Challenges for QTL Analysis in Crops

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Abstract

Quantitative trait loci, a genetic concept introduced in the 1940s, for explaining the inheritance of non-Mendelian traits, have been realized as particular fragments of chromosomes even unique genes in most crops in the 21st century. However, only very a small portion of QTL has been screened out by geneticists comparing to a great number of genes underneath the quantitative traits. These identified QTL even have been seldom used into breeding program because crop breeders may not find the QTL in their breeding populations in their field station. Several key points will be proposed to meet the challenges of QTL analysis today: a fine mapping population and the related reference genetic map, QTL evaluation in multiple environments, recognizing real QTL with small genetic effect, map integration.

Keywords: Quantitative trait, plant QTL analysis, current status, challenge

Introduction

The traits of organisms are determined by complicated gene expression – regulation network. The expression of each gene is different in the network. There are interactions of additivity, dominance and super-dominance existing among genes and alleles. The genetic architecture determining traits might vary slightly or greatly under different genetic backgrounds. Geneticists always use wild-types and mutants as parental plants to study target traits. Since a mutant is usual an alteration on DNA sequence of a single gene and other genes related to the trait remain unchanged, the qualitative traits of the generation accord with the law of segregation of single genes. Genetic research of several mutants or double-mutants is necessary to understand the genetic regulation network of the target trait.

If the genetic diversity between parents is significant, the performance of contrast characters differs. Parents have accumulated abundant mutations in relevant genetic network under respective historical and geographical conditions. Quantitative traits refer to multiple-gene controlled continuous variation characters in hybrid progeny. Each quantitative trait locus (QTL) is also a locus in the genetic regulation network. Thus, analysis on quantitative traits contributes to understanding genetic regulation network to some extent. Cross parents selected in breeding always have very distant genetic relationships and many different loci exist in the genetic regulation network, therefore molecular analysis on quantitative traits will directly help breeding.

Traditional quantitative genetics studies the multiple genes determining quantitative trait as an entity by using mathematical statistics (Mather 1941). But with this method, we cannot identify a single quantitative trait locus, determine the chromosomal location of QTL and its relationship with other genes, and analyze the molecular mechanism underlying quantitative trait phenotype variation. Thus, it has very limited significance on directing breeding. Molecular biology and DNA molecular marking techniques developed rapidly in 1980s. Quantitative trait research made a breakthrough when Paterson et al. (1988) located QTL in tomato by using genetic linkage map with RFLPs. In the subsequent decades, molecule labeling and mapping techniques made rapid progresses (For molecule marking: Collins et al. 1998; Rafalski and Tingey 1993; Monna et al. 1994; Williams et al. 1990; QTL mapping techniques: Jasen et al. 1993; Kao and Zeng 1999; Zeng 1993, 1994; Lander and Bostein 1989; for QTL cloning techniques: Arondel et al. 1992; Cardon and Bell 2001; Giraudat et al. 1992). QTL analysis becomes a leading edge of crop science research. Thousands of plant QTL have been located;

over 5,000 QTL have been revealed in rice (http://www.gramene.org/qtl/). The article briefly introduces the theory of QTL mapping, QTL identification method, QTL applicability, the current situation and issues on the biological role of QTL, and discusses the future of crop QTL research.

1 Theory of QTL mapping analysis

The theory of QTL mapping is to analyze the relationship between genotypes and phenotype variations based on molecular marker information and observed traits of special segregation populations, and calculate the position of QTL determining phenotype variation according to the known genetic linkage map.

Genetic linkage map and phenotype data are the basis of QTL mapping analysis. Any genetic segregation population (F_2, BC, DH, RIL) can be used to construct a genetic linkage map. The oldest mapping software was Mapmaker based on UNIX system and DOS system (Lander et al. 1987; Lincoln et al. 1992). The subsequent software Joinmap was based on the Windows system (Van Oojen et al. 2004).

But a temporary segregation population such as F_2 is not feasible to acquire phenotype data. Because since each single plant in the population has a specific genotype, it is very difficult to set repetition in field trials and exclude environmental effect and experimental error, and thus the acquired phenotype data is not accurate. For permanent segregation population, such as DH, RIL, and so on, experiments can be done based on the population lines, because each single plant has the same genotype in a line, and the genotype remains unchanged after self-crossing. Repeated trials can be conducted under different environments for this kind of population to separate the environmental effect and experimental error from the total effect and improve the accuracy of phenotype data as well as the precision of QTL position. At present, the latter kind of population is widely used in QTL mapping analysis.

