Finding the sources of missing heritability in a yeast cross

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Background

- GWAS studies have been extremely successful in identifying loci associated with many complex traits
- However large proportion of heritable contribution to trait variation is still “missing”

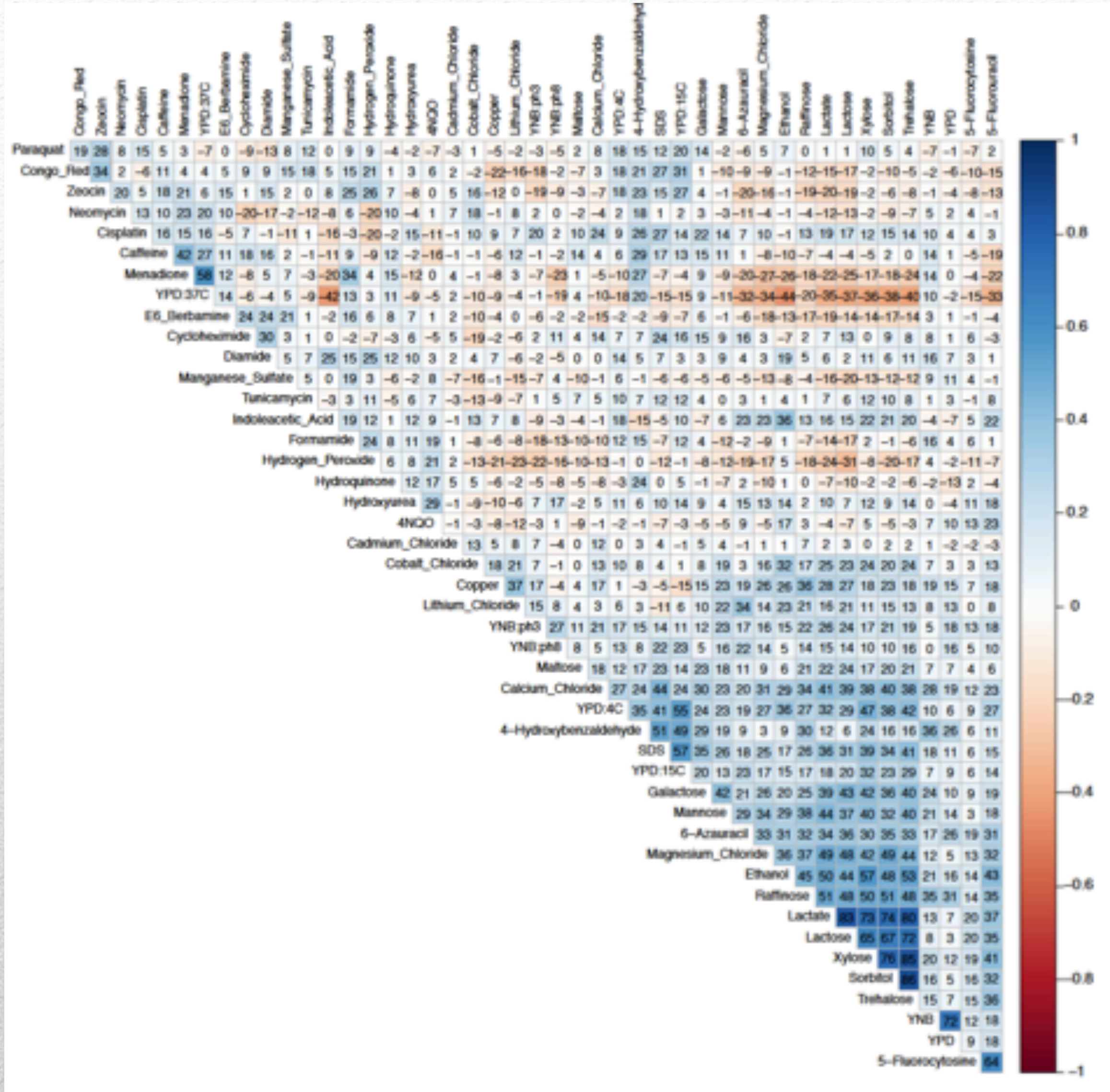
- Is it possible to find the entire “hidden heritability”, if we resequence everybody?

