The Past, Present, and Future of Maize Improvement: Domestication, Genomics, and Functional Genomic Routes toward Crop Enhancement

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ABSTRACT

After being domesticated from teosinte, cultivated maize (Zea mays ssp. mays) spread worldwide and now is one of the most important staple crops. Due to its tremendous phenotypic and genotypic diversity, maize also becomes to be one of the most widely used model plant species for fundamental research, with many important discoveries reported by maize researchers. Here, we provide an overview of the history of maize domestication and key genes controlling major domestication-related traits, review the currently available resources for functional genomics studies in maize, and discuss the functions of most of the maize genes that have been positionally cloned and can be used for crop improvement. Finally, we provide some perspectives on future directions regarding functional genomics research and the breeding of maize and other crops.

Key words: maize, domestication, genomics, functional genomics, improvement

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INTRODUCTION

After Columbus arrived in the New World and brought maize to Europe, it subsequently spread throughout the world (Brandolini and Brandolini, 2009; Nunn and Nancy, 2010). Nowadays, its production exceeds that of wheat (Triticum aestivum) and rice (Oryza sativa) (http://www.fao.org). Indeed maize has become the most productive cereal crop and therefore has a massively important role, directly or indirectly, in feeding human beings. At the beginning of the last century, a controversy arose concerning the origin of maize. One hypothesis stated that maize is a species resulting from hybridization of a close relative of maize and Tripsacum; a second stated that the oldest wild maize is the ancestor of modern maize (Beadle, 1972). Subsequent genetic and archaeological evidence indicated that one subgroup of teosinte, Zea mays ssp. parviglumis, is the only ancestor of maize, a finding that is now widely accepted (Benz, 2001; Piperno and Flannery, 2001; Matsuoka et al., 2002; Vallebueno-Estrada et al., 2016). The divergence between Z. mays ssp. parviglumis and maize occurred about 9000 years ago around the Balsas River of southwest Mexico (Matsuoka et al., 2002).

Some key traits of teosinte are very different from those of maize, for example, its abundant branches and tillers, increased number of ears per plant, reduced number of kernels per ear (5–12 per ear for teosinte and several hundred for maize), and small kernels with a hardened fruitcase (reviewed in Doebley, 2004). How many loci were involved in the domestication of maize? More than 40 years ago, Beadle (1972) reported that he had planted a teosinte–maize F2 population consisting of 50 000 individuals and found that the frequency of parental types was ~1 in 500, then estimated that there were four or five major loci involved in maize domestication. Later, Doebley and Stec (1993) mapped five major quantitative trait loci (QTLs) plus some minor-effect QTLs for key traits in which teosinte and maize differ. This result was consistent with Beadle’s estimation and indicated that a small number of loci were responsible for the teosinte–maize morphological difference. Wright et al. (2005) investigated 774 genes and estimated that 2%–4% of maize genes were selected during maize domestication and subsequent improvement. According to recently released gene annotations of high-quality maize

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have had an important role in maize domestication (Li et al., 2018; Yang et al., 2019a), indicating that \( tga1 \) is a single-nucleotide polymorphism (SNP) in the first exon that leads to a higher number of branches (Aguilar-Martinez et al., 2007); barley plants with the mutant allele of \( HvTB1 \) have a significantly higher number of tillers at the juvenile stage (Ramsay et al., 2011); and TaTB1 interacts with \( FLOWERING LOCUS T1 \) and regulates inflorescence architecture in bread wheat (\( Triticum aestivum \)) (Dixon et al., 2018). The conserved function of \( tb1 \) suggests its great potential for domesticating existing wild plants.

Another well-characterized maize domestication gene is \( tga1 \) (teosinte glume architecture 1), which encodes a squamosa-promoter binding protein (SBP) transcription factor. \( tga1 \) is responsible for the shift from kernels encased in a hardened fruit-case in teosinte to naked kernels exposed on the ear of modern maize. This QTL was mapped to a single Mendelian locus on chromosome 4 (Dorweiler et al., 1993) and was subsequently cloned (Wang et al., 2005). The causal variant of \( tga1 \) is a single nucleotide polymorphism (SNP) in the first exon that leads to a single amino acid change (Lys to Asn) at the sixth amino acid of TGA1, a change that affects the binding of TGA1 to its targets (Wang et al., 2005). Interestingly, \( tga1 \) is regulated by \( tb1 \) through direct binding of TB1 to two GGNCCC motifs in the promoter region of \( tga1 \) (Studer et al., 2017).

In addition to \( tb1 \) and \( tga1 \), dozens of genes have been isolated that control key traits for the transition from teosinte to maize (Table 1). Most of these domestication genes are transcription factors, and their expression levels were upregulated during domestication (Figure 1B–1D). Thus, their altered expression likely affected the expression of large numbers of downstream genes, including additional transcription factors, as illustrated by the regulatory network in which \( tb1 \) and \( tga1 \) are involved (Studer et al., 2017). This suggests that selection at the level of a regulatory network might be much more efficient in driving phenotypic changes as compared with variations that affect the function of an individual protein (Liu et al., 2015c).

Recently, two studies using ChIA-PET (chromatin interaction analysis by paired-end tag sequencing) technology mapped...
genome-wide chromatin interactions and revealed their connections to gene-expression regulation (Li et al., 2019b; Peng et al., 2019), including the chromatin interactions in which TB1, UB3, ZmCCT9, Vgt1 involved. Likely, population-scale identification of chromatin interactions would allow the detection of many more important regulatory elements, providing a number of useful selection targets for future maize improvement.

