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Genetic mapping of quantitative trait loci in crops

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ABSTRACT

Dissecting the genetic architecture of complex traits is an ongoing challenge for geneticists. Two complementary approaches for genetic mapping, linkage mapping and association mapping have led to successful dissection of complex traits in many crop species. Both of these methods detect quantitative trait loci (QTL) by identifying marker–trait associations, and the only fundamental difference between them is that between mapping populations, which directly determine mapping resolution and power. Based on this difference, we first summarize in this review the advances and limitations of family-based mapping and natural population-based mapping instead of linkage mapping and association mapping. We then describe statistical methods used for improving detection power and computational speed and outline emerging areas such as large-scale meta-analysis for genetic mapping in crops. In the era of next-generation sequencing, there has arisen an urgent need for proper population design, advanced statistical strategies, and precision phenotyping to fully exploit high-throughput genotyping.

1. Introduction

The objective of genetic mapping is to identify QTL responsible for natural phenotypic variation. Two strategies have been widely applied to genetic mapping in plants: (1) linkage mapping and (2) association or linkage disequilibrium (LD) mapping. Linkage mapping, a conventional mapping method, depends upon genetic recombination during the construction of mapping populations. Over the past two decades, linkage mapping has been commonly used in various plant species, and many QTL have been cloned or tagged [1]. However, linkage mapping has the disadvantages of relatively low mapping resolution, low allele richness, and low speed.

Association mapping, as a complement to linkage mapping, takes advantage of historic recombination events accumulated over hundreds of generations, thus providing higher resolution and greater allele numbers [2]. Since human diseases were successfully dissected, association mapping has been applied to crops [3]. Following its introduction to crops [4], association mapping has attracted increased attention in genetic studies. Owing to the dramatic reduction in costs of sequence technologies, association mapping has been conducted in plants from the model plant *Arabidopsis thaliana* [5] to many major crops, such as rice [6], maize [7], wheat [8], soybean [9], barley [10], sorghum [11], potato [12], and tomato [13].

The key distinction between association and linkage mapping lies in whether recombination events occur in populations or families. However, both of these methods share a consistent strategy for identifying molecular markers that are linked to QTL. As we step into the era of complete genome sequencing, the

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difference between the two methods will disappear [14]. Genetic mapping can be generally classified into family-based mapping when mapping is performed in progenies of biparental or multiparent crosses and natural population-based mapping when mapping is conducted in natural populations in which relationships are unknown. In this review, we describe the family-based mapping and natural population-based mapping of complex traits, highlight the statistical methods used for genetic mapping, and outline the developmental trends and perspectives of genetic mapping in crop genetics.

2. Family-based mapping

2.1. Biparental populations

The first and most important step in family-based mapping is constructing experimental populations, which may be biparental populations such as F_2, backcrosses (BC), doubled haploids (DH), recombinant inbred lines (RIL), and near-isogenic lines (NIL). These commonly used populations with their strengths and weaknesses are described in Table 1. The general process of biparental mapping includes: (1) collection of parental strains that differ for traits of interest, (2) selection of molecular markers such as RFLP, SSR and SNP that distinguish between the two parents, (3) development of a mapping population, (4) genotyping and phenotyping of the mapping population; and (5) detection of QTL using a suitable statistical method. The power of QTL detection is affected by QTL effects, allele frequencies, and the type and size of the mapping population. Biparental mapping has proven to be useful in crop breeding [15]. The main limitation of a biparental population is that only a few recombination events occur during the development of the population, allowing the localization of QTL to 10–20 cM intervals. Additionally, detection of QTL in biparental populations depends on the phenotypic diversity of the two parents, which may account for only a small part of the genetic variation in the species.

Table 1 – Commonly used biparental populations with their strengths and weaknesses.

