Genetic mapping of useful alleles

Prof. Karl Schmid, University of Hohenheim

This lecture is a modified version of a lecture by Ümit Seren, Gregor-Mendel-Institute, Vienna

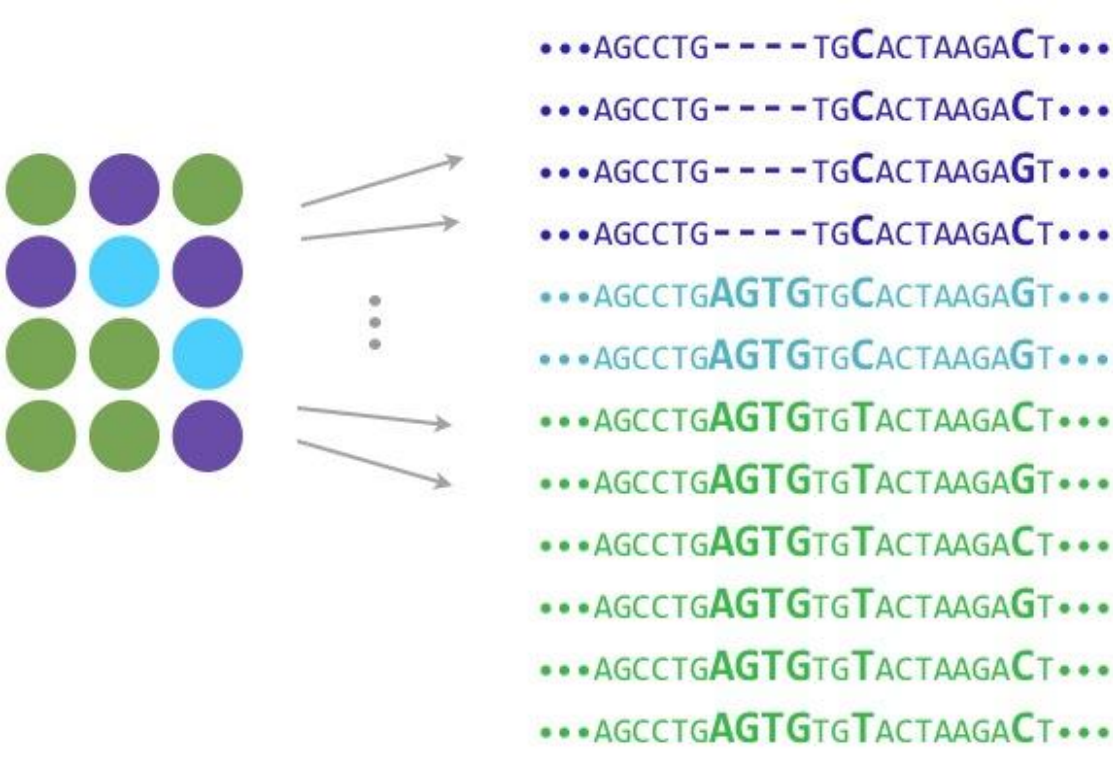
The original lecture is available from: https://goo.gl/bSX3De

Motivation

Motivation

- Studying the genetics of natural variation
- Understanding the genetic architecture of traits of ecological and agricultural importance
- Identifying the genomic regions that control genetic variation
- Test association at many variants instead of some and hypothesis-free instead of hypothesis-driven.

Phenotype ←→ Genomic marker



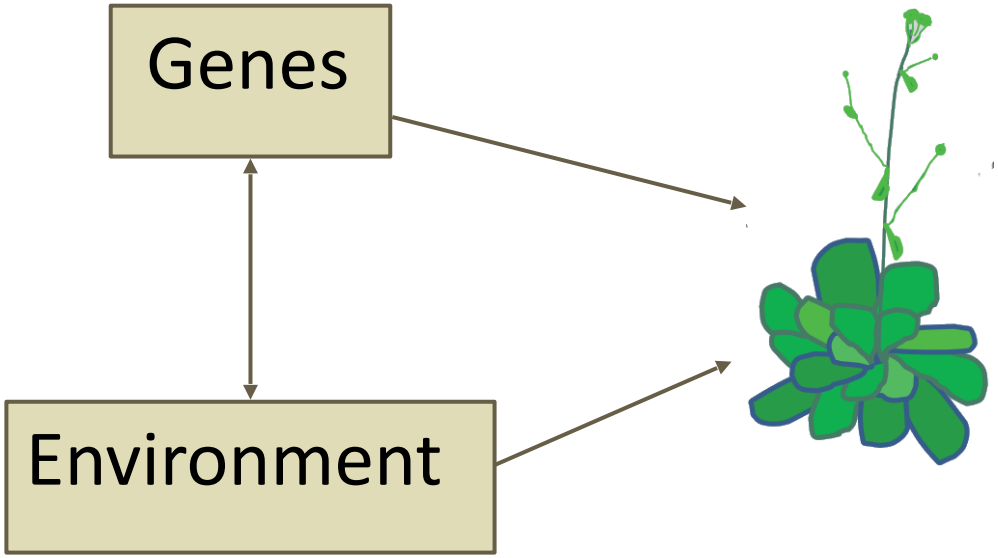
SNPs

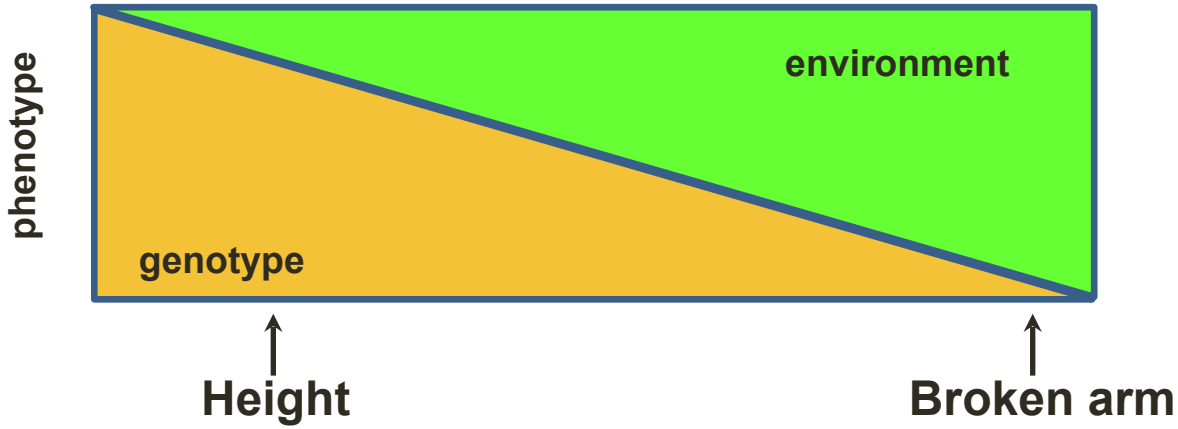
Indels

CNVs

Epigenetic markers

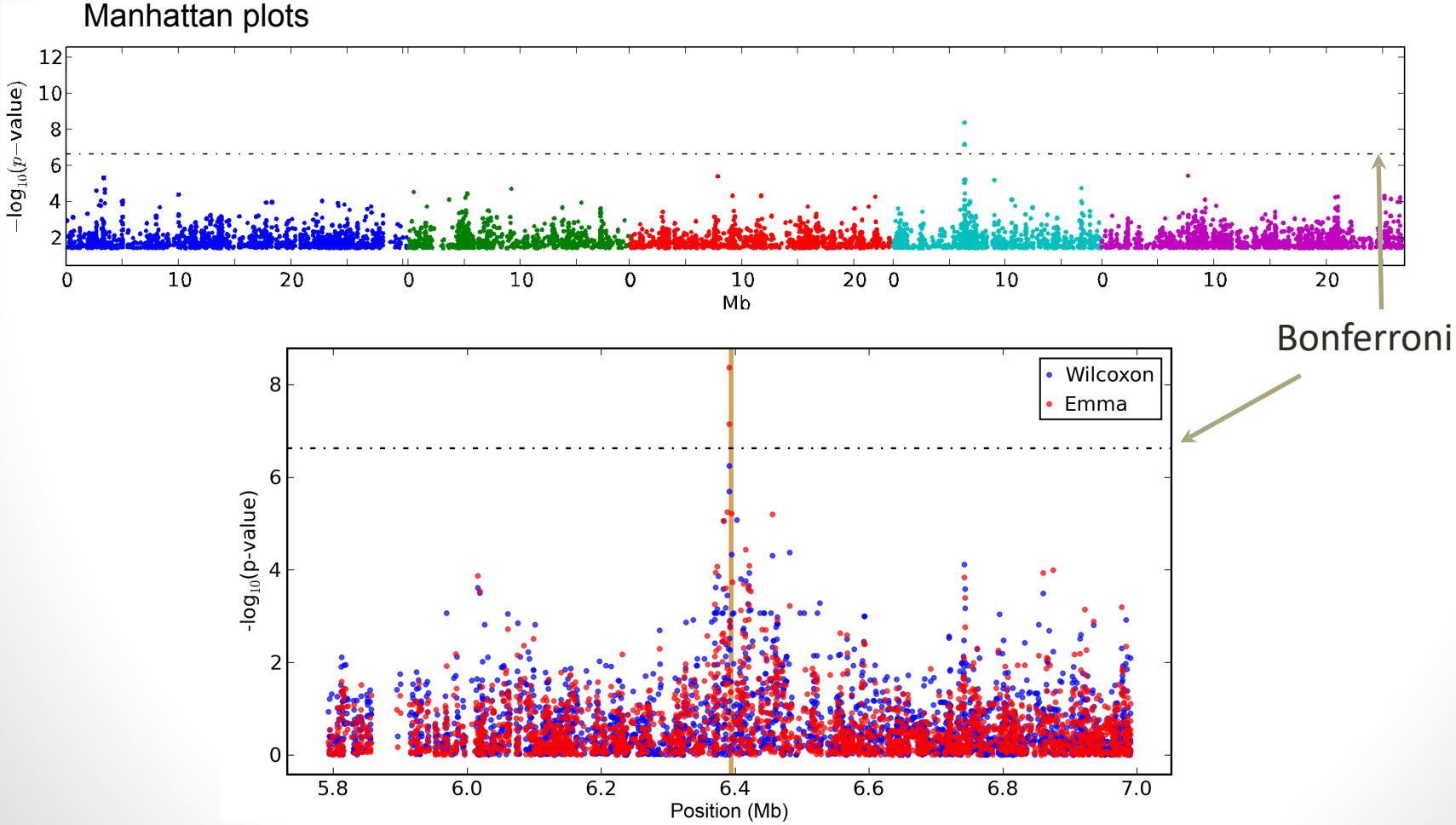
Phenotype = Genotype + Environment + GxE





A simple GWAS example

- Sodium concentration measured in *A. thaliana* leaves.



Multiple testing correction

- In GWAS a large number of marker tests are conducted, which leads to a multiple testing problem.
- Using a 5% significance threshold, we would expect 5% of the markers that have true marker effects of 0 to be significant.
- Solutions include:
  - **Bonferroni correction:** By assuming markers are independent we can obtain a conservative bound on the probability of rejecting the null hypothesis for one or more markers.

$$1 - P(T_1 \leq t, \ldots, T_m \leq t | H_0) \leq \alpha$$

for a given significance threshold α.

  - Other common methods include adjusted Bonferroni correction depending on rank, and permutations.