MAIZE FUNCTIONAL GENOMICS RESEARCH RESOURCES

Reference Genome Sequences

The first maize reference genome sequence (B73 RefGen_v1) was released in 2009 (Schnable et al., 2009) and relied on the sequencing of bacterial artificial chromosomes and fosmids; a subsequent release in 2017 was improved by the use of single-molecule technologies (Jiao et al., 2017). Since the release of the B73 reference genome sequence, it has been extensively used for maize functional genomics research. By comparing other inbred lines with B73, millions of SNPs and insertions/deletions (InDels; e.g., those of tb1 as illustrated in Figure 1) were identified, along with many structural variations (SVs) (examples of which are shown in Figure 2), presence/absence variation (PAV), expression presence/absence variation (ePAV), and copy-number variation (Springer et al., 2009; Lai et al., 2010; Jiao et al., 2012; Fu et al., 2013; Hirsch et al., 2014; Lu et al., 2015; Jin et al., 2016; Bukowski et al., 2018; Sun et al., 2018; Yang et al., 2019a).

The use of high-density SNPs, which were identified by resequencing maize lines and populations and mapping those sequences to the B73 reference genome, has greatly expanded our knowledge concerning maize domestication and development (Hufford et al., 2012) and the genetic basis of important traits such as flowering time (Buckler et al., 2009), disease resistance (Kump et al., 2011), oil and vitamin metabolism (Li et al., 2013; Wang et al., 2018a), plant height (Pan et al., 2017), and yield-related traits (Xiao et al., 2016; Liu et al., 2017c). Maize SNP arrays designed for molecular breeding by integrating SNPs associated with known genes and traits have been reported (Yan et al., 2010b; Xu et al., 2017). However, most resequencing research in maize and other crops has focused on identifying SNPs through mapping to a single reference genome, which limits the ability to make full use of genome data, detect SVs, and fully reveal the genetic diversity (Yang et al., 2019b). Recently, human graph-reference genomes, into which existing variations could be incorporated, have been used for alignments and genotyping (Garrison et al., 2018; Kim et al., 2019; Rakocevic et al., 2019). This strategy can take advantage of multiple genome sequences and reported variations and can increase the variant-calling accuracy, especially for SVs. We speculate that this graph-reference genome approach or other newly developed methods will soon be adopted by researchers studying maize and other crop genomes in order to integrate the increasing amounts of variation data and genome sequences that are becoming available.

A further disadvantage of resequencing studies is that most of them fail to detect associations between SVs and traits, despite
growing evidence that SVs affect important agronomic traits, e.g., flowering time, plant height, kernel weight, disease resistance, and metabolic traits (Hirsch et al., 2014; Lu et al., 2015; Zuo et al., 2015; Jin et al., 2016). At a genome-wide level, it was demonstrated that 22% of SVs could not be detected using SNPs (Yang et al., 2019a). This indicates that more reference genome sequences are required to fully characterize the maize functional genome.

With the development of new sequencing technologies and the decreased costs of sequencing, several additional maize genome sequences have been reported since 2016. These include the genomes of PH207 (Hirsch et al., 2016), mexicana (Yang et al., 2017a), Mo17 (Yang et al., 2017a; Sun et al., 2018), W22 (Springer et al., 2018), HZS (Li et al., 2019a), and SK (Yang et al., 2019a). Among these released genomes, the B73, Mo17, W22, and SK genomes have high-quality assemblies (Table 2) and thus could be representative genomes for maize genomics research. The high-quality assemblies enabled by single-molecular sequencing, which are currently available for B73 Ref_V4, Mo17, and SK, have greater advantages in annotation of genome features and identification of important elements (such as promoters and TEs) and variations (especially structure variations) compared with assemblies based on short-read sequencing (Jiao et al., 2017; Sun et al., 2018; Yang et al., 2019a). Without the high-quality assembly of SK achieved by long-read sequencing, it would have taken tremendous effort to identify the large structure variations located upstream of ZmBAM1d, the gene underlying a major QTL affecting maize kernel size and weight (Yang et al., 2019a). There is no doubt that these genome sequences will greatly facilitate the revelation of maize genetic diversity, the connection between genetic variation and phenotypic variation, and the maize improvement process.

Mutant Libraries
Mutants are important resources for plant functional genomics research. Unlike Agrobacterium T-DNA insertion mutant libraries in Arabidopsis and rice (Alonso et al., 2003; Wu et al., 2003; Zhang et al., 2006), maize researchers mainly use transposon mutagenesis approaches to tag genes for cloning. Many genes for important agronomic traits have been cloned by transposon tagging. The most well known is tb1, a major domestication locus affecting tiller number and inflorescence development (Doebely et al., 1997). Several research programs have tagged maize genes with active Mu, including the Trait Utility System for Corn, Maize Targeted Mutagenesis database, Mu array, RescueMu, Photosynthetic Mutant Screen, and UniformMu (reviewed in Brutnell, 2002). Among these programs, UniformMu is currently the most widely used (McCarty et al., 2005). However, only ~30% of maize genes have UniformMu insertions. Apart from transposon mutagenesis, targeting induced local lesions in genomes (TILLING) has also been used to construct maize mutant libraries (Till et al., 2004; Lu et al., 2018). In this approach, point mutations, caused by exposure to ethyl methanesulfonate, are detected with high-throughput methods or NGS. The mutant library constructed by Lu et al. (2018) covers ~80% of maize genes (32 069 of 39 591), with each line containing on average 4500 mutations.