Aim

- Cross between two yeast strains (*S. cerevisae*) – lab strain and wine strain
- Large panel on yeast segregants were genotyped and phenotyped individually – 1,008 prototrophic haploid segregants were used to estimate heritability and detect underlying loci
- 46 phenotypes, with strong heritable component, were measured

Study design

Spearman correlation coefficients for all pairs of traits



- *proportion of phenotypic variance attributable to genetic variance*

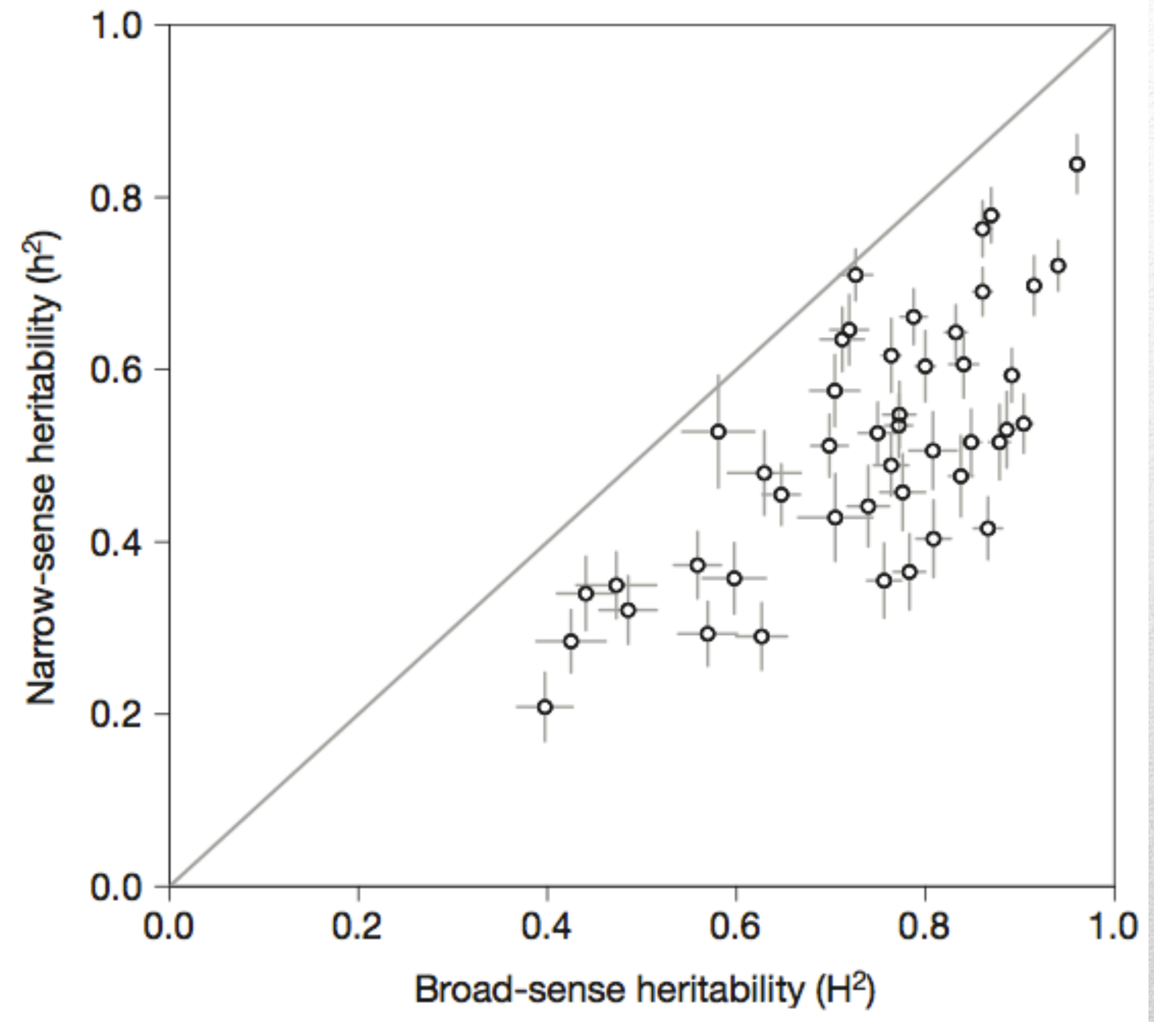
- *Broad-sense heritability: all the genetic contributions to a population's phenotypic variance including **additive**, dominant, and **epistatic** (multi-genic interactions), GxE*

