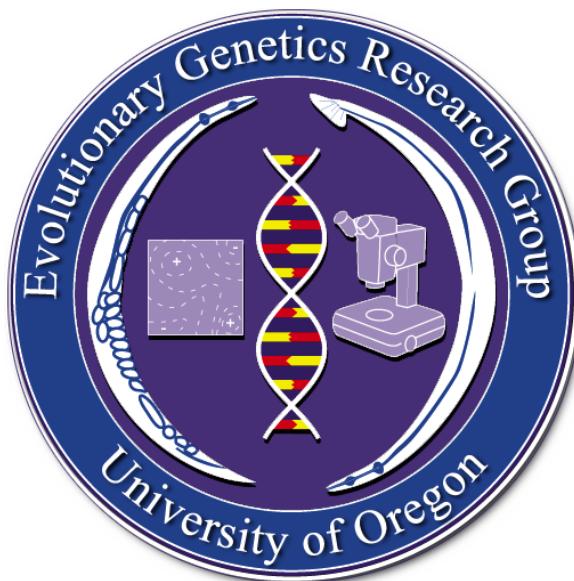


Molecular Quantitative Genetics

Theory and Practice



Patrick Phillips

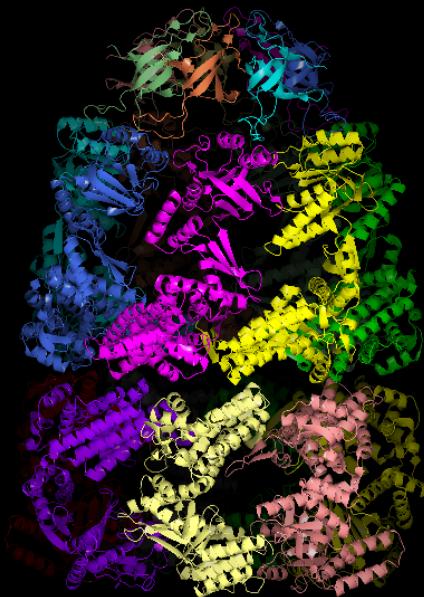
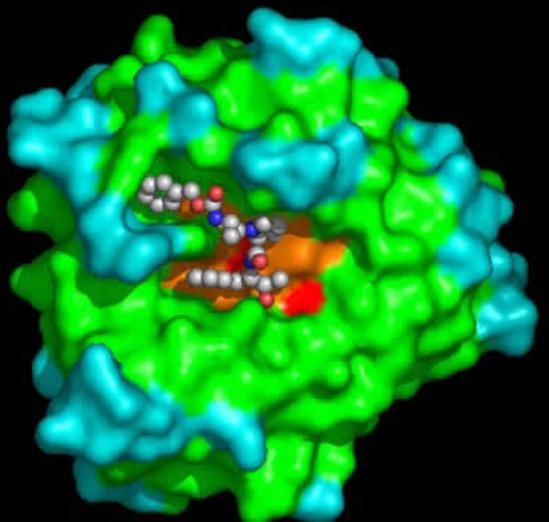
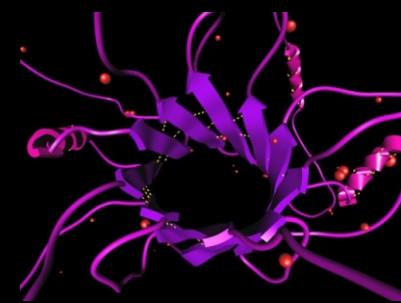
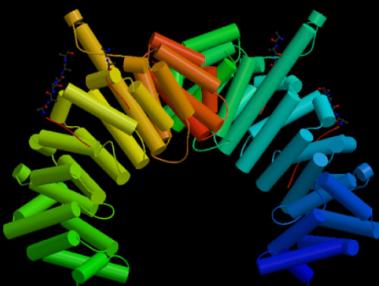
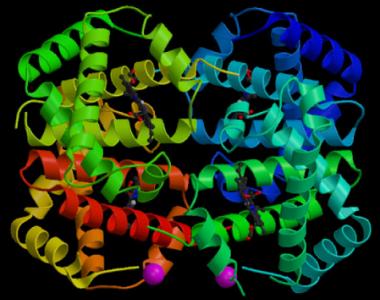
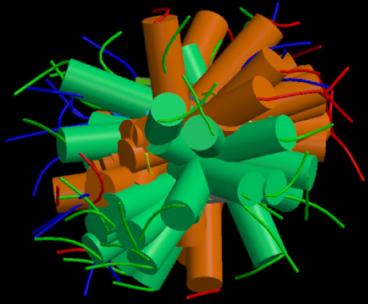
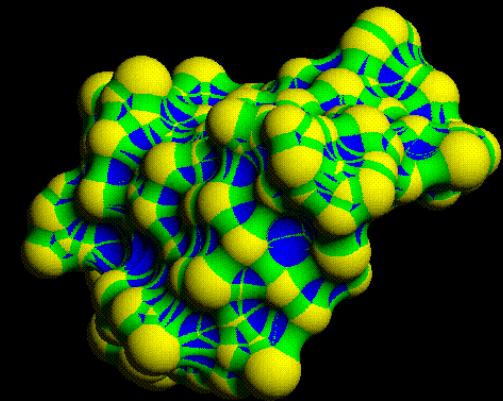
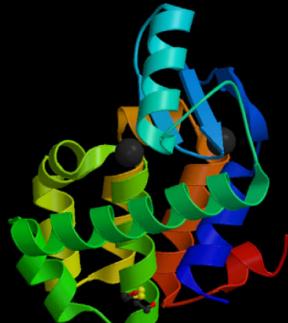
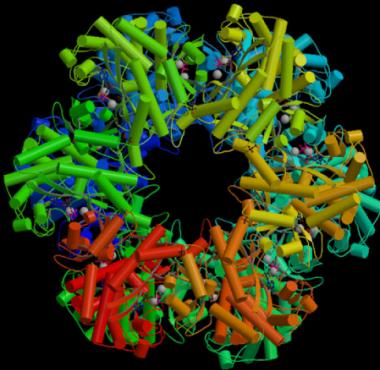
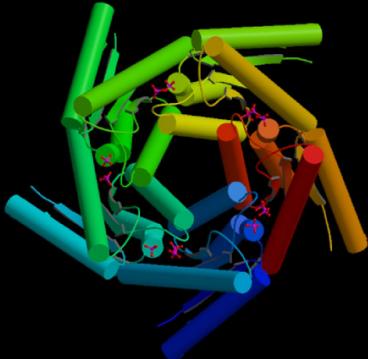
Institute of Ecology and Evolution (IE²)

Department of Biology

University of Oregon

pphil@uoregon.edu





Mendelian Genetics **Population Genetics** **Molecular Genetics** **Quant. Genetics** **Comp Meth Phylogen**

Diversification

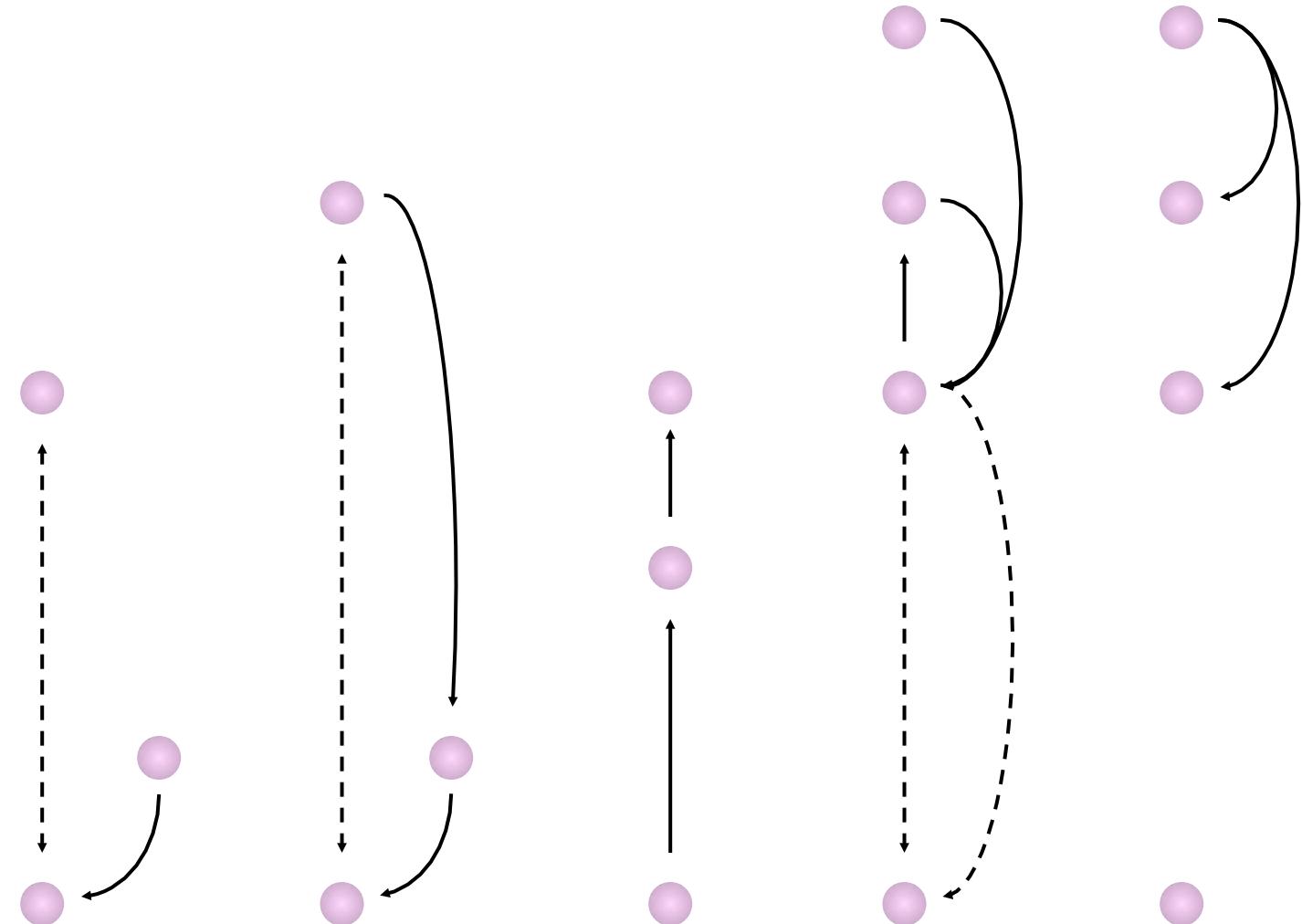
Ecological Context

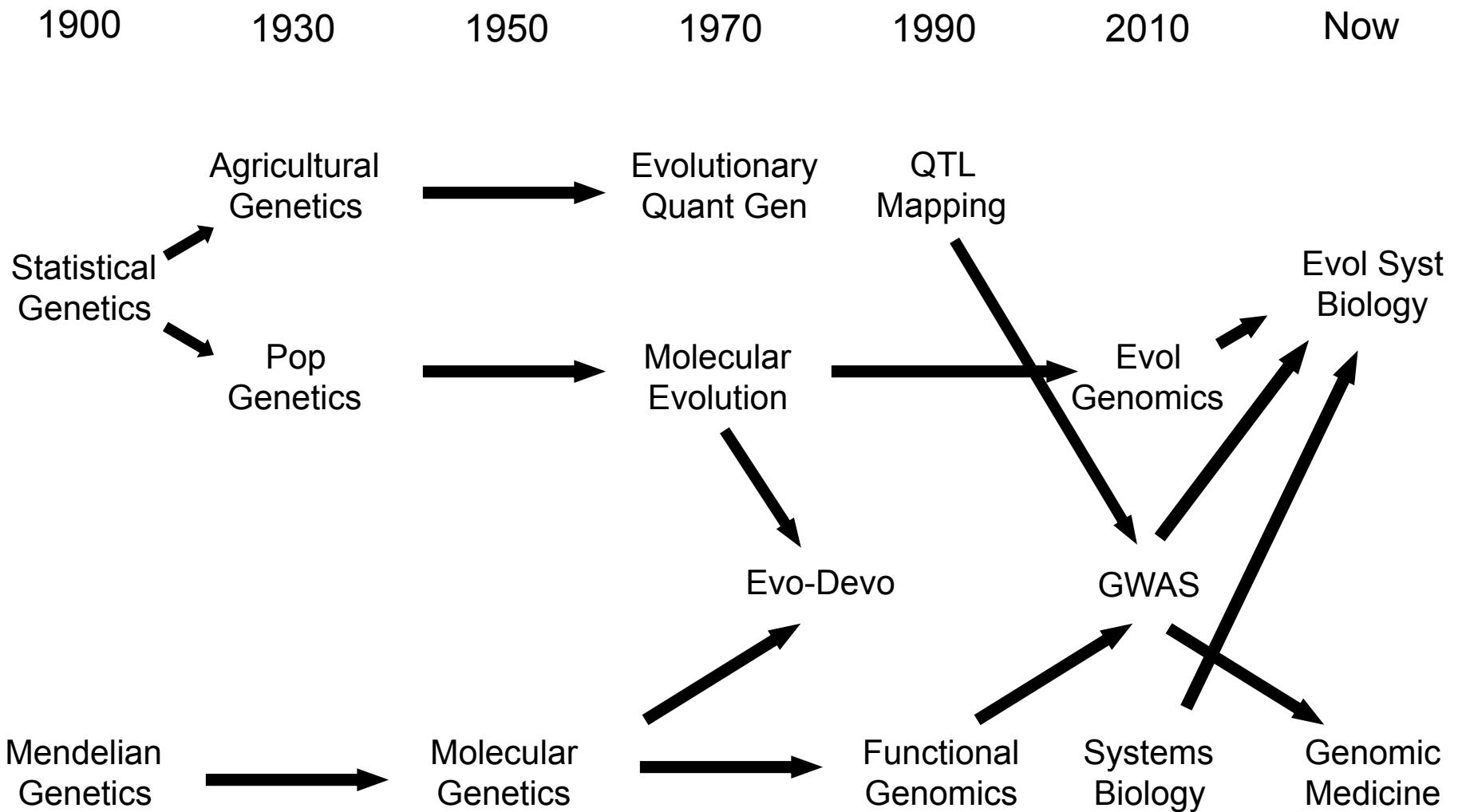
Phenotype

Genic Effects

Transmission

Genes





The fundamental distinction

Fundamental genetic unit

- ◆ Mendelian/molecular biology
 - The locus
 - Comparison between wildtype and mutant (usually a knockout)
- ◆ Quantitative genetics
 - The allele
 - Each allele can have a quantitative effect that is independent of the effects of other alleles