Nurtured and Natural Populations
As molecular markers were applied to construct linkage maps and to map QTLs for quantitative traits, many different kinds of mapping populations were generated, not only in maize but also in other crops, including classic F2, backcross, chromosome segment substitution line, recombinant inbred line (RIL), and multi-parent advanced generation intercross populations. In

Figure 2. Examples of Large Structural Variations between Two Maize Lines, B73 and Mo17.
(A) An ~2-Mb inversion on chromosome 7, as indicated by blue dots and dashed box.
(B) Two adjacent inversions covering ~2 Mb on chromosome 1, as indicated by blue dots and dashed boxes.
(C) An ~3-Mb deletion in Mo17, as compared with B73, on chromosome 6.
(D) An ~3-Mb insertion in Mo17, as compared with B73, on chromosome 6.
The alignment was performed using MUMMER 3.23 (Kurtz et al., 2004) with a minimum match length of 1 kb.
addition to these commonly used populations, maize researchers have constructed other types of high-resolution mapping populations that have been used extensively for genetic mapping. One such population is the intermated B73-Mo17 (IBM) population, a type of intermated RIL (IRIL) population. Unlike regular RIL populations, the F₂ progenies of crosses between B73 and Mo17 were intermated for four generations before repeated selfing by single-seed descent to generate RILs. Because of the extra generations of intermating, the genetic map of this population has a 2.7-fold greater recombination fraction distance and a 3.86-fold longer map length (Lee et al., 2002), thus significantly improving the QTL mapping resolution. Another such population is a nested association mapping (NAM) population consisting of 25 RIL populations with a common parent line (B73) with a sequenced genome (Yu et al., 2008). This population captured ~136,000 recombination events with three recombinations per gene on average. This genetic design took advantage of both linkage mapping and association mapping (McMullen et al., 2009). Both IBM and NAM populations have been used to dissect the genetic basis of complex traits, such as flowering time and disease resistance (Balogh et al., 2007; Buckler et al., 2009; Kump et al., 2011), and the population resources, including parental lines, are now publicly available (https://maizegdb.org/stock_catalog). Recently, Xiao et al. (2016) developed a random-open-parent association mapping population. This type of population has several advantages, the most impressive of which is that newly developed populations can be integrated into existing populations (reviewed in Xiao et al., 2017). It has been successfully used to dissect the genetic basis of cob traits (Xiao et al., 2016), kernel traits (Liu et al., 2017c), and plant architecture (Pan et al., 2017).

An association test between *dwarf8* and flowering time was the first instance of association analysis being applied in plant genetics. This analysis tested associations between 123 polymorphic sites covering *dwarf8* and flowering time in an association mapping population consisting of 92 maize inbred lines, and used 141 simple sequence repeat loci to control for population structure (Thornsberry et al., 2001). Thereafter, many maize natural populations were used for candidate-gene-association analyses (reviewed in Yan et al., 2011; Xiao et al., 2017; Liu and Yan, 2019), and association tests were subsequently extended to genome-wide association studies (GWASs) in maize and other plants including, but not limited to, *Arabidopsis* (Atwell et al., 2010), barley (Cockram et al., 2010), rice (Huang et al., 2011), and tomato (Sauvage et al., 2014). In maize, some natural populations have been widely used for GWAS research. One such population is the “Goodman” maize diversity panel, which contains 302 inbred lines and captures the diversity present in public breeding programs (Flint-Garcia et al., 2005). This panel has been genotyped using the Illumina MaizeSNP50 Array (Olukolu et al., 2013) and genotyping-by-sequencing (GBS; Romay et al., 2013), and is now covered by maize HapMap 3 (Bukowski et al., 2018). The “Goodman” panel has been used to dissect the genetic basis of ear rot resistance (Zila et al., 2013), iron homeostasis (Benke et al., 2015), aflatoxin resistance and important agronomic traits (Farfan et al., 2015), resistance to *Fusarium verticillioides* infection (Stagnati et al., 2019), and metabolite production (Zhou et al., 2019b). Another panel-based resource is the MaizeGo panel (http://www.maizego.org/Resources.html), which consists of 540 well-chosen lines and represents the largest association mapping population panel assembled for maize (Yang et al., 2011; Liu et al., 2017a). Many efforts to dissect the genetic architecture of complex traits have been carried out with this population or with a subset of this population, including analyses of expression traits (Fu et al., 2013; Liu et al., 2015c, 2017b), metabolite levels (Li et al., 2012, 2013; Wen et al., 2014, 2018; Deng et al., 2017; Wang et al., 2018a), agronomic traits (Yang et al., 2013, 2014), disease resistance (Chen et al., 2015; Ding et al., 2015; Li et al., 2019d), and drought tolerance (Liu et al., 2013; Mao et al., 2015; Wang et al., 2016; Xiang et al., 2017).

### Databases and Datasets

The most valuable database for the maize research community is the Maize Genetics and Genomics Database (MaizeGDB; https://www.maizegdb.org/) (Portwood et al., 2019). This database was first released in the early 1990s and has since evolved into a “Swiss army knife” of datasets and tools for maize functional genomics research. First, it supports genome sequences of several maize inbred lines with a user-friendly genome browser. It also contains, among other features, large numbers of datasets covering stocks, polymorphisms, mutants and phenotypes, genetic maps, QTLs, gene annotations, and transcriptomic and proteomic data. Furthermore, it provides many tools for querying and visualizing datasets, such as SNPversity, which allows the visualization of the SNP diversity of a selected genomic region, and qTeller (https://qtagle.maizegdb.org/), which allows the exploration of the expression of genes of interest. Finally, it provides additional services for the maize community such as the...
coordinated expression of genes and proteins. This has led to the identification of key regulatory elements and transcription factors that coordinate the development of different tissues in maize. The maize community has generated large numbers of datasets, but in this review we will focus on population-scale genotypic variation and gene-expression datasets given their important proven connections with phenotypic variation. Accompanying the release of the maize B73 reference genome, the first-generation haplotype map of maize was also released. This HapMap 1 was constructed with 3.3 million SNPs and InDels identified within the founder lines of the NAM population (Gore et al., 2009). This HapMap subsequently evolved into HapMap 2 following the deep sequencing of 103 inbred lines covering 19 teosinte accessions, 23 landraces, and 60 improved lines, including the NAM founders of HapMap 1. HapMap 2 consists of 55 million SNPs, 21% of which are located in genic regions (Chia et al., 2012), and has been used to identify genomic regions that underwent selection during maize domestication and improvement (Hufford et al., 2012). More recently, maize HapMap 3 was built from NGS data from ~1200 lines covering those used for HapMap 2, International Maize and Wheat Improvement Center (CIMMYT) lines, China Agricultural University (CAU) lines, and the Goodman panel. HapMap 3 contains ~83 million polymorphisms (Bukowski et al., 2018). In addition to the HapMap populations, the MaizeGo panel has been genotyped with SNP arrays, RNA sequencing (RNA-seq), and GBS and also has a very high SNP density (2.65 million SNPs) (Yang et al., 2011; Fu et al., 2013; Liu et al., 2017b). All information about MaizeGo panel was integrated into a database called MODEM (http://modem.hzau.edu.cn/) (Liu et al., 2016).