Multiple testing correction

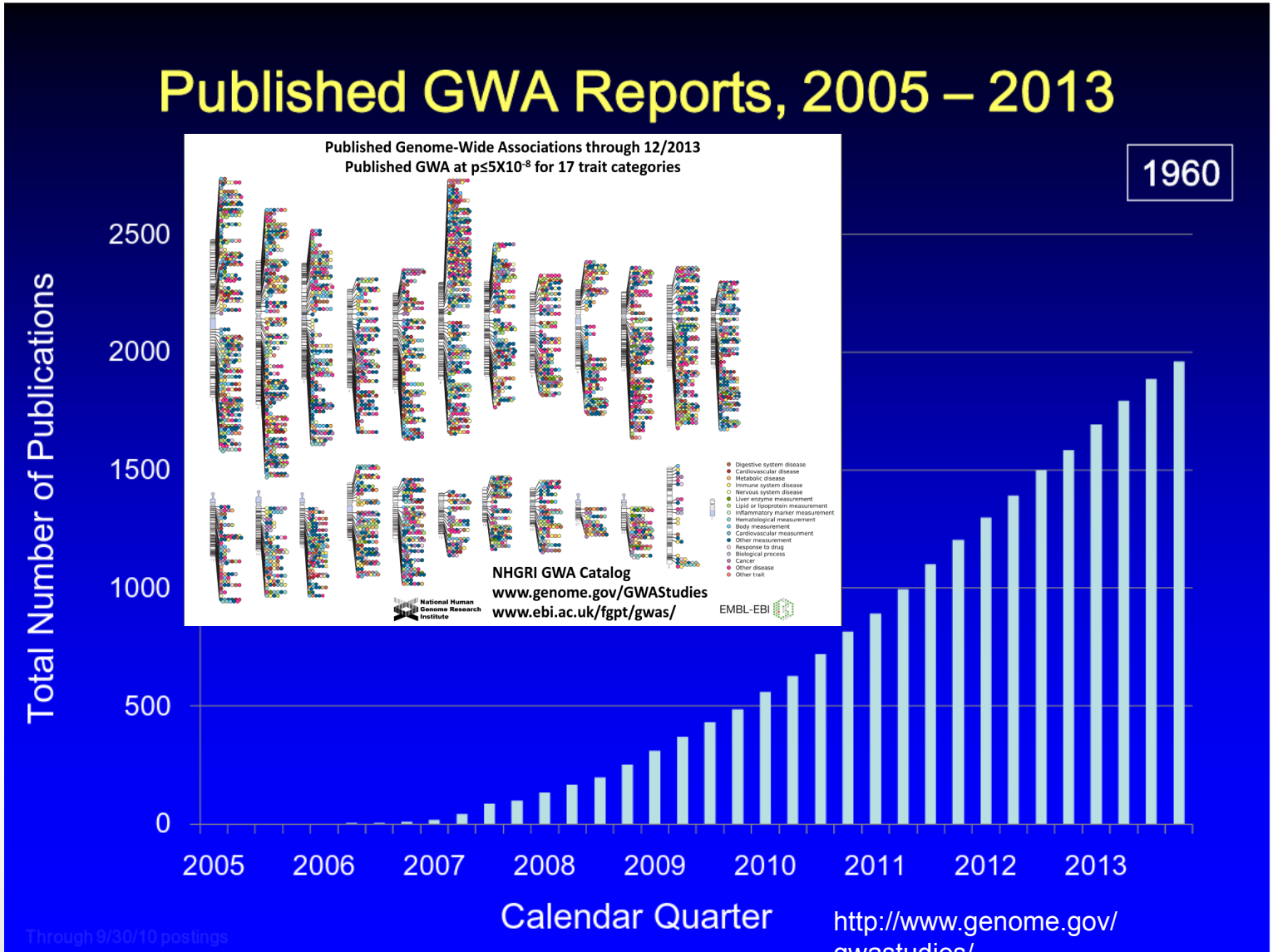
- Many SNP markers -> multiple testing problem.
- 5% of the markers with true marker effects of 0 are significant.
- Possbile solutions:
  - **Bonferroni correction:** Conservative bound on the probability of rejecting the null hypothesis for one or more markers.

$$1 - P(T_1 \leq t, \ldots, T_m \leq t | H_0) \leq \alpha$$

for a given significance threshold .

  - Other common methods include adjusted Bonferroni correction depending on rank, and permutations.

GWAS - a success story

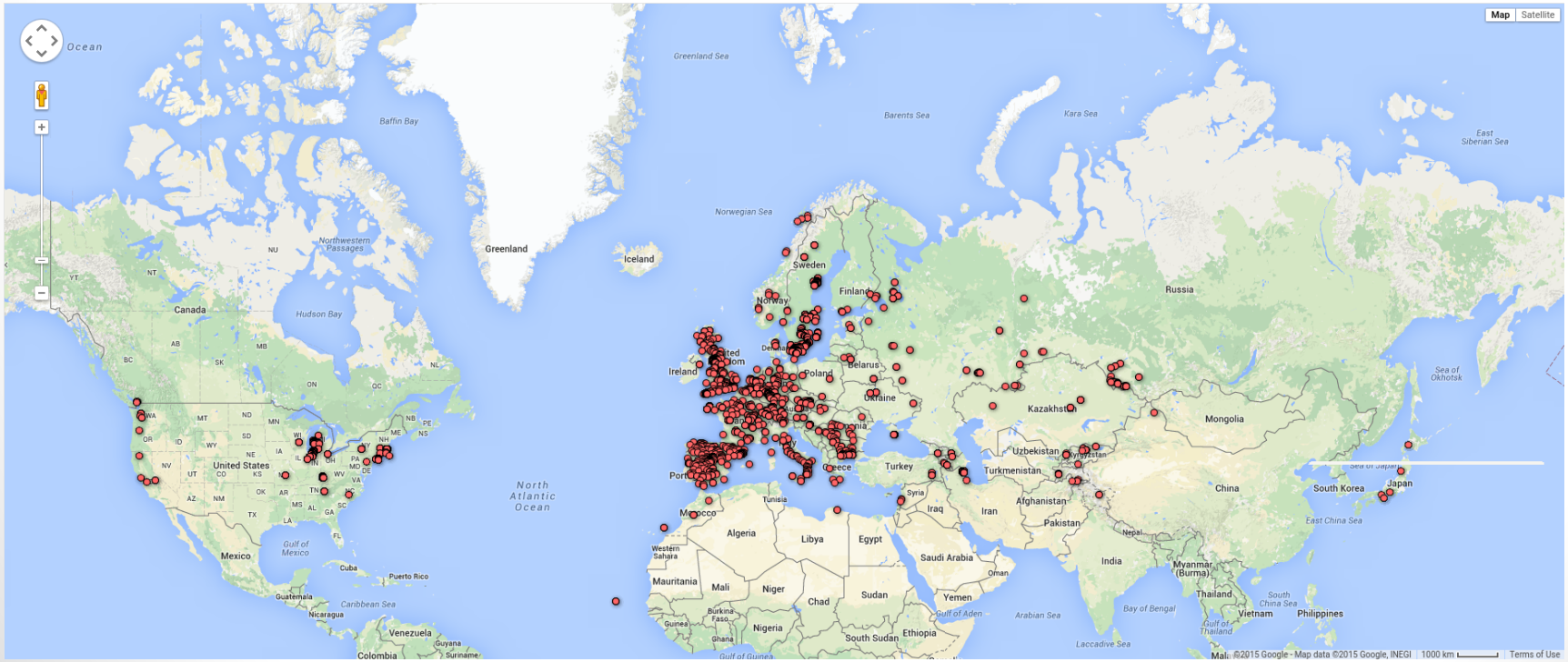


Why plants (*A. thaliana*)?

- Replicates usually available either through clonal propagation or the existence of inbred lines
- Relationship with breeding
- *A.thaliana*: the model plant
  - small size
  - rapid life cycle
  - small genome (~150 Mb, 5 Chr.)
  - inbred (self-fertilization)
  - transgenics (follow up)
  - mutant collections (follow up)

Why plants (*A. thaliana*)?
Availability of lines

- Curated information about 7522 accessions (https://goo.gl/IwGah)



Why plants (*A. thaliana*)?
Availability of genotypes

Genotyping data:

- 250k Affymetrix genotyping array (Horton *et al*., 2012)
  - 250.000 probes → after filtering 214.051 SNPs for 1307 accessions.
  - Expected resolution is pretty good (average SNP density 1 per 550 bp | LD decays on average within 10 kb. Kim *et al.*, 2007)

Full-sequence data:

- Small sets:
  - Long et al., 2013 (181 accessions)
  - Cao *et al.*, 2010 (80 accessions)
  - Schmitz *et al.*, 2013 (195 accessions)
- 1001genomes (http://the1001genomes.org):
  - Joint effort of MPI, GMI, Salk and Monsanto
  - 10 Million SNPs and 500k structural var. for 1135 accessions
  - Imputation → 2029 accessions

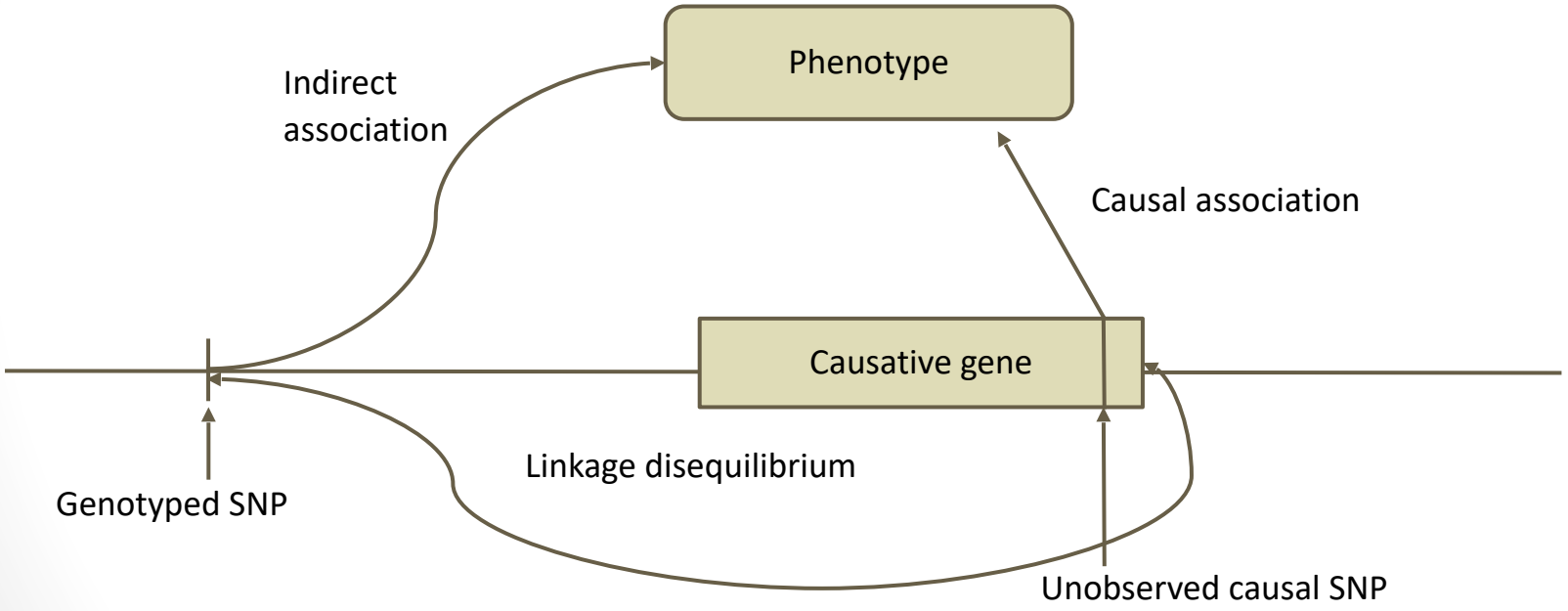
Why plants (*A. thaliana*)?
Availability of phenotypes

- Atwell *et al.*, 2010:
  - 107 phenotypes on up to 197 accessions
  - 4 categories: flowering (23), defence (23), ionomics (18), development (18)
  - https://github.com/Gregor-Mendel-Institute/atpolydb

- Other sources on larger datasets:
  - Baxter *et al.*, 2010: sodium concentration on 342 accessions.
  - Li *et al.*, 2010: flowering time for 473 accessions grown in 4 controlled environments
  - Unpublished data: flowering time, germination, leaf morphology, metabolite levels, gene expression

