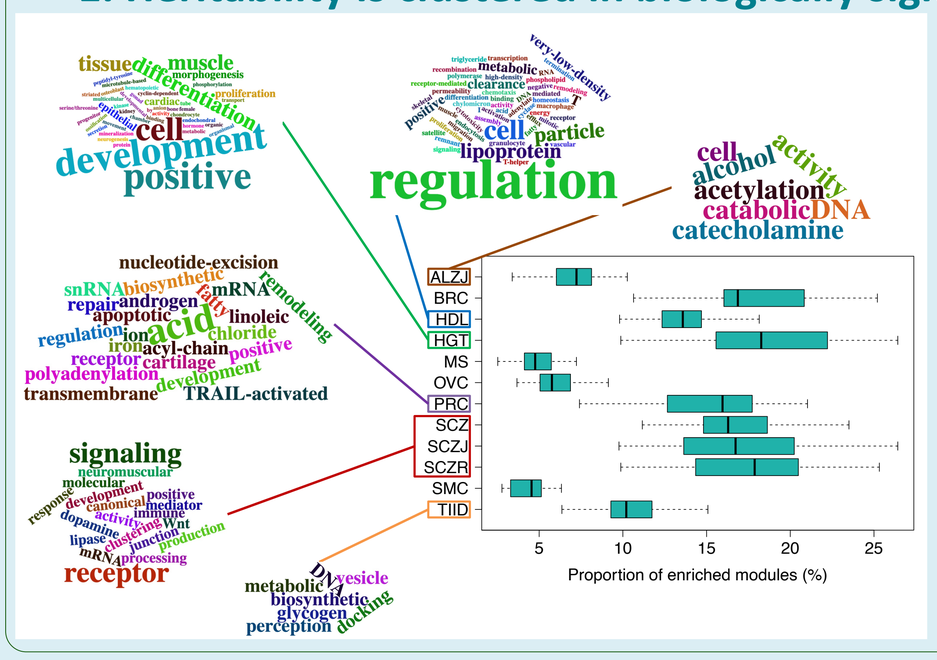






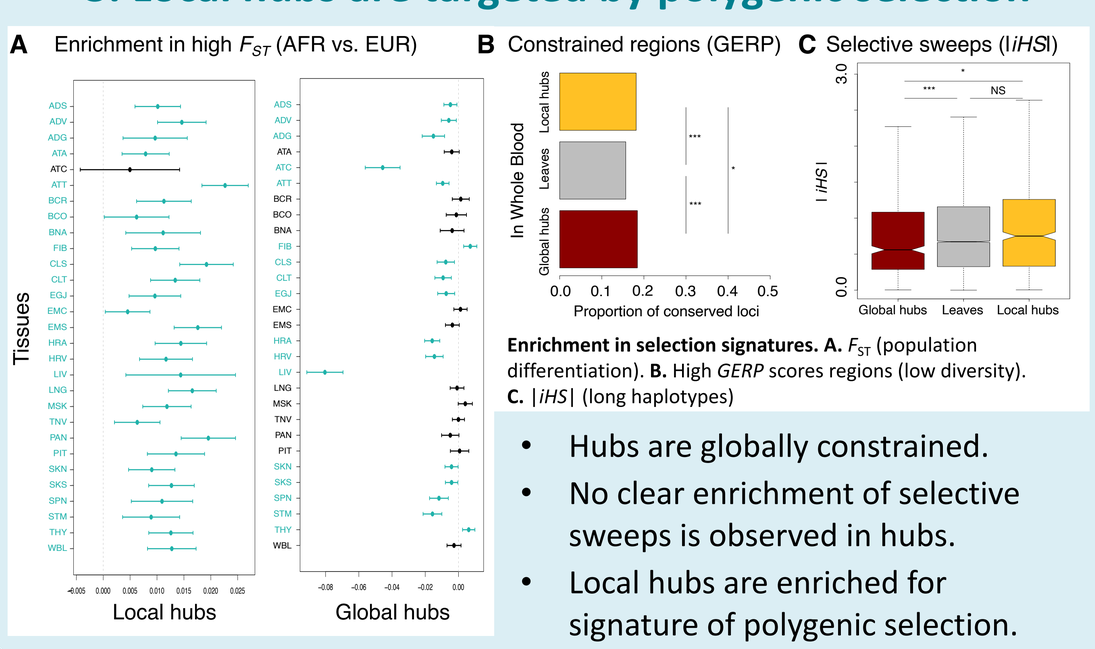
3 Results

1. Heritability is clustered in biologically significant modules



- eQTL networks are highly structured.
- SNPs explaining the heritability of a phenotype are clustered in a few tissue-specific modules
- Modules enriched for heritability regulate biological functions related to the phenotype.