Temporal and spatial gene-expression profiles are critical both for the functional analysis of genes and for understanding developmental processes. Most gene-expression profiling studies in maize have focused on maize seeds or seed parts at different stages of development in order to identify networks important for kernel and endosperm development and, thus, crop yield. Using deep RNA-seq, Fu et al. (2013) profiled the expression levels of 28,769 genes and 42,211 transcripts in kernels at 15 days after pollination (DAP) from 368 inbred lines, which were a subset of the MaizeGo panel. Similarly, Li et al. (2014) reported the temporal patterns of gene expression in kernels and endosperm during eight stages within 0–12 DAP; Chen et al. (2014) and Yi et al. (2019) quantified gene-expression levels in the embryo, endosperm, and whole seed at 0–38 DAP and 0–144 h after pollination, respectively. Recently, Zhan et al. (2019) used laser-capture microdissection technology to isolate five different endosperm compartments from B73 kernels at 8 DAP and then quantified the transcription level of genes within these compartments using RNA-seq. In addition to gene-expression quantification in kernel-related tissues, there have been other reports of gene-expression profiling in multiple tissues across the entire maize life cycle. These include 79 tissues from B73 (Stelplugs et al., 2016), 23 tissues from B73 (Valley et al., 2016), and 23 tissues from B73, Mo17, and their F1 hybrid (Zhou et al., 2019a). These diverse gene-expression profiles have already contributed much toward identifying networks for development and could also provide the first hints of the functions of genes of interest.

GENES UNDERLYING IMPORTANT QUANTITATIVE TRAITS

There are thousands of QTLs, and hundreds of genes have been identified that are important for maize agronomic traits. Among the resulting cloned genes, 464 “classic” genes were cloned based on visible morphological mutant phenotypes (Schnable and Freeling, 2011). Although these cloned mutant genes are functionally important for maize development, most of them cannot be used directly in maize-breeding programs due to their deleterious effects. In this review, we will pay much more attention to genes (Table 3) identified by positional cloning whose genetic polymorphisms are responsible for natural variation in important quantitative traits and are additionally promising candidates for marker-assisted selection (MAS).

Flowering Time-Related Genes

In the late 1990s, Vladuțu et al. (1999) identified two tightly linked QTLs for flowering time and named them Vegetative to generative transition 1 and 2 (Vgt1 and Vgt2). Vgt1 was then mapped to a 1.3-cM interval (Salvi et al., 2002) and was finally cloned (Salvi et al., 2007). Vgt1 consists of a non-coding regulatory element located ~70 kb upstream of an AP2-like transcription factor, ZmRap2.7. The role of ZmRap2.7 as a negative regulator of flowering time was confirmed in both overexpression and downregulation studies carried out by means of transgenesis (Salvi et al., 2007). Three polymorphisms (G/A/indel1324, MITE, and ATindel434) in Vgt1 were found to be significantly associated with flowering time in two independent association mapping studies (Salvi et al., 2007; Ducrocq et al., 2008). The miniature inverted-repeat transposable element (MITE) insertion in Vgt1 was demonstrated to be highly methylated, and its flanking region was significantly more methylated compared with alleles without this MITE insertion (Castelletti et al., 2014). Allele-specific expression analysis of ZmRap2.7 in F1 plants showed that the two allele-specific transcripts exhibited significantly different expression levels (Castelletti et al., 2014).

ZmCCT is another major flowering-time QTL and was first mapped to a ~170-kb region containing five putative genes in one parental line and eight in the other (Ducrocq et al., 2009). A CCT gene, ZmCCT10, which is homologous to rice Ghd7 (a large-effect locus for grain number, plant height, and heading date) (Xue et al., 2008), was proposed to be the candidate for this QTL (Ducrocq et al., 2009). This QTL was independently mapped to a ~202-kb region that includes part of ZmCCT10, the only gene present in the QTL interval (Hung et al., 2012). The effect of ZmCCT10 on flowering time was confirmed by association analyses in two independent diverse panels (Hung et al., 2012; Yang et al., 2013) and also by transgenic analysis (Yang et al., 2013). The causal variation of ZmCCT is a 5122-bp CACTA-like TE located ~2.5 kb upstream of ZmCCT10. This TE could lead to a change in the methylation level of the ZmCCT10 promoter that would affect the expression level of the gene (Yang et al., 2013). Another CCT gene, ZmCCT9, is the gene underlying qDTA9, a QTL for days to anthesis (DTA). This QTL was narrowed down to a ~2.4-kb region located ~57 kb
upstream of ZmCCT9. A Harbinger-like TE was the most significant polymorphism associated with DTA based on an association analysis. In addition, knocking out ZmCCT9 with CRISPR/Cas9 resulted in earlier flowering under long-day conditions (Huang et al., 2018).

Interestingly, all three causal TEs underwent selection during maize adaptation to temperate regions. The frequency of the MITE allele of Vgt1 varies from 0.3 in tropical lines to 0.87 in the European and Northern elite lines, and there is a significant correlation between latitude and MITE frequency (Ducrocq et al., 2008). The frequency of the TE alleles of ZmCCT10 and ZmCCT9 increased from 51.4% and 10.3% in tropical lines to 85.4% and 79% in temperate lines, respectively (Huang et al., 2018).