$$H^2 = \frac{Var(G)}{Var(P)}$$

- *Narrow-sense heritability: **additive** effects only*

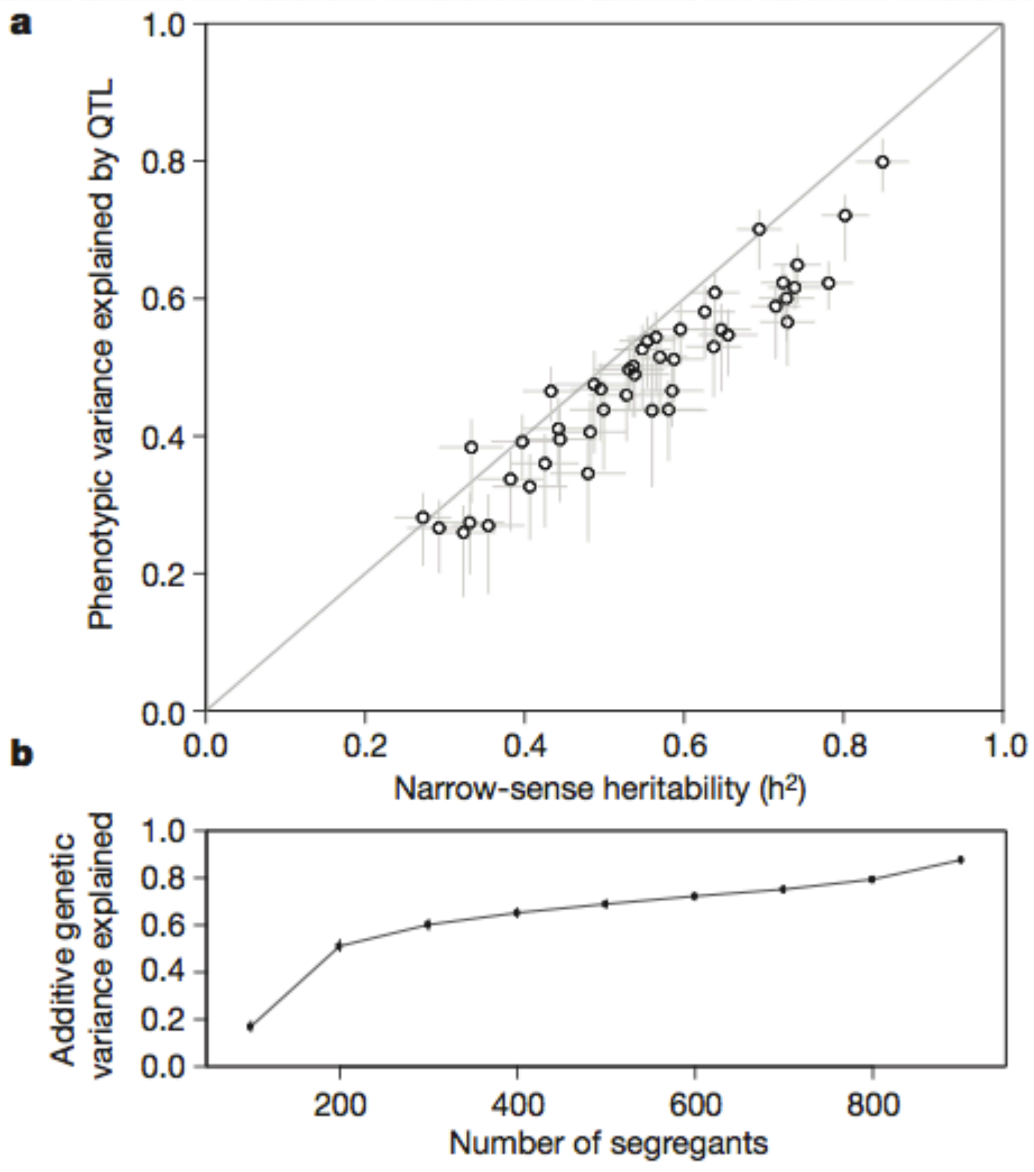