Analysis methods and softwares

Certain statistical analysis methods are required in QTL mapping analysis. The methods have experienced a rapid development. The oldest method is single marker analysis. Afterward, a series of methods was developed, including interval mapping (Lander and Bostein 1989), composite interval mapping (Jansen 1993; Zeng 1994), multi-trait mapping analysis (Jiang and Zeng 1995), composite

interval mapping based on Least Squares estimation (Wu 1996), composite interval mapping based mixed linear model (Zhu and Weir 1998), and interval mapping (Kao and Zeng 1999), in which CIM is used most frequently. The method keeps the strength of single interval mapping by using a likelihood map to estimate the possible position and significance of a QTL. Under the conditions without epistasis and interaction between QTL and environment, since cofactor is introduced to control genetic background in the statistical model, the estimation of QTL location and effect is asymptotically unbiased.

The common software for QTL mapping analysis is QTL Cartographer (Basten et al. 1994; http://statgen.ncsu.edu/qtlcart/index.php), which is compatible with multiple operation systems. The WinQTLCart2.5 for Windows system can be used to conduct interval mapping, composite interval mapping and multiple interval mapping (Wang et al. 2007). Other QTL analysis software, such as MapQTL (Van Ooijen 2004), PlabQTL (Utz and Melchinger 1996, QTLmapper (Wang et al. 1999) can be downloaded in public webpages (http://www.stat.wisc.edu/~yandell/statgen/software/biosci/linkage.html#linkage).

With the QTL mapping analysis method, researchers have mapped thousands of QTLs in the genetic maps of various plants, which greatly promoted quantitative genetics. But the current situation of QTL analysis is far from optimal no matter for the theoretical need for revealing quantitative trait gene network or the application need from plant breeding. There are still severe challenges in identification, applicability, and biological explanation of QTL.

2. Method of QTL identification

Criteria for distinguishing QTL

Certain criteria (significance and threshold) are necessary to identify the QTL locus in some positions of linkage groups with different statistical methods. Taking CIM for example, the permutation test (Churchill and Doerge 1994) is currently widely used to determine the LOD value or threshold judging QTL existence under different significance. Since the likelihood value of QTL is relevant to genotype effect, and the likelihood value of non-QTL is relevant to trial and error, during QTL identification, threshold values can thus be easily approached when genotype effect is relatively major and the trial error is minor (20 ± 2); on the contrary, the threshold values are hardly reached when genotype effect

is minor and the trial error is major (2 ± 1). It is also very difficult to control the experimental error within a small range in field trials (most phenotype data for the QTL analysis determining important crop characters comes from field trials). Therefore, QTL identification based on the threshold of certain significance levels ensures the statistical accuracy of QTL. Actually, many loci with less genetic effect and under statistical threshold are ignored.

Multi-environments field trails for detecting QTLs

Meanwhile, since quantitative traits are instable to the environment, researchers always conduct environmental trials to examine the stability of QTL. Generally, QTLs with overlapping confident intervals repeatedly examined under multiple environments are considered the same one; while QTLs examined under single environments are considered instable and are ignored. In fact, people realized very early that the expression of genes depends on the particular environment (Mather 1941). The gene expression of plants depends on certain environments more than animals due to its immobility. Therefore, recognizing and studying environment-specific QTL (the so-called instable QTL) is an important issue of plant QTL analysis. For example, when our laboratory examined the QTL of flowering time traits, we detected the main-effect QTL of flowering (LOD＝36, explained 52% of phenotypic variance) in the N10 linkage group in the spring cultivate environments for *Brassica napus*, which then disappeared in the winter environments. A large number of important instable QTLs were found in the QTL analysis of *Brassica napus*. For example, 36 flowering time QTL are detected in multiple-location-multiple-year environments, in which 23 QTL are under the threshold and “instable” in certain environments.