ZmCCT10, ZmCCT9, and CCT genes in other plants (such as rice Hd1 and Ghd7) have important roles in regulating flowering time, which indicates a conserved function among CCT genes. In maize there are 53 CCT genes, among which 15 are significantly associated with flowering time based on candidate-gene association analysis (Jin et al., 2018). These results underscore the substantial role of CCT genes and their related pathways in flowering-time manipulation.

### Table 3. Positionally Cloned Maize Genes Related to Important Quantitative Traits

| Gene         | Phenotype                  | Functional annotation                  | Causal variation                                                   | References                  |
|--------------|----------------------------|----------------------------------------|-------------------------------------------------------------------|-----------------------------|
| ZmRap2.7     | Flowering time             | AP2-like transcription factor          | MITE TE ~70 kb upstream of this gene                              | Salvi et al., 2007;         |
|              |                            |                                        |                                                                   | Castelletti et al., 2014    |
| ZmCCT10      | Flowering time             | CCT transcription factor               | CACTA-like TE ~2.5 kb upstream of this gene                       | Hung et al., 2012;          |
|              | Disease resistance         |                                        |                                                                   | Yang et al., 2013;          |
|              |                            |                                        |                                                                   | Wang et al., 2017           |
| ZmCCT9       | Flowering time             | CCT transcription factor               | Harbinger-like TE ~57 kb upstream of this gene                    | Huang et al., 2018          |
| ZmCLA4       | Leaf angle                 | Ortholog of LAZY1 in rice              | −                                                                 | Zhang et al., 2014          |
| ZmRAVL1      | Leaf angle                 | B3 domain–containing protein           | 2-bp InDel ~9.5 kb upstream of this gene                          | Tian et al., 2019           |
| brd1         | Leaf angle                 | Brassinosteroid C-6 oxidase            | −                                                                 | Tian et al., 2019           |
| ZmGA3ox2     | Plant height               | GA3 β-hydroxylase                      | Two small InDels in the promoter                                  | Teng et al., 2013           |
| qph1         | Plant height               | ABC transporter                        | A mis-sense SNP                                                   | Xing et al., 2015           |
| UB3          | Kernel row number          | SBP-box transcription factor           | 1.2-kb transposon-containing insertion located ~60 kb downstream  | Liu et al., 2015b           |
|              |                            |                                        |                                                                   |                             |
| ids1/Ts6     | Kernel row number          | AP2 transcription factor               | −                                                                 | Wang et al., 2019           |
| ZmBAM1d      | Kernel size and weight     | CLV1/BAM-related receptor kinase-like protein | −                                                                 | Yang et al., 2019a          |
| DGAT1-2      | Oil content and composition| Diacylglycerol acyltransferase         | Extra phenylalanine insertion                                    | Zheng et al., 2008          |
| Zmfatb       | Palmitic acid              | Acyl-ACP thioesterase                  | 11-bp InDel in the sixth exon                                    | Li et al., 2011             |
| ZmPORB2      | Tocopherol concentration   | Protochlorophyllide oxidoreductase      | A small InDel in 5’ UTR                                           | Zhan et al., 2019           |
| ZmAuxRP1     | Disease resistance         | Domain of unknown function 966        | −                                                                 | Ye et al., 2019             |
| ZmPLA1/MTL/NLD|Haploid induction rate      | Phospholipase A                        | A 4-bp insertion led to a frame shift                            | Gilles et al., 2017;        |
|              |                            |                                        |                                                                   | Kelliher et al., 2017;      |
|              |                            |                                        |                                                                   | Liu et al., 2017a           |
| ZmDMP        | Haploid induction rate     | DUF679 domain membrane protein         | One single-nucleotide change                                    | Zhong et al., 2019          |

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plants with larger leaf angles showing lower expression, indicating the negative role of ZmCLA4 in controlling leaf angle. This negative role was confirmed by RNAi of ZmCLA4 in maize and overexpression of ZmCLA4 in rice (Zhang et al., 2014). Rice plants that overexpressed ZmCLA4 had much smaller leaf angles than did controls, suggesting that ZmCLA4 has a conserved role in regulating leaf angle among different crops. This is supported by the finding that both mutant and RNAi lines of OsLAZY1 have larger tiller angles compared with their respective control lines (Li et al., 2007).

Recently, Tian et al. (2019) cloned two QTLs (Upright Plant Architecture1 and 2 [UPA1 and UPA2]) for upright plant architecture. The underlying genes for these two QTLs are brassinosteroid C-6 oxidase1 (brd1) and ZmRAVL1, which is a homolog of rice RAVL1. The functional variant in UPA2 is a 2-bp InDel located 9.5 kb upstream, which alters the binding affinity of the protein DRL encoded by drooping leaf1, another maize leaf-angle gene (Strable et al., 2017). While LG1, encoded by ligeuleless1, which is essential for leaf ligule and auricle development (Moreno et al., 1997), activates the expression of ZmRAVL1, the physical interaction between DRL1 and LG1 represses this activation (Tian et al., 2019). Interestingly, ZmRAVL1 regulates the expression level of brd1 and thus alters the endogenous brassinosteroid level and leaf angle (Tian et al., 2019).

qPH3.1 is a major QTL for plant height with a 10.0-cm additive effect and 3.7-cm dominant effect. This QTL was narrowed down to a 12.6-kb region, within which ZmGA3ox2 was shown to be responsible for both qPH3.1 and the dwarf-1 mutant (Teng et al., 2013). This gene, which encodes a gibberellin (GA) 3-oxidase, is expressed constitutively, and higher expression results in greater endogenous GA, (a bioactive gibberellin) levels and taller plants. Association mapping results subsequently indicated that two 3-nucleotide repeats within this gene might be the causative polymorphism for plant-height variation (Teng et al., 2013).

qph1, another major QTL for plant height with a 17.7-cm additive effect and a 7.8-cm dominant effect, was mapped to a 1.59-kb region covered by the fifth exon of Br2. A mis-sense SNP leading to an amino acid change from Arg to Leu is the causal variant for this QTL (Xing et al., 2015). Mutants of maize Br2, which encodes an ATP-binding cassette transporter belonging to the multidrug-resistant class of P-glycoproteins, show shortening of the lower stalk internodes due to reduced auxin transport. In addition, an 882-bp duplication in exon 5 of the Br2 homolog in sorghum is responsible for the dw3 mutant phenotype and the instability of dw3 caused by unequal recombination at this duplication site (Multani et al., 2003).