Population	Strengths	Weaknesses
F_2	Rapid construction, estimation of both additive and dominant effects	Lower power, limited recombination, temporary nature
BC	Utility for introgressing specific genes	Impossibility of estimation of dominant effects, time requirement, temporary nature
DH	Rapid construction, immortality, easy replication	Limited recombination, expense, impossibility of estimation of dominant effects
RIL	Abundance of recombination, immortality, easy replication	Impossibility of estimation of dominant effects, time requirement

2.2. Multiparent mapping populations

Multiparent mapping populations have been constructed to overcome the limitations of biparental populations. The genetic diversity of multiple parents leads to a population with large phenotypic diversity, making it suitable for high-resolution QTL mapping. Increasing in popularity are two experimental designs of multiparent populations that include nested association mapping (NAM) and multiparent advanced generation intercrosses (MAGIC). Recently published multiparent mapping studies in crops are summarized in Table 2.

NAM is an excellent multiparent population design suggested by Yu et al. [16] for dissecting the genetic architecture of maize flowering time. A NAM population was created by crossing 25 diverse inbred maize lines to the B73 inbred, chosen as a reference line, resulting in 5000 RILs from 25 families, with 200 RILs per family. As a combination of several high-resolution biparental populations in one large population, the NAM population affords very high resolution and power for detecting QTL. In maize, a NAM population has been used for large-scale genetic mapping for several important traits including leaf architecture and disease resistance [17–19]. The use of MAGIC populations was first proposed for QTL mapping in mouse by Threadgill et al. [20]. In crops, Kover et al. [21] first developed a MAGIC population in *A. thaliana* that consisted of 527 lines derived by intermating a heterogeneous panel of 19 founders. MAGIC populations have been used for identification of QTL for hectoliter weight and plant height in wheat [22]. MAGIC populations including several indica and japonica rice parents have been developed for QTL mapping and varietal development in rice [23]. Compared with other multiparent populations, MAGIC populations involve intermating multiple inbred founders for multiple generations prior to the construction of inbred lines, considerably improving the precision of QTL detection. Undoubtedly, MAGIC populations offer great opportunities for dissecting complex traits and improving breeding populations. Statistical approaches for QTL mapping in MAGIC populations have become available, some of them based on the general linear model (GLM) used in biparental populations [24].

3. Natural population-based mapping

With the advantages of high resolution, high allelic richness, and absence of need of the tedious development of a mapping population, natural population-based mapping has become a powerful tool for detection of natural variation underlying complex traits in more than a dozen crops since 2001. The main steps in natural population-based mapping are depicted in Fig. 1. They consist of first, collection of a sample population including elite cultivars, landraces, wild relatives, and exotic accessions; second, phenotyping traits, estimating broad-sense heritability of traits of interest and determining the genotypes of the population entries, either for candidate genes or genome-wide; third, quantification of the LD extent of the selected population; fourth, identification of the influence of population structure and kinship; and fifth, testing the associations between genotypes and phenotypes using appropriate statistical approaches. Subsequent experimental validations such as mutagenesis and gene

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Table 2 – Examples of multiparent mapping in various crop species.

Crop species	Population	Trait	Model or software	Reference
Arabidopsis	Nineteen-parent MAGIC	Germination date, bolting time	R/HAPPY Empirical Bayes MLM, Hierarchical Bayesian	Kover et al. [21]
Wheat	Four-parent MAGIC	Plant height, hectoliter weight	R/mpMap	Huang et al. [22]
Rice	Indica MAGIC, MAGIC plus, Japonica MAGIC, Global MAGIC	Biotic and abiotic stress tolerance, yield, grain quality	MLM and GLM	Bandillo et al. [23]
Wheat	Eight-parent MAGIC	Awn presence/absence	R/Popgen	Mackay et al. [25]
Barley	Eight-parent MAGIC	Flowering-time	Binary approach (BA), Haplotype approach (HA)	Sannemann et al. [26]
Tomato	Eight-parent MAGIC	Fruit weight	R/mpMap	Pascual et al. [27]
Maize	NAM	Flowering time	Joint GLM, JICIM	Buckler et al. [28,29]
Maize	NAM	Southern leaf blight resistance	ASReml	Kump et al. [17]
Maize	NAM	Northern leaf blight resistance	Joint GLM	Poland et al. [18]
Maize	NAM	Leaf architecture	Joint GLM	Tian et al. [19]

expression analysis are required. The statistical power of natural population-based mapping is strongly dependent upon the extent of LD and population structure, as well as the sample size and minor allele frequency (MAF).