Concept of Micro-real QTL (MR-QTL)

Since a large number of minor QTLs and environment-specific QTLs are ignored, the recognized “stable” QTLs are not many. The results of QTL analysis are that the typical features of minor quantitative trait genes disappear and the characters influenced by the environment are covered. Since the recognized QTLs are few, the genetic architecture determining the traits is only partially revealed. Thus, we recommend that environment-specific QTLs should be recognized and emphasized. We proposed the concept of micro-real QTL to protect the minor QTLs (Fig. 1, Long et al. 2007). MR-QTLs refer to QTLs under the threshold ($P \leq 0.05$) but above certain standard ($P \leq 0.5$) in

multiple-environmental trials. MR-QTLs accounts for 10-15% of all examined QTls in *Brassica napus*. A MR-QTL in one population may be a main effect QTL in another population. When we mapped the QTL determining oil content in the TN DH population, we found the confident interval of a MR-QTL in the A9 linkage group overlapping with a major effect QTL for oil content in the SG population reported by Zhao et al. (2005). Recognition of MR-QTL will obviously reduce the risk of missing potential major effect QTLs in breeding selection. But a theoretical statistical method for minor QTL examination is necessary to avoid false positive result.

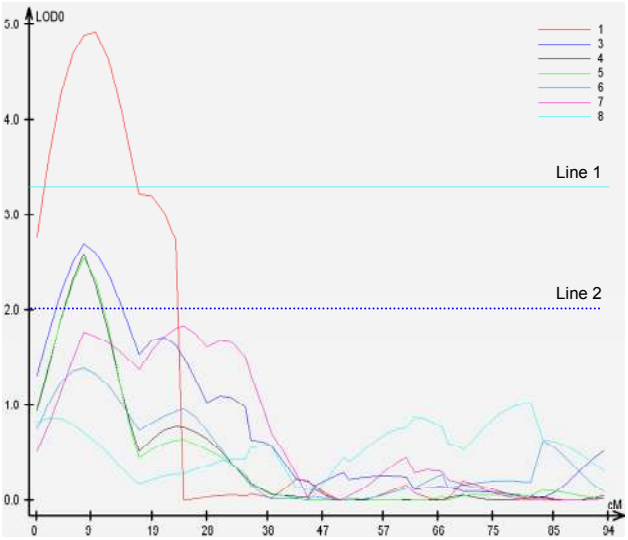

Fig. 1. Analysis of MR-QTL determining flowering time in *Brassica napus* in different natural environments. Line 1 and Line 2 indicate the average thresholds in the eight environments at P = 0.05 and P = 0.5, the former threshold is usually used. In environments 3, 4, and 5, since the LOD value screened near 9cM of chromosome is between the two significance levels, a MR-QTL exists here. The QTL reaches the significance level of P = 0.05 in environment 1, thus the QTL is environment-specific.

3. Applicability of identified QTL

The significant difference among alleles in the target segment of parental genomes is the biological basis for QTL examination in segregation population. And the environment required for allele expression is the precondition for QTL examination. Therefore, whether QTLs detected in a mapping population can be detected in other populations depends on whether a similar allele difference exists in

other populations and whether their environments are similar. Since different researchers always use populations with a distinct genetic basis and examine QTL under distinct natural environments, the foregoing two conditions are hardly consistent for different reseaches. This is the reason that a QTL discovery by a researcher is hardly repeated by others in most cases. And this is also why plant breeders always complain that the QTLs in the linkage map provided by scientists cannot be applied in genetic improvement of crops.

So how can we make the QTLs examined in genetic mapping populations universal? In addition to examining the phenotype traits under multiple environments, a more direct method is to construct a high density reference map with a set of molecular markers existing in the crops, integrate all the genetic maps of each QTL mapping population based on reference map, and finally map QTLs examined under different genetic backgrounds and environments in a common map. QTLs in the integrated map reflect the genetic variations of the crop genome and interactions with multiple environments to a large extent, which can be a reference for crop scientists and breeders. For example, Li et al. (2005) discovered 15 universal drought-resistant QTLs by integrating 181 QTLs of drought-resistant related traits under drought environment.

The accuracy of QTL position varies due to the different density of genetic maps. It is difficult to determine their number and accurate positions for the QTLs with overlapping confident interval and from different populations when conducting QTL analysis in integrated map. Goffinet and Gerber (2000) proposed meta-analysis method to analyze QTL in different populations in integrated map. This method can optimize QTL, reduce QTL confident interval and improve the accuracy and validity of QTL positon by establishing a mathematical model based on integrated QTL. Meta-analysis has been successfully used in QTL analysis of integrated genetic map in maize (Chardon et al. 2004), bean (Guo et al. 2006), and cotton (Rong et al. 2007), guaranteeing the accuracy of QTL position information.