Examples

◆ Pleiotropy

- *Mol bio*: property of a locus. Either pleiotropic or not
- *Quant gen*: property of an allele. Pleiotropy can be variable both within and between loci (and it can evolve)

◆ Epistasis

- *Mol bio*: Mutation at one locus blocks ("stands upon") effects of mutations at a second locus
- *Quant gen*: Many possible types of interaction, allele-by-allele across loci

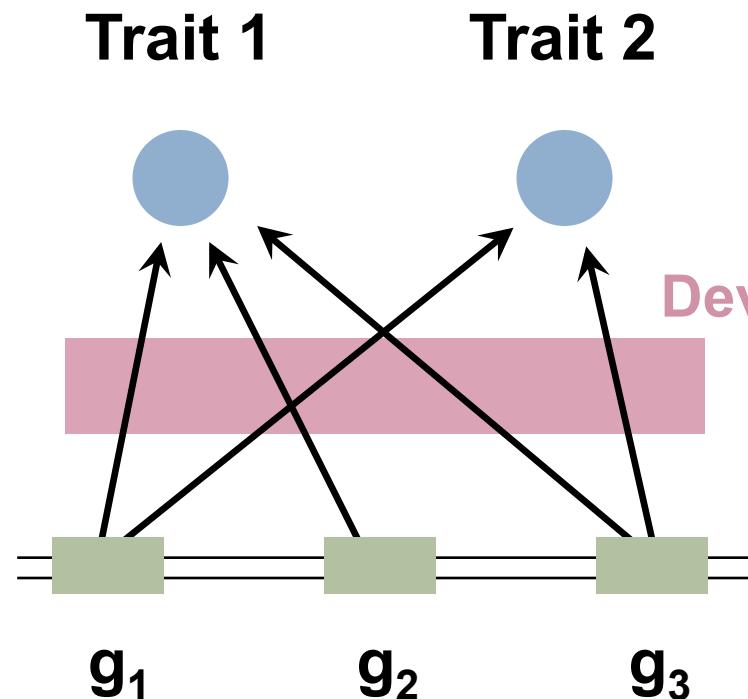
Multivariate selection

$$\Delta \bar{z} = G\beta$$

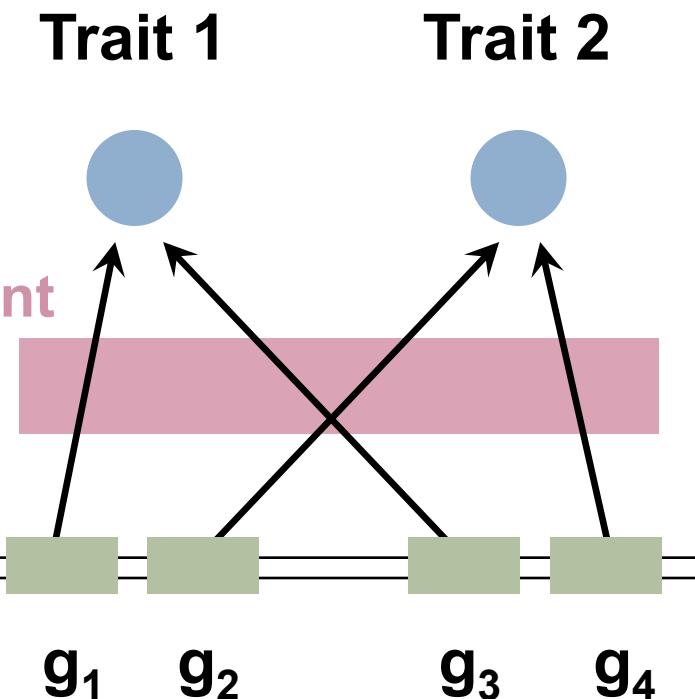
Lande 1979
Lande & Arnold 1983

Evolution of genetic architecture

Pleiotropy

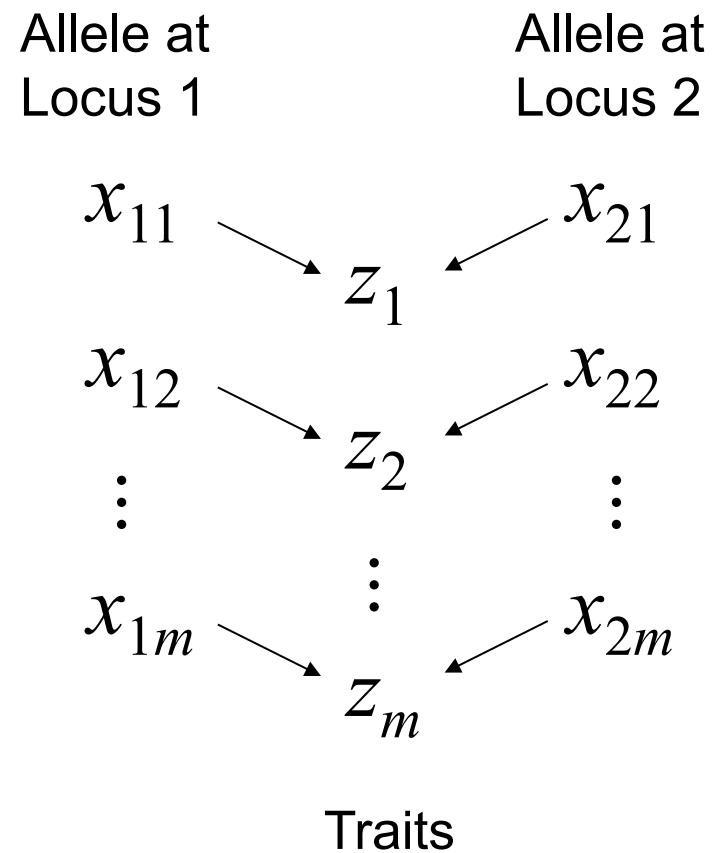
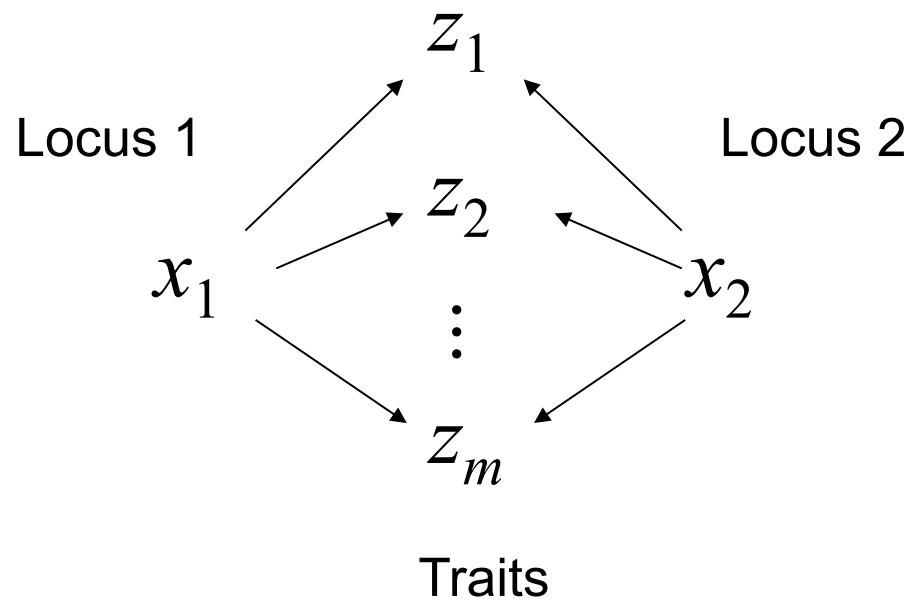


Linkage



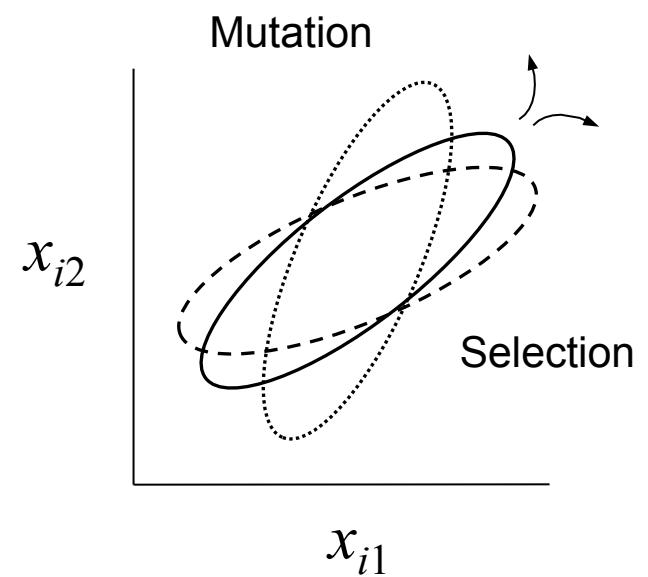
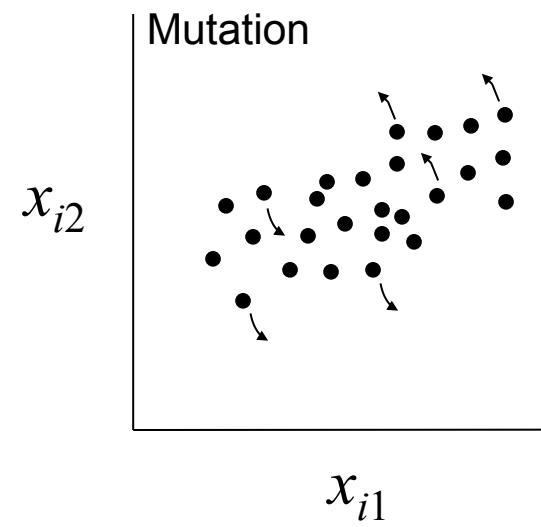
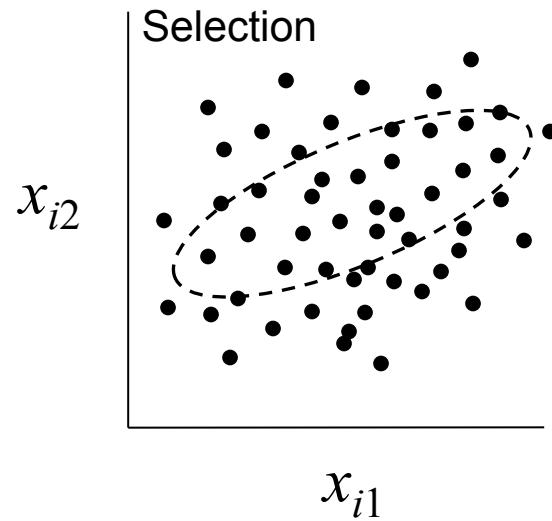
Development

Distributions of pleiotropic effects



Phillips and McGuigan 2006

Evolution of the G matrix



Finding the alleles that matter

- ◆ Understand the functional basis of adaptation
 - Connect molecular evolution to phenotypic evolution
- ◆ Understand the role of historical processes in shaping evolutionary change
 - Connect phylogenetics and biogeography to phenotypic evolution
- ◆ Understand the distribution of allelic effects
- ◆ Understand and predict the structure of the genotype-phenotype map

Approaches

◆ Quantitative trait locus (QTL) mapping

- *Strengths*: Controlled genetic crosses, strong linkage between markers and potential causal loci
- *Weaknesses*: Limited sample of alleles, strong linkage can confound effects of different loci

◆ Genome-wide association (GWAS) mapping

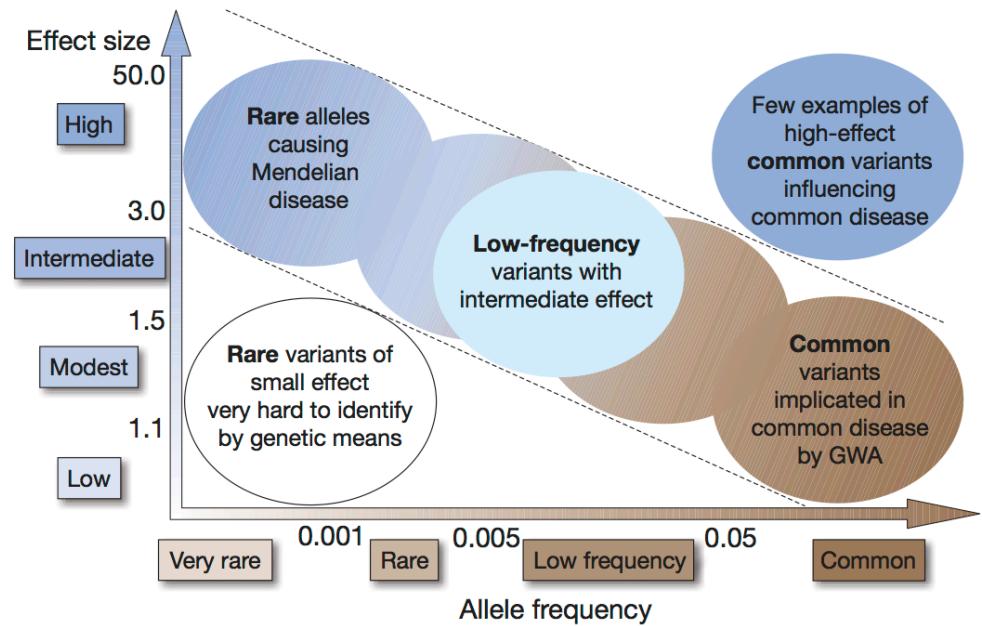
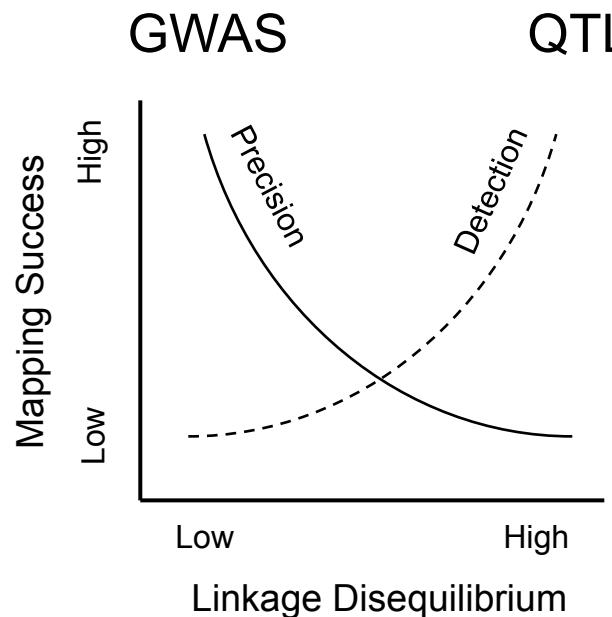
- *Strengths*: Potential to sample all relevant alleles, historical breakdown of linkage increases precision
- *Weaknesses*: Genetic heterogeneity means large samples are required, undetected population structure can bias results

