BIS180L

Genome-Wide Association Mapping

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Association Mapping

- Goals
  - find genes associated with diseases or other traits
  - assess relative risk based on genotype (personalized medicine)

- Association mapping
  - look at associations at a few loci (you have *a priori* candidates)

- Genome Wide Association Mapping (GWAS)
  - scan the whole genome for associations

- Takes advantage of historical recombination

Many GWAS publications

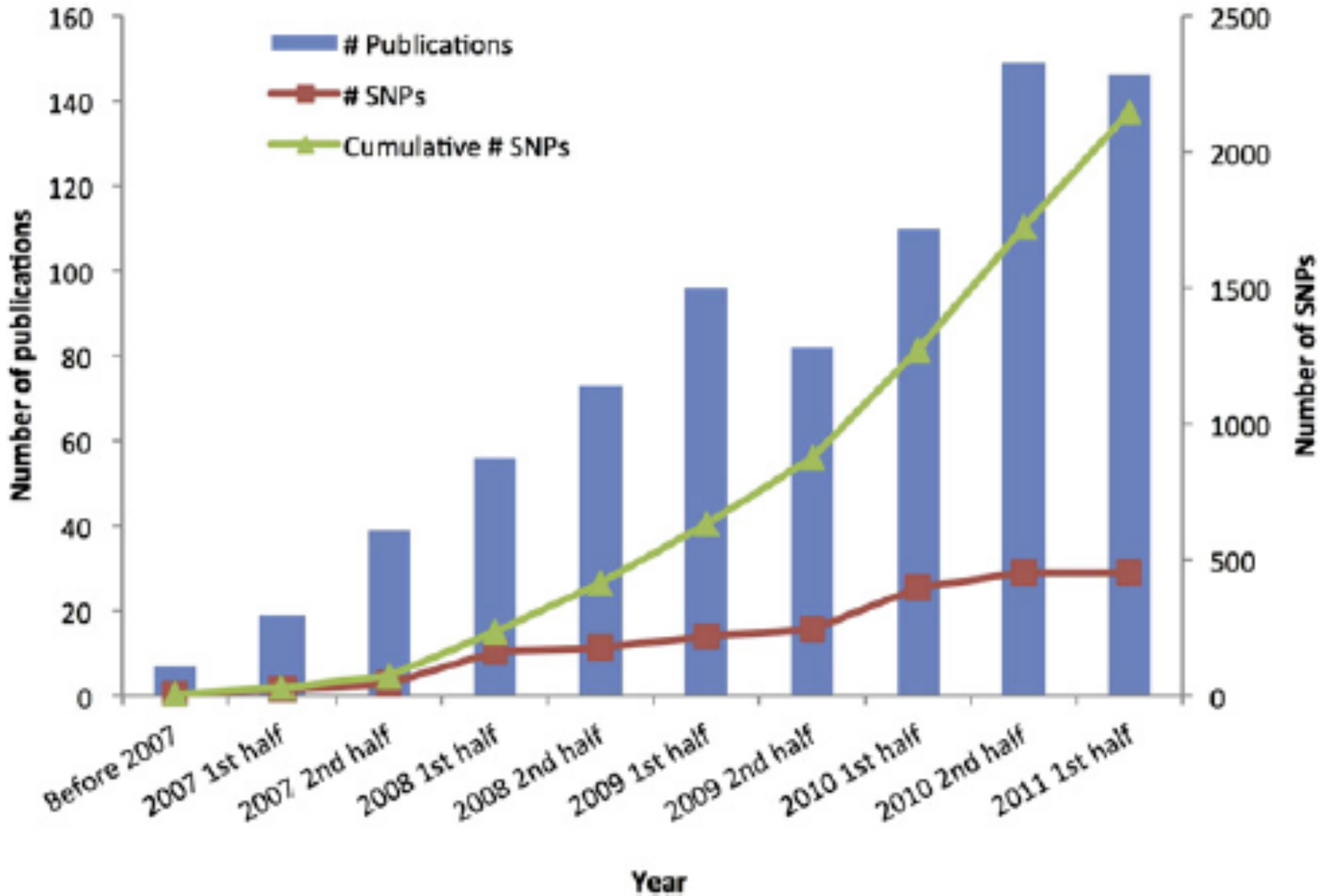


Figure 1. GWAS Discoveries over Time

Visscher et al, 2012

Lecture Outline

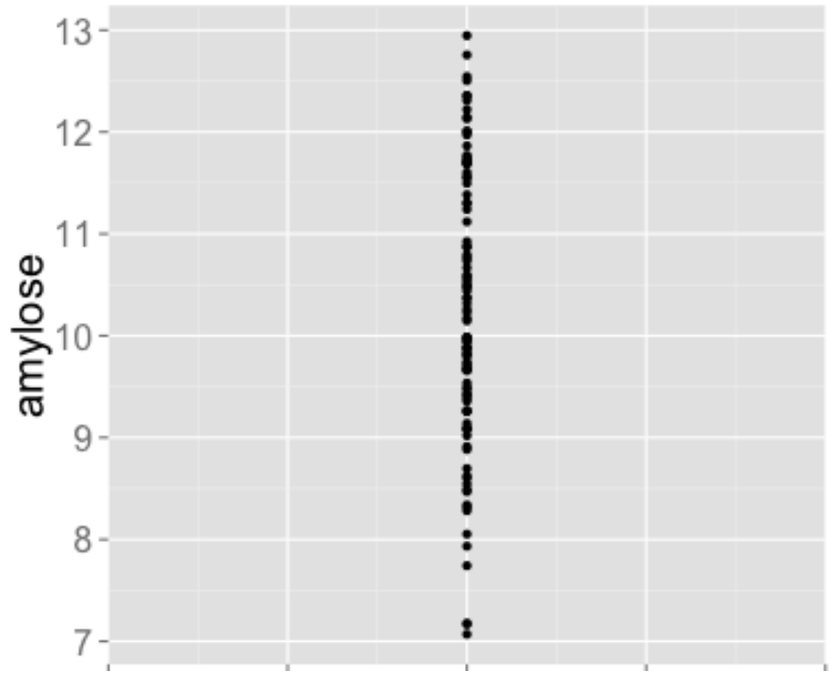
- Association Mapping
- Genome-Wide Association Mapping (GWAS)
- The problem of population structure

Association Mapping

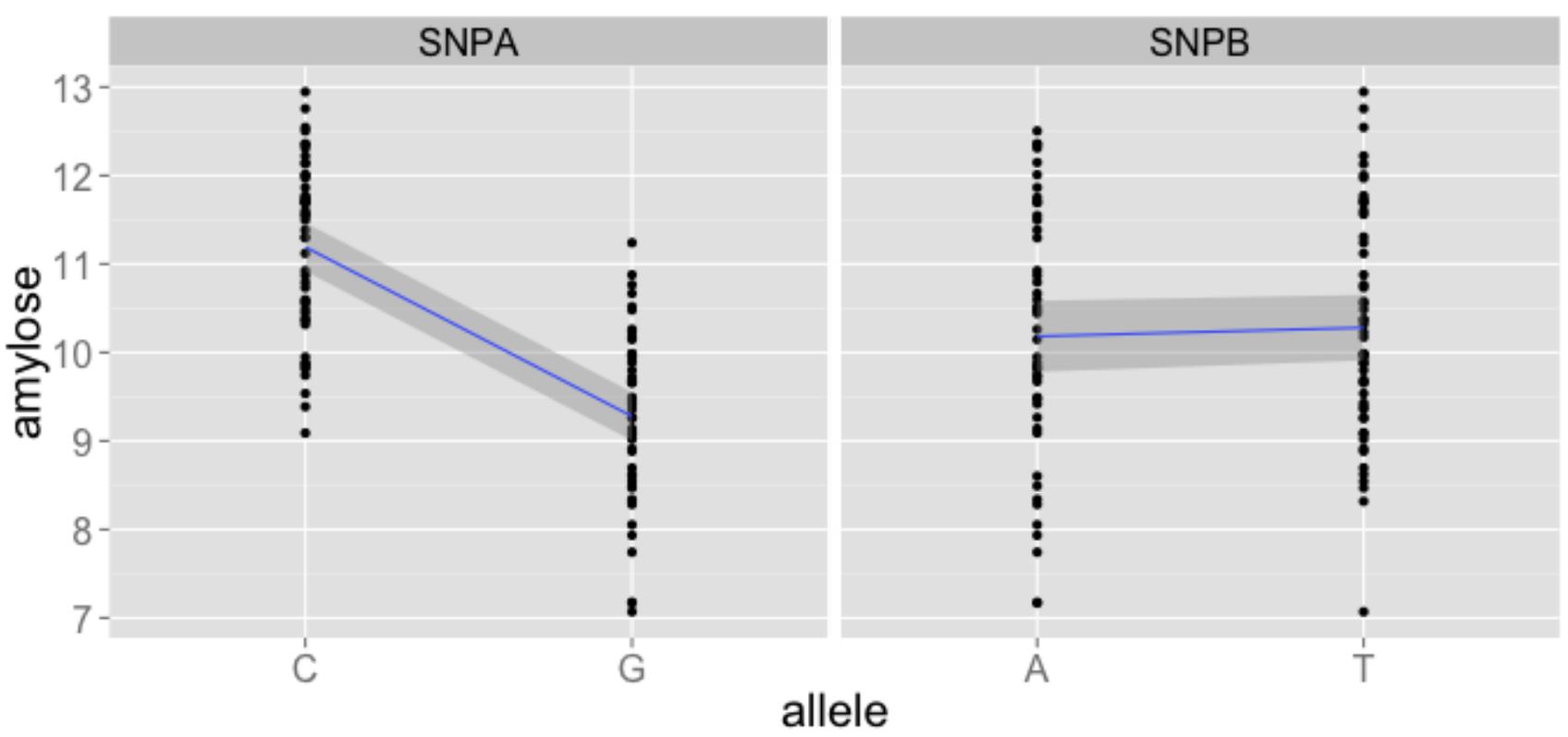
- Trying to find genetic basis for a trait or disease
- Look for statistical association between a SNP allele state and a phenotype
-

