

Genome-wide association mapping

Brian Kissmer

USU Department of Biology

Nov. 14th, 2024

What is genome-wide association mapping?

Genome-wide association (GWA) mapping is a set of methods used to identify genetic variants associated with variation in particular traits or disease susceptibility.

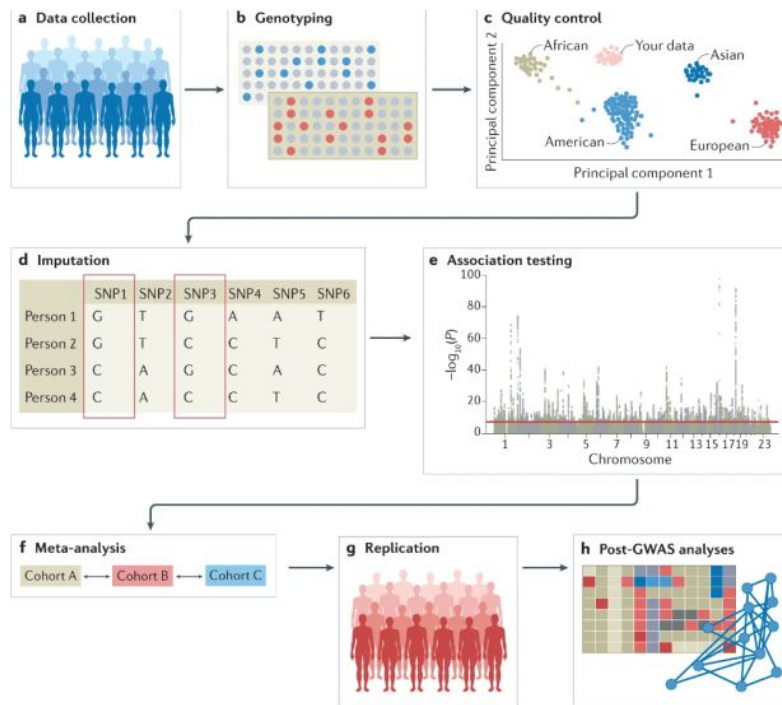
Why is genome-wide association mapping useful?

1. Provides insights into the genetic basis of complex traits and diseases
2. Medical applications: helps identify potential therapeutic targets.
3. Evolutionary biology: aids in understanding the genetic architecture of traits in diverse populations and species.

Basic principles of genome-wide association mapping

- Observational study of a genome-wide set of genetic variants in different individuals.
- Tests for statistical association between genetic variants and traits.
- Typically use single-nucleotide polymorphisms (SNPs) genetic variants.
- Statistical association is NOT equivalent to causal effect.

Overview of steps for conducting GWA mapping



[Uffelmann et al., 2021]

Linear regression models for GWA mapping

Standard linear model for phenotype (y_i) as a function of genotype (g_i) for individual i :

$$y_i = \beta_0 + \beta_{SNP} g_i + \epsilon_i$$

Linear regression models for GWA mapping

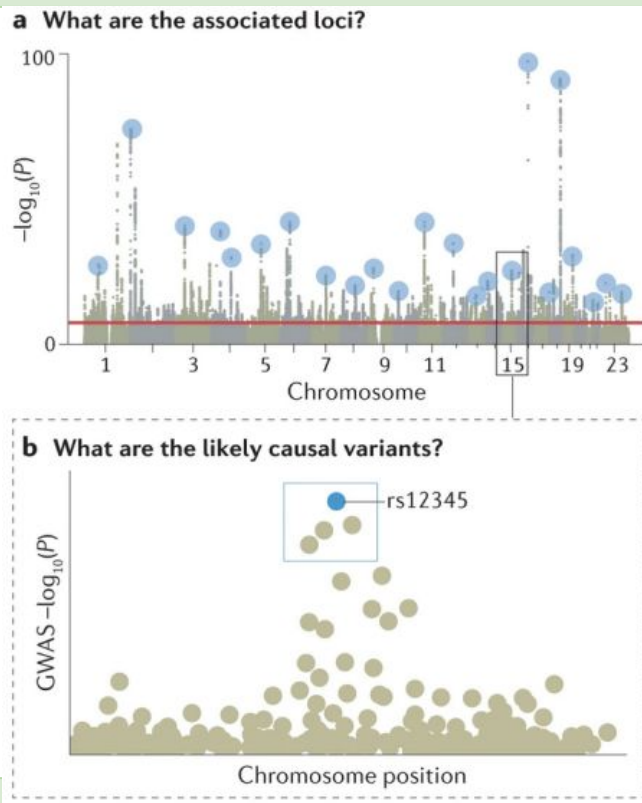
Standard linear model for phenotype (y_i) as a function of genotype (g_i) for individual i :

$$y_i = \beta_0 + \beta_{SNP} g_i + \epsilon_i$$

Models can include additional covariates (x), such as environmental effects, organism attributes (sex, age, etc.), or genetic background:

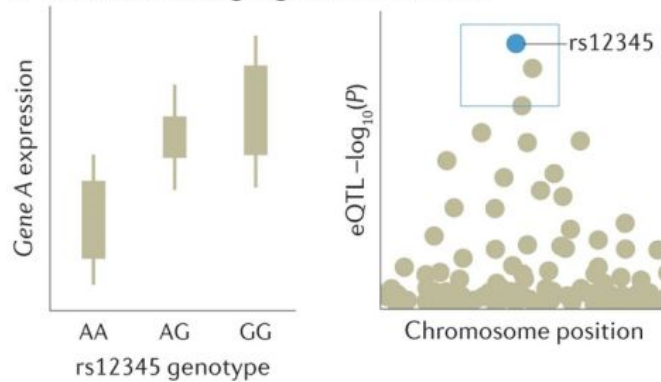
$$y_i = \beta_0 + \beta_{SNP} g_i + \alpha_1 x_{1i} + \dots + \alpha_k x_{ki} + \epsilon_i$$

Putative causal variants prioritized based on patterns of association

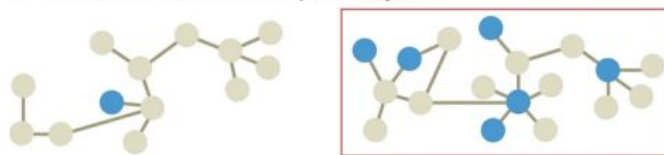


GWA signals can be associated with changes in gene expression and molecular pathways

d What are the target genes in the locus?



e What are the affected pathways?



Challenges for genome-wide association mapping

- Many traits are polygenic, i.e., influenced by many genes often with small and contingent effects.
- Population stratification and environmental influences can lead to false associations.
- Very large sample sizes are often needed to increase the power to detect “true” (useful) associations.

GWA mapping methods to increase power

Common methods test one genetic variant (SNP) at a time, this leads to low power

$$y_i = \beta_0 + \beta_{SNP} g_i$$

How to fit a multilocus model

- Traditional regression methods do not work when the number of parameters exceeds the number of observations, which is often the case for multi-locus GWA mapping analyses.
- Two possible solutions:
 - Use penalized regression, e.g., LASSO (last week)
 - Use machine learning, e.g., Random Forest (more on this later)

GWA in practice

See programming project 5