Linkage disequilibrium

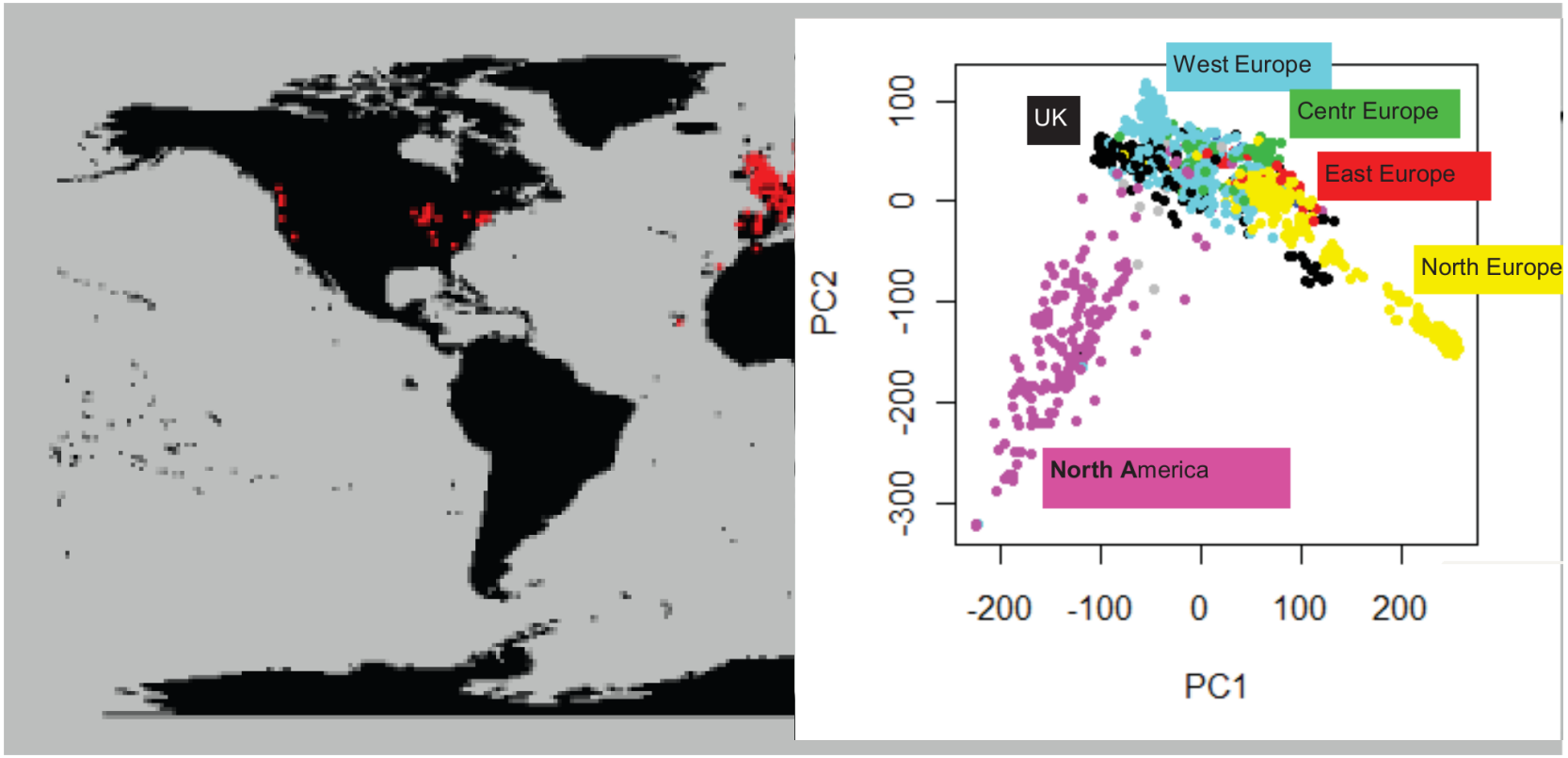
- Neighboring markers will tend to be inherited together, causing linkage disequilibrium (LD) between the two markers



- Since LD causes correlations between markers, in a given population we expect a lot of redundancy in the genotypes.

Population Structure

- Isolation by distance (Platt *et al*, 2010)
- Accessions tend to cluster in sub-populations according to their geographic origin

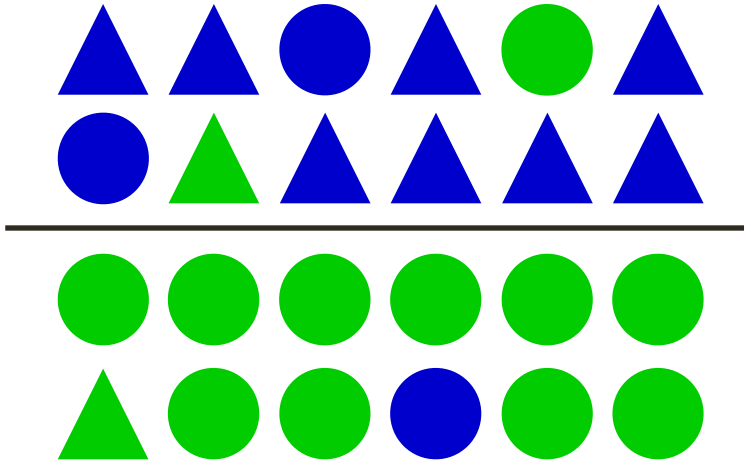


Population Structure

- Confounding due to population structure may arise if it correlates with the trait in question.

Sub-population 1

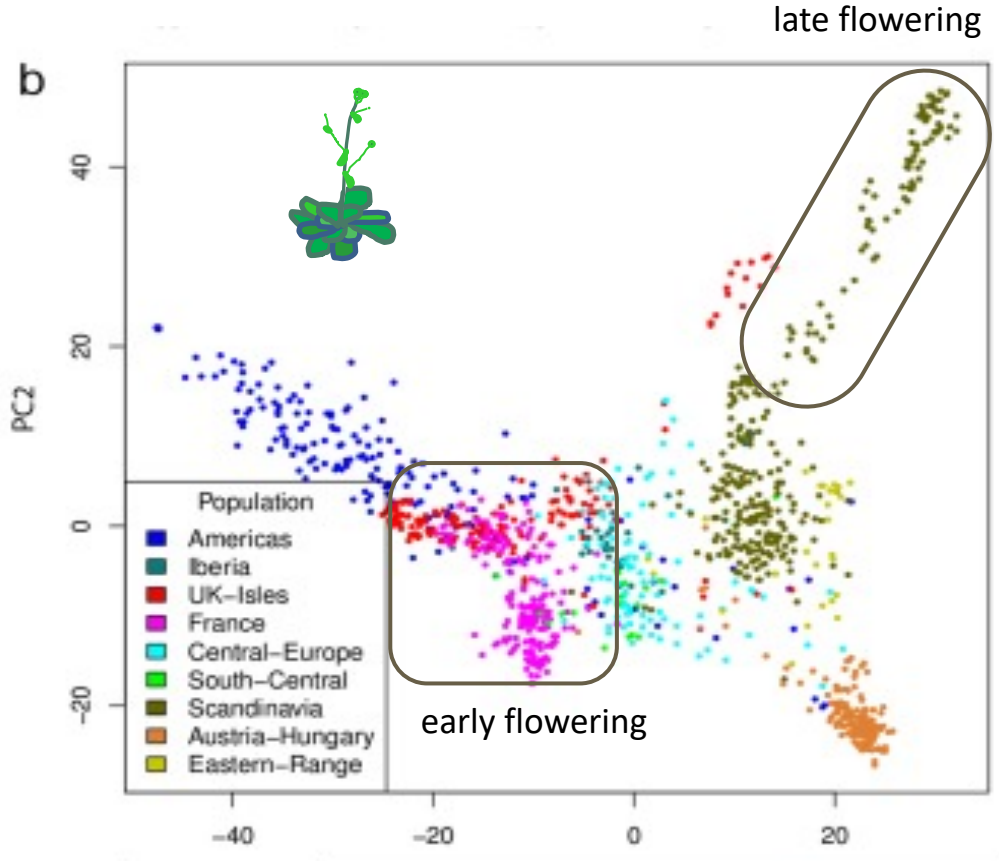
Sub-population 2



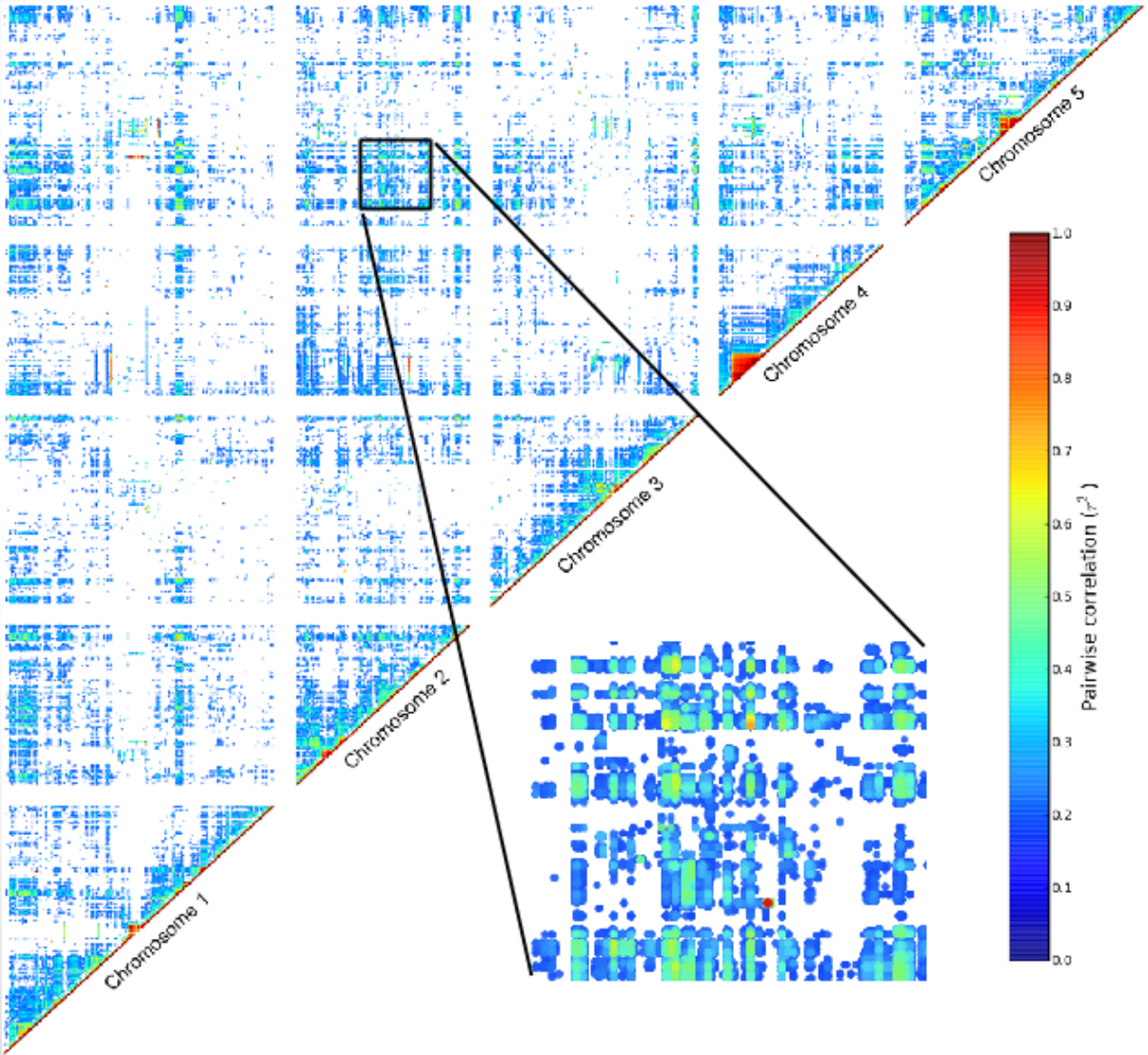
- Any variant which is fixed for different alleles in each sub-population will show an association.

Examples of Population Structure Confounding

- Humans:
  - Genetic marker for skin color might also be associated with malaria resistance because the trait is correlated with the population structure.
- *A. thaliana:*
  - Flowering time is correlated with latitude
  - Disease resistance is **NOT** correlated with population structure



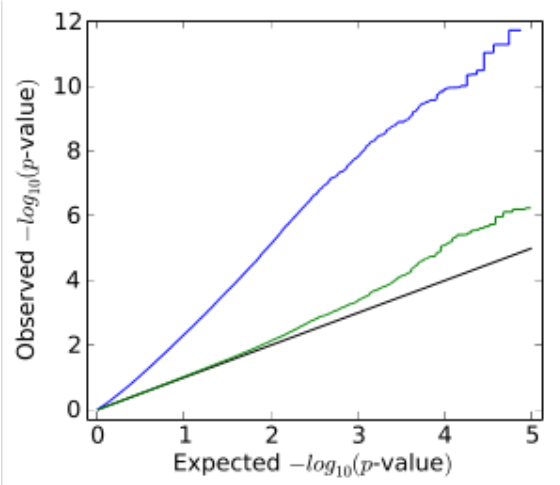
Population Structure is reflected in long range LD.

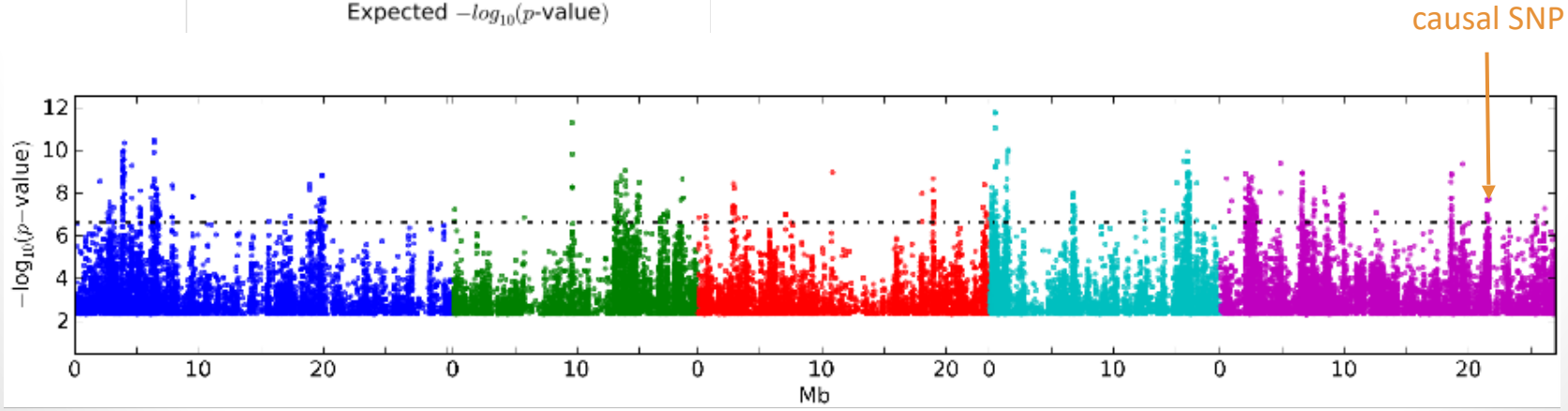


Linkage disequilibrium in *A. thaliana*, 214K SNPs and 1307 accessions.

