

Module 6: Association Testing and Mapping

Introduction

Genetic maps have proven to be useful in a variety of ways, particularly for demonstrating the feasibility of dissecting quantitative traits. For marker breeding, however, the utility of such maps is limited by their low resolution—caused by lack of genetic recombination in a limited number of generations. Association mapping, on the other hand, takes advantage of genetic recombination over 10's to 1000's of generations and if done properly, can thereby be accomplished with greater accuracy. In this module, we move beyond the use of genetic maps to locate QTL (Module 5), and introduce association mapping. In addition to phenotypic data, association mapping requires critical analyses of multiple markers, statistical controls to account for false positives, and an understanding possible confounding factors that might wrongly suggest causal associations between genetic markers and phenotypes. Association mapping provides the scientific underpinnings for MAS and MAB applications introduced in Modules 7 & 8.

Key Messages

- Association mapping has only recently become feasible given abundant sequence data and high throughput genotyping platforms
- Association mapping can be done at the level of whole genomes, or for selected genomic targets, e.g. for candidate genes
- Association mapping depends on detecting non-random associations between markers and phenotypes, typically maintained by LD
- Significant LD does not necessarily indicate causal associations since LD can also be influenced by population history. Therefore, LD needs to be interpreted cautiously, using appropriate experimental controls
- Methods for association mapping are developing rapidly in humans, model organisms, and in selected agricultural plants and animals, as well as forest trees

Outcomes

Course attendees will:

- learn how LD in segregating families limits resolution in genetic maps, while enabling the creation of fine-scale maps using association approaches
- learn how various kinds of potential confounding factors need to be accounted for in order to properly interpret results from association studies
- understand how association mapping approaches have been strongly influenced by studies of genetic epidemiology in humans
- understand how neutrality theory is used to formulate null hypotheses against which to test the statistical significance of LD and marker-phenotype associations

Module 6: Association Testing and Mapping Outline

- I) Background and introduction
 - A) Genetic and QTL mapping require pedigreed families
 - B) Association testing/mapping: can be done with or without families
- II) General Testing/Mapping Strategies
 - A) Where to look?
 - 1) Genome-wide? (requires more sequence info)
 - 2) Or a subset—candidate genes (can be done based on ESTs)
 - B) What to look for
 - C) What type of mapping population?
 - 1) Unrelated individuals
 - 2) Family-based studies
- III) Association testing depends on LD. How do we evaluate LD?
 - A) Quick review of LD statistics and properties
 - B) HapMap Project (and human diversity)
 - C) Other examples in plants and animals
- IV) Association Tests: Additional background details
 - A) Early studies: Examples and caveats in humans
 - B) Testing and experimental considerations
 - C) Factors affecting success
- V) Case studies
 - A) Maize I: Dwarf8 and flowering time (Thornsberry et al)
 - B) Maize II: TASSEL
 - C) Maize III:
 - D) Loblolly I: Gonzalez-Martinez 2007
 - E) Loblolly II: Gonzalez-Martinez et al 2008 Family assn testing
- VI) Lab: Assn mapping
 - A) TASSEL
 - B) STRUCTURE
 - C) Excoffier and Heckel 2006 (NatRevGenet: Software Survival Guide)