Yield-Related Genes

Ear- and kernel-related traits are important components of maize yield. Two major QTLs (KRN4 and KRN1) have been cloned for kernel row number (KRN) and one (qHKW1) has been cloned for kernel size and weight. KRN4 was mapped to a 3-kb intergenic region located ~60 kb downstream of an SBP-box gene, UB3 (unbranched3), which negatively affects KRN (Chuck et al., 2014). A 1.2-kb PAV with a harbinger TE in this 3-kb region and a SNP (S35) in the third exon of UB3 additively contribute to KRN, and these two sites both underwent selection during maize improvement (Liu et al., 2015a). In both rice and maize, the UB3 protein binds to genes encoding inflorescence-related transcription factors that are involved in the cytokinin pathway, and UB3 additionally targets genes involved in the auxin pathway and CLV-WUS pathway in maize (Du et al., 2017).

Krn1 was identified in an F2,3 population derived from crosses between the tropical line CML220 and landrace 1091AF, and had a phenotypic variation explained (PVE) value of 22%. This QTL was then fine-mapped to a 6.6-kb region, and the causal gene, which was confirmed by association analysis and two other independent mutation events, was shown to be a previously reported mutant gene, ids1/Ts6 (indeterminate spikelet 1/Tassel seed 6) (Wang et al., 2019). This gene is homologous to the wheat gene Q (Simons et al., 2006). Mutants of these two genes have similar phenotypes including altered spike length, spike density, grain size, and plant height, and both genes also underwent selection during the domestication of these two crop species (Debernardi et al., 2017; Xie et al., 2018; Wang et al., 2019).

qHKW1 accounts for 18.4% of the variation in hundred-kernel weight (HKW) in an RIL population derived from the modern elite maize inbred line ZHENG58 and the landrace SK (Raihan et al., 2016; Liu et al., 2017c). This QTL was fine-mapped to a ~177-kb region containing only one gene, ZmBAM1d, which encodes a CLAVATA1 (CLV1)/BARELY ANY MERISTEM (BAM)-related receptor kinase-like protein. The increased expression of ZmBAM1d, which is caused both by disrupted chromatin interactions resulting from distal large InDelS in the promoter and altered methylation levels in the promoter region, leads to enhanced HKW. A similar effect was noted in transgenic lines that overexpress ZmBAM1d, which show a ~1.9-g increase in HKW (Yang et al., 2019a).

Disease Resistance-Related Genes

Disease is one of the largest contributors to maize yield loss. Strategies for cloning quantitative disease-resistance genes and the characterization of some of these cloned genes have been extensively reviewed in Yang et al. (2017b). Therefore, we focus here solely on two recently cloned disease-resistance genes, ZmCCT10 and ZmAuxRp1.

Two major QTLs (qRfg1 and qRfg2) conferring resistance to Gibberella stalk rot were identified, and qRfg1 was mapped to a ~500-kb region (Yang et al., 2010a). qRfg1 was then narrowed down to a ~170-kb region (Wang et al., 2017). Interestingly, ZmCCT10 was the gene underlying this QTL, and the CACTA-like TE, which had been shown to be the causal polymorphism for flowering time (Yang et al., 2013), was also the causal variant for stalk rot resistance. This TE results in altered histone modification and DNA methylation in the cis-regulatory region of ZmCCT10, which leads to changes in its expression and, thus, enhanced disease resistance (Wang et al., 2017).

qRfg2 was first mapped to a ~300-kb region (Zhang et al., 2012) and then to a ~2.6-kb region containing only one gene,
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ZmAuxRP1, which encodes a protein with a domain of unknown function (DUF966). RNAi of ZmAuxRP1 results in plants with greater resistance, whereas plants that overexpress this gene are more susceptible to Gibberella stalk rot (Ye et al., 2019). It turns out that this gene regulates resistance to Gibberella stalk rot by affecting the biosynthesis of both indole-3-acetic acid (IAA) and benzoxazinoids (Ye et al., 2019).

Nutrition-Related Genes

The 21st century has seen an increase in concerns about nutrition, as indicated by a PubMed search with the keywords “nutrition” or “metabolome,” which reveals a rapid increase in published studies since 2010. Searches with the phrase “maize nutrition” or “maize metabolome” produce similar results. Biofortification, the process of increasing nutrition in crops through plant breeding (Nestel et al., 2006), has been successfully applied in maize nutrition improvement through MAS for, for instance, protein content and provitamin A (Muthusamy et al., 2014; Zunjare et al., 2018). Improvement through MAS for, for instance, protein content and provitamin A (Muthusamy et al., 2014; Zunjare et al., 2018).

Selection of the recessive allele of Opaque2 increases the lysine content of kernels (Mertz et al., 1964) while favorable alleles of Opaque2 increase tocopherol content in both the leaf and kernel (Zhan et al., 2019), which suggests great potential in vitamin E biofortification.