$$h^2 = \frac{Var(A)}{Var(P)}$$

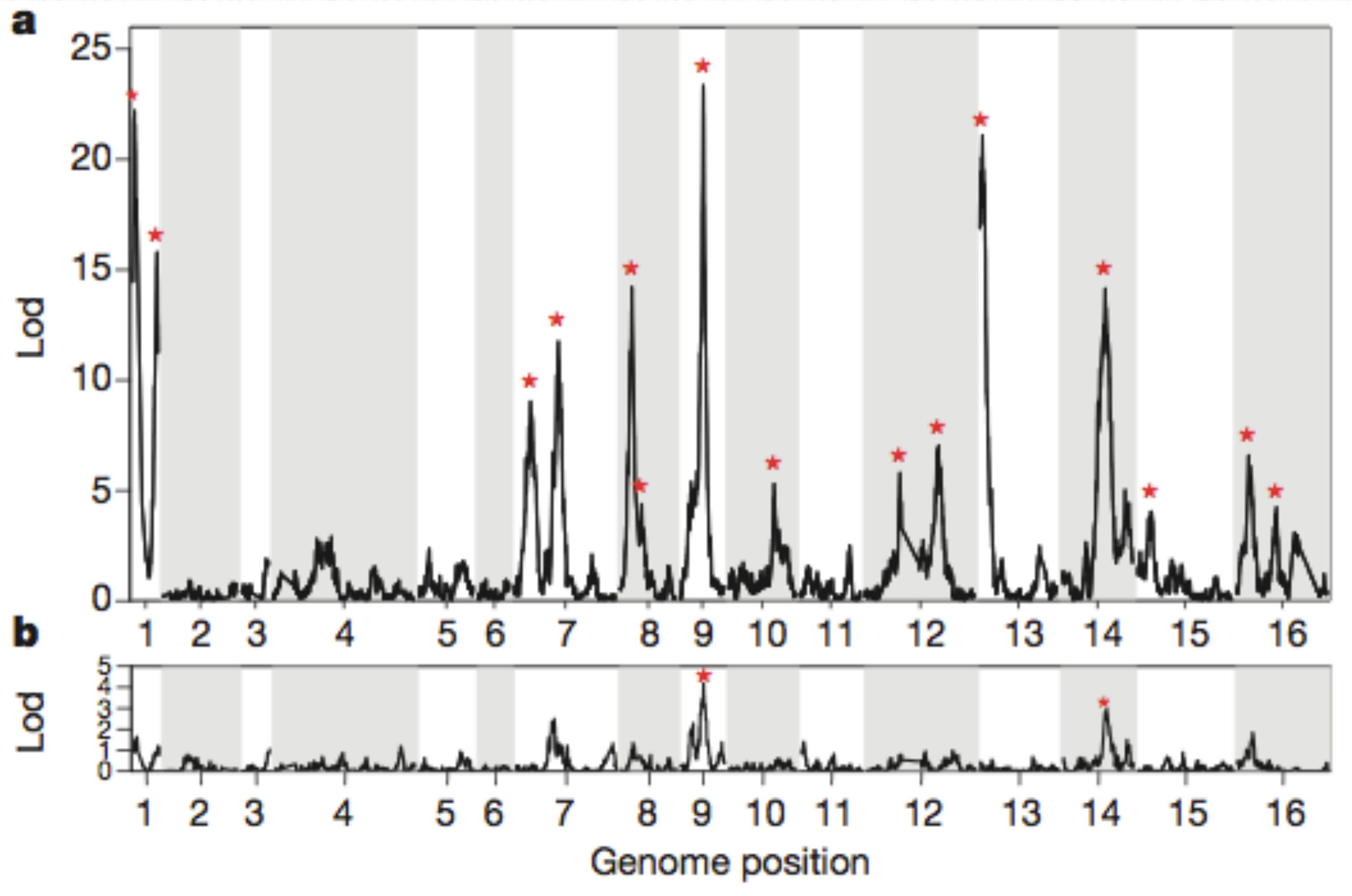
Heritability