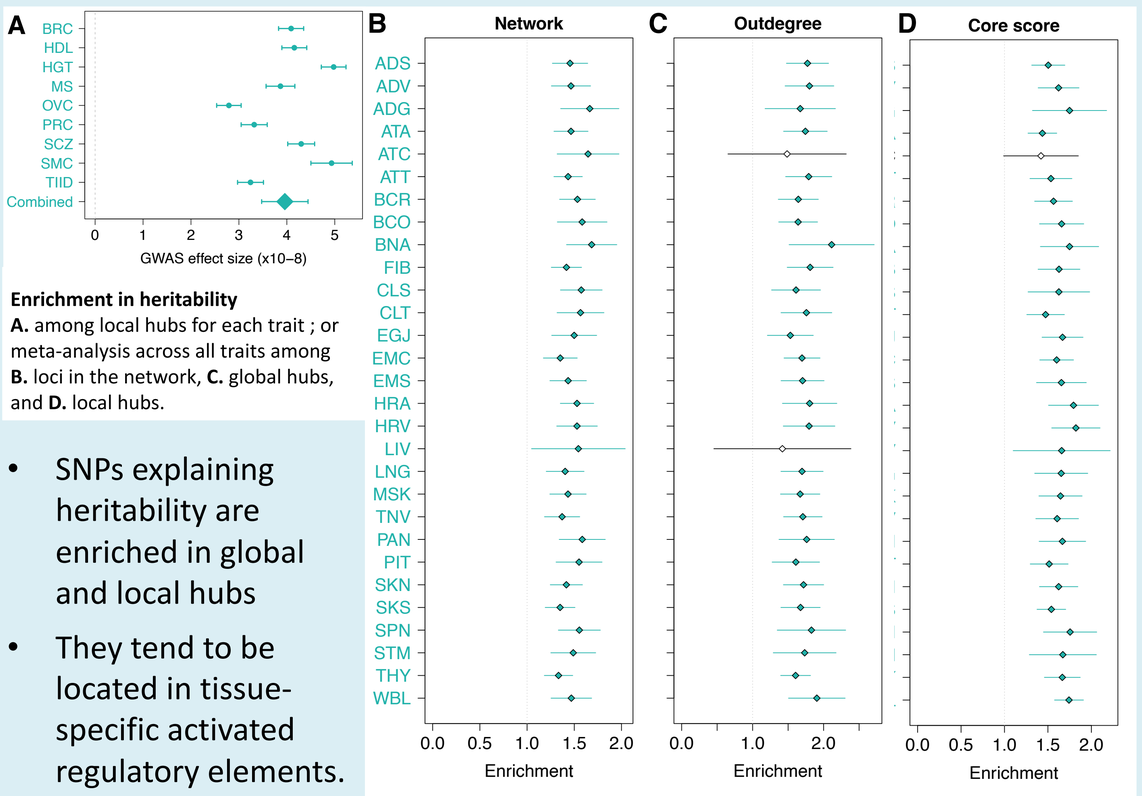
3. Local hubs are targeted by polygenic selection



Enrichment in selection signatures. A. F_{ST} (population differentiation). **B.** High *GERP* scores regions (low diversity). **C.** |*iHS*| (long haplotypes)

- Hubs are globally constrained.
- No clear enrichment of selective sweeps is observed in hubs.
- Local hubs are enriched for signature of polygenic selection.

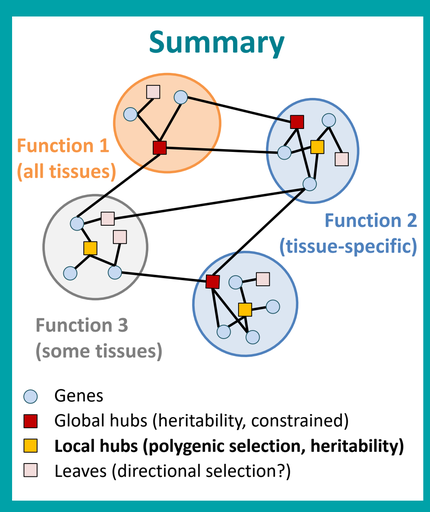
2. Heritability is clustered in global and local hubs

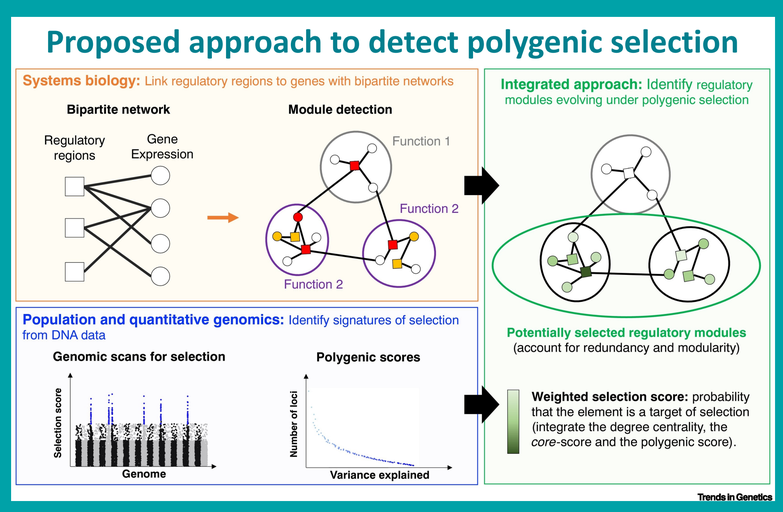


Enrichment in heritability
A. among local hubs for each trait ; or meta-analysis across all traits among **B.** loci in the network, **C.** global hubs, and **D.** local hubs.

- SNPs explaining heritability are enriched in global and local hubs
- They tend to be located in tissue-specific activated regulatory elements.

4 Conclusions and Perspectives





Local hubs are major players in determining complex traits: they explain a more heritability than expected and have been preferential targets of polygenic selection. Altogether, these results provide **a model to understand how polygenic phenotypes can evolve despite pervasive pleiotropy**. Based on the results, we have elaborated an approach to detect polygenic selection[7].

Bibliography: [1]Freedman *et al.* (2011) *Nature Genetics* **43**:513-518. [2]Kirschner M.W. (2015) *Cell* **121**:503-504. [3]Boyle *et al.* (2017) *Cell* **169**:1177-1186. [4]GTEx Consortium (2018) *Nature Genetics* **50**(7):956-967. [5]Platig *et al.* (2016) *PLoS Computational Biology* **e1005033**. [6]Finucane *et al.* (2015) *Nature Genetics* **47**:1228–1235. [7]Fagny & Austerlitz (2019) *Trends In Genetics* 37(7):631-638.