3.1. How LD affects natural population-based mapping

LD describes the degree of nonrandom association of alleles at different loci in a population. LD is affected by many factors including recombination and mutation, mating system, admixture, genetic drift, and selection. The power of natural population-based mapping depends on the degree of LD between genotyped markers and QTL. Several statistics have been proposed for estimation of LD, of which the most commonly used are known as D' and r^2. Generally, r^2 values of 0.1 or 0.2 are used to present a graphical view of LD decay. How quickly LD decays with physical distance in the population determines the marker density required and the level of resolution that can be obtained. If LD decays slowly within a region, a small number of markers are required to scan the genome, but the mapping resolution will be low. In contrast, if LD decays rapidly, a relatively large number of markers are required but the mapping resolution is increased.

The extent of LD varies enormously across different species owing to differences in mating systems. Generally, selfing species such as rice, soybean, and foxtail millet tend to have extended LD. In rice, Garris et al. [30] found that LD extended to 100 kb with r^2 of 0.1 surrounding locus *Xa5*. Outcrossing species such as maize show more rapid LD decay. Even within a species, LD extent is highly variable. In maize, for instance, LD decays rapidly within 1 kb in landraces [31], and 2 kb in diverse inbred lines [32], whereas it can extend up to 100 kb in commercial elite inbred lines [32]. Rapid LD decay and great genetic diversity make maize a promising model with high power in natural population-based mapping. However, the average extent of genome-wide LD in the gene pool may not reflect the LD extent in a specific genomic region, and it is always more informative to estimate intrachromosome than genome-wide LD decay [33].

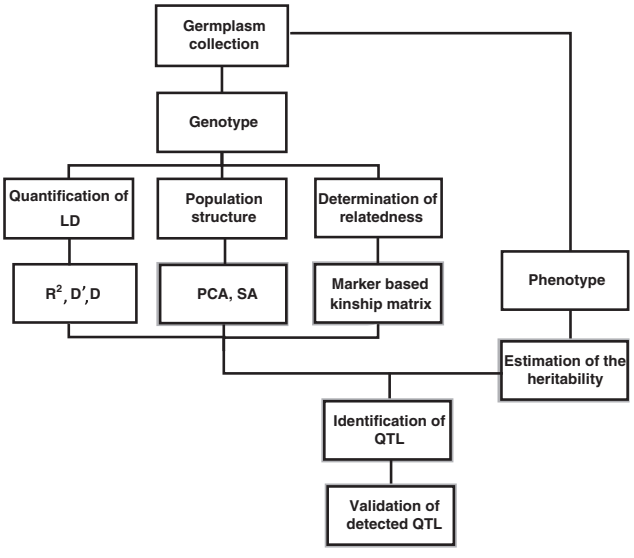

Fig. 1 – A flowchart of natural population-based mapping using diverse crop varieties.