◆ Evolve and re-sequence (experimental evolution)

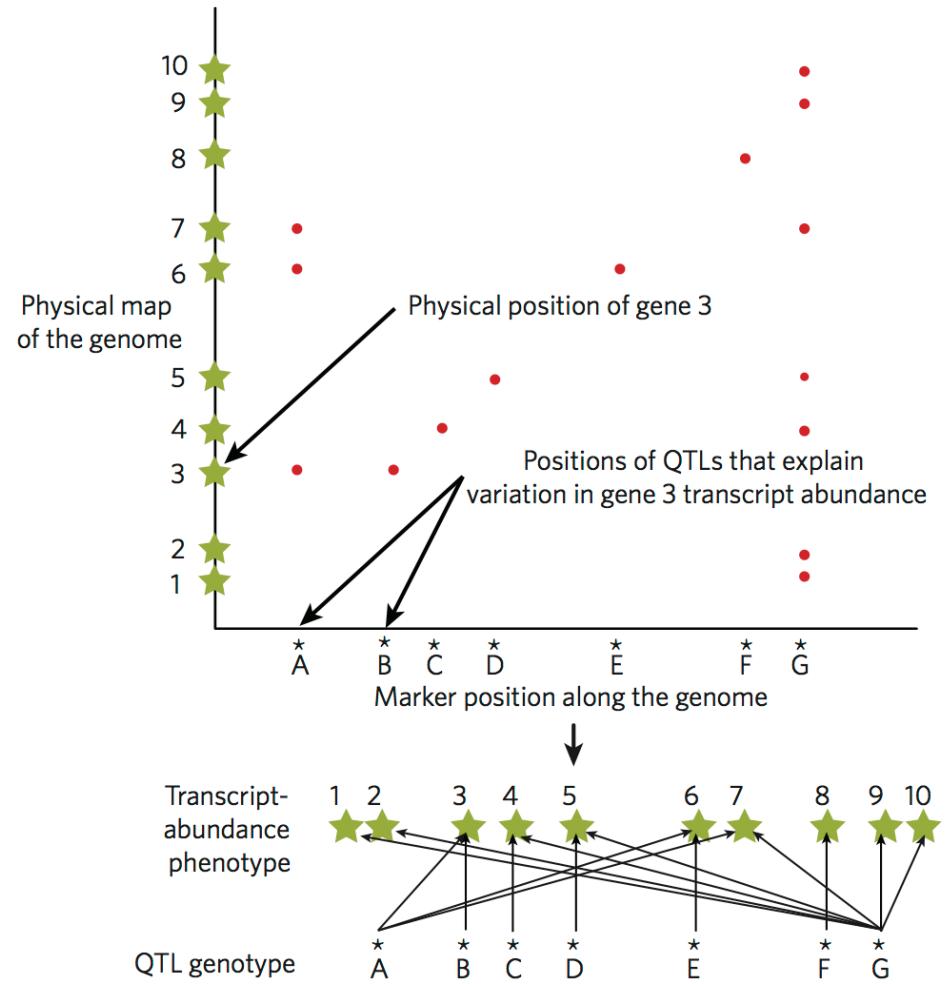
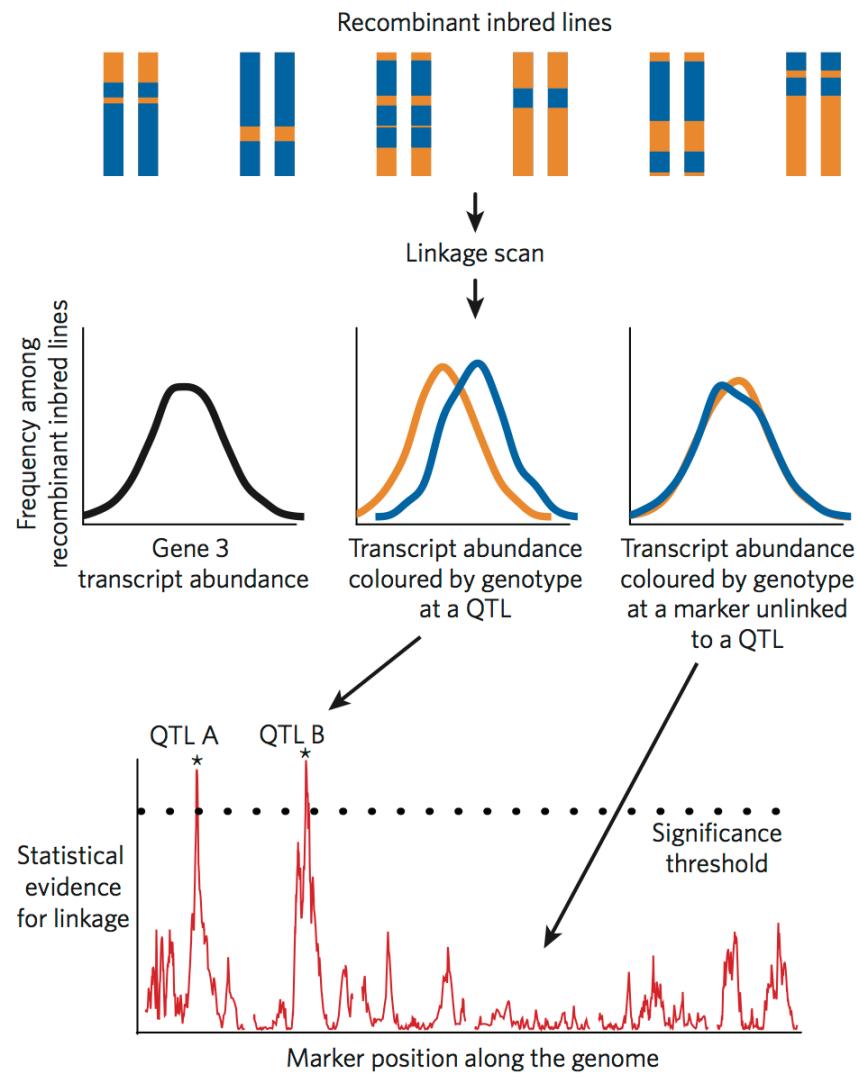
- *Strengths*: Comparison to ancestor allows hypothesis testing and increased power, find alleles relevant to adaptation
- *Weaknesses*: Only a subset of variants will be detected, selective sweeps could obscure signal, difficult to separate selection from drift

Challenges

- ◆ Structure of genetic architecture determines power of detection
- ◆ Tradeoff on the effects of linkage on detection and specification