Association Mapping, simulated example for amylose

- Measure amylose in many rice varieties



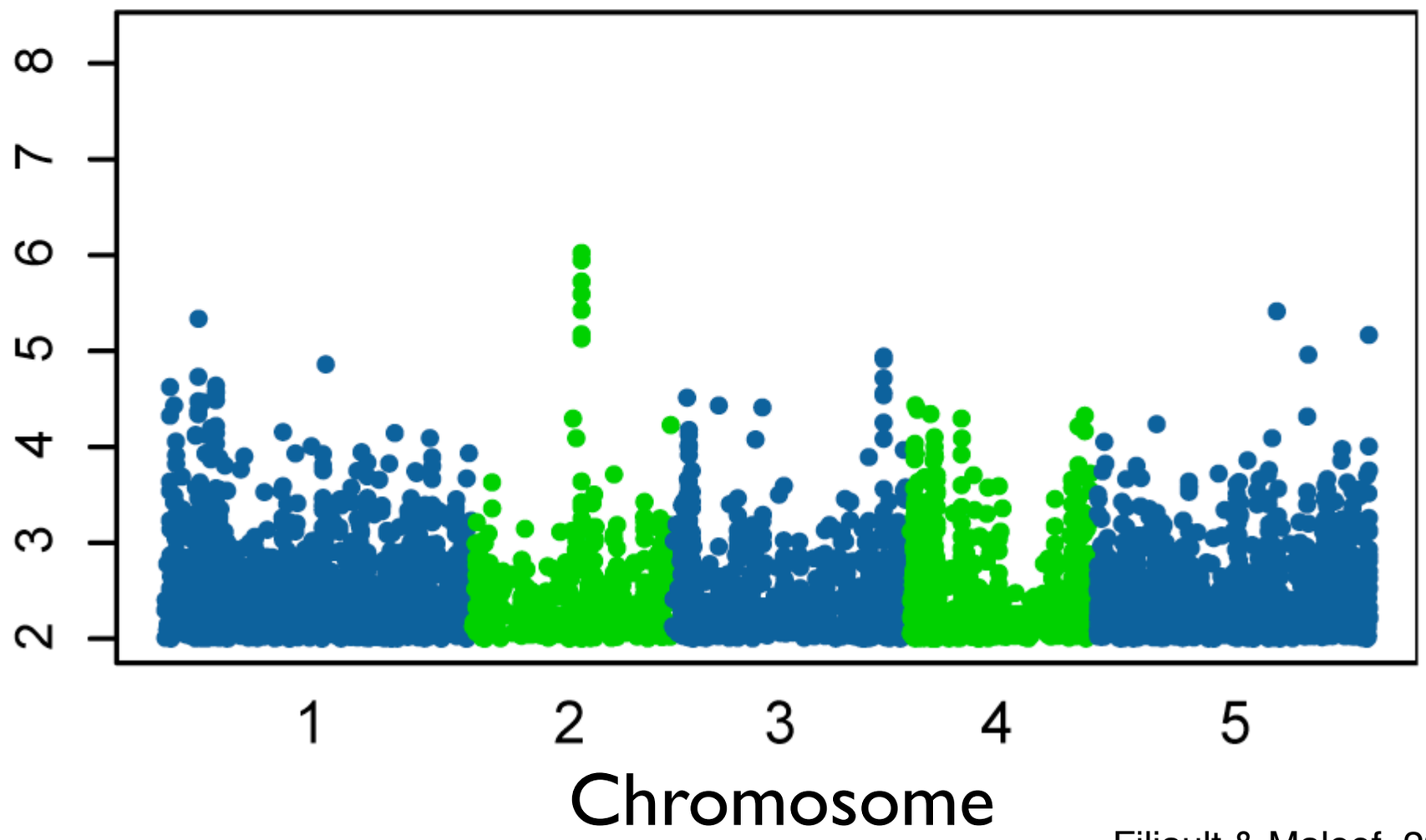
- Separate measurements according to SNP allele



- Test for association. Slope not equal to 0 = association.