3.2. Major limitations of natural population-based mapping: population structure, relatedness, and MAF

The most vital constraint for the use of natural population-based mapping for crops is population structure, which may lead to false positives because many neutral markers are significantly correlated with trait differences among subpopulations. The mixed linear model (MLM) is an effective method to correct for population structure (Q matrix) in natural population-based mapping, and this method treats population structure as a fixed effect [34]. This model will be discussed later in more detail. The Q matrix can be obtained by any of the following methods: genomic control (GC) [35], structured association (SA) analysis [36], or principal component analysis (PCA) [37]. GC is the first method for statistically controlling population structure and uses a set of random markers to estimate the influence of population structure on the association test statistics, assuming that such structure has equal effects on all loci. GC is used mainly for case–control studies in humans and is seldom used in crops. In contrast, SA is commonly used in crops and uses a set of random markers to infer the number of subpopulations and then estimates the probability of an individual's belonging to

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each subpopulation. Alternatively, PCA analysis summarizes the original genotype data as a small number of underlying components. Compared with SA, PCA is computationally more effective without requiring assumptions about the true number of subpopulations. However, correction using only population structure (the Q matrix) is not always adequate for avoiding spurious association. Relatedness between pairs of individuals also accounts for a proportion of phenotypic variation and can be corrected using a marker-generated kinship matrix (K matrix) in MLM. Some researchers have found that correction involving the Q + K matrix results in more accurate effect estimation than correction involving only the K matrix, especially in some populations with complex relationships. Nevertheless, it remains a challenge to correct for the population structure and relatedness effectively while maintaining statistical power.

MAF is another constraint for natural population-based mapping, and functional alleles present at low frequency (MAF < 0.05) can hardly be detected unless they exert enormous effects. However, rare alleles account for a substantial proportion of natural variation in several species. Family-based mapping is a good choice for dealing with such rare alleles because allele frequency can be artificially increased via construction of a mapping population.

4. Statistical analysis in genetic mapping

4.1. *Statistical methods for family-based mapping*

Single-marker analysis is used for initial QTL mapping in biparental populations and identifies QTL according to the difference between the average phenotypes of different genotype groups without using information about genetic distances in the linkage map. To improve the power of mapping, Lander and Botstein [38] proposed interval mapping (IM) based on maximum-likelihood parameter estimation, which efficiently estimates the effect and position of a QTL within two flanking markers. A regression version of IM developed by Haley and Knott [39] is used to simplify computation of IM. IM assumes that only one QTL affects quantitative traits of interest and ignores the effects of other QTL. However, it is well known that quantitative traits are usually controlled by several loci, and therefore QTL can be mapped more accurately by analysis of multiple QTL simultaneously. To overcome the limitation of IM, composite interval mapping (CIM), combining regression and interval mapping, selects a subset of markers as covariates that can account for the effects of linked QTL and reduce residual error [40]. The key question in CIM is how to choose appropriate marker covariates, and this question can be addressed by stepwise regression or preliminary interval mapping. A modified algorithm called inclusive composite interval mapping (ICIM) better controls sampling variance and avoids the complicated selection of marker covariates while retaining all the advantages of CIM [41]. Multiple interval mapping (MIM), an extension of interval mapping to multiple QTL, tends to be more powerful and precise than CIM in identifying QTL and allows the simultaneous estimation of multiple QTL with epistasis [42]. A large number of software packages implementing the above methods are available for biparental mapping, including QTL Cartographer, QTL Network, and R/qtl. Although many dense marker maps have been constructed, QTL interval mapping remains useful today because complete genomic information and high-density marker maps are not available for all crop species.

