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Association mapping an effective tool for gene mapping: A review

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Abstract
Many agriculturally important variations such as productivity and quality, tolerance to environmental stresses, and some of forms of disease resistance are controlled by polygenes. These complex traits are referred to as quantitative trait loci (QTLs), and it is challenging to identify QTLs based on only traditional phenotypic evaluation. Linkage analysis and association mapping are the two most commonly used tools for dissecting complex traits like QTLs. Association mapping examines the linked inheritance of functional polymorphisms and adjacent molecular markers in a set of genotypes with unknown ancestry. Association mapping is also known as linkage disequilibrium mapping as LD is used for association study.

Keywords: association mapping, effective tool, gene mapping, QTLs

Introduction
The level of the genetic diversity is pivotal for world food security and survival of human civilization on earth. The narrow genetic base of modern crop cultivars is the serious obstacle to sustain and improve crop productivity due to rapid vulnerability of genetically uniform cultivars by potentially new biotic and abiotic stresses. However, plant germplasm resources worldwide, comprising of wild plant species, modern cultivars, and their crop wild relatives, are the important reservoirs of natural genetic variations, originated from a number of historical genetic events as a respond to environmental stresses and selection through crop domestication. The efficient exploiting these *ex situ* conserved genetic diversities is vital to overcome future problems associated with narrowness of genetic base of modern cultivars. However, many agriculturally important variations such as productivity and quality, tolerance to environmental stresses, and some of forms of disease resistance are controlled by polygenes and "multifactorial" that greatly depends on *genetic* × *environmental* (G × E) interactions. These complex traits are referred to as quantitative trait loci (QTLs). Identification of QTLs of agronomic importance and its utilization in a crop improvement further requires mapping of these QTLs in a genome of crop species using molecular markers. Linkage analysis and association mapping are the two most commonly used tools for dissecting complex traits like QTLs.

Genetic mapping
Gene mapping describes the methods used for determining the location of gene and relative distances between genes on a chromosome. Genes can be viewed as one special type of genetic markers in the construction of genome maps. The two most commonly used methods to dissect quantitative traits are linkage mapping and association mapping. Linkage mapping exploits the linked inheritance of functional polymorphisms and adjacent molecular markers within pedigrees of known structures. In plants, such experiments typically are conducted with experimental populations that were derived from crosses of two homozygous genotypes. In contrast, association mapping examines the linked inheritance of functional polymorphisms and adjacent molecular markers in a set of genotypes with unknown ancestry. By exploring deeper population genealogy rather than family pedigrees, association mapping offers mainly three advantages over linkage mapping: higher mapping resolution, higher number of alleles and broader reference population and less research time in establishing an association.

Linkage mapping

A linkage map may be thought of as a 'road map' of the chromosomes derived from two different parents (Paterson, 1996a) [5]. Linkage maps indicate the position and relative genetic distances between markers along chromosomes, which is analogous to signs or landmarks along a highway. The most important use for linkage maps is to identify chromosomal locations containing genes and QTLs associated with traits of interest; such maps may then be referred to as 'QTL' (or 'genetic') maps. 'QTL mapping' is based on the principle that genes and markers segregate via chromosome recombination (called crossing-over) during meiosis (i.e. sexual reproduction), thus allowing their analysis in the progeny (Paterson, 1996a) [5]. The frequency of recombinant genotypes can be used to calculate recombination fractions, which may be used to infer the genetic distance between markers. By analyzing the segregation of markers, the relative order and distances between markers can be determined–the lower the frequency of recombination between two markers, the closer they are situated on a chromosome conversely, the higher the frequency of recombination between two markers, the further away they are situated on a chromosome.

Association mapping

Association mapping identifies quantitative trait loci (QTLs) by examining the marker trait associations that can be attributed to the strength of linkage disequilibrium between markers and functional polymorphisms across a set of diverse germplasm. As association mapping is carried out with the help of linkage disequilibrium (LD), it is also known as 'linkage disequilibrium mapping'. LD mapping detects and locates quantitative trait loci (QTL) by the strength of the correlation between a trait and a marker. It is a tool to resolve complex trait variation down to the sequence level by exploiting historical and evolutionary recombination events at the population level. Diverse germplasm lines are used as mapping population in contrast to conventional genetic mapping where family based population is required. Offers greater precision in QTL location than family-based linkage analysis. (Chengsong *et al*., 2008) [2] The basic objective of association mapping (AM) studies is to detect correlations between genotypes and phenotypes in a sample of individuals on the basis of linkage disequilibrium (LD).