Implication for Association Studies

- Test statistic is inflated
- High false positive rate





Association mapping in structured populations

- **Genomic contro**l**:** Scale down the test-statistic so that its median becomes the expected median. Heavily used, but does not solve the problem (Devlin & Roeder 1999, Biometrics)!
- **Structured association** (Pritchard et al. 2000, Am.J.Hum.Genet.)
- **PCA approach:** Accounting for structure using the first **n** principle components of the genotype matrix (Price *et al.*, 2006). However when population structure is very complex, e.g. in *A. thaliana*, too many PCs are needed.
- **Mixed Model approach:** Model the genotype effect as a random term in a mixed model, by explicitly describing the covariance structure between the individuals (Yu et al. 2006, Nature Genet.; Kang et al. 2008, Genetics).

Linear Model, Non-parametric test, Linear Mixed Model, Advanced Linear Mixed Models & Caveats & Problems

GWAS Methods

Linear Model (LM)

A linear model generally refers to linear regression models in statistics.

$$y_j = \sum_{j=1}^{P} \beta_j x_{ij} + \epsilon_i \qquad Y = X'\beta + \epsilon$$

- **Y** typically consists of the phenotype values, or case-control status for **N** individuals.
- **X** is the **N**x**P** genotype matrix, consisting of **P** genetic variants (e.g. SNPs).
- **β** is a vector of P effects for the genetic variants.
- **ϵ** is still just known as the *noise* or *error* term.

Linear Mixed Model (LMM)

- Linear model and Non-parametric tests don't account for population structure

$$Y = X\beta + u + \epsilon, \quad u \sim N(0, \sigma_g K), \quad \epsilon \sim N(0, \sigma_e I)$$

- Initially proposed in association mapping by Yu et al. (2006)
- **Y** typically consists of the phenotype values, or case-control status for N individuals.
- **X** is the **N**x**P** genotype matrix, consisting of **P** genetic variants (e.g. SNPs).
- **u** is the random effect of the mixed model with var(u) = σ g K
- **K** is the **N** x **N** kinship matrix inferred from genotypes
- **β** is a vector of **P** effects for the genetic variants.
- **ϵ** is a **N** x **N** matrix of residual effects with var(ε) = σ e I

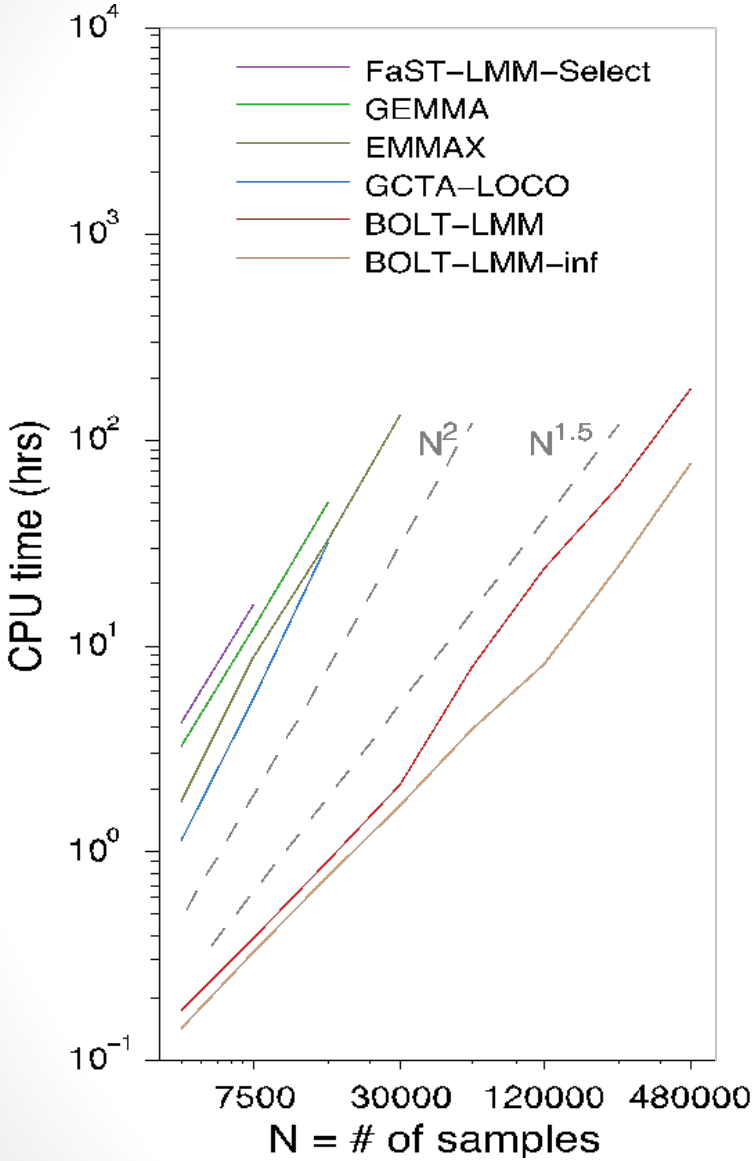
Kinship

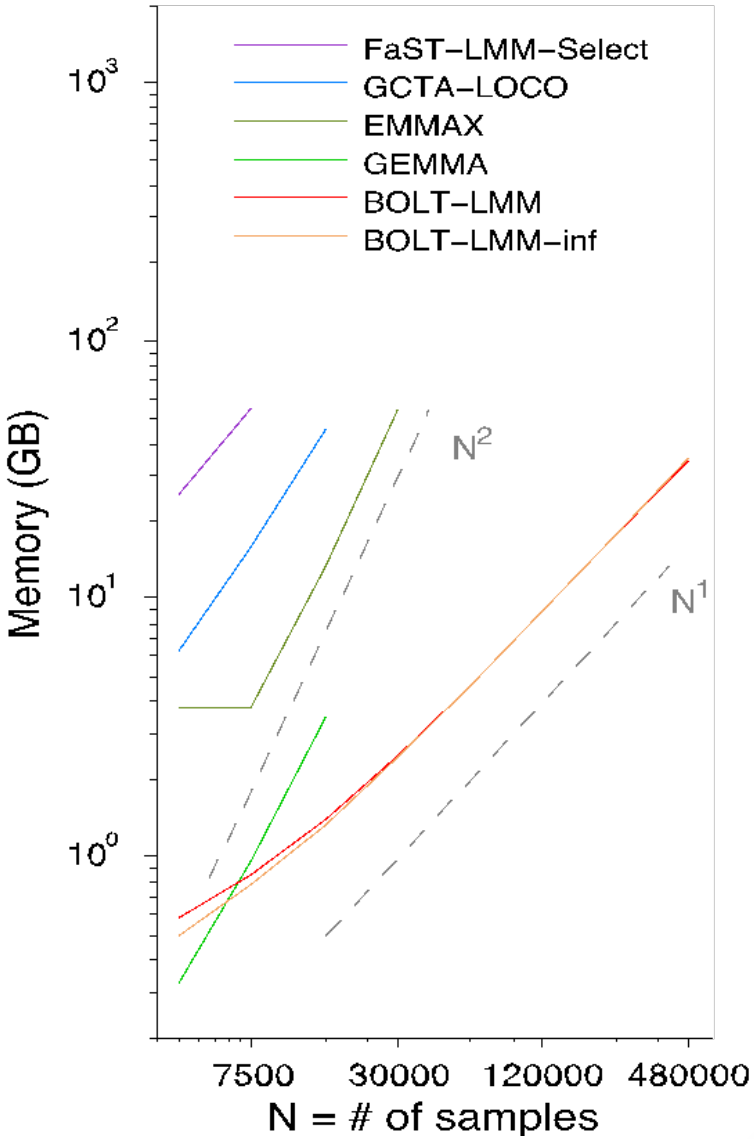
- The kinship measures the degree of relatedness, and is in general different from the covariance matrix.
- It is estimated using either pedigree (family relationships) data or (lately) using genotype data.
  - When estimating it from pedigree data, one normally assumes that the ancestral founders are “unrelated”.
  - They are sensitive to confounding by cryptic relatedness.
- Alternatively the kinship can be estimated from genotype data.
  - Genotype data may be incomplete.
  - Weights or scaling of genotypes can impact the kinship.
- *A. thaliana* using an IBS matrix works pretty well (Zhao *et al.*, 2007, Atwell *et al.*, 2010)

Linear Mixed Model (LMM)

- Original implementation: EMMA (Kang *et al.*, 2008)
  - Problem: $O(PN^3)$ → 1 GWAS in 1 day (500k individuals)
- Approximate methods $O(PN^2)$:
  - GRAMMAR (Aulchenko *et al.*, 2007) http://www.genabel.org/packages/GenABEL
  - P3D (Zhang *et al.*, 2010) http://www.maizegenetics.net/#!tassel/c17q9
  - EMMAX (Kang *et al.*, 2010) http://genetics.cs.ucla.edu/emmax/
- Exact methods:
  - FaST LMM (Lippert *et al.*, 2011) http://mscompbio.codeplex.com/
  - GEMMA (Zhou *et al.*, 2012) http://www.xzlab.org/software.html
- This is too slow for large samples (>20000 individuals), i.e. exactly the sample sizes where one might expect to see most gains.
  - BOLT-LMM (Loh *et al.*, 2015), **O(PN)** https://data.broadinstitute.org/alkesgroup/BOLT-LMM/?

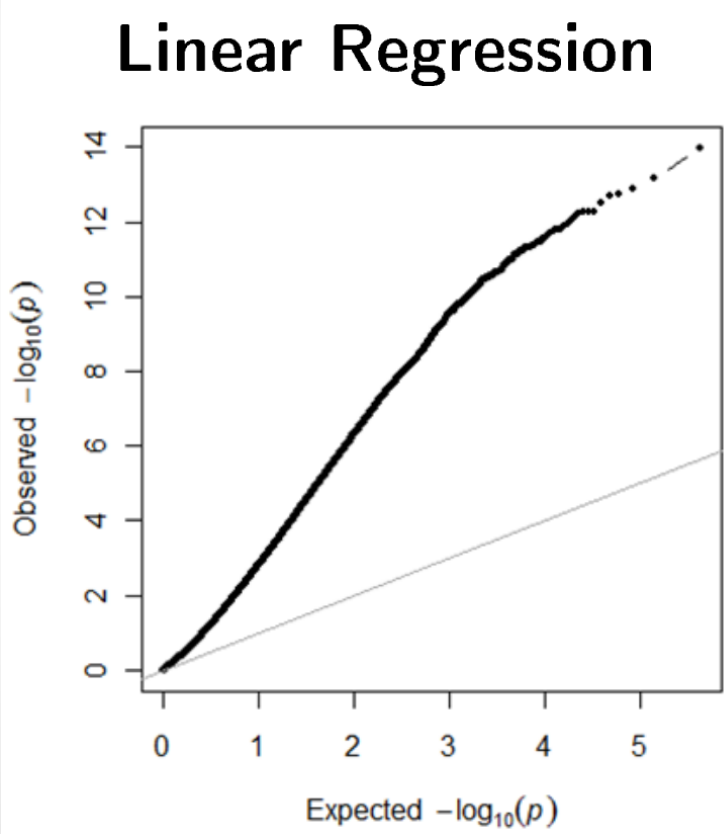
BOLT-LMM

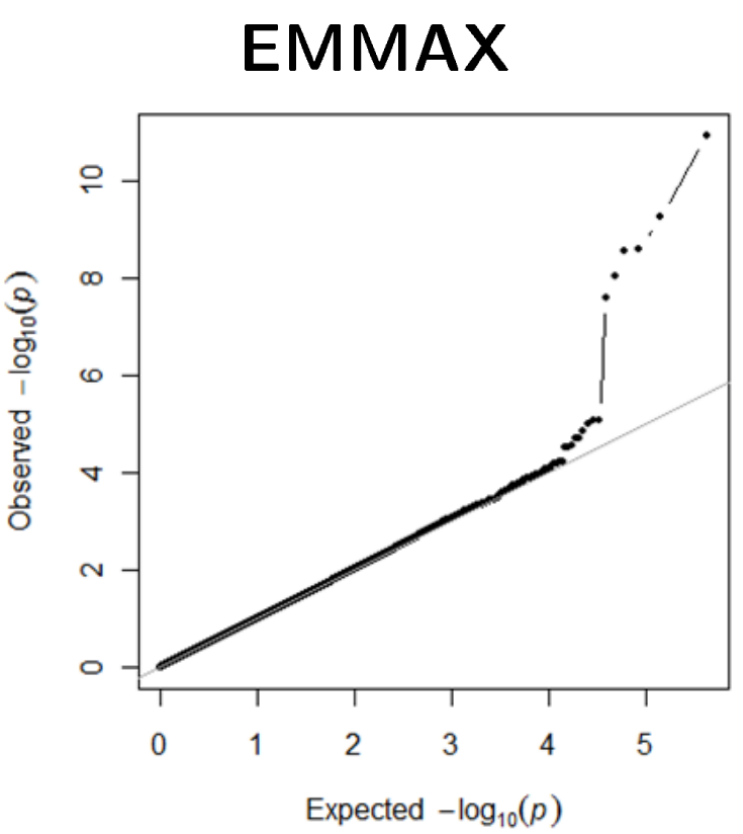




Po-Ru Loh *et al.* (Nat Genet 2015)