Analysis of multiparent populations has much in common with that of biparental populations, but it cannot intuitively yield the parental origin of alleles from the observed marker information. For this reason, methods developed for biparental mapping cannot be directly used for multiparent mapping. Xu [43] first proposed an interval mapping approach for a four-way cross design based on multiple linear regression analysis, demonstrated by later simulation studies that fixed- and random-model approaches perform equally well for multiparent mapping, and estimated the parameters of the fixed model via an iteratively reweighted least squares algorithm that disentangles QTL variance from residual variance [44,45]. Software has been designed for mapping QTL in multiparent populations. For example, assuming that QTL locations are the same in all crosses, Jourjon et al. [46] developed MCQTL software to perform QTL mapping in multicross designs using CIM and iterative QTL mapping. Mott et al. [47] developed an R package, HAPPY, for fine QTL mapping in outbred mice stocks. HAPPY estimates the probability that an allele descends from each founder strain using a hidden Markov model (HMM). This package was successfully used to detect QTL in MAGIC populations of *A. thaliana* [21]. Another R package, mpMap, was developed for QTL mapping of multiparent RILs and accommodates linear mixed models [48]. However, all of the above methods are limited to IM and CIM. Whole-genome average interval mapping (WGAIM), a QTL mapping method for biparental populations that simultaneously incorporates all intervals or marker information, has been shown to be superior to CIM and has been modified for multiparent populations (MPWGAIM) by use of the probability of inheriting founder alleles [49,50]. The founder probabilities can be determined using three-point or HMM methods. Under a MLM framework, MPWGAIM allows for population structure to be modeled and uses a forward selection approach to reduce model complexity. However, it still incurs a high cost if the numbers of markers and QTL included are large. Wei and Xu [51] developed a random-model approach for MAGIC populations by assuming founder effects at each locus to be random effects following a common normal distribution and showed this approach to be more powerful and substantially faster than MPWGAIM. Bayesian methods, such as hierarchical Bayes and empirical Bayes, are also useful in multiparent mapping because of their flexibility to deal with uncertainty of founder allele inheritance [21]. However, when a Bayesian method is used, a dataset with a large number of markers creates a heavy computational demand resulting from frequent Monte Carlo sampling. Although several methods have been developed for multiparent mapping, they have yet to take full advantage of these special designs. There remains an urgent need for statistical methods that permit rapid and accurate identification of QTL in multiparent populations.

4.2. *Statistical methods for natural population-based mapping*

Several powerful natural population-based mapping methods have been proposed. The MLM approach suggested by Yu et al.

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[34] is becoming more and more popular, as it successfully corrects for population structure and family relatedness [2]. However, with its requirement of large sample size and high marker density (~1 million markers) to improve the power of QTL identification, the computational demand of the MLM approach is high. Under the framework of the MLM model, several methods have been developed to substantially improve computational speed (Fig. 2). For example, efficient mixed model association (EMMA) takes advantage of eigendecomposition to evaluate the likelihood functions, making matrix inversion and determinant calculation into simple summations and thus decreasing the computational time [52]. Another new method called the genome-wide efficient mixed model (GEMMA) suggested by Zhou and Stephens [53] has proven much faster than EMMA. Lippert et al. [54] developed an improved method called the factored spectrally transformed linear mixed models (FaST-LMM), which selects a set of markers to extract the polygenic effect and permits short computation times even for 120,000 individuals. All three methods mentioned above are also called exact methods, because the polygenic variance is re-estimated with each marker analyzed. Some approximate approaches that do not involve re-estimating polygenic variance include EMMAX (efficient mixed-model association eXpedite) [55], P3D (population parameters previously determined) [56], compressed MLM [56], and FaST-LMM-Select [57]. These approximate approaches substantially increase speed at the cost of accuracy. The search for new mapping methods with high precision and speed is a current trend. Recently, Wang et al. [58] presented the SUPER method, which retains the computational advantage of FaST-LMM and improves the statistical power. Loh et al. [59] proposed BOLT-LMM, an efficient Bayesian mixed model analysis, which dramatically reduces running time and increases power by using a mixture of two Gaussian distributions as a prior on marker effect sizes.

Multilocus association mapping, in which multiple loci are identified simultaneously, has the potential to increase power and avoid multiple testing [60]. In earlier research, many multilocus methods, such as least-squares kernel machines [61] and generalized ridge logistic regression [62], have been developed without consideration of population structure. Recently, three powerful methods combining the mixed model and sparse regression have been proposed to deal with multiple loci and population structure. The multi-locus mixed model (MLMM) proposed by Segura et al. [63] shows promising performance in terms of false positives and power, using a forward–backward stepwise approach. Rakitsch et al. [64] presented the linear mixed model-Lasso (LMM-Lasso) method, which employs MLM and sparse lasso regression, applying a Laplacian shrinkage to the fixed effects and assuming the effects of the majority of markers to be equal to zero. Also, the Bayesian sparse linear mixed model (BSLMM) sets an appropriate prior for hyper-parameters and uses the Markov chain Monte Carlo algorithm for posterior inference, yielding reliable results for large datasets [65].