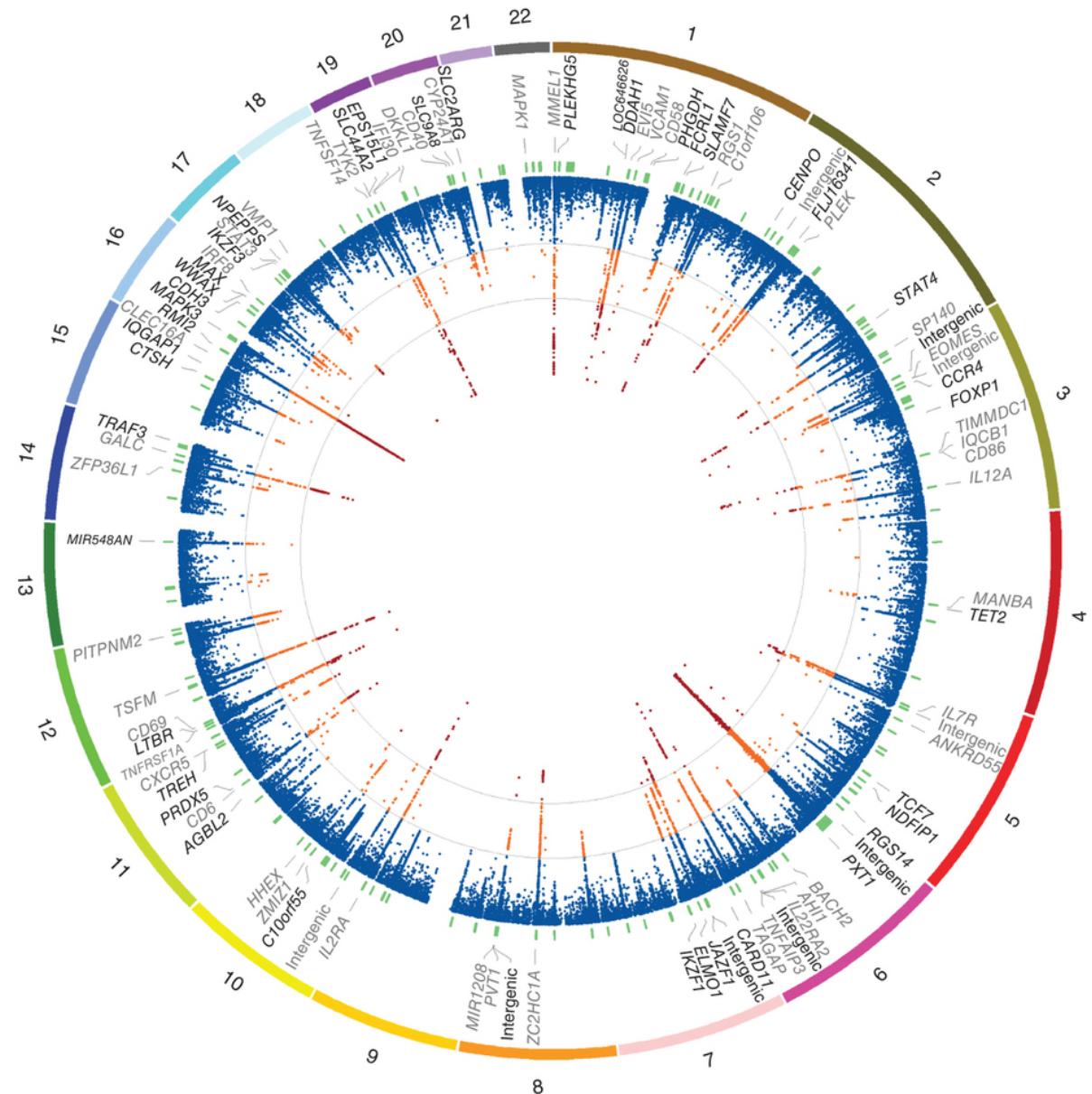
QTL Mapping



GWAS: Complexity of complex traits

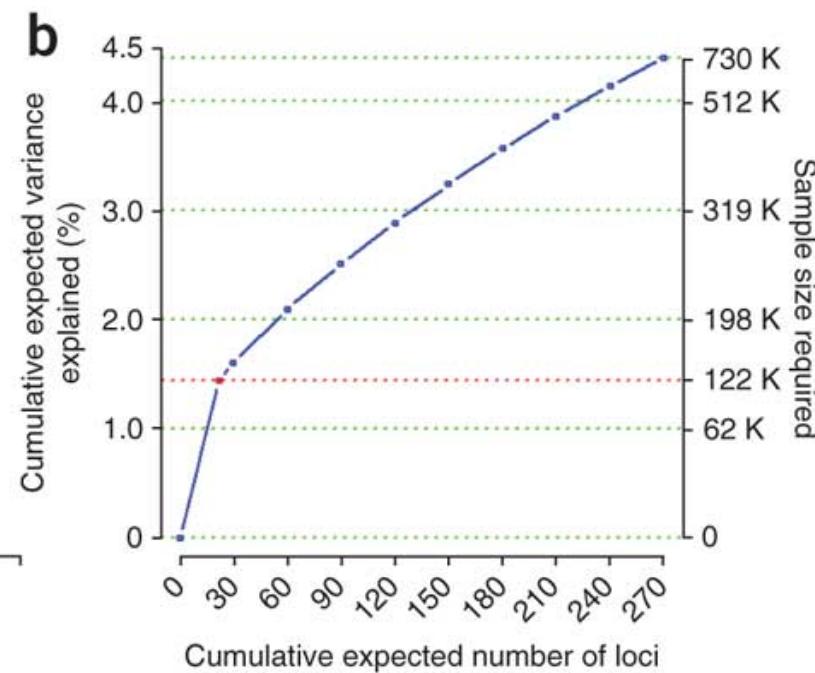
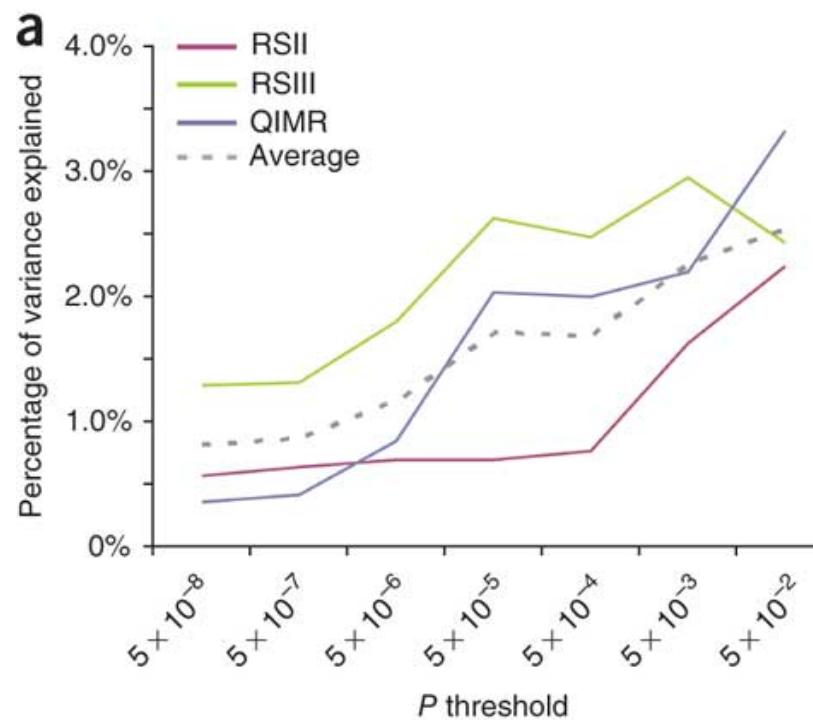
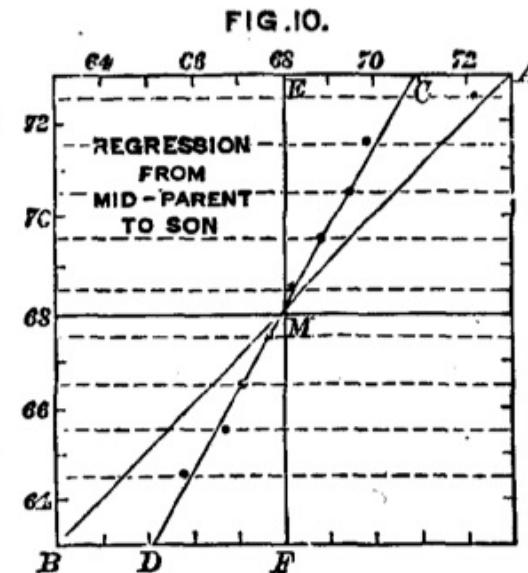
GWAS of multiple sclerosis

- 14,498 subjects
- 24,091 controls
- 161,311 SNPs
- 103 loci detected
- ~28% variation explained



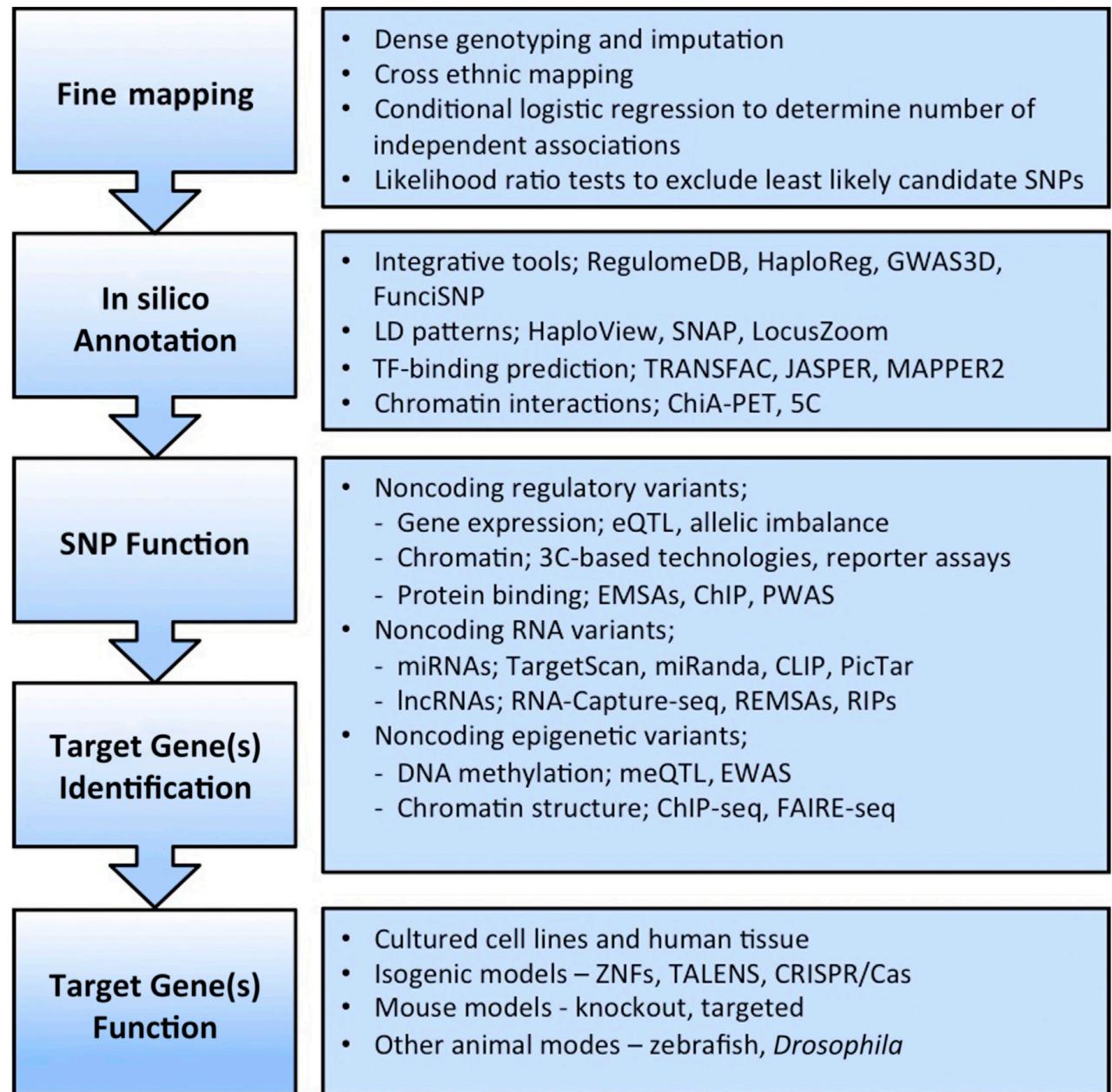
GWAS for human height

Francis Galton, Natural Inheritance (1889)

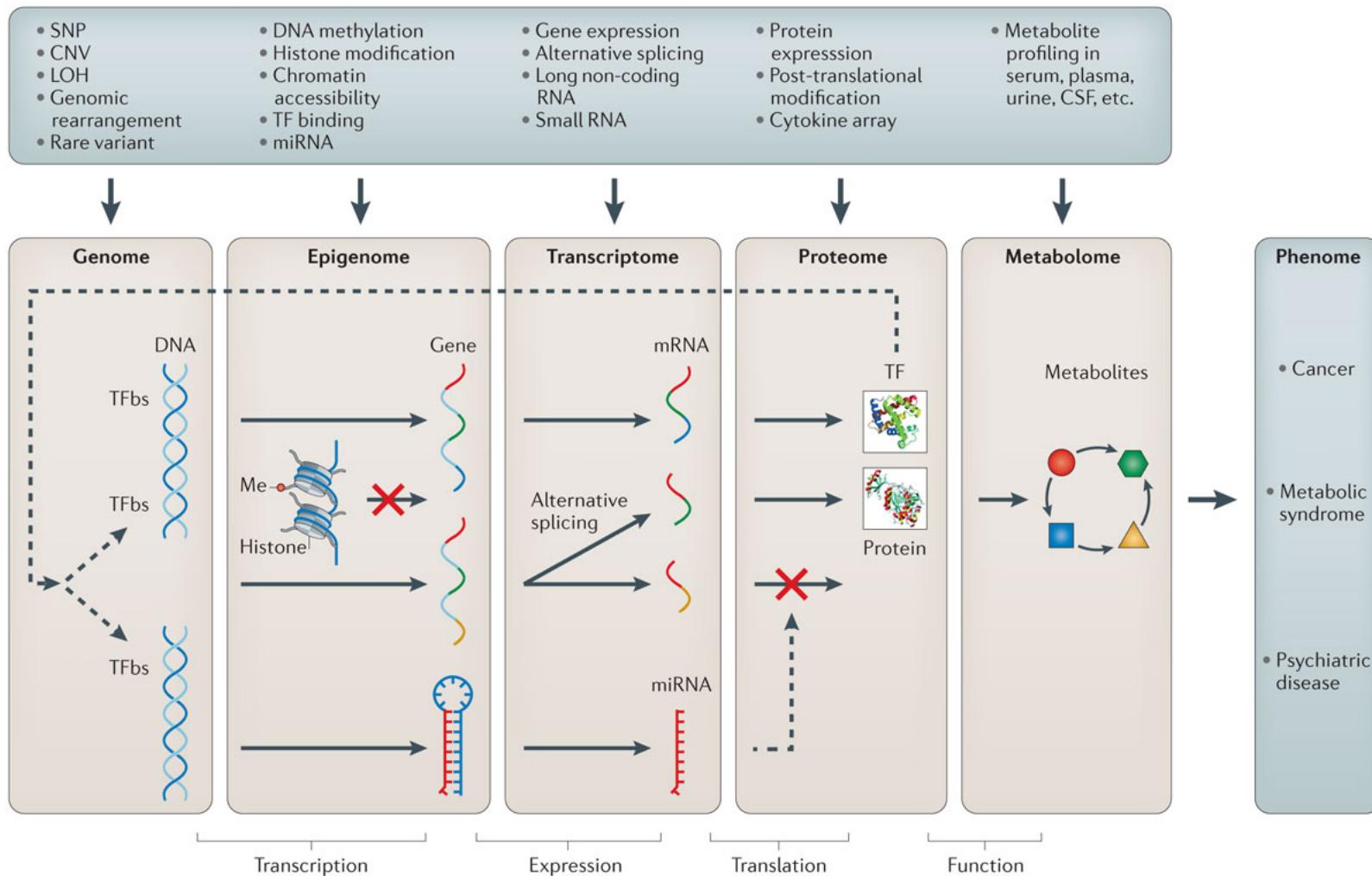


Speliotis et al. 2010 Nature

Determining SNP function



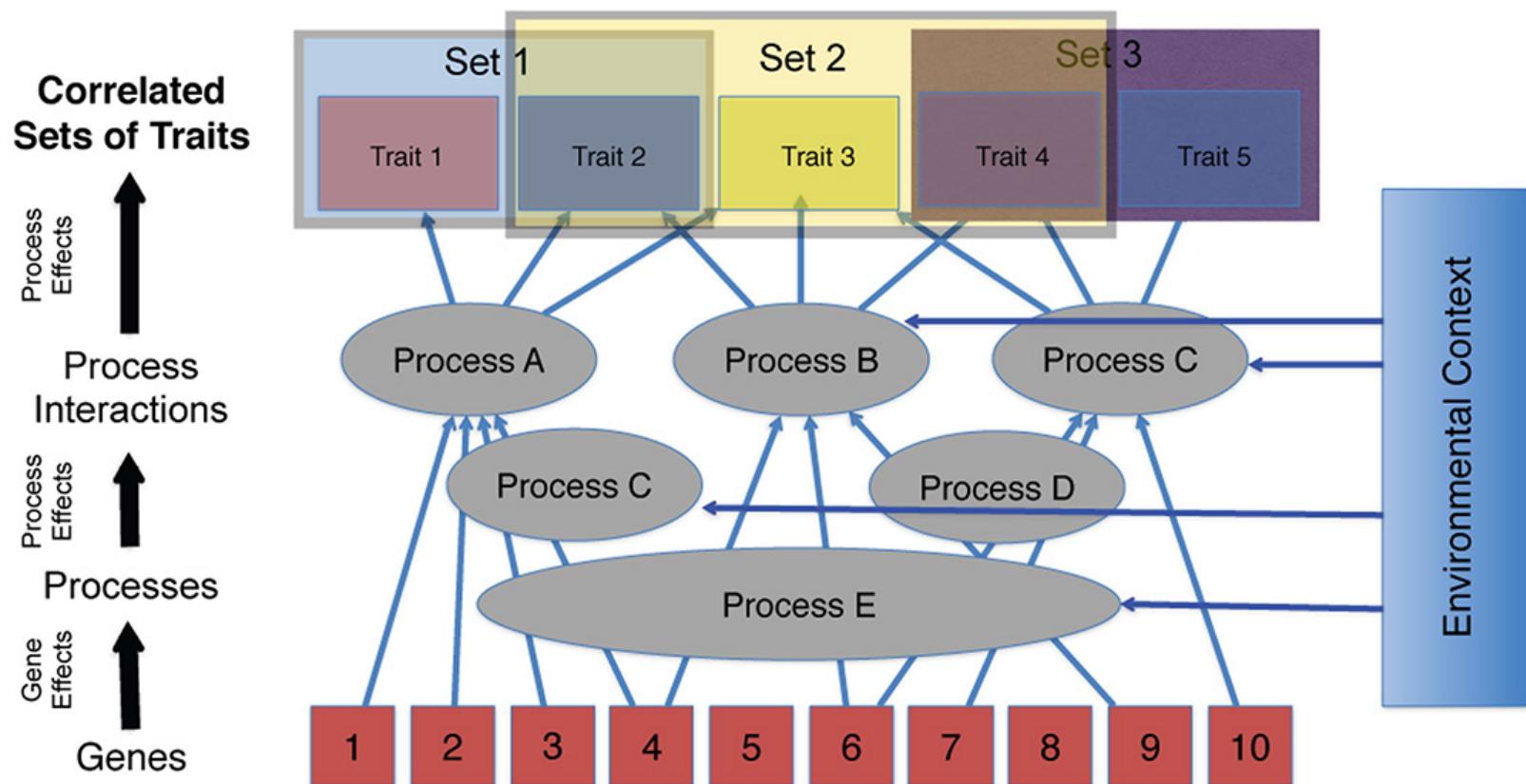
What is systems biology?