LMM reduces test statistic inflation

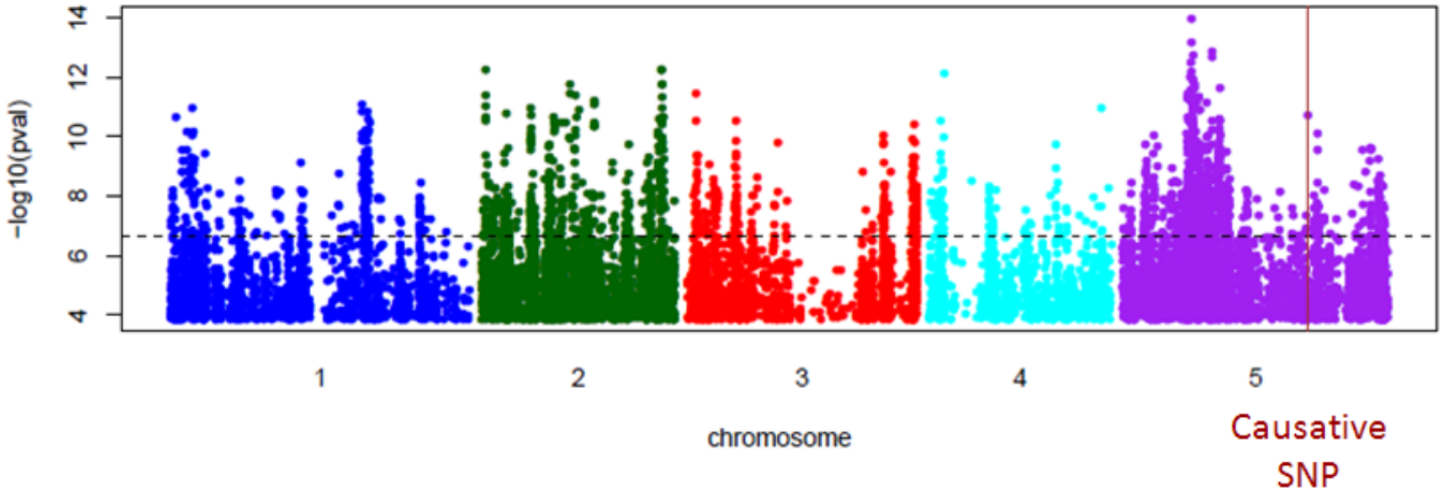




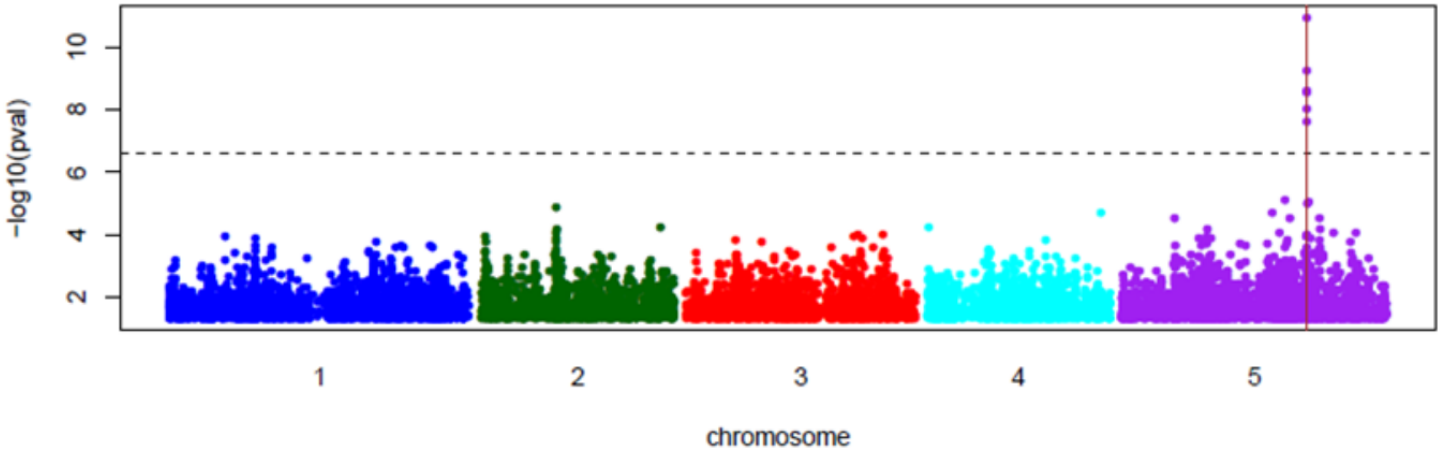
LMM reduces false positive rate

GWAS for a simulated phenotype

Linear Regression



EMMAX



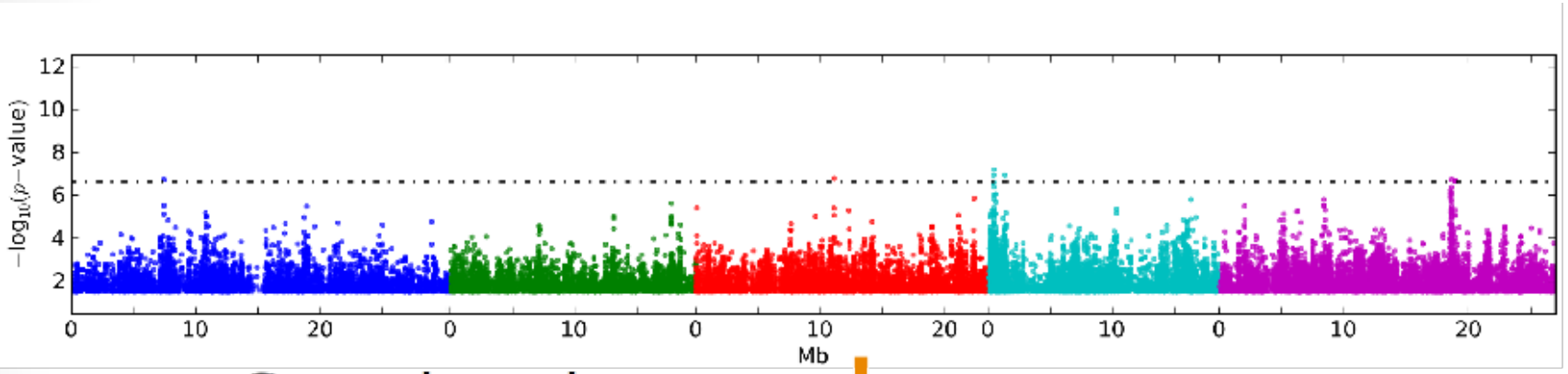
Advanced Mixed Models

The mixed-model performs pretty well, but GWAS power remain limited and need to be improved:

- **M**ulti **L**ocus **M**ixed **M**odel (MLMM, Segura *et al.*, 2012):
  - Single SNP tests are wrong model for polygenic traits
  - Increase in power compared to single locus models
  - Detection of new associations in published datasets
  - Identification of particular cases of (synthetic associations) and/or allelic heterogeneity
- **M**ulti **T**rait **M**ixed **M**odel (MTMM, Korte *et al.*, 2012):
  - Traits are often correlated due to **pleiotropy** (shared genetics) or **linkage** between causative polymorphisms.
  - Combining correlated traits in a single model should thus increase detection power
  - When multiple phenotypes consists in a single trait measure in multiple environments, **plasticity** can be studies through the assessment of GxE interaction

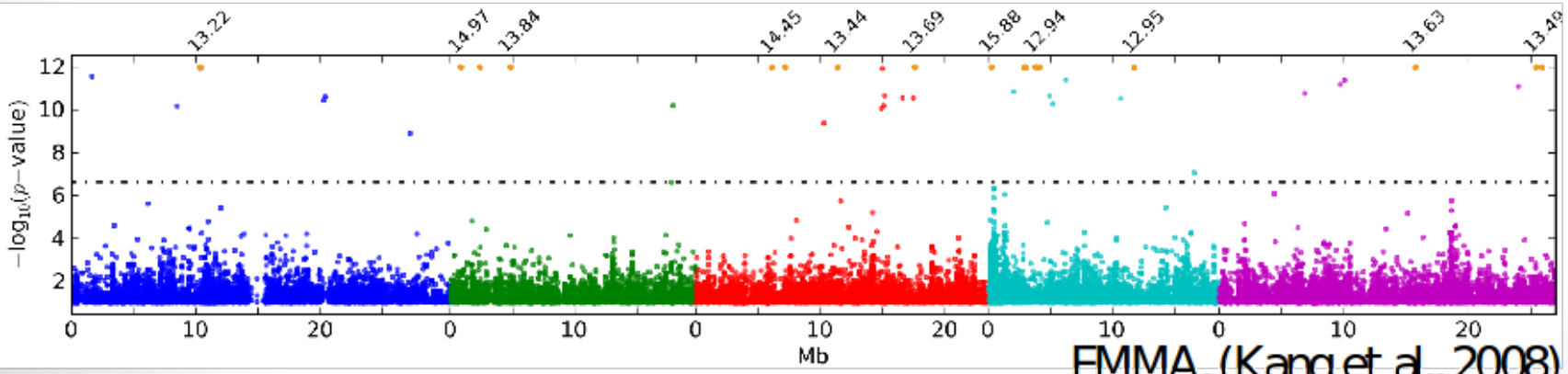
Caveats & Problems

Accounting for population structure does not alway work:



Wilcoxon rank sum test

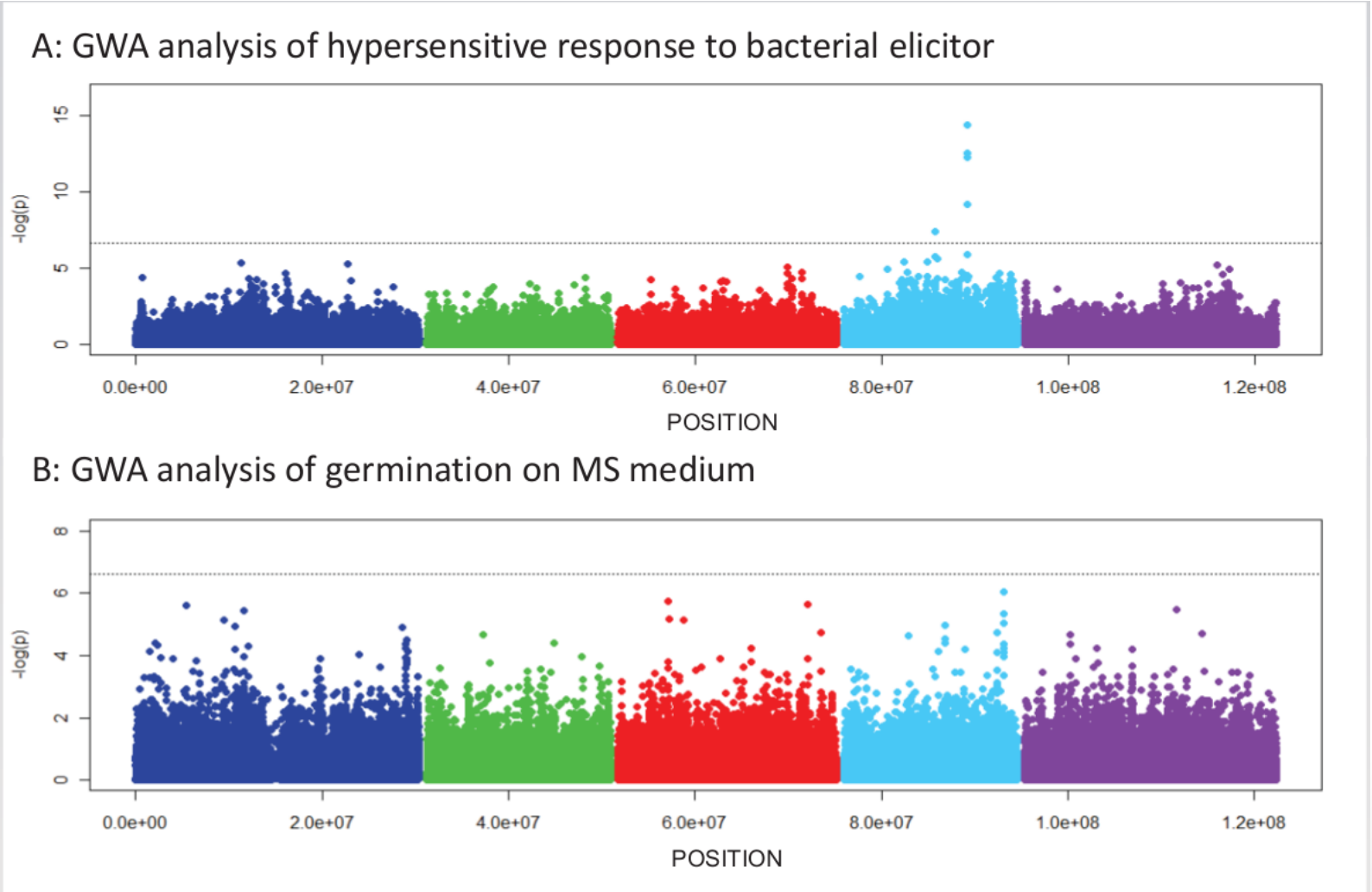
Sometimes it doesn't



EMMA, (Kang et al., 2008)