In addition to acquiring universal QTL based on integrated genetic map, we can construct a segregation population consisting of multiple parents and then conduct QTL examination in the population. RIL population from eight parents has been constructed for QTL mapping analysis in *Arabidopsis thaliana* (Huang et al. 2007). Valuable QTLs can be discovered and provided to plant breeders for application by using multiple parents-segregation population for QTL analysis.

4. Biological meaning of QTLs

Though we can analyze quantitative traits on system level with QTL mapping analysis, we only know the number, position, effect, and interactions of genes determining quantitative traits based on statistical theory. Little is known to us about the DNA sequence structure, expression regulation, mechanism, and molecular basis underlying allele variation. Thus, molecular cloning of QTL becomes necessary.

The common QTL cloning methods include map-based cloning (Coulson et al. 1986), candidate gene approach, and association analysis. The map-based cloning method is used most frequently in successfully cloning QTLs. The first successful cloning case of QTL *fw2.2* determining the size of tomato uses the method (Frary et al. 2000). Generally, the procedures of map-based cloning can be summarized as follows: (1) precise location of QTL, (2) determination of QTL corresponding physical maps, (3) determination of candidate gene, and (4) determination of candidate gene function (genetic transformation, function complementation test). Discovery of molecular markers closely linked to target genes and fine mapping of QTL is a key step in map-based cloning, which always has a high cost in human and material resources. The candidate gene approach is to first determine the candidate genes based on understanding of target traits, design primers according to known sequence of candidate gene in other crops and then map them in the genetic map. If the candidate gene is located near the target QTL peak, the correlation between genotype and phenotype can be proved genetically by using advanced generation segregation population. Finally, the role of candidate genes in phenotype variation can be further established by conducting transgenic experiments or association mapping analysis. Currently, there have been successful reports on QTL cloning by the candidate gene approach in plant (Ishimaru et al. 2004; Loudet et al. 2007). We primarily analyzed a QTL determining the flowering time of *Brassica napus* by using this approach. Since large-scale precise mapping is unnecessary for the candidate gene approach, it gains obvious advantages over the map-based method. Association mapping analysis can verify candidate genes and even the effect of polymorphic locus of candidate genes on phenotype by using natural resource population materials efficiently and effectively. Konishi et al. (2006) analyzed the DNA sequence difference of *qSH1* alleles and found 13 polymorphic loci after locating and separating QTL *qSH1* determining kernel shattering in rice. Afterward, the relevant polymorphic regions of *qSH1* in 118 rice cultivars were sequenced and found

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two polymorphic loci relevant to kernel shattering, which proved the function of the gene on determining kernel shattering. Further study on the two polymorphic loci found one SNP locus is common in all *indica* cultivars, and that variation occurs in two subclasses of *japonica* cultivars. The genotype of one of the *japonica* rice subclasses is the same as that of *indica* rice, and the kernels shed more, reflecting the original character of rice; the genotype of the other *japonica* rice subclass is different from the *indica* rice, and the kernels shed less, reflecting the evolutional character. Therefore, the SNP is thought to be attained by human selection during rice domestication. Also, Wilson et al. (2004) and Wang et al. (2005) discovered the candidate gene *sh2* determining protein and starch synthesis and QTL *tgal* determining shell evolution in maize with association analysis respectively.

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QTL cloning can not only help us clarify the molecular mechanism of allele variation but also apply this valuable DNA sequence information to crop breeding. Breeders can develop allele-specific markers according to DNA sequence variation among alleles to assist selection and more rapidly improve crop quality by transferring agronomically favorable genes cloned through transgenesis.

Though the molecular mechanism of QTL can be analyzed by QTL cloning, the successful cases are few due to the tremendous workload. Only a few QTLs have been cloned successfully in plants in the five years since the first QTL cloning (Salvi and Tuberosa 2005). Flint (2005) pointed out that it might take 1,500 years to clone all reported QTLs in the mouse genome at the current QTL cloning rate. It is obvious that the biological significance of QTL cannot be revealed universally only by cloning within a rather long time.