These are by no means the only metabolic QTLs that are important for nutrition in maize, with several recent QTL studies based on maize introgression or RILs, or alternatively on association panels, profiling such nutritionally important compounds as essential amino acids, lipids, vitamins and flavonoids, and other antioxidants (Riedelheimer et al., 2012; Wen et al., 2015, 2016). In a similar vein, although such studies have not yet been reported on a large scale in maize, a huge number of QTLs for taste have been found in studies in many species, most notably in tomato (Tiemann et al., 2017; Gao et al., 2019; Zhao et al., 2019) and cucumber (Shang et al., 2014; Zhu et al., 2019). Encompassing both traits, the first papers studying the domestication of the plant metabolome have recently been published for wheat, tomato, and maize (Beleggia et al., 2016; Zhu et al., 2018; Li et al., 2019c; Xu et al., 2019). The first of these studies carried out in wheat demonstrated that a reduction in unsaturated fatty acids was associated with selection during domestication of emmer while changes in the amino acid content due to selection mark the domestication of durum wheat (Beleggia et al., 2016). Similarly, tomato domestication was characterized by a shift in the ratios of nutritional and anti-nutritional steroidal glycoalkaloids as well as alterations in phenylpropanoid content driven by the Asian preference for pink tomatoes and considerable changes in metabolism that were due to genes hitchhiking on those genes selected to improve tomato yield (Zhu et al., 2018). Two recent studies have carried out a detailed comparison of metabolism in large populations derived from maize-by-teosinte crosses, revealing large-scale changes in both primary (particularly in amino acids and lipids [Li et al., 2019c; Xu et al., 2019]) and secondary (particularly in alkaloids and terpenoids [Xu et al., 2019]) metabolism that occurred during domestication. A current complication in using insights derived from the metabolomics data described above for crop improvement is that often the metabolite function is not well characterized (Alseekh and Fernie, 2018). With increasing use of wild germplasm, such studies identifying the changes that occurred during domestication to make our food more palatable (Zhu et al., 2018) will, however, become essential in order to prevent the reintroduction of antinutritional compounds.

Lessons Learned from Characterization of Positionally Cloned Genes

One lesson we have learned from these positionally cloned genes is that SVs and TEs are of great importance in shaping plants and enhancing their fitness. SVs and TEs are causal variations not only for important QTLs (tb1, Vgt1, ZmCCT, ZmCCT9, KRNN, qHKW1) for taste have been found in studies in many species, most notably in tomato (Tiemann et al., 2017; Gao et al., 2019; Zhao et al., 2019) and cucumber (Shang et al., 2014; Zhu et al., 2019). Encompassing both traits, the first papers studying the domestication of the plant metabolome have recently been published for wheat, tomato, and maize (Beleggia et al., 2016; Zhu et al., 2018; Li et al., 2019c; Xu et al., 2019). The first of these studies carried out in wheat demonstrated that a reduction in unsaturated fatty acids was associated with selection during domestication of emmer while changes in the amino acid content due to selection mark the domestication of durum wheat (Beleggia et al., 2016). Similarly, tomato domestication was characterized by a shift in the ratios of nutritional and anti-nutritional steroidal glycoalkaloids as well as alterations in phenylpropanoid content driven by the Asian preference for pink tomatoes and considerable changes in metabolism that were due to genes hitchhiking on those genes selected to improve tomato yield (Zhu et al., 2018). Two recent studies have carried out a detailed comparison of metabolism in large populations derived from maize-by-teosinte crosses, revealing large-scale changes in both primary (particularly in amino acids and lipids [Li et al., 2019c; Xu et al., 2019]) and secondary (particularly in alkaloids and terpenoids [Xu et al., 2019]) metabolism that occurred during domestication. A current complication in using insights derived from the metabolomics data described above for crop improvement is that often the metabolite function is not well characterized (Alseekh and Fernie, 2018). With increasing use of wild germplasm, such studies identifying the changes that occurred during domestication to make our food more palatable (Zhu et al., 2018) will, however, become essential in order to prevent the reintroduction of antinutritional compounds.

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(Bommert et al., 2013). Liu et al. (2017b) found that some kernel-related mutant genes are enriched in QTLs for kernel traits and that SNPs in some of these genes are significantly associated with kernel traits, with the most significant SNPs being either located in the regulatory region or being synonymous substitutions. These findings together highlight the possibility of improving maize via a combination of knowledge concerning mutant genes and CRISPR/Cas9 technology, which, as has already been demonstrated (Eshed and Lippman, 2019; Fernie and Yan, 2019), could be used to generate considerably more favorable alleles.

The genetic basis of different traits varies substantially in maize. For flowering time and oil concentration, dozens of loci, each with a small effect, have been identified (Buckler et al., 2009; Li et al., 2013). Yield-related traits, such as plant architecture and ear and kernel traits, have a much more complex genetic architecture as indicated by the detection of several hundreds of loci (Xiao et al., 2016; Liu et al., 2017c; Pan et al., 2017). In contrast, there are fewer mapped QTLs for disease resistance. Taking gray leaf spot (GLS) as an example, only 16 loci were mapped in the NAM population, among which three had a large effect (Benson et al., 2015). This situation is not the same across crops. Unlike maize, rice heading and seed size and weight are regulated by only a handful of genes, each with a large effect (Huang et al., 2011). These differences suggest that the road to maize improvement may vary significantly among different crops.
improvement should differ from that of rice, and researchers should select an appropriate method based on the genetic complexity of the desired traits. For traits mainly controlled by major QTLs, i.e., disease resistance, MAS would be a more efficient strategy, whereas genomic selection would be more suitable for traits with a much more complex genetic basis, such as flowering-time and yield-related traits (Figure 3A–3C).

**PERSPECTIVES**

Based on the tremendous genotypic diversity revealed by resequencing studies in both maize and other plants (especially rice and Arabidopsis), we believe that more high-quality genome assemblies, including assemblies for teosinte, landraces, and tropical lines, are needed to comprehensively reveal maize variations. Another challenge is to rapidly clone and validate genes responsible for important agronomic traits. The step forward in methodology has greatly accelerated this process, especially the progress in transformation, CRISPR/Cas9 technology, statistical methods for speeding up QTL cloning (such as QTL sequencing [QTL-seq] and quantitative trait gene sequencing [QTG-seq] [Takagi et al., 2013; Zhang et al., 2019], and haploid induction technologies.