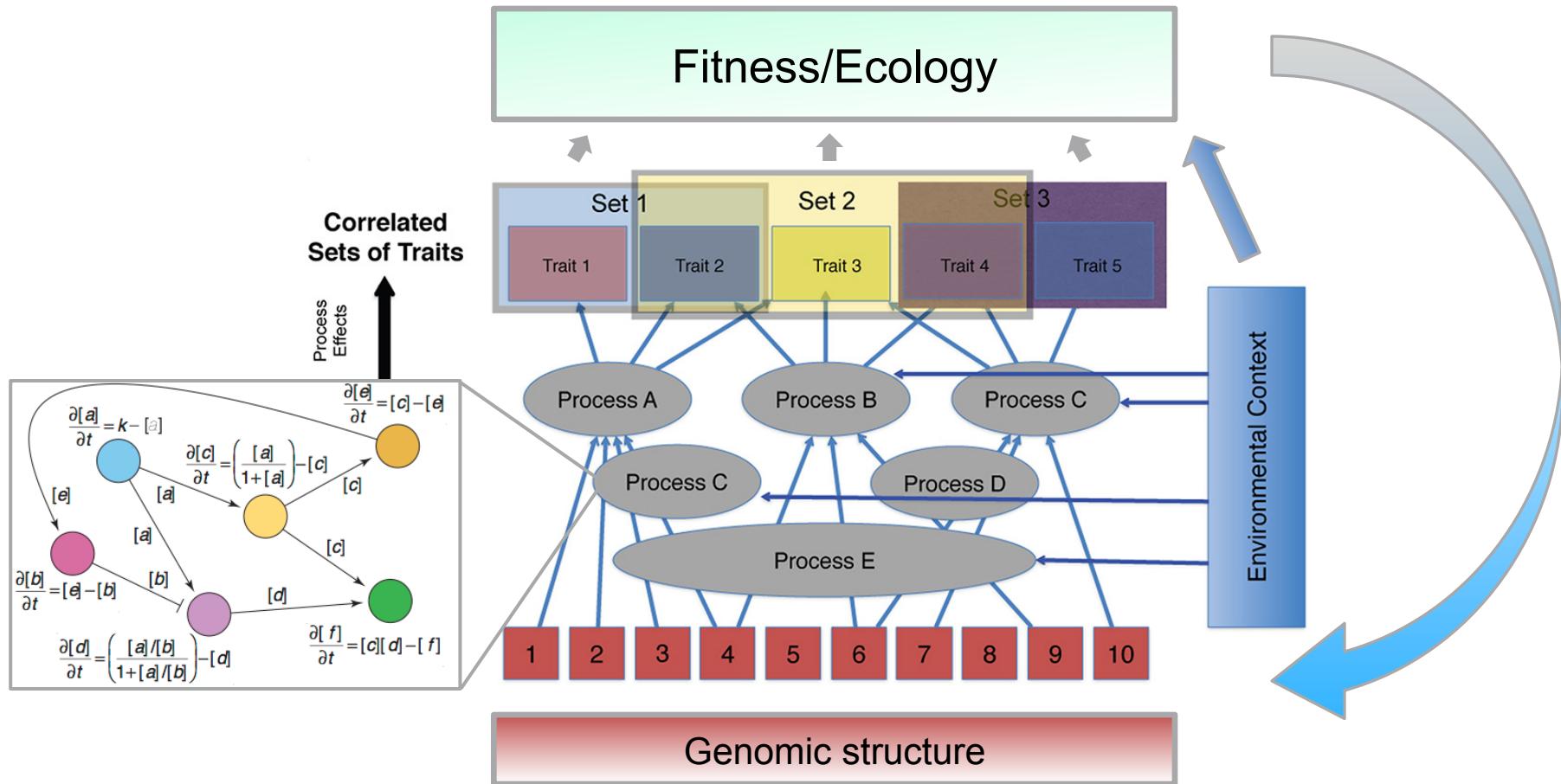
Nature Reviews | Genetics

Ritchie et al. 2015 Nat Rev Gen

Systems biology



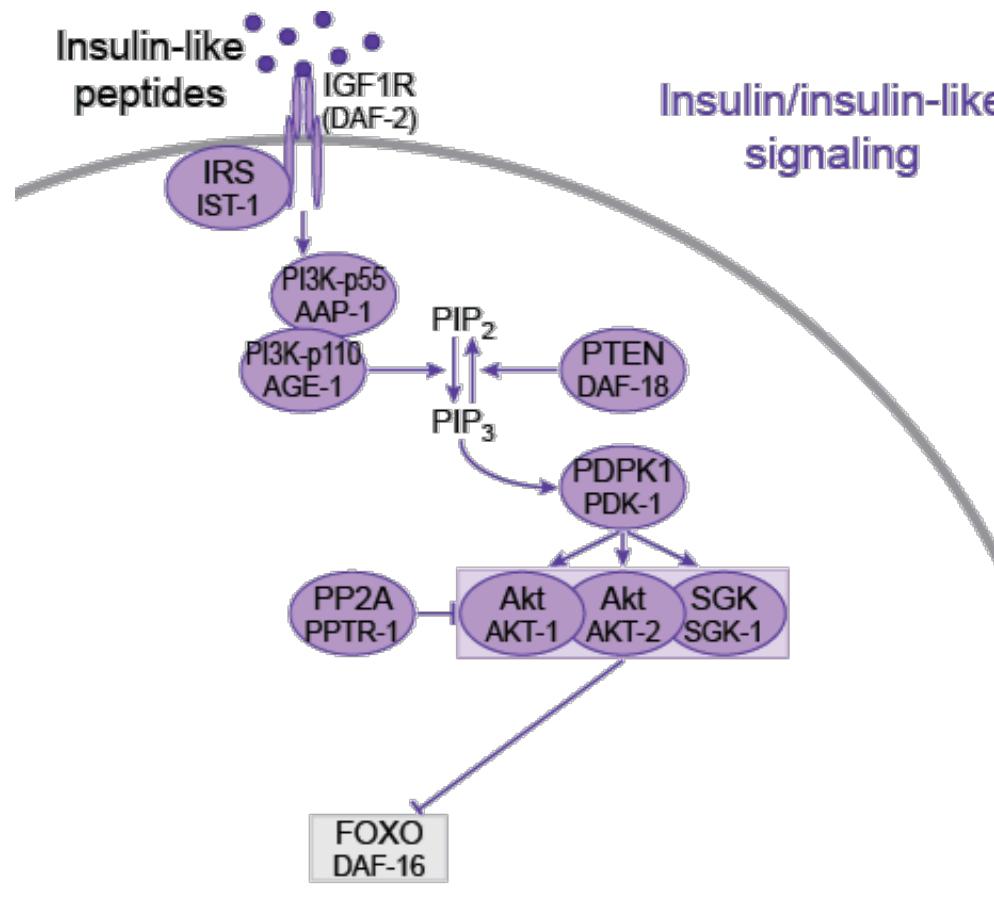
Evolutionary systems biology



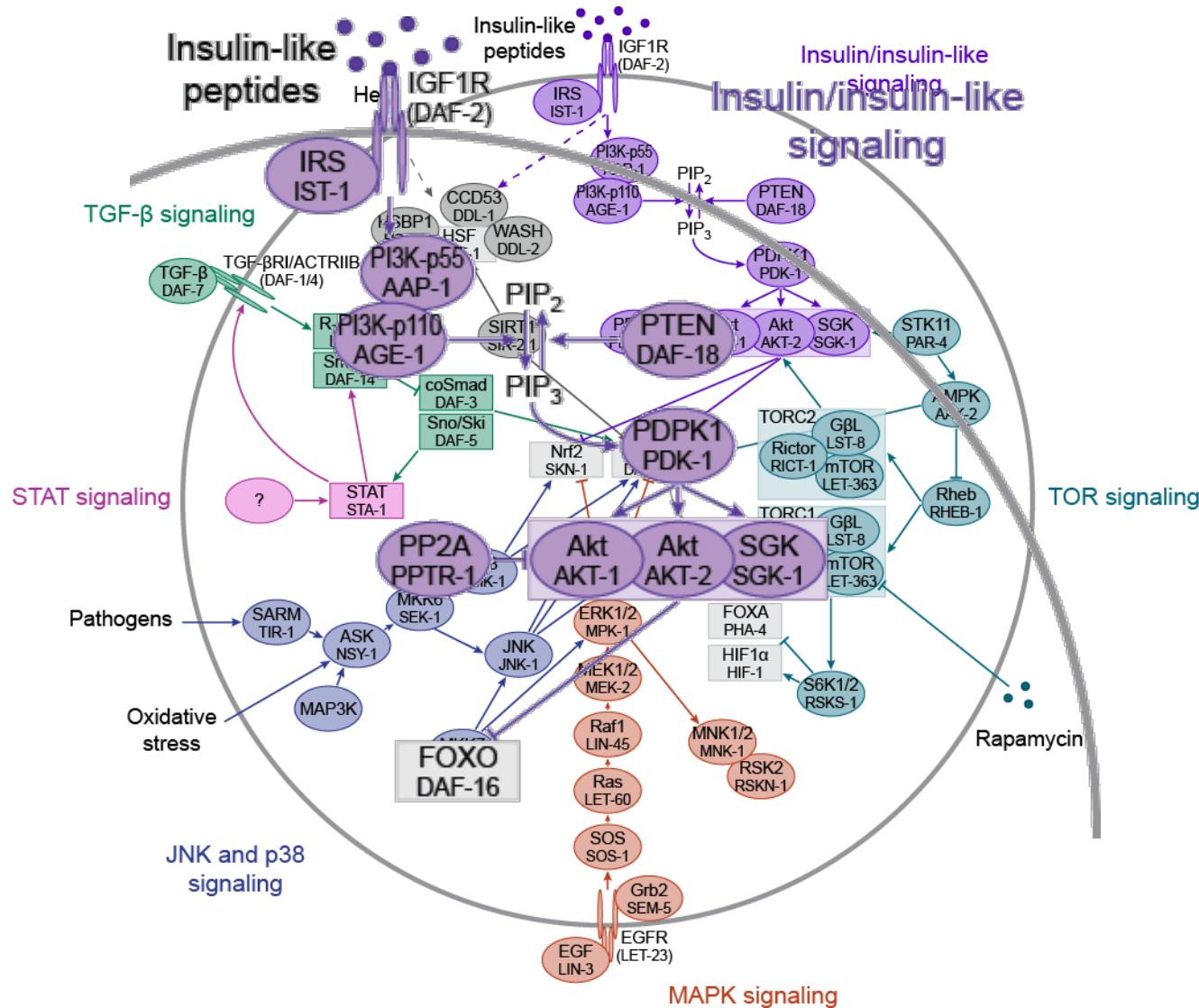
An assessment [of potential adaptive variation] will depend on an understanding of the relation between gene and organism that far transcends any present knowledge of development, physiology, and behavior. **In fact, it demands the answer to every other question that now lies open in biology.**