Single-trait approaches are most commonly used in natural population-based mapping, but recently, multitrait approaches are attracting interest because detection power may be increased by taking into account the correlation structure of multiple traits. Many multi-trait methods are available for linkage mapping, but they are hard to implement in natural population-based mapping

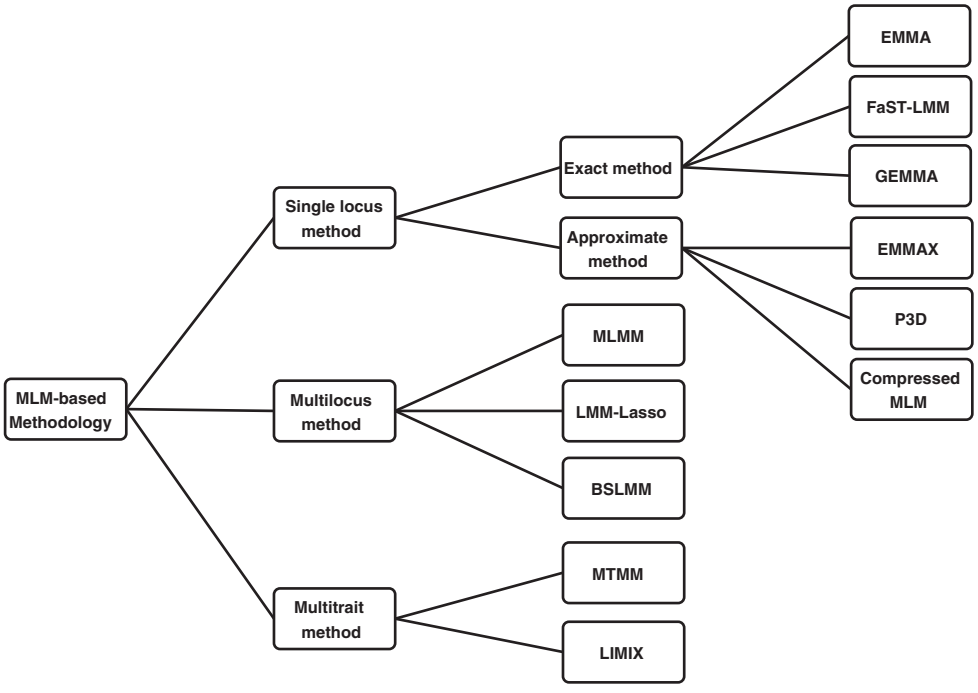

Fig. 2 – MLM-based statistical methods available for single locus, multilocus and multitrait mapping. EMMA: efficient mixed model association; FaST-LMM: factored spectrally transformed linear mixed models; GEMMA: genome-wide efficient mixed model; EMMAX: efficient mixed-model association eXpedite; MLMM: multi-locus mixed model; LMM-Lasso: linear mixed model-Lasso; BSLMM: Bayesian sparse linear mixed model; P3D: population parameters previously determined; MTMM: multitrait mixed model.

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owing to computational complexity and failure to control for population structure. Korte et al. [66] first proposed the multitrait mixed model (MTMM), which extends the MLM approach to multiple correlated traits, permitting the identification of both interactions and pleiotropic loci while correcting for population structure. Then, Lippert et al. [67] developed LIMIX, a multitrait mixed-modeling framework that allows the joint analysis of numerous traits with high computational efficiency and power by combining multitrait models and stepwise multilocus regression. With the many approaches now available to identify QTL, one should choose an approach appropriate for a given dataset, leading to higher statistical power and lower numbers of false positives.