Association Mapping vs Genome-Wide Association Mapping

- For GWAS repeat the analysis for SNPs across the whole genome.
- Can plot the results as a manhattan plot:
  - each point is a SNP
  - X-axis is position in the genome. In this case there are 5 chromosomes
  - Y-axis is -log10(P) for association with the trait. Higher values are more significant.

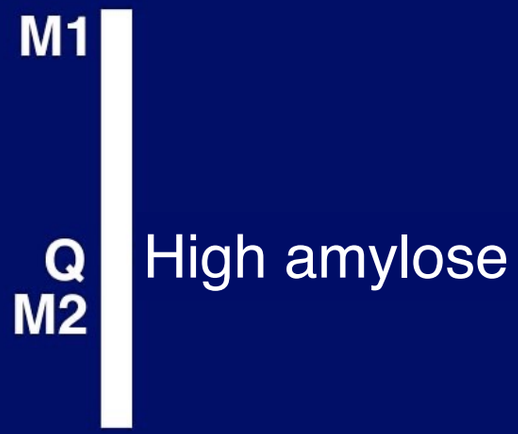


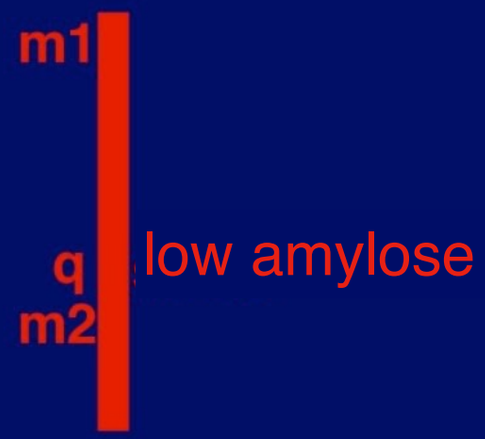
Filiault & Maloof, 2012

Association Mapping: historical recombination

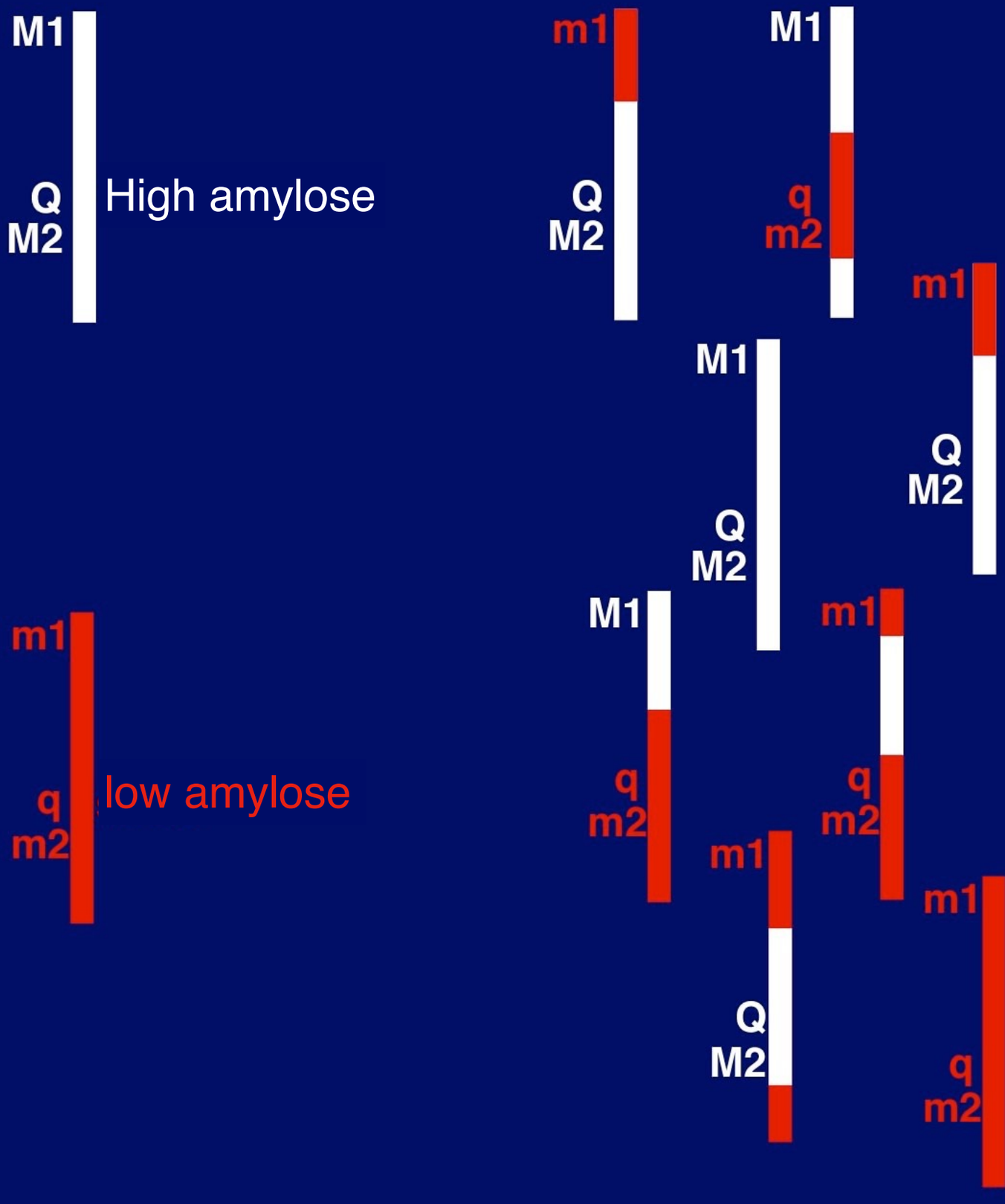
- Why might some SNPs be associated with a trait and not others?
- Historical Recombination!