After the sequencing of Arabidopsis genome, the genomes of rice and aspen were sequenced one after the other (Arabidopsis Genome Initiative 2000； International Rice Genome Sequencing Project 2005; Tuskan et al. 2006). The number, location, and structure of genes in these genomes have been very clear. The genome sequencing of 18 crops including maize, bean, and cabbage is in progress (Pennisi 2007). For those unsequenced crops with a comparative genomics strategy, we can align the genome segment of model organisms with the genetic map of unsequenced relatives by in silico mapping and establish the relationship between the genetic map of the crop and gene location. For example, Parkin et al. (2005) mapped more than 1,100 loci marked by 500 sequenced RFLP in the genetic map of *Brassica napus* in the corresponding positions of Arabidopsis chromosomes by sequence comparison and established a precise collinear map of *Brassica napus* and *Arabidopsis thaliana*. The whole

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genome sequencing of model organisms and the establishment of a collinear map with its relatives makes it possible to reveal the biological significance of QTLs in all plants. Gilliland (2006) found that five of the 14 examined QTLs contained genes involved in the vitamin E synthesis pathway after examining QTL determining vitamin E content in *Arabidopsis thaliana* seed, which provide cues for further illustrating the biological role of QTLs. In addition to the model plant itself, the biological role of QTLs determining agricultural traits in other unsequenced crops can also be analyzed by this method. For example, researchers found *FLC* may be the key gene controlling anthesis time in *Brassica napus* by comparison with the Arabidopsis genome (Osborn et al. 1997); Raman (2005) found the polyphenol oxidase gene in rice might be the corresponding gene in wheat QTLs by in silico mapping of QTLs determining polyphenol oxidase activity in the wheat and rice genomes.

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If we locate QTL in 0.5cM confident interval in a high-density genetic map by multiple-environment planting, integration of QTL by using meta-analysis, and confirm the environment required for the QTLs expression, the possibility of screening genes related to the trait in the confident interval (about 10-20 genes) will be very high. Further bioinformatics analysis will help us understand the biological role of each QTL in the gene network more comprehensively and accelerate the deep comprehension on quantitative traits.

5. The future of plant QTL analysis

It has been 60 years since the origin of plant QTL. During this time, especially since the end of the 20th century, the abundant, stable, and efficient molecular markers and rapid development of QTL analysis methods and software has made QTL estimation more accurate. QTL cloning is no longer an insoluble problem. The rapid progress of plant QTL study makes the abstract and boring quantitative trait genetics more vivid and fascinating. This is the garden of genomics, where many flowers called “complicated agricultural trait” are blooming. There is a respective gene regulation network behind each flower, which is gradually revealed along with the discovery of QTLs. Though the *Arabidopsis thaliana* genome sequencing has been completed and gene cloning is very easy, botanists still analyze the important traits by locating corresponding QTL. For example, analyzing QTL determining vitamin E and plant shape, which demonstrate that QTL analysis still has broad development space.

As genome sequencing of various crops is completed and massive sequence information is released,

the development of molecular markers will greatly accelerate, high throughput molecular marking technique combining SNP and chip is emerging, and the commercialization of molecular marking is an obvious trend. The restriction factor of constructing high density genetic maps becomes the size of a mapping population rather than polymorphic molecular markers. As genetic maps become denser, plant QTL analysis will finally reach the ideal situation of one marker from one gene for one QTL. QTL cloning will become very easy.

Multiple-parent strategy is expected to be widely used in the construction of mapping populations. Since the loci with allele differences will increase by time; the efficiency of QTL examination will be greatly improved. Statistical methods and software for composite QTL analysis are required to deal with the increased multiple alleles in multiple-parent populations.

Along with the economic development and increase in investment, the conditions of field trials will be improved, the experimental error will be reduced, and the detection rate and repeatability will be further increased. Some advanced laboratory might be able to estimate the phenotype of plants under manual manipulation. It can not only improve the efficiency of QTL improvement, but also predict the QTL by simulating complex soil conditions and varied climates.

As the cost of gene chips decreases, expressed QTL analysis will be developed. Epigenetics will cross with QTL analysis. It is estimated that plant QTL analysis will become an important component of plant functional genomics and even plant system biology in the near future. Meanwhile, the “whole” QTL map determining all important agricultural traits will be improved, which will become the sketch where breeders conduct plant variety design and molecular-marker-aided breeding.

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