4.3. *Multiple-testing corrections*

Methods for identifying appropriate critical values are important for declaring significant QTL effects in single-marker scanning approaches and also pose a challenge for multiple-testing correction. Several methods developed to deal with this problem include Bonferroni correction, permutation, false discovery rate (FDR) and others. Bonferroni correction is a conventional way to correct for multiple tests but is highly conservative, correcting the P-value (0.05) by division by the number of statistical tests conducted. Holm proposed a Bonferroni step-down correction procedure that is considered less stringent [68]. An alternative to adjusting for multiple testing is permutation, which generates an empirical distribution of a test statistic by randomly reassigning phenotypes among individuals, thus yielding reliable results but requiring too much time for large datasets [69]. Also, FDR as originally proposed by Benjamini and Hochberg [70] is commonly used and is considered less stringent than any of the above methods. An additional adjustment for Bonferroni correction is the replacement of the number of independent tests with the effective number estimated based upon the linkage relationships of the markers, thus reducing the actual number of tests [71]. As there are several methods of correction for multiple testing, it is necessary to compare the results of different methods and choose an appropriate method according to the research objective.

5. Future perspectives for genetic mapping in crops

5.1. *High-density genotyping*

Historically, SNP array-based approaches to genotyping have been widely used in genetic mapping for many plants. As sequencing cost continues to decrease, researchers are developing novel methods that leverage next-generation sequencing (NGS) platforms for genotyping. Genotyping by sequencing (GBS) is a simple, highly multiplexed technology used for creating reduced-representation libraries for marker discovery and genotyping [72]. As a relatively rapid, robust and cost-effective tool, GBS is currently being successfully applied to genotype several crop species with complex genomes [73]. In maize, Romay et al. [74] used GBS to genotype 2815 maize inbred accessions and identified 681,257 SNPs across the entire genome, some of which were close to known candidate genes for flowering time. Sequencing of reduced-representation libraries for the diverse set of 304 soybean genotypes produced over 47,000 SNPs, of which some were significantly associated with five complex traits and most were located in genomic regions identified by previous studies [75].

Integrating GBS and biparental mapping is becoming a powerful tool for dissecting complex traits in plants. For example, a 384-plex GBS protocol was used for adding 30,984 markers to an indica × japonica mapping population with 176 rice RILs and a previously unreported QTL associated with aluminum tolerance was identified [76]. In barley, Liu et al. [77] used GBS to construct a genetic map of 136 RILs and precisely mapped the dwarfing gene *Breviaristatum-e* on chromosome 5H. In oil palm, of 21,471 SNPs identified from GBS libraries of 108 F_2 progeny, 1085 SNPs distributed over 17 linkage groups were used to construct a linkage map and three QTL associated with trunk height and a single QTL controlling bunch weight were identified [78]. Recently, a high-density GBS consensus map including 28,644 markers was constructed in bread wheat, and three rust-resistance genes and 15 published QTLs were validated with high resolution [79].

To analyze GBS data, the TASSEL GBS pipeline is available for large quantities of data from a large number of samples with a reference genome [80], while the UNEAK pipeline is designed for species without a reference genome [81]. One potential limitation of GBS, however, is the large proportion of missing data per marker due to low-fold sequencing. It is necessary to impute missing markers before GBS data can be used for genetic analyses. Some accurate algorithms have been developed for imputation in related and unrelated individuals [82]. However, for species without a reference genome and a complete reference linkage map, the imputation of GBS data remains challenging [83]. Recently, a population-sequencing approach was proposed to order and impute GBS markers in hexaploid wheat [84]. The major advantages of GBS are that it is less expensive than other genotyping platforms and can be adapted to species that lack preliminary sequence or genotypic information. As the quality and amount of sequencing information produced per run continuously increase, it is anticipated that GBS will be extensively applied to genetic mapping in numerous species.