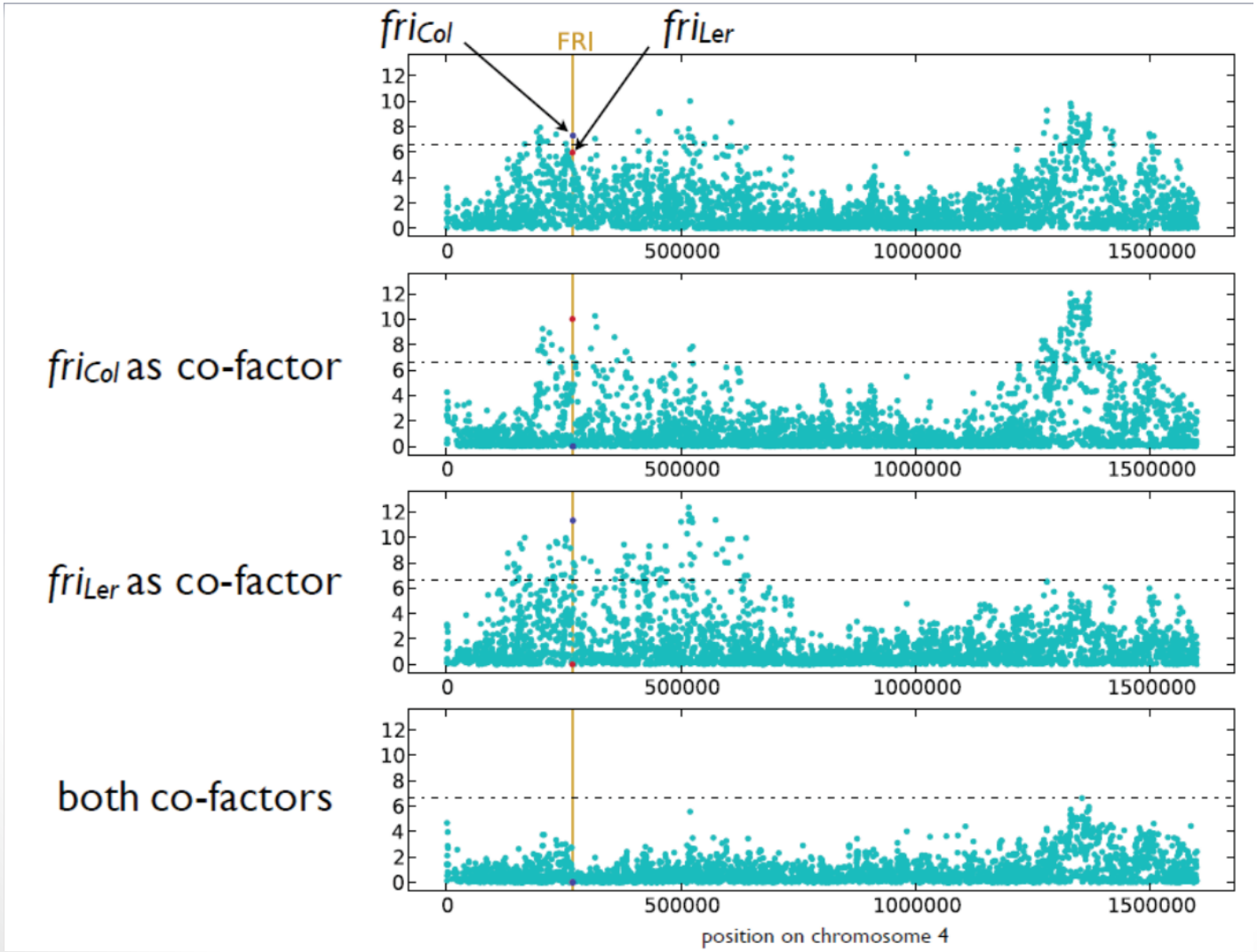
Caveats & Problems

Difficult to decide which peaks are significant (Solution: permutation)



Caveats & Problems

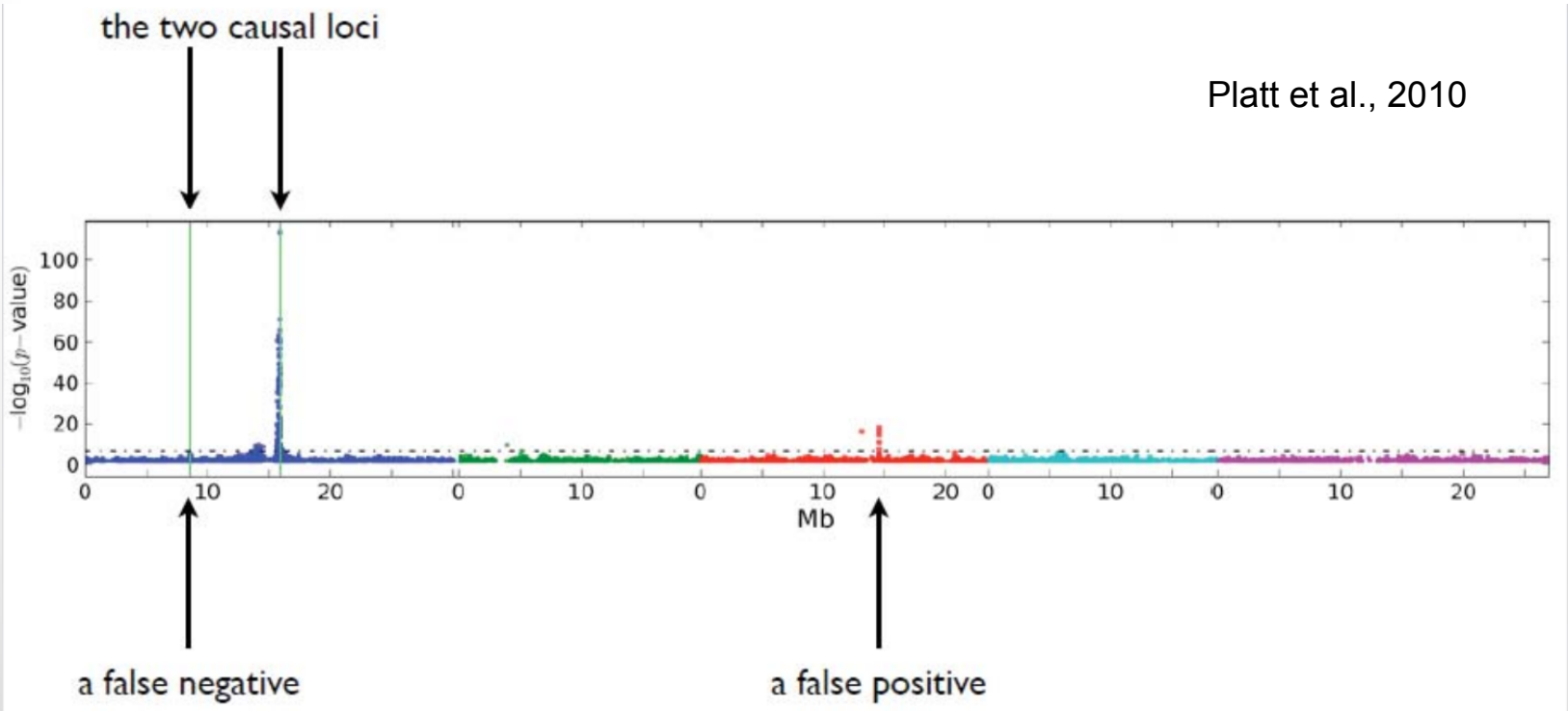
Peaks are complex and make it difficult to pinpoint causative site



Caveats & Problems

Condition under which GWAS will be positively misleading:

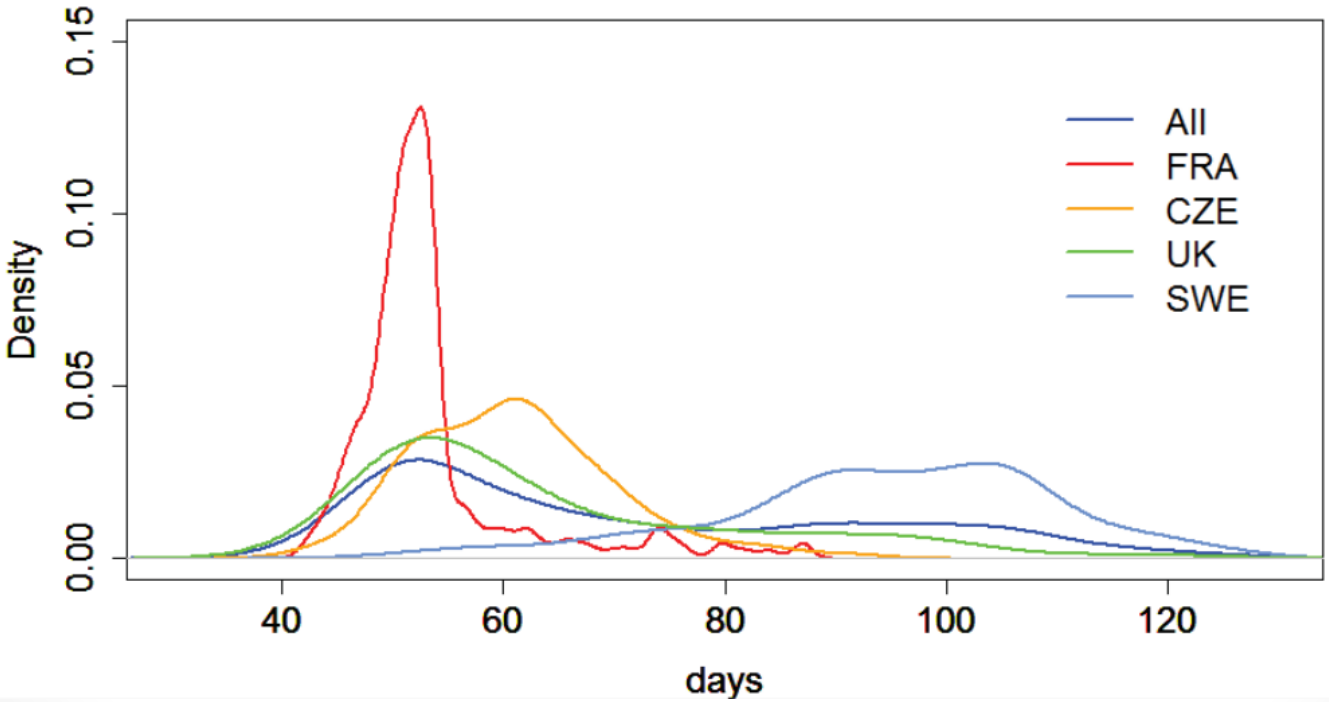
- Correlation between causal factors and unlinked non-causal markers
- More than one causal factor
- Epistasis