– Lewontin 1974

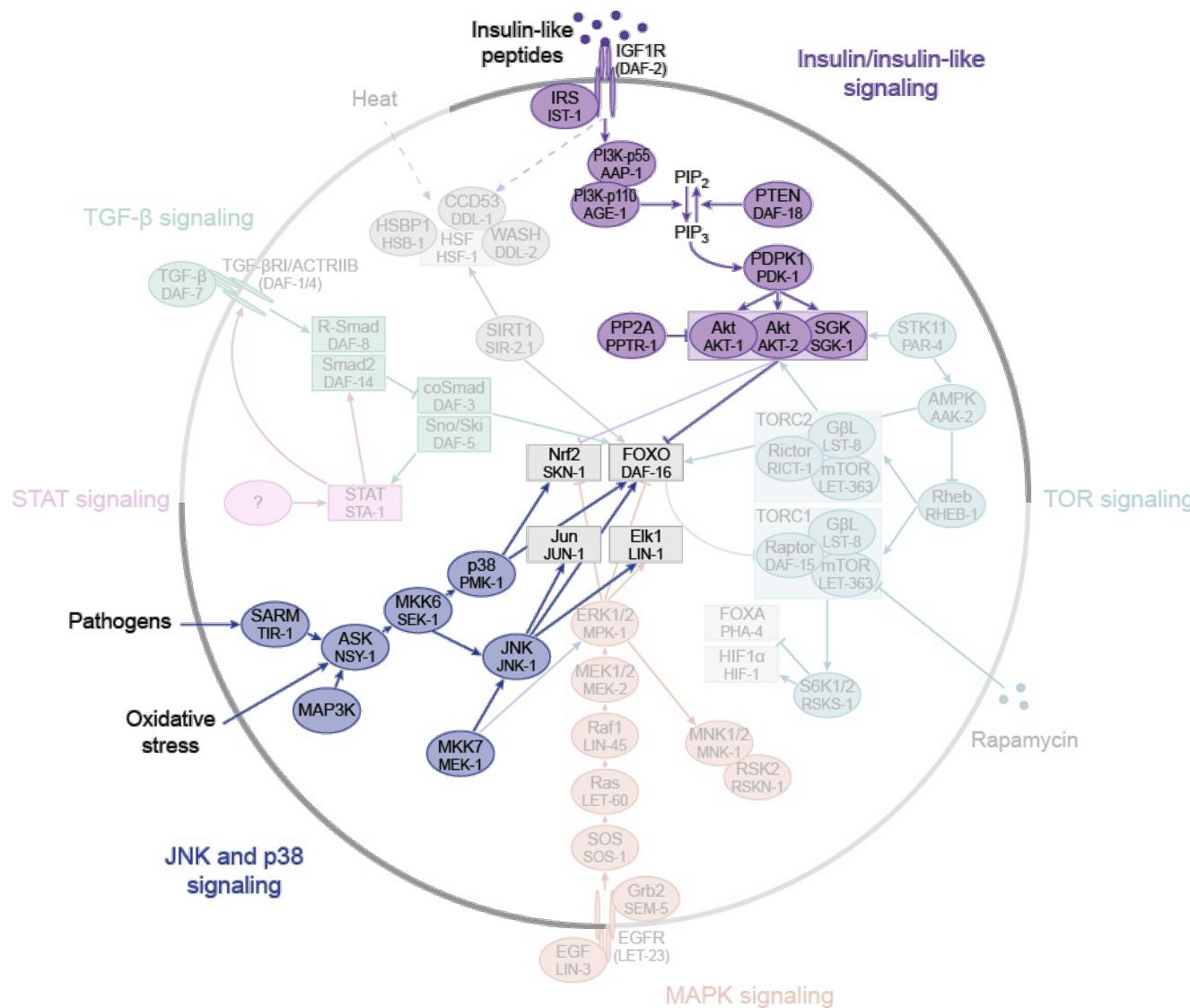
Stress response pathways



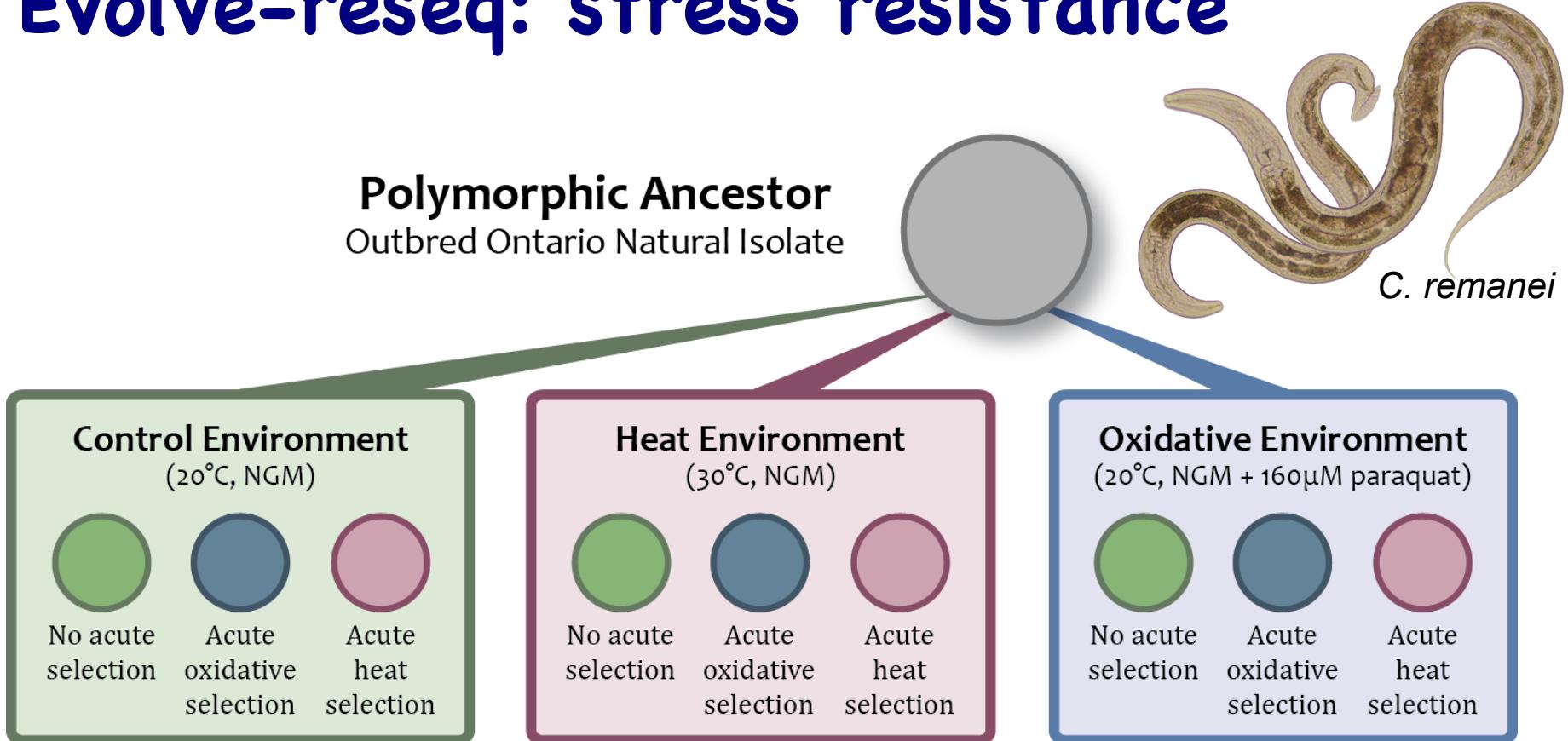
Stress response pathways



Stress response pathways



Evolve-reseq: stress resistance



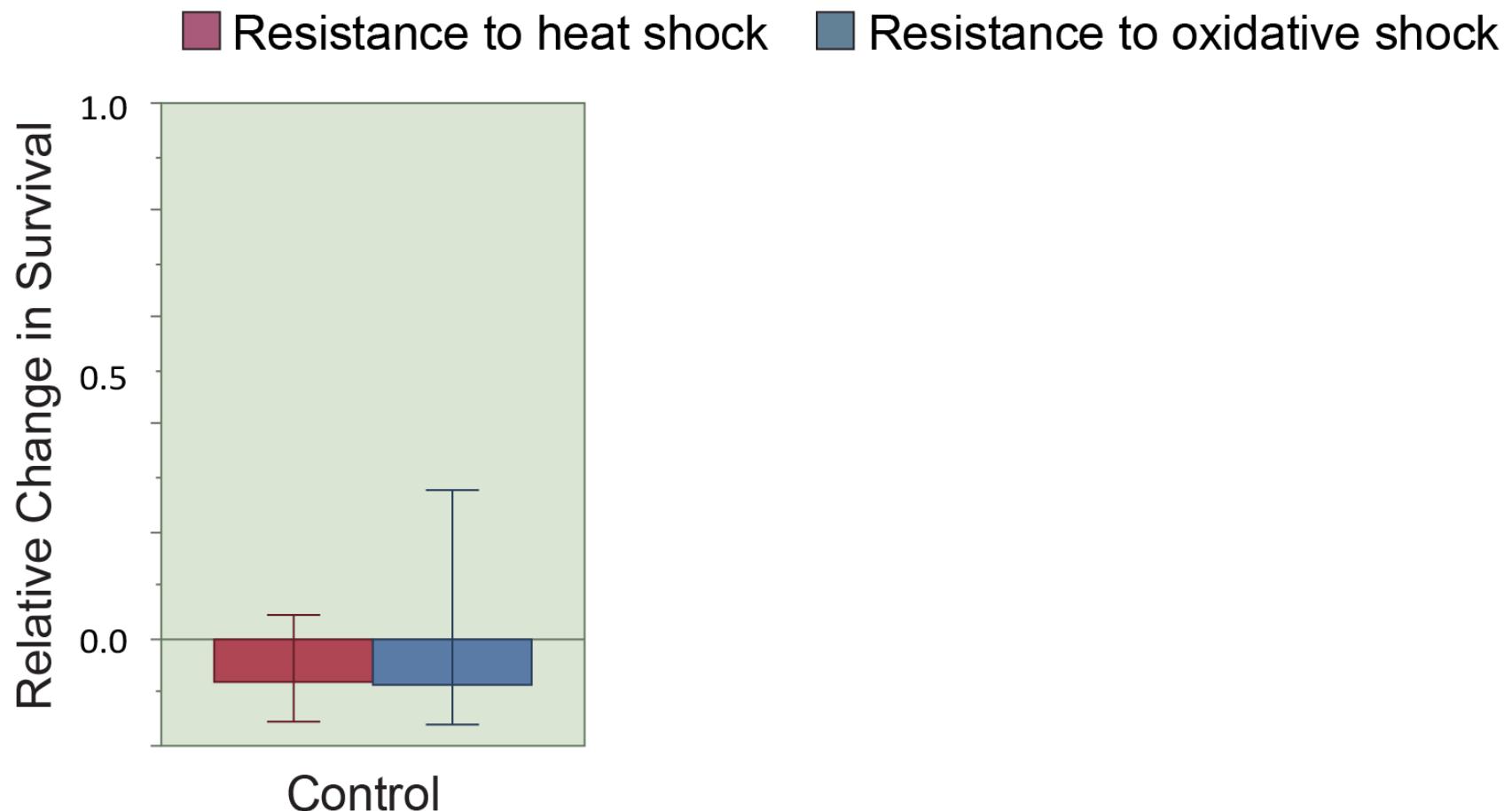
- ◆ Chronic conditions every generation (30 total)
- ◆ Acute selection every 3 generations (10 total)
- ◆ 2 replicates of each of the 9 conditions, phenotyped in 3 environments, N ≈ 10,000



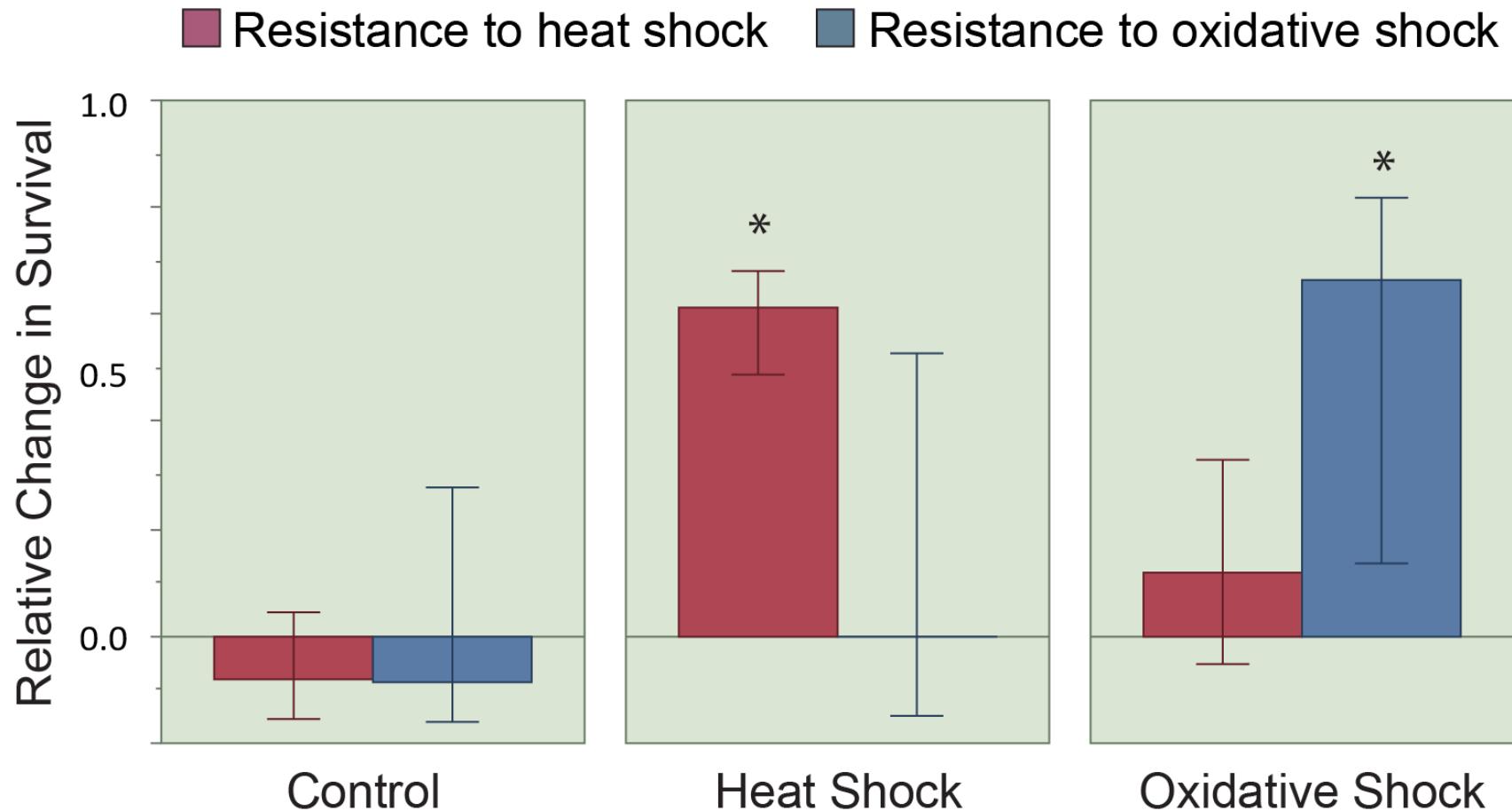
Kristin Sikkink Rose Reynolds

Sikkink et al. 2015 Evolution

Integrated stress responses?