5.2. *Phenotyping*

The last decades have seen a revolution in our understanding of genotypes, and now genotypes can be determined to the level of individual nucleotides and rapidly sequenced genome-wide at dramatically declining cost [85]. However, the precision of phenotype characterization remains the main bottleneck in genetic mapping, because most phenotypes are affected by interactions between genes and environment and some developmental traits change dynamically at different developmental stages [70]. Phenomics, as a high-throughput phenotyping technology, has the potential to increase phenotyping precision and facilitates dynamic measurement, thus relieving this bottleneck. With recent advances in computing, robotics, spectroscopy and image analysis, phenomics is becoming available in crops [86]. To date, phenomics has been applied to important traits such as abiotic stress resistance and yield, and it is expected to erase the boundaries between genomics, plant function, and agricultural traits [87].

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5.3. *Bulked sample analysis*

Compared to conventional genetic mapping, which requires analyzing all individuals for traits of interest in sample populations, selective genotyping and bulked-segregant analysis are more efficient and cost-effective, especially for major gene-controlled traits and QTL with large effect. With the development of NGS technologies, bulked-segregant analysis can be used not only for biparental segregating populations but also for natural populations. Recently, Zou et al. [88] defined bulked sample analysis (BSA) as a sampling–bulking method that selects extremes or representative samples from any populations and pools them as bulks. The power of bulked sample analysis is greatly affected by sample selection and sample size. A selected sample can be generated by bidirectional selection when the two tails of a distribution are considered or by single selection when only one tail is considered [89]. Bidirectional selection is widely used and generally more effective, as it avoids the effect of segregation distortion. However, single selection is more suitable for traits under strong negative or lethal selection pressure. With the development of high-throughput genotyping platforms, chip-based BSA has been successfully used to detect QTL for traits of agronomic importance, such as rust resistance in wheat [90], kernel row number in maize [91], and salt tolerance and blast disease in rice [92,93]. Owing to its reduction in genotyping cost and high detection power, BSA will become increasingly prominent in genetic mapping.

5.4. *Large-scale meta-analysis*

The statistical power to detect QTL is determined by the sample size used for a study. One can perform a single study using a large sample, but this approach is much too costly [94]. To overcome this limitation, meta-analysis has been used to combine results from multiple studies and increase the power of genetic mapping. Recently, several large-scale meta-analyses have been successfully performed for human diseases, and the approach is thus a promising method for the detection of new genetic loci in crops. A major difficulty in performing meta-analysis stems from heterogeneity due to genetic and environmental factors. Heterogeneity is usually measured using the Q statistic and the I2 index [95]. Although random-effects models have been used to deal with this problem [96], some studies with high heterogeneity should be removed from a meta-analysis [97]. Besides increasing the chances of finding true positives, random effects-based meta-analysis (Meta-G × E) can be applied to identify gene-by-environment interactions by treating the interactions as heterogeneity, an approach that has proven powerful in mouse data analysis [98]. Thus, it will be desirable to apply this method for identification of loci involved in gene-by-environment interactions in crops.

6. Conclusions

Family-based mapping and natural population-based mapping are the two major approaches for genetic mapping of QTL and detected QTL can be used for the improvement of quantitative traits via marker-assisted selection (MAS). These approaches have complementary advantages and limitations. Population structure and rare alleles remain problems for natural population-based mapping. For this reason, multiparent designs such as NAM and MAGIC are becoming popular in crop genetics and breeding, making it urgent to develop more efficient methods for identification of QTL in these population designs. Although the advent of a series of MLM-based methods facilitates the genetic mapping of complex traits, there is still a need for advanced and powerful methodology to address challenges such as multiple-testing corrections and large-scale meta-analysis. With the development of high-throughput genotyping, phenotyping will be a major challenge for genetic mapping studies. We believe that high-quality phenotyping and appropriate experimental design coupled with new statistical models will accelerate progress in dissecting the genetic architecture of complex traits.

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