Association mapping and historical recombination

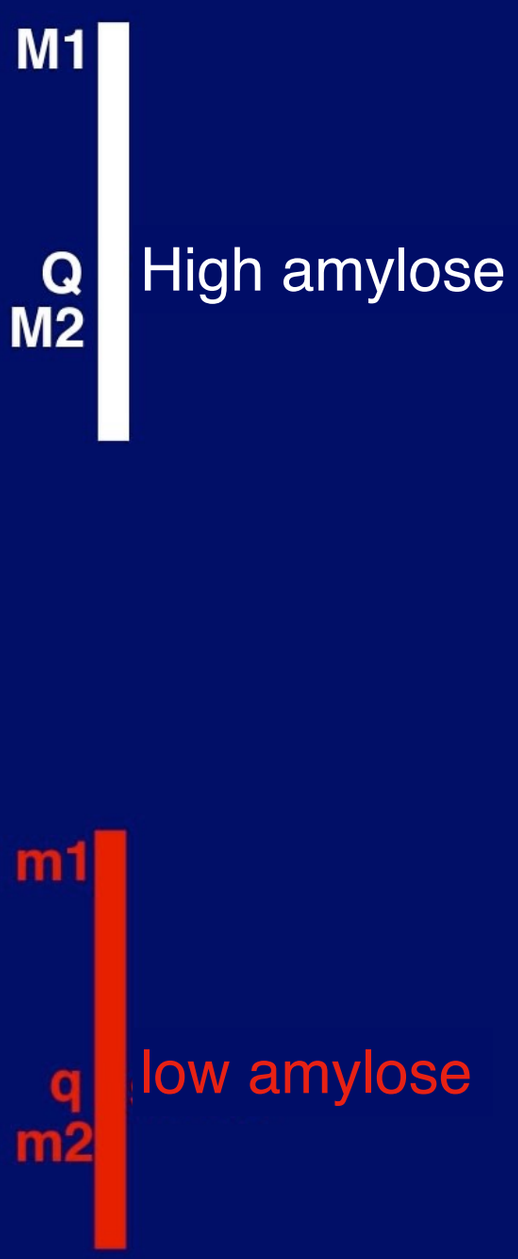


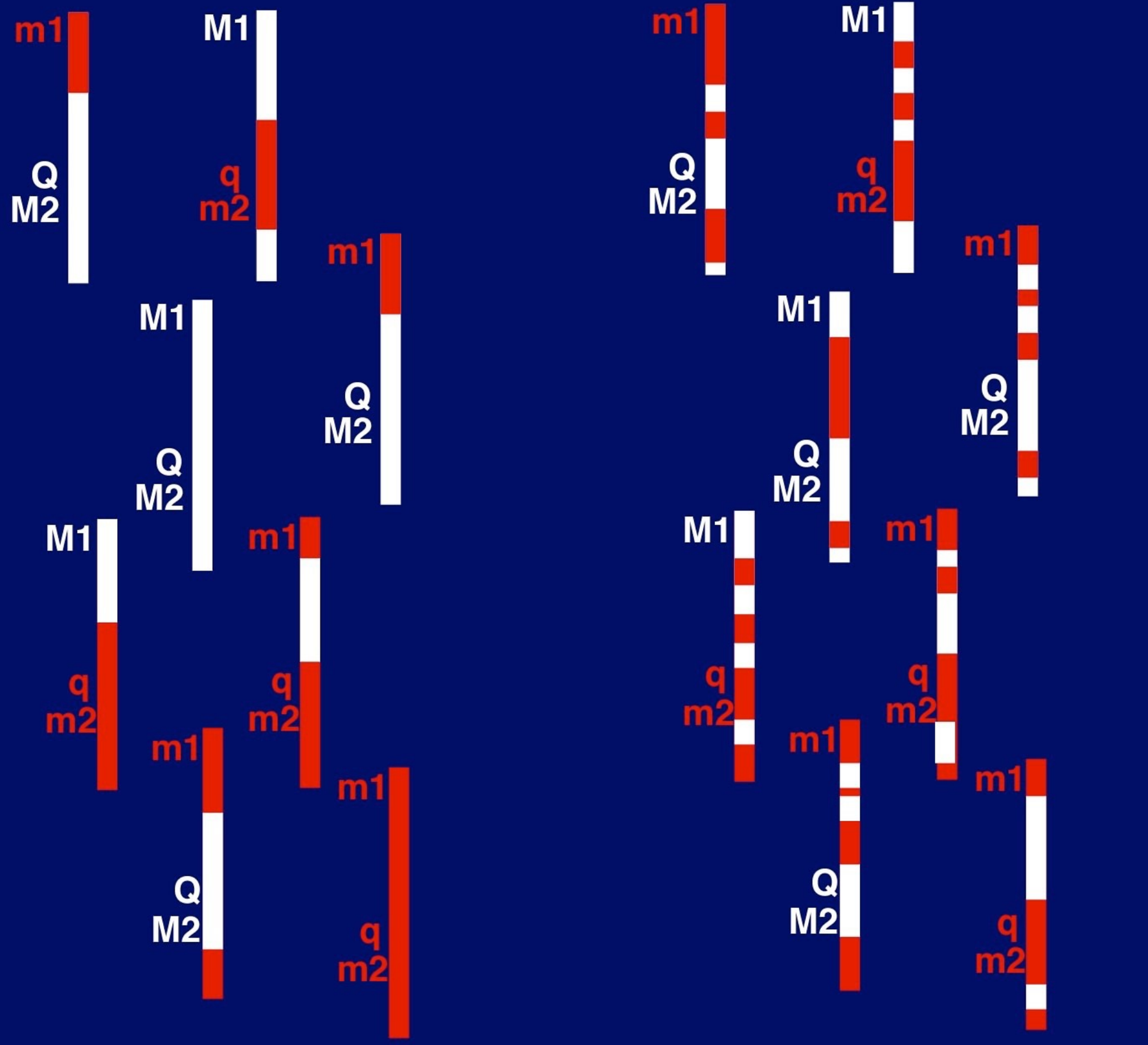


Association mapping and historical recombination



Association mapping and historical recombination

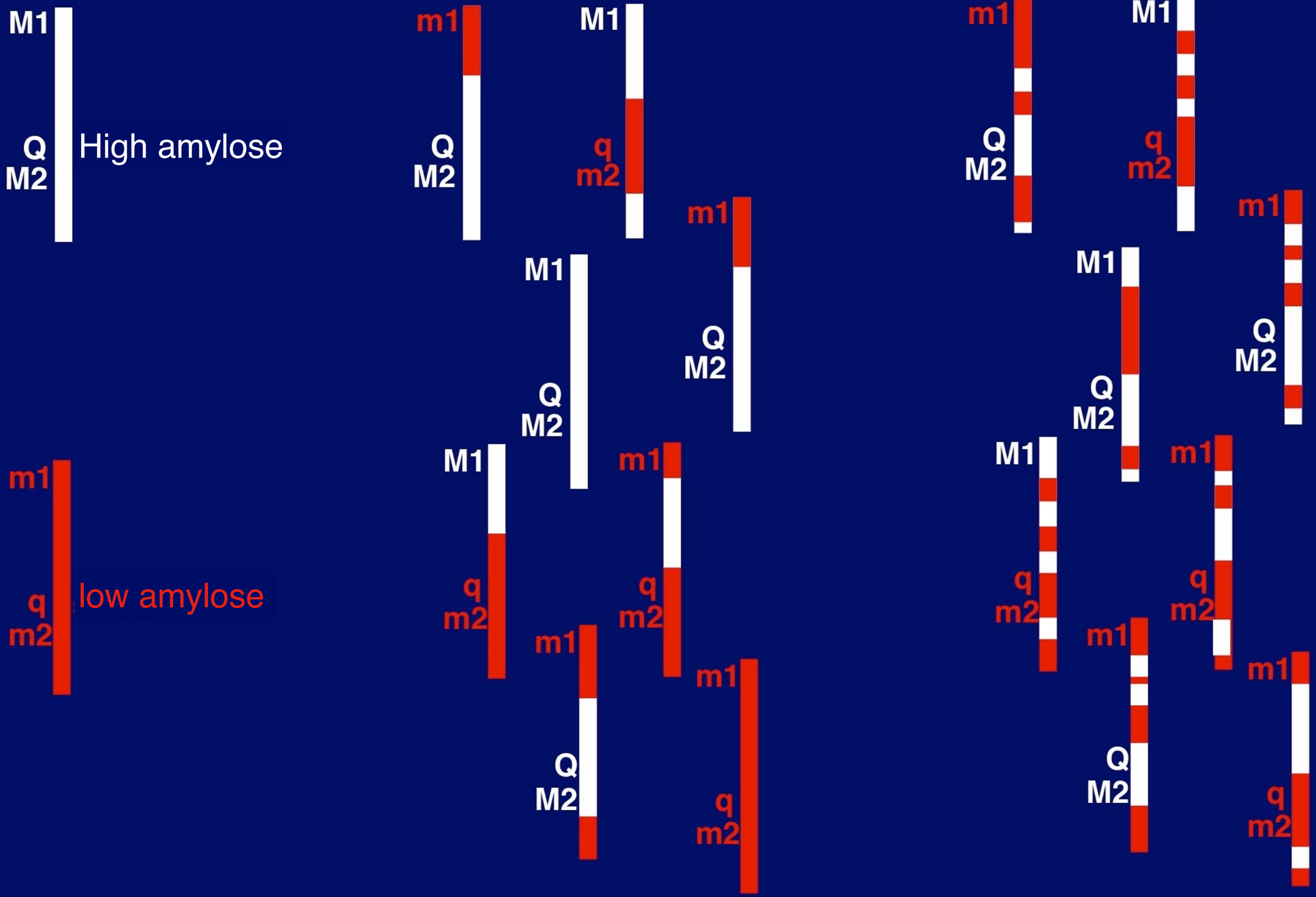




The importance of tagSNPs

- Our rice SNP data set has ~44,000 SNPs.
- There are ~500,000 SNPs segregating among the rice varieties.
- Is it hopeless?
  - Do we have less than a 1 in 10 chance of finding an association because we are assaying less than 10% of the SNPs?
- Not hopeless
  - Because of linkage disequilibrium there is a strong correlation among closely linked SNPs

Not hopeless: SNPs near to one another are correlated...