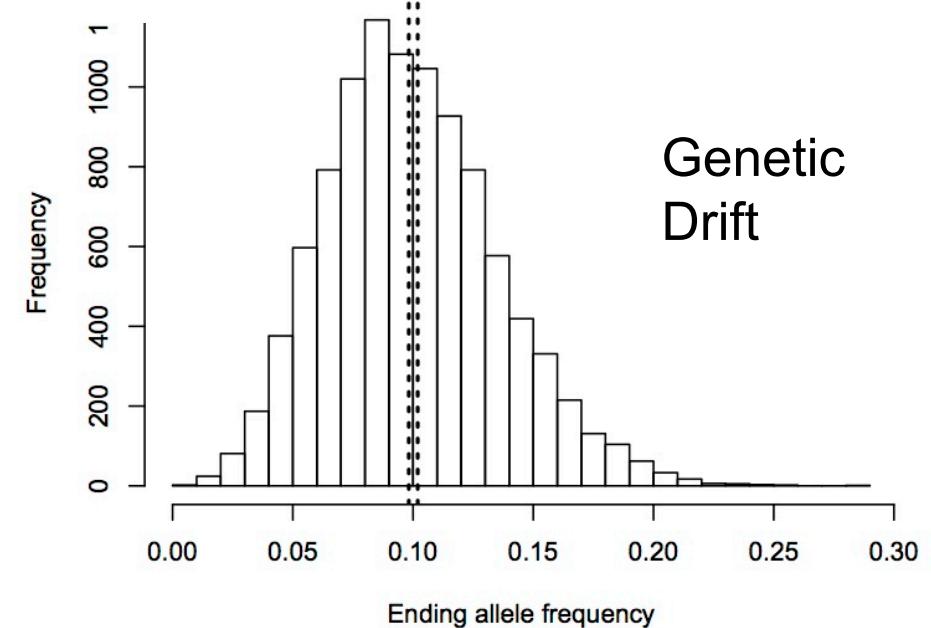
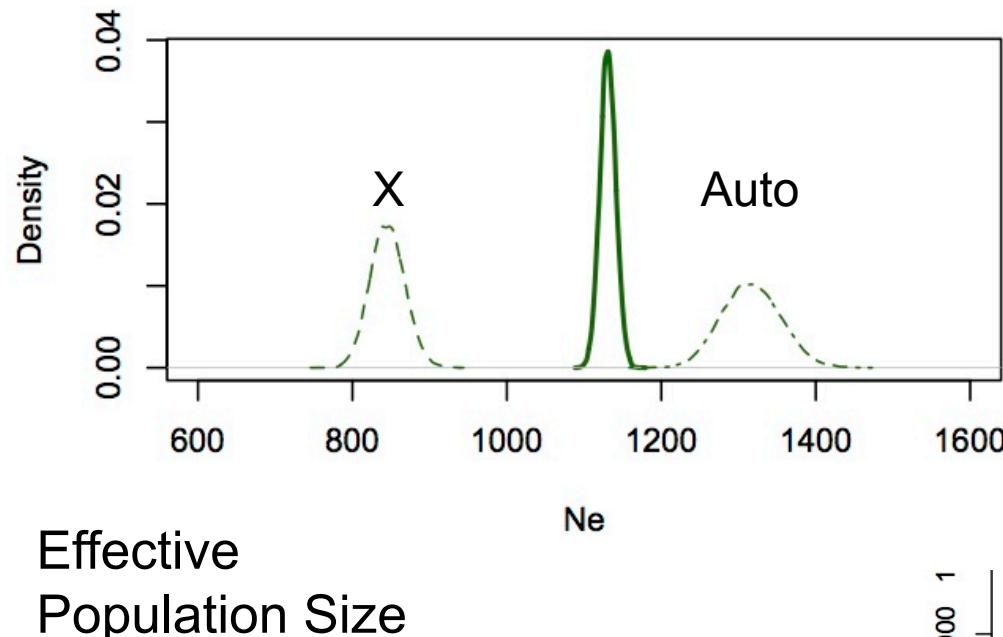


Integrated stress responses?