The advantages of population-based association study, utilizing a sample of individuals from the germplasm collections or a natural population, over traditional QTL-mapping in biparental crosses primarily are due to (1) availability of broader genetic variations with wider background for marker-trait correlations (i.e., many alleles evaluated simultaneously), (2) likelihood for a higher resolution mapping because of the utilization of majority recombination events from a large number of meiosis throughout the germplasm development history, (3) possibility of exploiting historically measured trait data for association, and (4) no need for the development of expensive and tedious biparental populations] that makes approach timesaving and cost-effective (Braulio *et al*., 2012) [1].

Turning the gene-tagging efforts from biparental crosses to natural population of lines (or germplasm collections), and from traditional QTL mapping to linkage disequilibrium (LD)-based association study became a powerful tool in mapping of the genes of interest. This leads to the most effective utilization of *ex situ* conserved natural genetic diversity of worldwide crop germplasm resources.

What is linkage disequilibrium?

LD refers to the non-random association of alleles at different loci in a given population. LD refers to a historically reduced (nonequilibrium) level of the recombination of specific alleles at different loci controlling particular genetic variations in a population LD is a nonrandom association of alleles at different loci, describing the condition with nonequal (increased or reduced) frequency of the haplotypes in a population at random combination of alleles at different loci. LD is not the same as linkage, although tight linkage may generate high levels of LD between alleles. Usually, there is significant LD between more distant sites or sites located in different chromosomes (Hedrick, 1987) [3].

Factors affecting LD

There are many genetic and demographic factors that play a role in the shaping of the haplotypic LD blocks in a genome .Mutation and recombination are one of the strong impact factors influencing LD, generally, factors affecting LD can be grouped into two categories: (1) factors that increasing LD, and (2) factors that decreasing LD. (Ibrokhim and Abdusattor, 2008) [4]. Factors like inbreeding, new mutation, relatedness (kinship), genetic drift, epistasis, genomic rearrangements, selection increases linkage disequilibrium while Factors like High recombination, High mutation, Outcrossing, Genetic conservation decreases LD.

LD decay

LD decays as LD decreases. LD will tend to decay with genetic distance between the loci under consideration. LD decays by one-half with each generation of random mating. Thus, LD declines as the number of generations increases, so that in old populations LD is limited to small distances. Threshold value of LD is r2 = 0.1, below which LD decay is considered. The resolving power of LD mapping depends on how rapidly LD decays with genetic distance.

Different stages of association mapping for tagging a gene of interest

A. Assembly of Association Mapping Population

The choice of germplasm is crucial to the success of association analysis as genetic diversity, the extent of genome-wide LD, as well as the level of population structure and relatedness in the population under consideration determine the mapping resolution. Suitable populations for AM are like ideal sample with subtle population structure and familial relatedness, multi-family sample without population structure, sample with population structure but without familial relatedness, sample with both population structure and familial relatedness and sample with severe population structure and familial relatedness.

B. Genotyping

In association mapping studies, genotyping is required for inferences on population structure and familial relatedness, marker-phenotype associations. The genotyping of a set of selectively neutral background markers distributed throughout the genome is required. Random amplified polymorphic DNA (RAPD) and amplified fragment length polymorphism (AFLP) markers can serve as background markers, but as a result of their dominant inheritance demand special statistical methods if used to estimate population genetic parameters. Conversely, codominant simple sequence repeats (SSRs) and single nucleotide polymorphisms (SNPs) are more powerful

in estimating population structure and familial relatedness.

C Phenotyping the Association Mapping Population

Obtaining robust phenotypic data remains a hurdle for large-scale association mapping projects. Because association mapping often involves a relatively large number of diverse accessions, phenotypic data collection with adequate replications across multiple years and multiple locations is challenging. An efficient field design with an incomplete block design (e.g. a-lattice) has the potential to increase the mapping power

D. Association Analysis

Different approaches have been designed to deal with statistical association analysis. Case and control approach, Linear mixed effect model, HHR (Haplotype relative risk approach), TDT (transmission disequilibrium test) approaches are used for marker trait association analysis among germplasm lines. STRUCTURE association model is combination of two or more association analysis models. While, HAS (Hplotype sharing analysis) and DHS (decay of haplotype sharing) are used for family based population.

Advantages of Association mapping over linkage mapping

Association mapping counter the limitations of classical linkage mapping by increasing mapping resolution, mapping of greater no. of allels, border allel coverage. It is Cost effective and time saving as there is no requirement of developing mapping population. Historical recombination and natural genetic diversity can be exploited as several recombination events are studied from ancestry to current generation of germplasm.

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