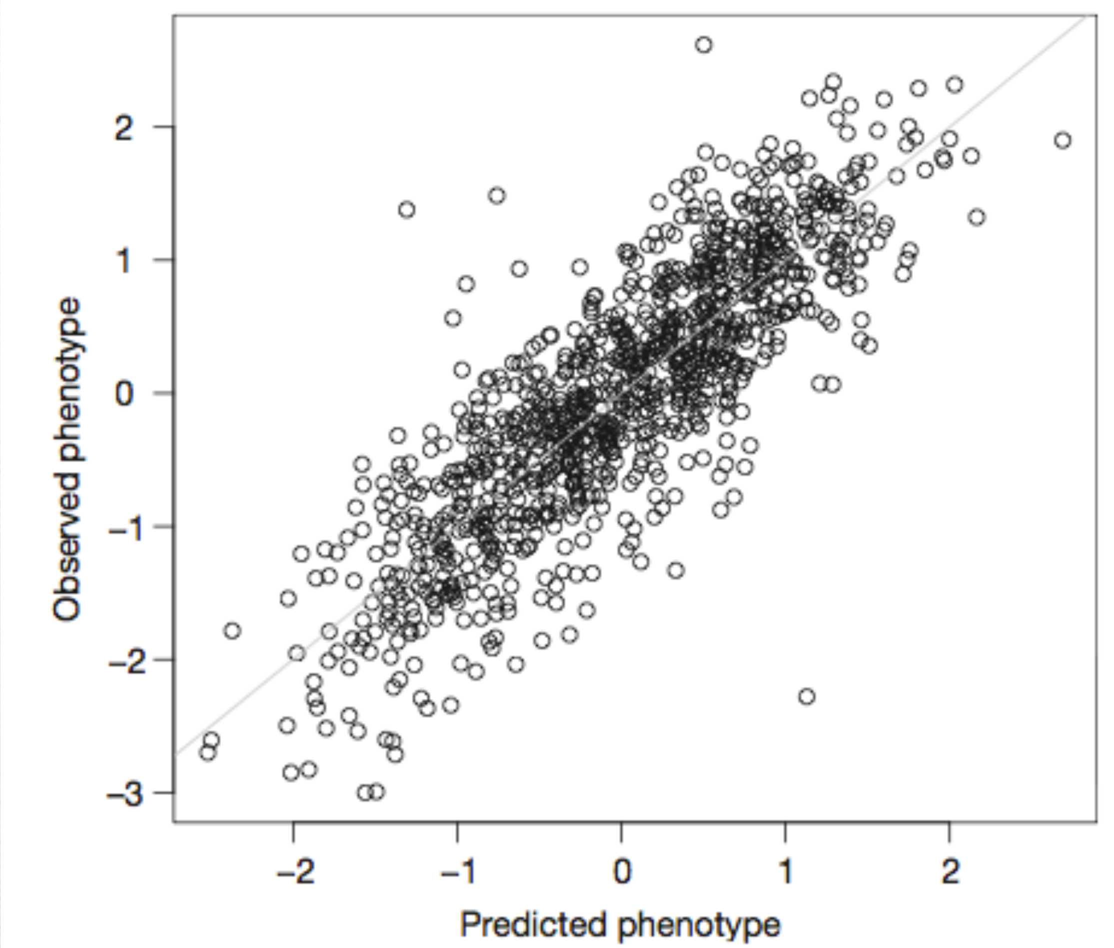
Heritability of 46 yeast traits

Most additive heritability is explained