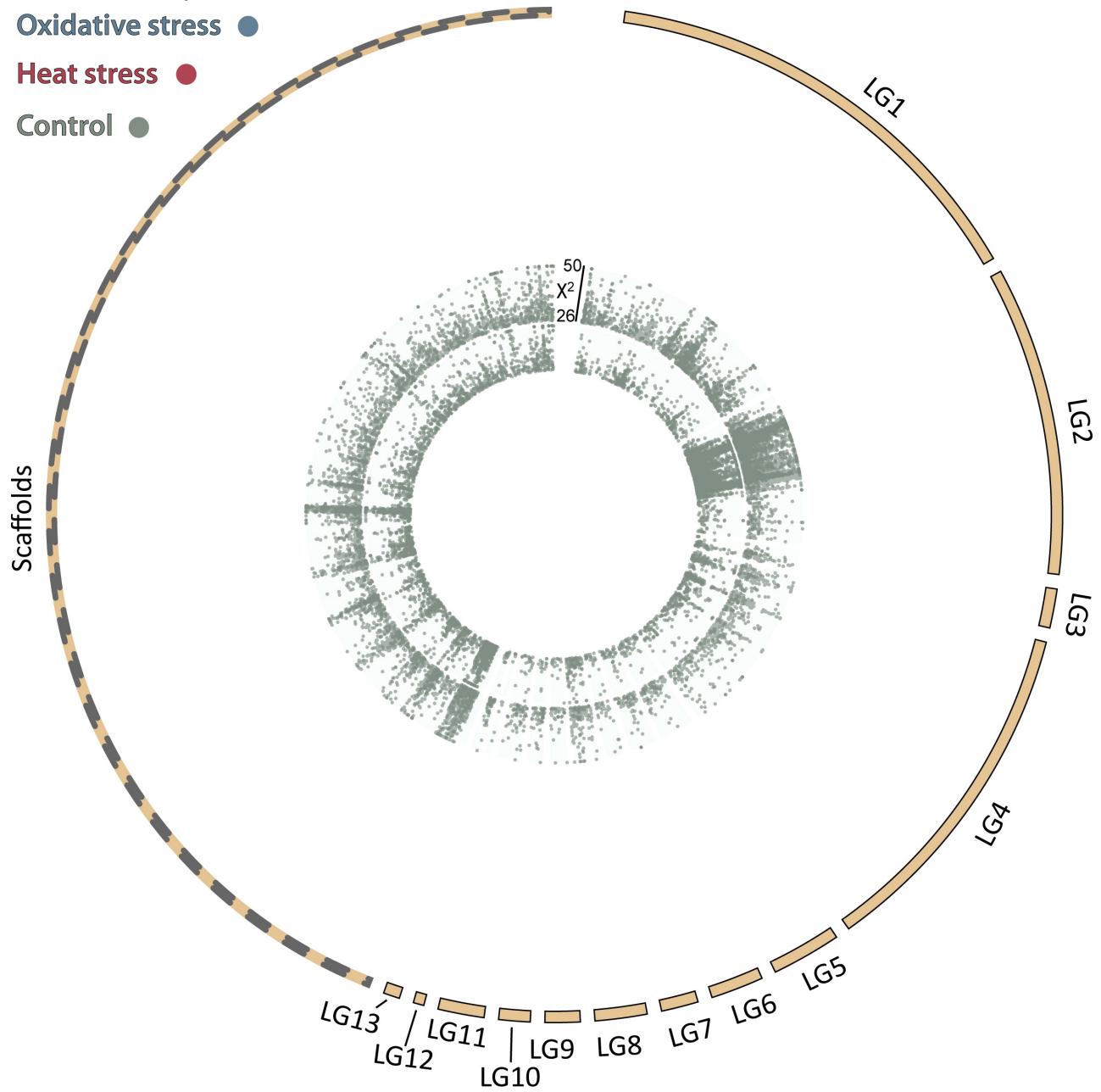


No pleiotropy for segregating variation for
heat and oxidative shock resistance

Population genomics

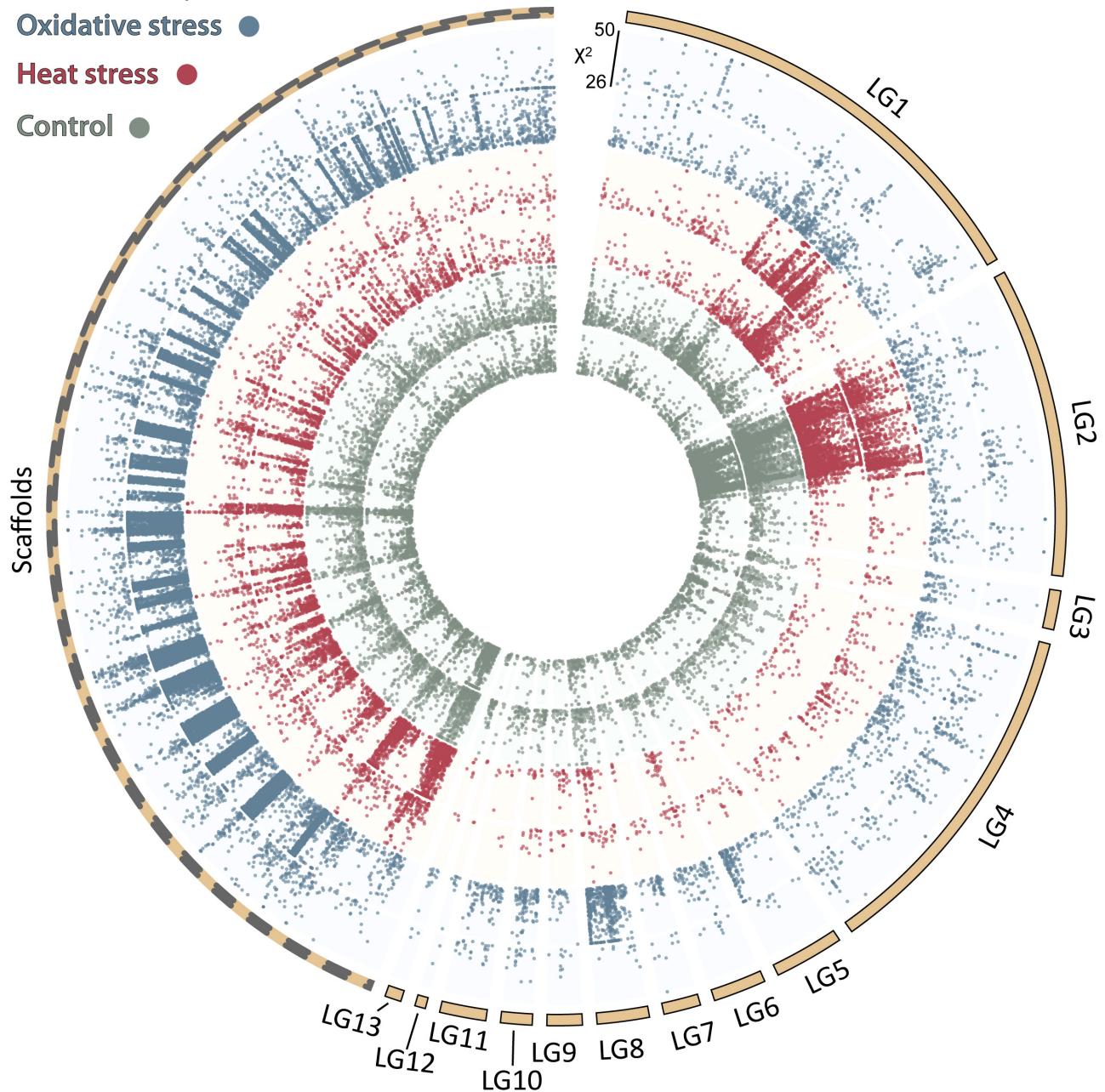


Genomic data analysis

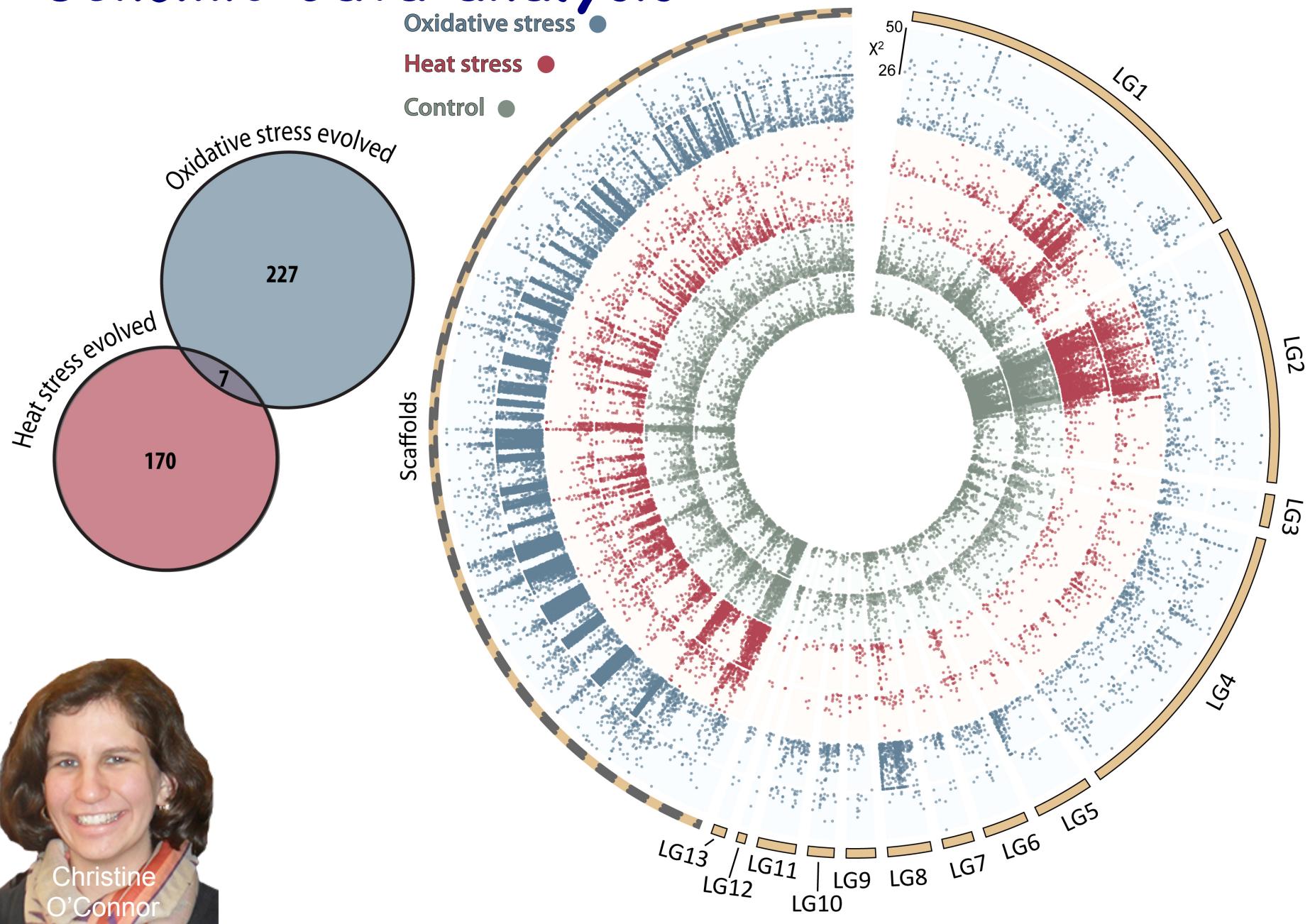


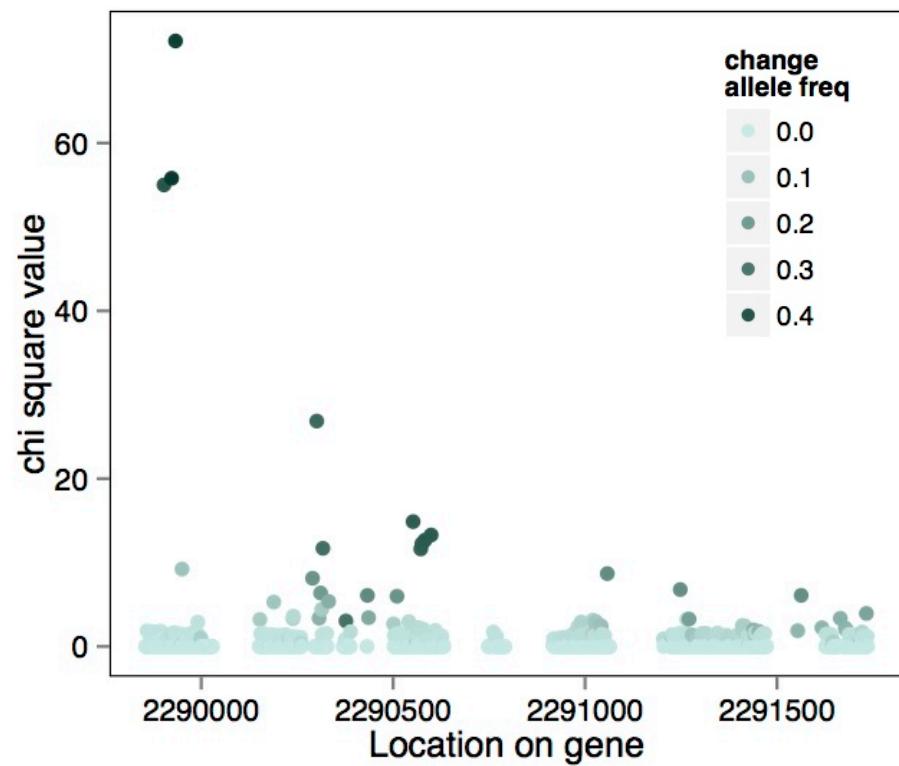
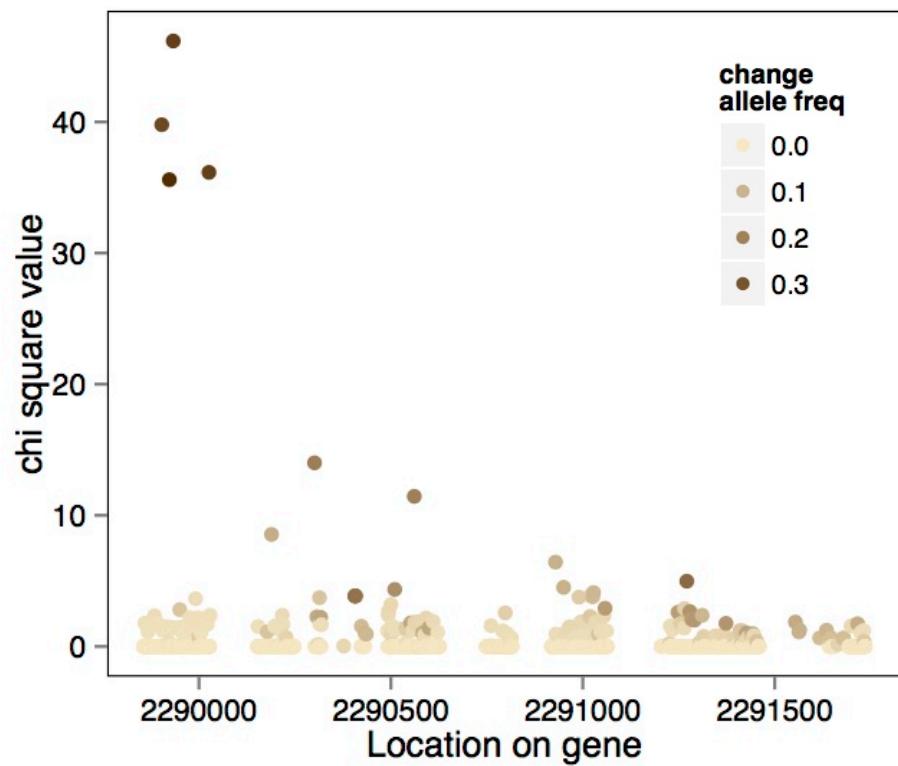
Christine
O'Connor

Genomic data analysis



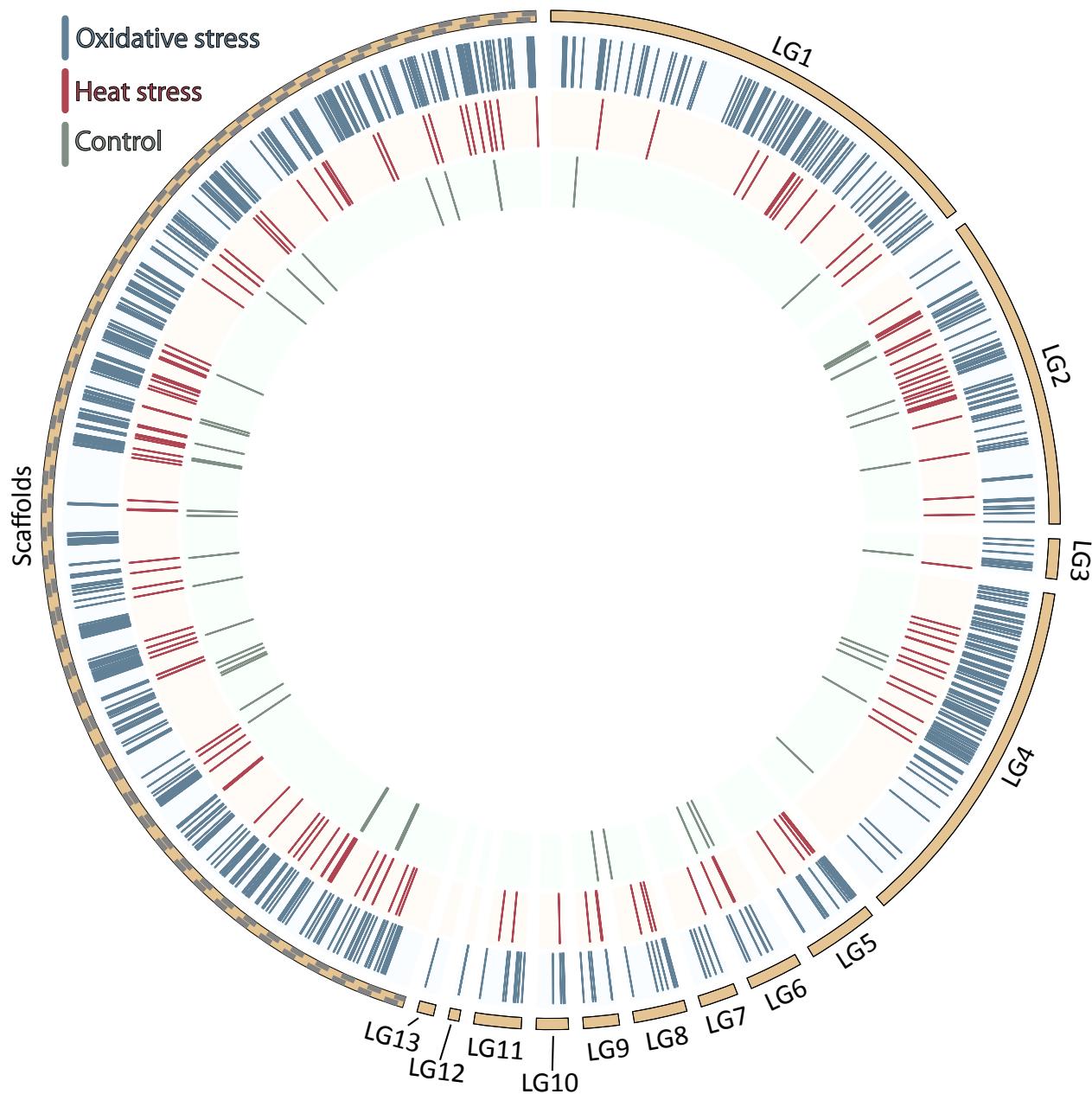
Genomic data analysis



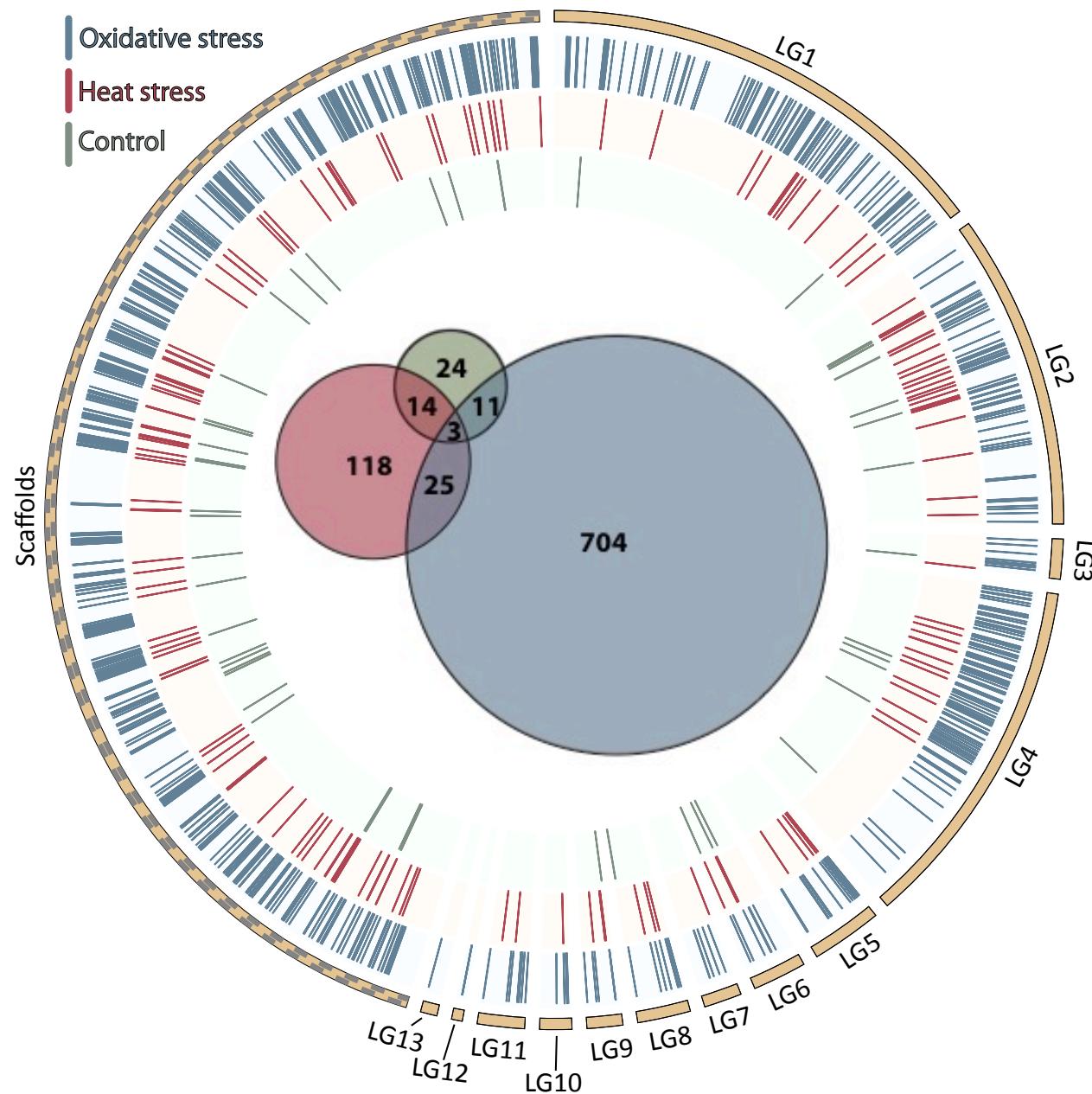


daf-2 Insulin growth factor 1 receptor

Constitutive changes in gene expression



Constitutive changes in gene expression



Summary

- ◆ Selection on stress response pathways largely leads to independent responses
- ◆ Pleiotropic responses depend on environmental milieu is a complex fashion
- ◆ Genetic correlations across environments (phenotypic plasticity) can also rapidly evolve
- ◆ Can use experimental evolution to identify genetic changes at nucleotide resolution within *C. remanei*