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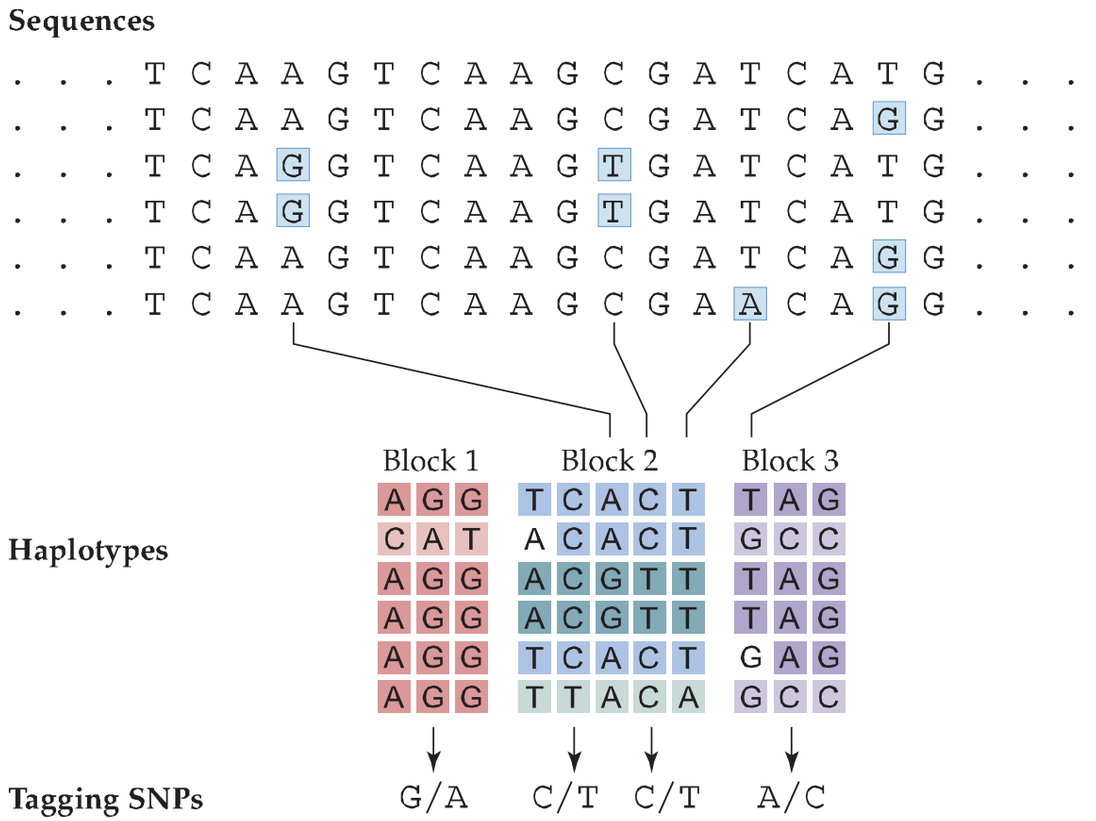
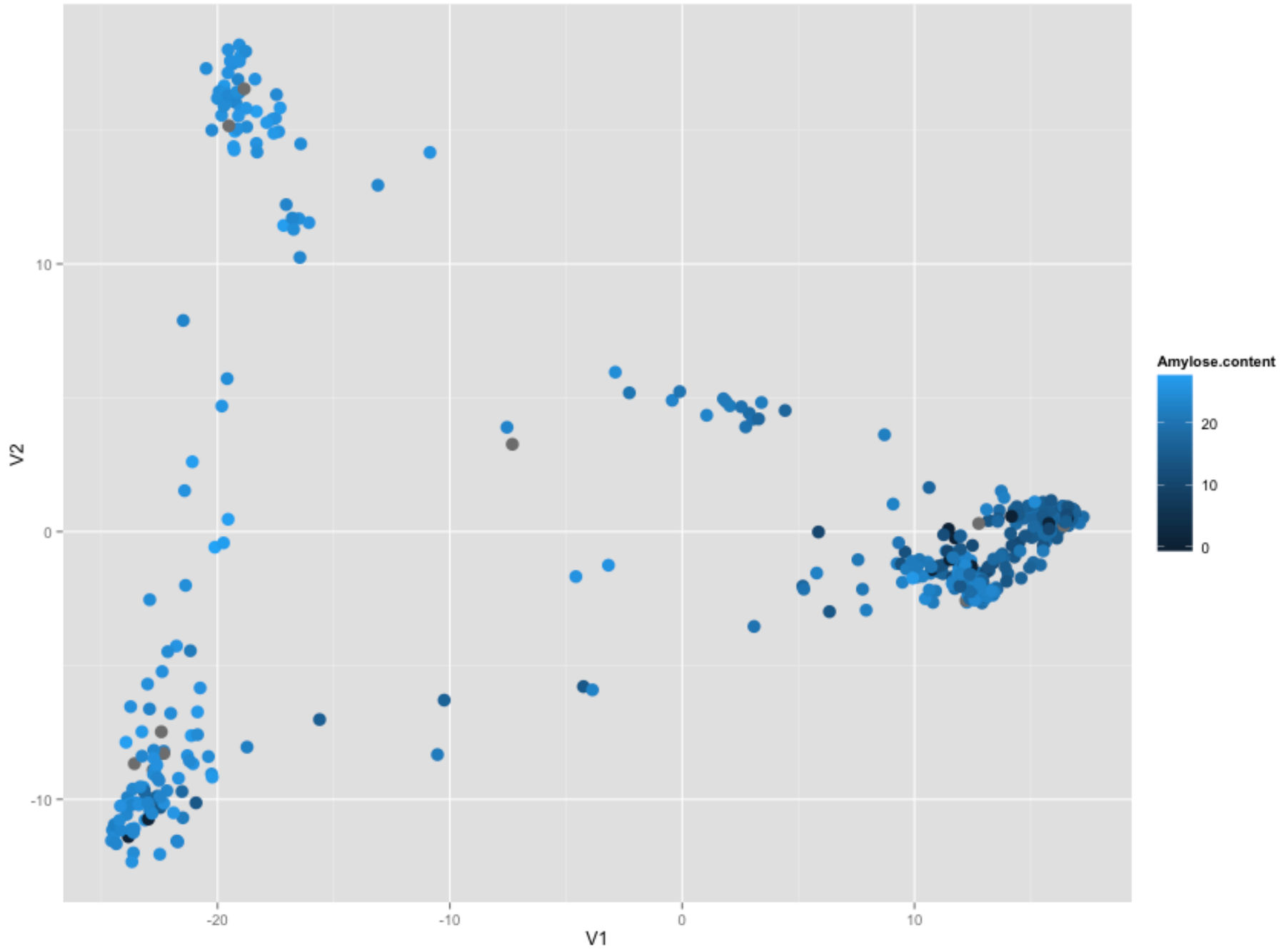


Figure 3.5 Tagging SNPs and haplotype blocks. Extraction of the polymorphisms from a set of sequences typically reveals a blocklike pattern of haplotypes. In this hypothetical example, Block 1 has two classes of haplotypes, one rare and one common; Block 2 has three classes of haplotypes; and Block 3 has two classes of haplotypes. Note that the boundaries between blocks are relatively sharp. The tagging SNPs can be used to define most of the variation in the sample.

Population Structure can present a problem for GWAS

- What is the potential problem with a GWAS for amylose content?



Population structure corrections

- Analyze within each population
- OR
- include structure information in the statistical model.
  - instead of: amylose ~ SNPgenotype
  - use: amylose ~ SNPgenotype + population_membership
- Often it is best to include BOTH population membership and a kinship matrix (genetic relatedness). We will not use that method today (but checkout GAPIT)