by detected QTL

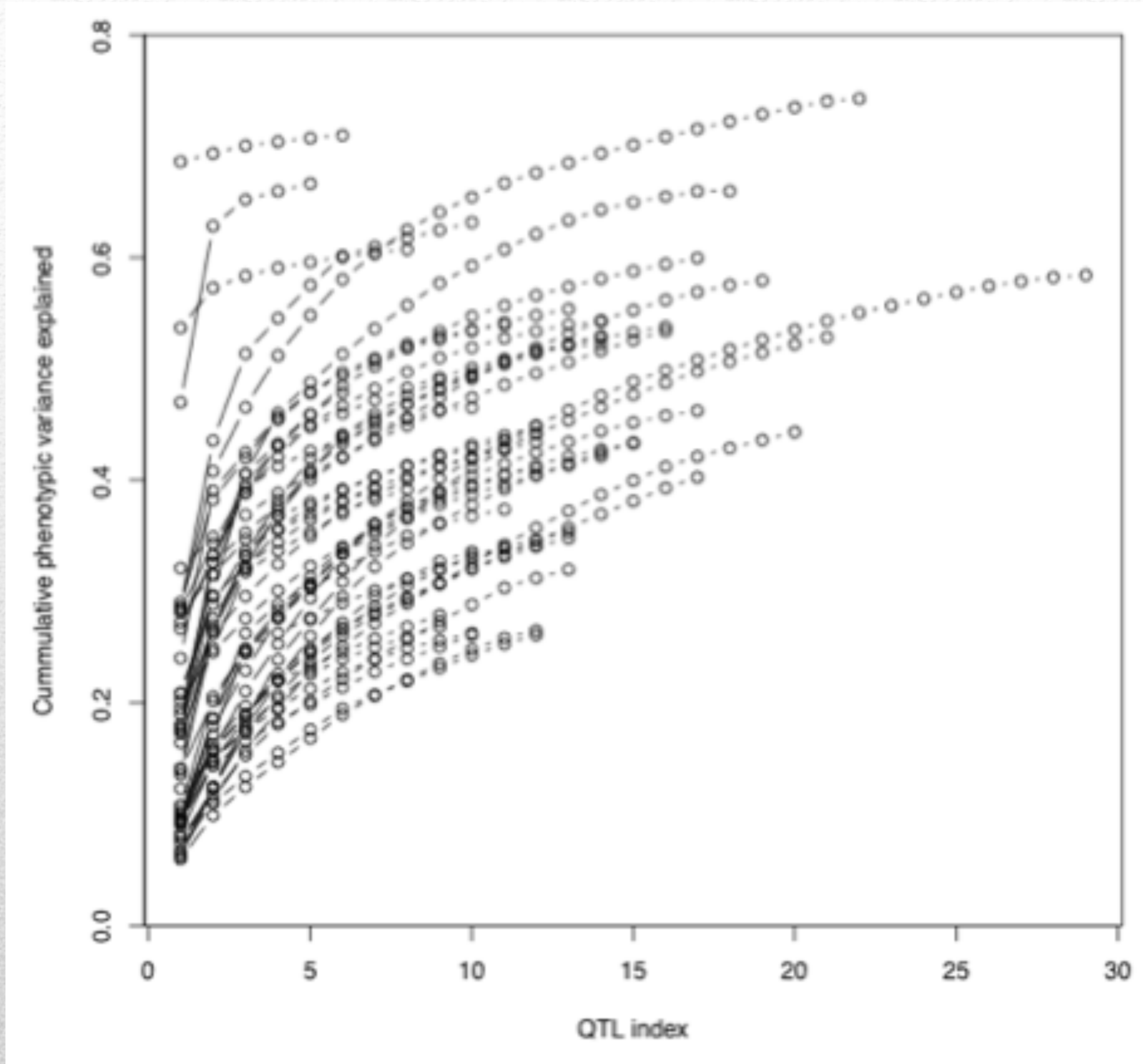




QTL detection for a complex trait (E6 berbamine)