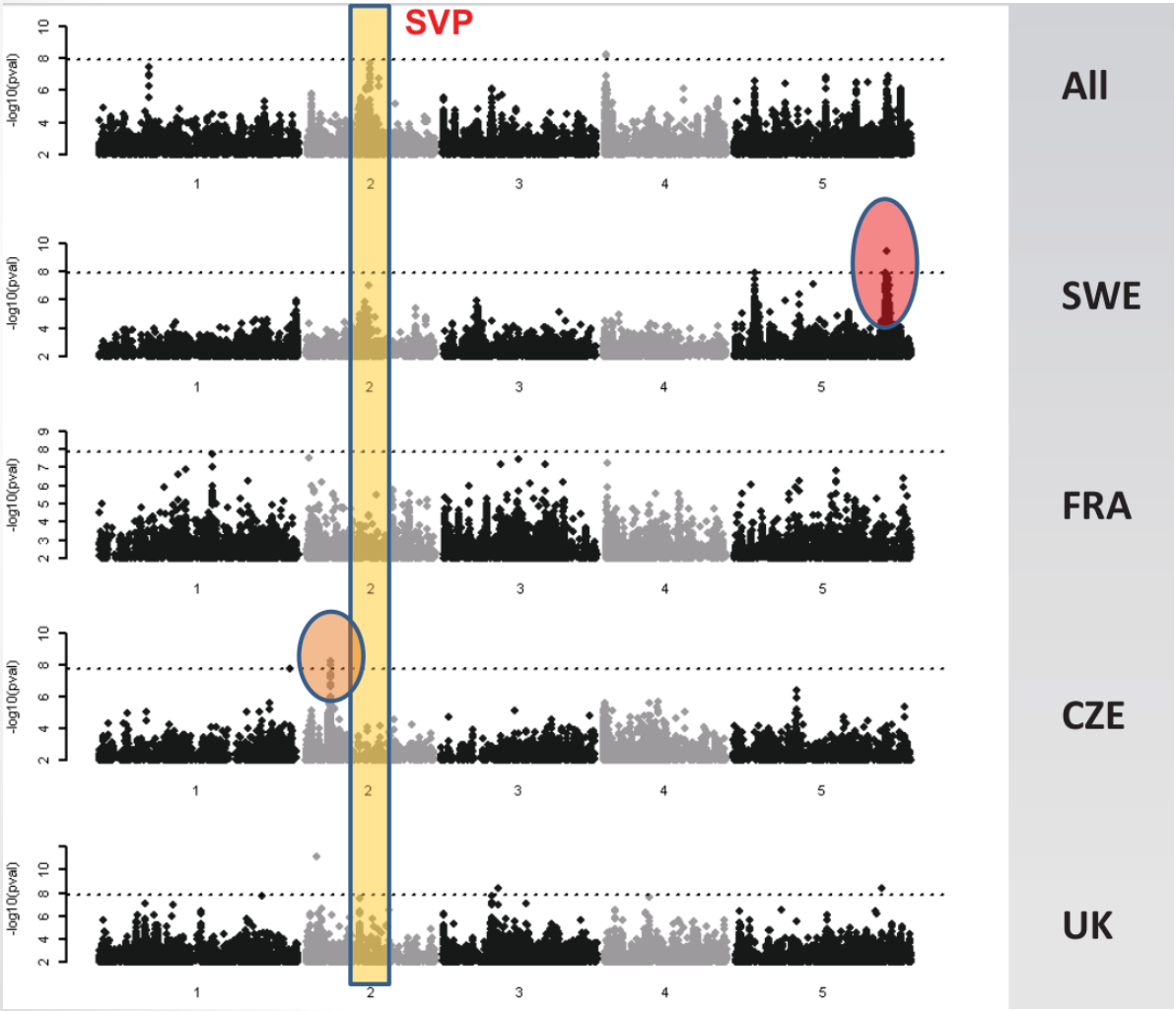
Caveats & Problems

Different associations for different subsets (i.e. Flowering time at 10 °C

- Highly heritable, easy to measure, polygenic trait
- 925 worldwide accessions
- Flowering time greatly varies in different populations



Caveats & Problems



Significance and effect size differ dramatically in different subsets

Reasons:

- False positives
- Effect depends on genetic background (Epistasis)
- Differences in allele frequency of the causal marker
- Artefact of LMM

Caveats & Problems

Korte and Farlow *Plant Methods* 2013, **9**:29
http://www.plantmethods.com/content/9/1/29

PLANT METHODS

REVIEW Open Access

The advantages and limitations of trait analysis with GWAS: a review

Arthur Korte*† and Ashley Farlow†

Abstract

COMMENT

The nature of confounding in genome-wide association studies

Bjarni J. Vilhjálmsson[1,2] and Magnus Nordborg[3,4]

The authors argue that population structure per se is not a problem in genome-wide association studies — the true sources are the environment and the genetic background, and the latter is greatly underappreciated. They conclude that mixed models effectively address this issue.

Thanks to dramatically decreasing genotyping and sequencing costs, genome-wide association studies (GWASs) are becoming the default method for studying the genetics of natural variation. The increasing number and diversity of GWASs will require appropriate statistical analysis methods. The most basic problem is assessing the significance of an association in the light of confounding effects that may cause spurious associations.

The aspect of this problem that has received the most attention is the danger of false positives in structured populations. If the study population is a mixture of populations that differ with respect to allele frequencies as well as the trait of interest, spurious correlations in 'unrelated' individuals. Variation in relatedness is a basic property of natural populations, as is correlation between causative loci. This issue is familiar to quantitative geneticists[5] but has not been widely appreciated in other fields. It is important for GWASs and will become crucial as sample sizes increase.

To demonstrate this, let us return to the chopstick example but fast-forward to the era of millions of SNPs. Genetic differentiation between East Asians and other populations means that vast numbers of markers in addition to *HLA-A1* would be associated with chopstick skill. These markers would also be correlated with *HLA-A1*, with each other and with any trait (genetic or not) that

Review Highly accessed

Genome-wide association studies in plants: the missing heritability is in the field

Benjamin Brachi, **Geoffrey P Morris** and **Justin O Borevitz***

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Genome Biology 2011, **12**:232 doi:10.1186/gb-2011-12-10-232

The electronic version of this article is the complete one and can be found online at:
http://genomebiology.com/2011/12/10/232

Published: 28 October 2011

Abstract

Genome-wide association studies (GWAS) have been even more successful in plants than in humans. Mapping approaches can be extended to dissect adaptive genetic variation from structured background variation in an ecological context.

Examples of GWAS in PGR

nature genetics

ARTICLES

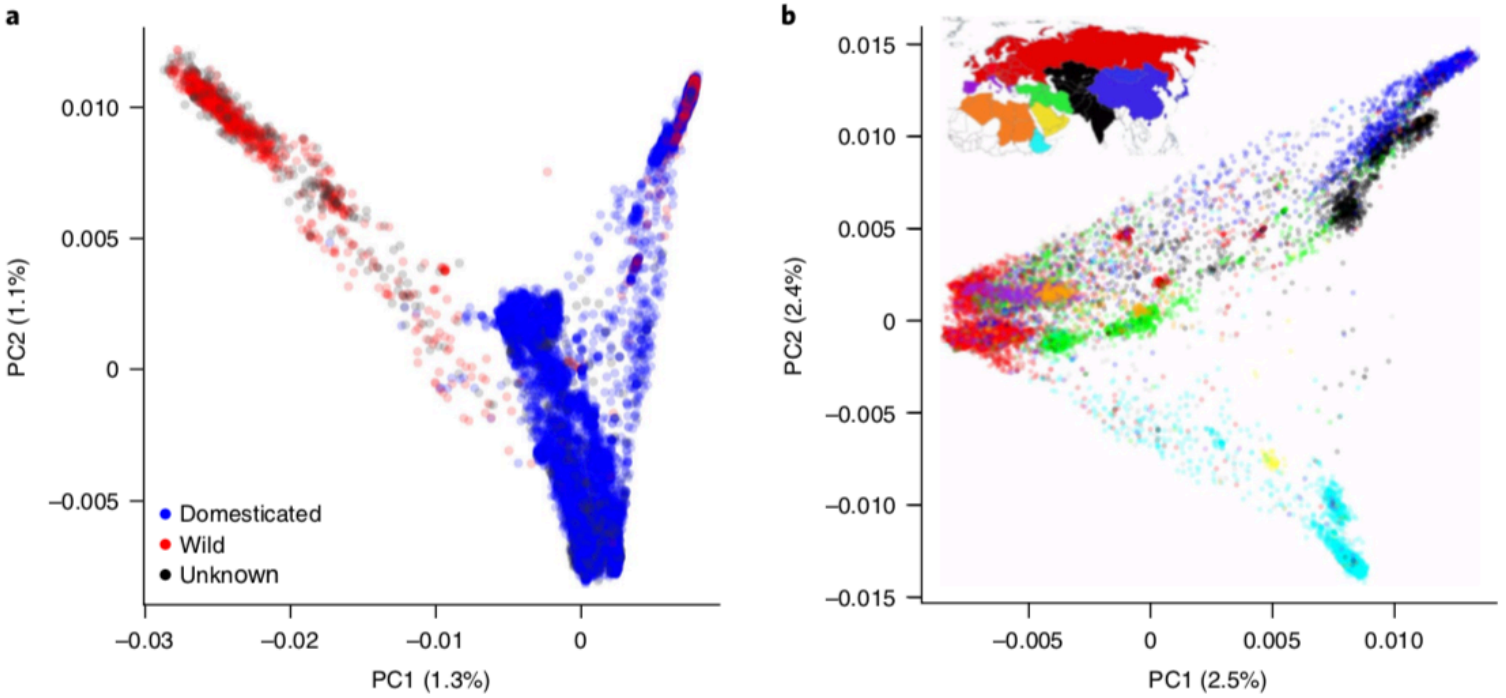
https://doi.org/10.1038/s41588-018-0266-x

Genebank genomics highlights the diversity of a global barley collection

Sara G. Milner[1,12], Matthias Jost[1,9,12], Shin Taketa[2], Elena Rey Mazón[1], Axel Himmelbach[1], Markus Oppermann[1], Stephan Weise[1], Helmut Knüpffer[1], Martín Basterrechea[1], Patrick König[1], Danuta Schüler[1], Rajiv Sharma[1,10], Raj K. Pasam[1,11], Twan Rutten[1], Ganggang Guo[3], Dongdong Xu[3], Jing Zhang[3], Gerhard Herren[4], Thomas Müller[4], Simon G. Krattinger[4,5], Beat Keller[4], Yong Jiang[1], Maria Y. González[1], Yusheng Zhao[1], Antje Habekuß[6], Sandra Färber[6], Frank Ordon[6], Matthias Lange[1], Andreas Börner[1], Andreas Graner[1], Jochen C. Reif[1], Uwe Scholz[1], Martin Mascher[1,7*] and Nils Stein[1,8*]

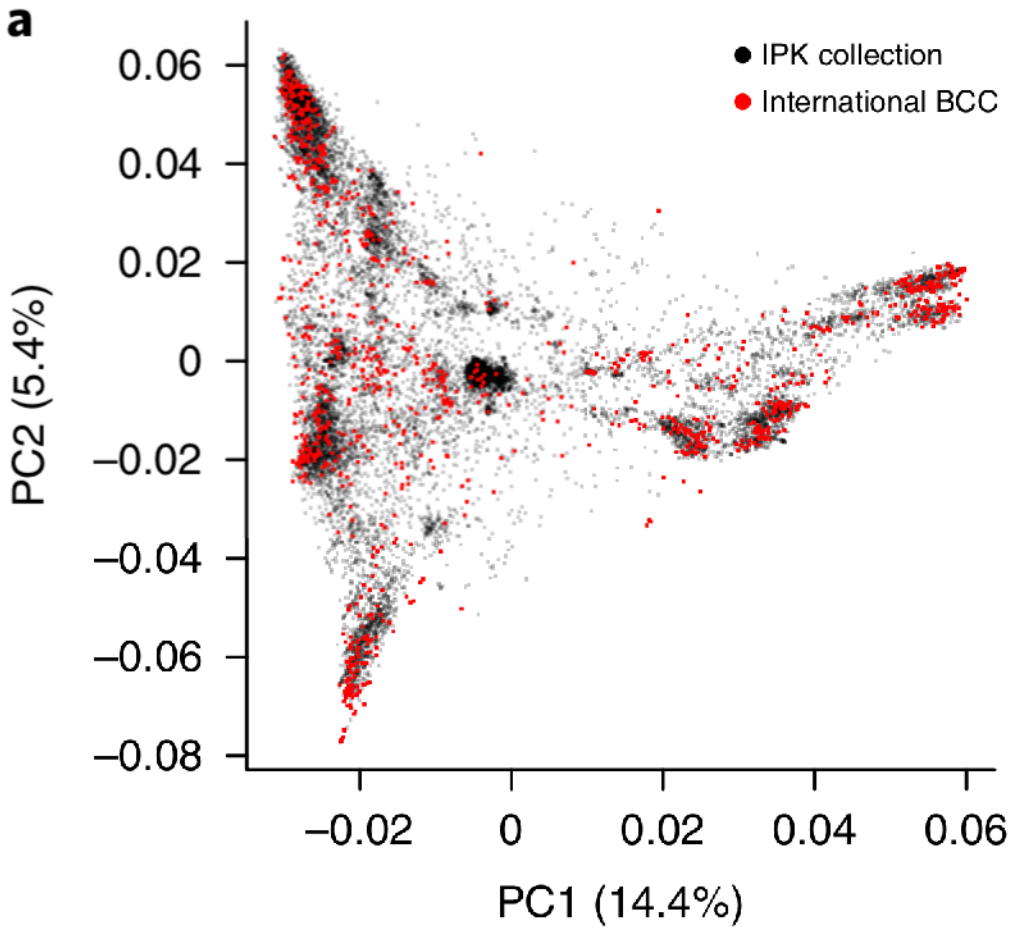
Table 1 | Number of segregating SNPs detected by GBS in wild and domesticated barley samples

	Number of SNPs	SNPs with MAF ≥ 1%	SNPs with MAF ≥ 5%
All samples ($n = 22,626$)	171,263	23,908	15,683
Domesticated barleys ($n = 19,778$)	76,102	22,356	15,872
Wild barleys ($n = 1,140$)	127,408	46,392	20,511



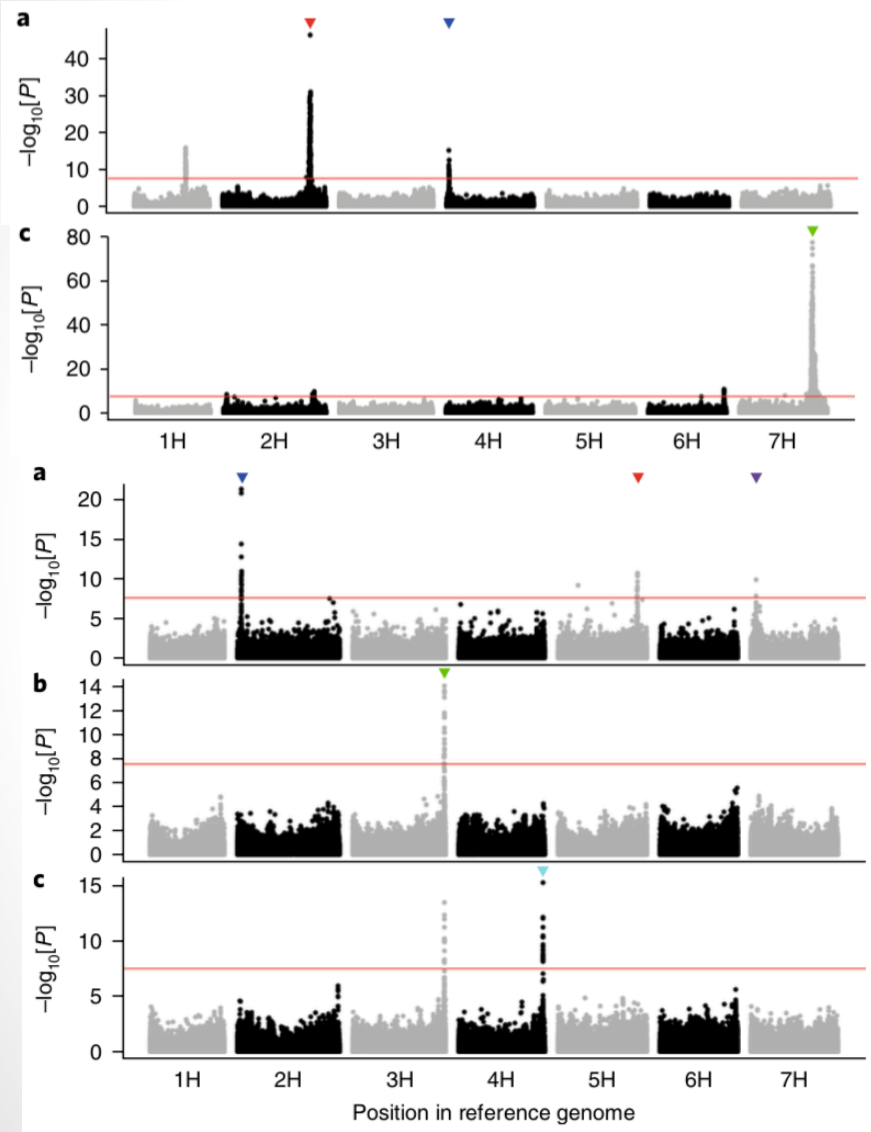
Milner et al., Nature Genetics (2019)

Comparison of IPK with International Barley Core collection



Milner et al., Nature Genetics (2019)

Large-scale GWAS study



Domestication genes:

Row type genes

Hull adherence gene

Agronomic genes:

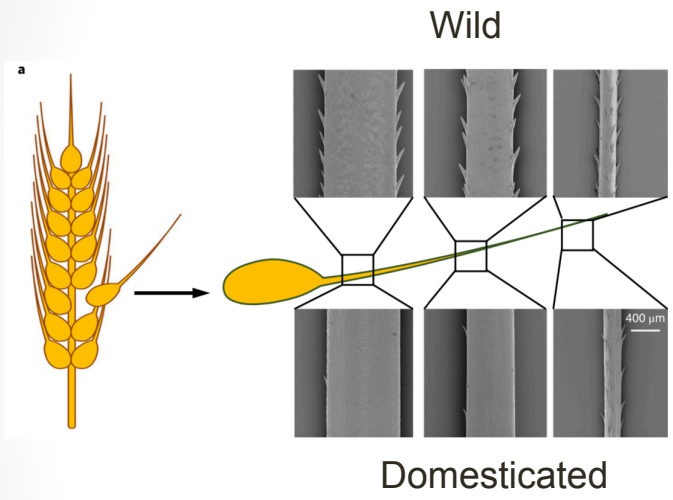
Flowering time genes

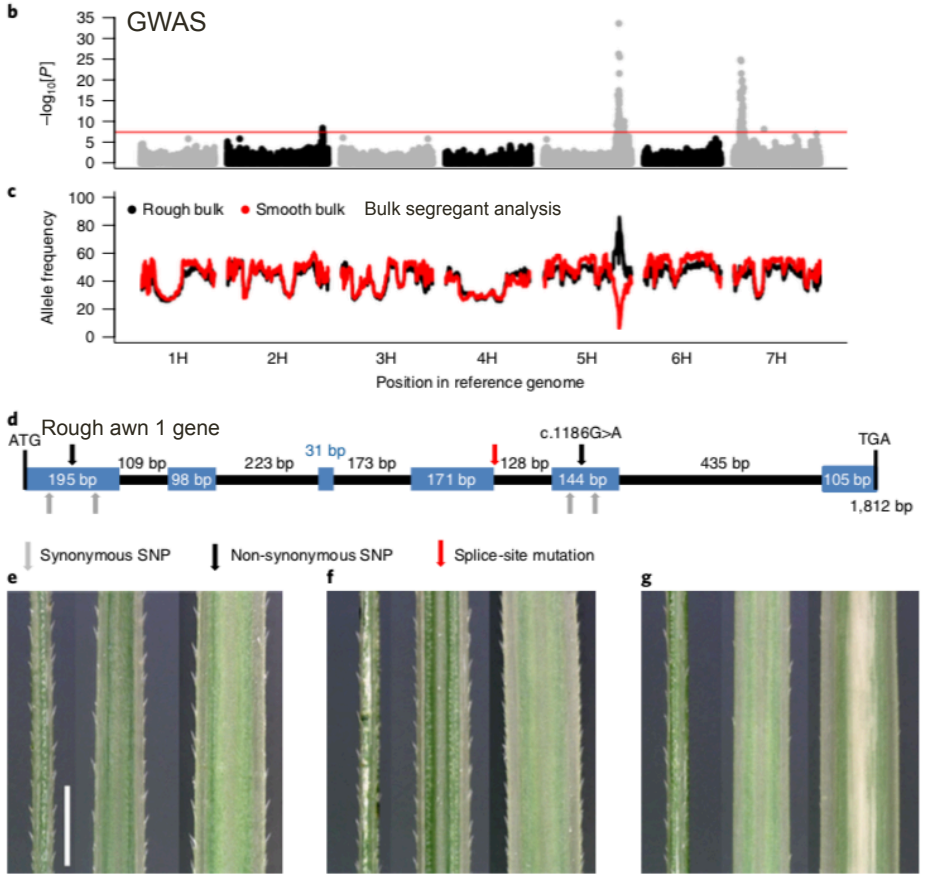
Disease resistance gene

Disease resistance gene

Milner et al., Nature Genetics (2019)

Mapping of novel genes: Awn roughness

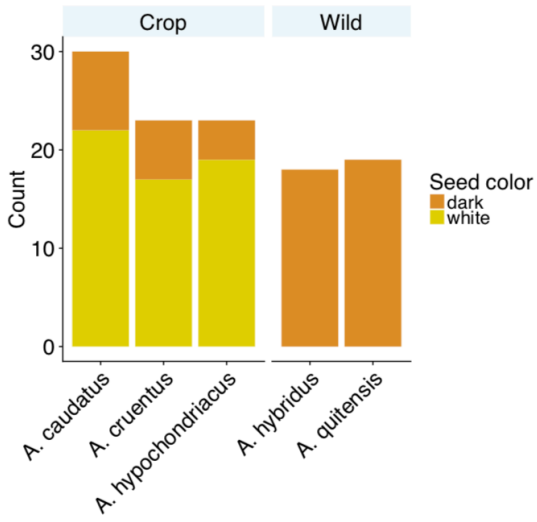




Validation by mutagenesis

Milner et al., Nature Genetics (2019)

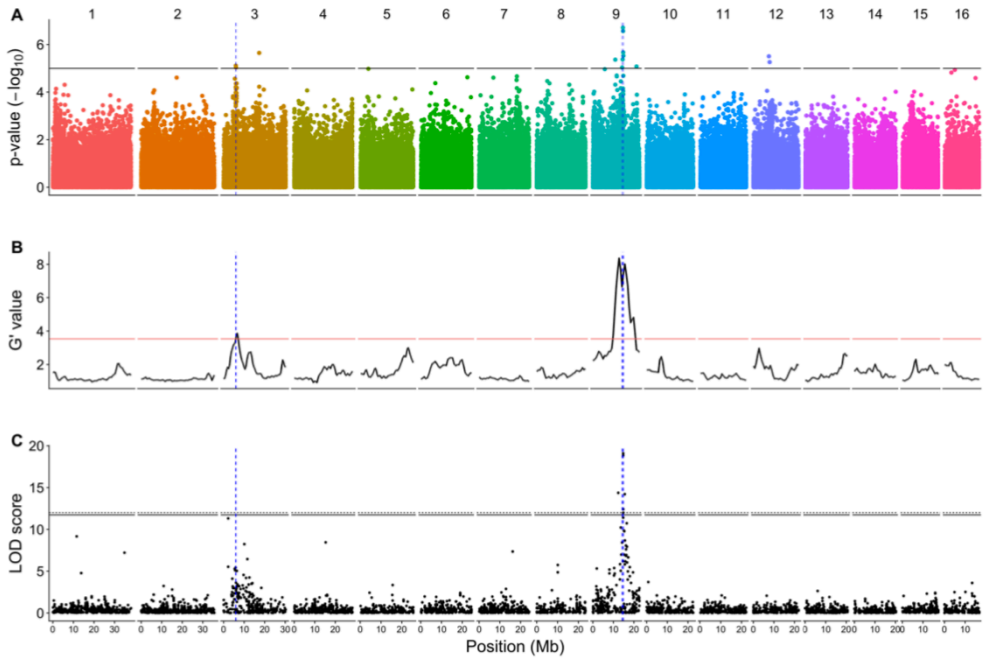
Seed color in Amaranth



GWAS

BSA

QTL



Parallel Seed Color Adaptation during Multiple Domestication Attempts of an Ancient New World Grain

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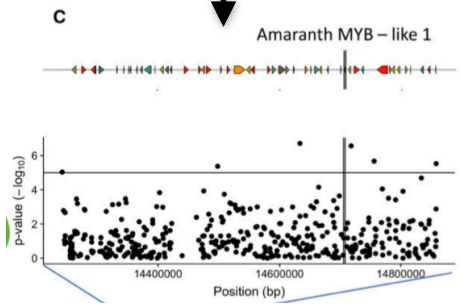

Stetter et al., Mol. Biol. Evol. (2020)

Summary

- GWAS is a powerful tool to understand the genetics of natural variation.
- Methods are fast enough to do GWAS on big sample sizes in reasonable time
- Population structure confounding can cause issues
  - Linear Mixed Model can help address this issue
- BUT GWAS is not without challenges to be aware of
  - Epistatic interaction
  - Allelic heterogeneity
  - GWAS on sub-samples
  - …
- Web-based tools like GWA-Portal allow to mine the GWAS data, look at the information from different perspectives and uncover previously unknown pleiotropic effects.

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