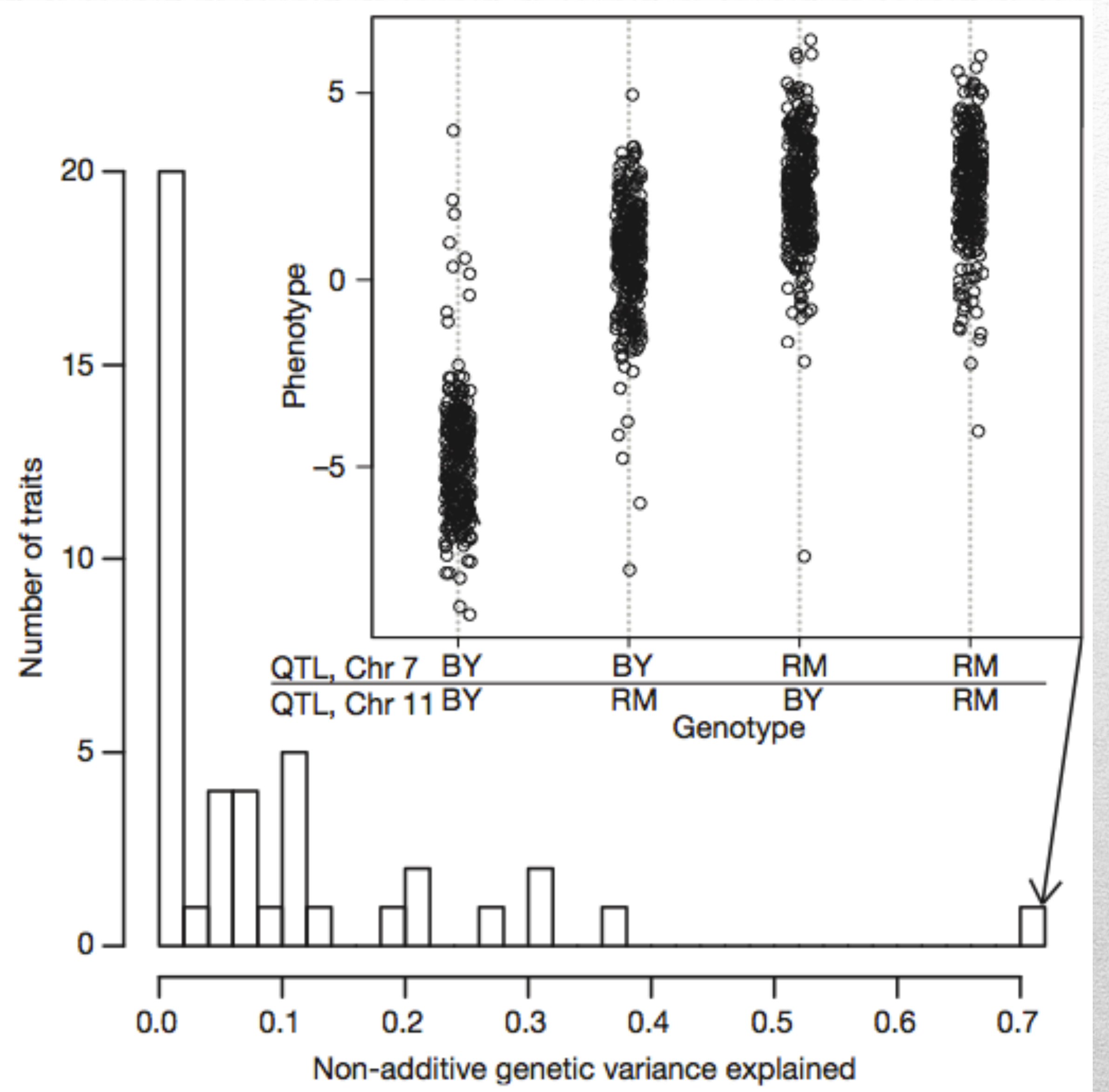


Prediction of segregant trait values from QTL phenotypes



Cumulative phenotypic variance explained

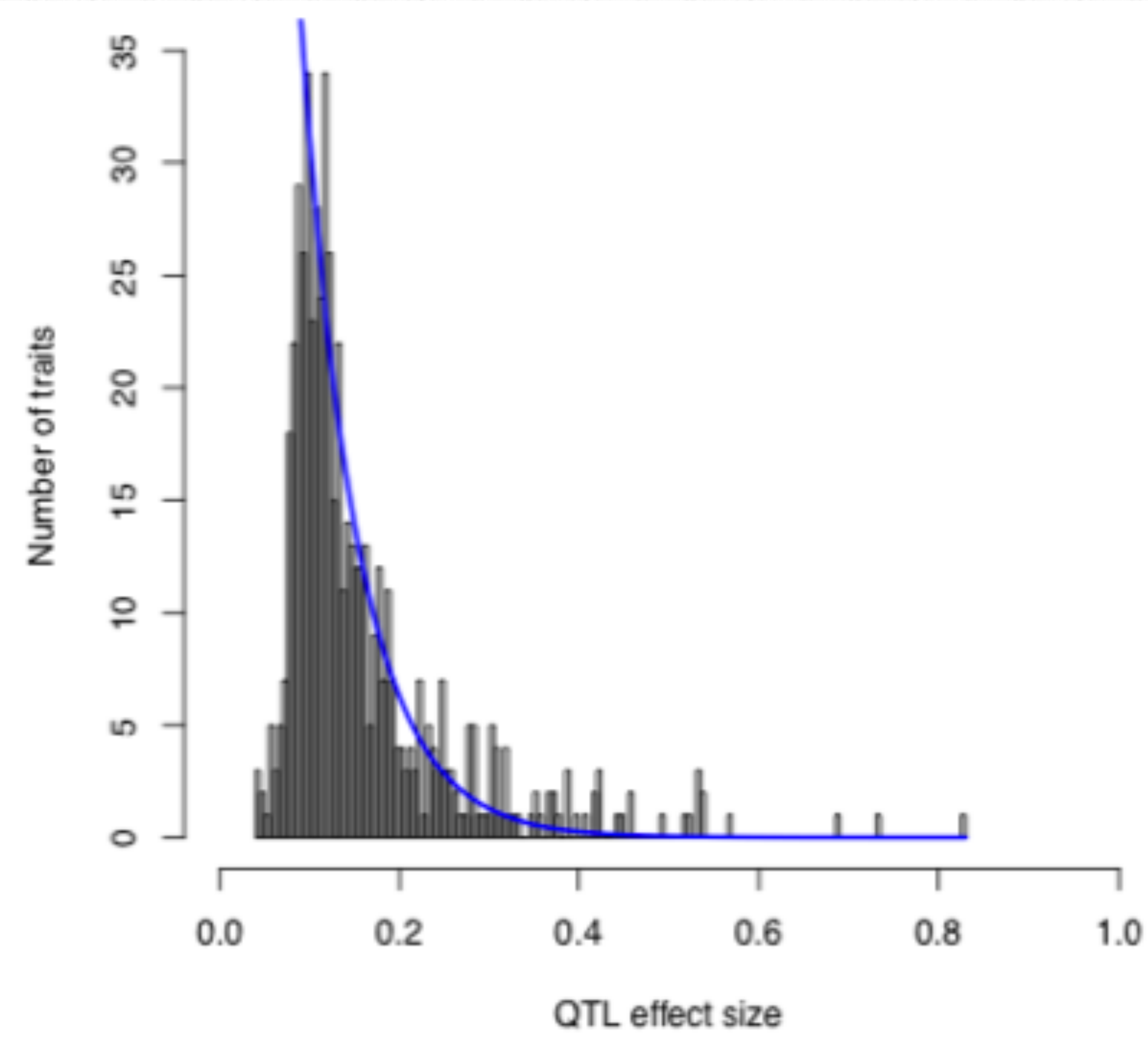
Non-additive genetic variance explained by QTL–QTL interactions



- Up to 54% of genetic variations in GxG
- QTLxQTL interactions only describe small part of that variability – most of it remains elusive

- Statistical power is lower for detecting interactions
- Interaction effects are expected to be smaller
- There might be high number of interactions with more than 2 loci

Genetic interactions



QTL effect sizes across all traits

- It is possible to find all the “hidden heritability” if the sample size is large enough as most of the genetic variance comes from many loci with small (but not infinitesimal) effects
- Gene-gene interactions play important role for some phenotypes (up to 50%) and two-locus interactions explain only minority of this contribution

Conclusions

References