Using a combination of these methods to quickly map and validate candidate genes (with CRISPR/Cas9) could provide a revolutionary way to rapidly clone genes and generate favorable alleles that could be directly used in future breeding programs (Figure 3). In addition, many important QTLs, including tb1, UPA1, and UPA2, were mapped within populations derived from teosinte and cultivated maize, which indicates that teosinte is full of treasures waiting to be found. What studies with teosinte can provide is not only insights into domestication but also directions for future improvement and de novo domestication new crops (Fernie and Yan, 2019).

**The Need for Additional Whole Genome Sequences from Diverse Maize Lines**

Population-scale genome projects (the human 1000 Genomes Project, the Arabidopsis 1001 Genomes Project, and the rice 3000 Genomes Project) have shown that a handful of reference genome sequences is not enough to reveal the genetic variation within a species, especially low-frequency and rare variants that are also important components of the genetic basis of human diseases or plant traits. For example, according to the pilot phase results of the human 1000 Genomes Project, 55% of the ~15 million SNPs identified are novel (1000 Genomes Project Consortium, 2010); According to pan-genome analysis results from the rice 3000 Genome Project, each rice accession has at least 26.5% distributed gene families (Wang et al., 2018b).

The genetic diversity of maize is much higher than that of humans (more than 10-fold higher; Tenaillon et al., 2001). However, most of the maize genome sequences released to date are from temperate lines. Genome sequences from tropical lines, landraces, and teosintes have seldom been reported, although many known variations exist that are specific to teosinte or tropical lines (examples are shown in Figure 1). With the advancement of sequencing technologies, it will become much easier and also cheaper to assemble many more maize genome sequences to fully reveal genetic variations, including widespread genome-structure variations (representative inversions and InDels >1 Mb are illustrated in Figure 2), and their relationship to phenotypes.

**Technologies**

Although some maize genome sequences and abundant variations are already available, the functions of most genes and also the genes underlying many traits and biological processes remain unclear. In the past decades, genotype limitations and the low efficiency of maize genetic transformation made maize genetic analysis much slower than that of Arabidopsis and rice. However, the greatly increased transformation efficiency that results from ectopic expression of Baby Boom (Bbm) and Wuschel 2 (Wus2) and the use of promoters from Zm-PLTP and Zm-Axig1 (which encode a phospholipid transferase protein and an Aux/IAA transcription factor, respectively) opened the gates for efficient and genotype-independent maize transformation (Lowe et al., 2016, 2018).

Rooted in these improved transformation approaches, CRISPR/Cas9 technology can be used to generate both multiple mutated alleles for a single gene and mutations of multiple genes in a single maize plant by integrating multiple guide RNAs into one vector and using just a single guide RNA targeting a conserved region of homologous genes, respectively (Doll et al., 2019). This would be a very convenient method for studying gene families with functional redundancy, as demonstrated in rice (Ma et al., 2015). Furthermore, the CRISPR/Cas9 system has been successfully used to construct genome-wide mutant libraries in rice (Lu et al., 2017; Meng et al., 2017). Lines in mutant libraries derived from TILLING or Mu tagging usually have many randomly mutated loci, and mutant loci caused by Mu insertions are sometimes not stable (Brutnell, 2002; Lu et al., 2018), which could exacerbate the difficulty in phenotype investigation and validation of gene function. In contrast, the CRISPR/Cas9 system introduces stable mutations precisely at specific sites as dictated by the single guide RNA with a much cleaner genetic background. There are also increasing reports about the application of CRISPR/Cas9 technology in maize. For example, Svitashev et al. (2016) delivered a Cas9-guide RNA ribonucleoprotein assembly into maize embryos and successfully obtained edited plants and achieved DNA-free genome editing; Feng et al. (2018) reported highly efficient genome editing using the dmc1 promoter combined with the U3 promoter to drive the CRISPR/Cas9 system. Thus, the technique shows great promise in both functional research and breeding of maize (Figure 3D–3G).

Traditional QTL mapping in populations derived from multiple generations of selfing, backcrossing, or intercrossing and positional cloning are time-consuming methods. There are two approaches, referred to as QTL-seq (Takagi et al., 2013) and QTG-seq (Zhang et al., 2019), that take advantage of both bulked segregant analysis and NGS to rapidly identify QTLs (Figure 3B). Using QTG-seq, researchers even mapped a plant-height QTL to a ~300-kb region (Zhang et al., 2019). There is also another way to quickly construct populations and, hence, map QTLs, which depends on the application of doubled haploids. A haploid, which contains only one set of chromosomes, could become a diploid inbred line in only one generation after a...
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chromosome-doubling process. One method widely used in maize to produce haploids is to cross plants with haploid inducer lines. A number of QTLs for haploid induction rate (HIR) have been reported, with qhir1 and qhir8 explaining most of the variation (66% and 20%, respectively) in this trait (Prigge et al., 2012; Hu et al., 2016). The cloning of these two loci and the dissection of the mechanisms underlying this process were reported recently (Gilles et al., 2017; Kelliher et al., 2017; Li et al., 2017; Liu et al., 2017a; Zhong et al., 2019). A 4-bp insertion and a nucleotide change in ZmPLA1 (also named MTL, NLD) and ZmDMP, respectively, led to increased HIR (Gilles et al., 2017; Kelliher et al., 2017; Liu et al., 2017a; Zhong et al., 2019). Li et al. (2017) found severe chromosome fragmentation in pollen of an inducer line using single nucleus sequencing technology, which might be the reason for haploid induction. These findings have great promise for accelerating the breeding process, and there are already reports about the genetic manipulation of ZmPLA1 in other crops to promote haploid induction, for example in rice and wheat (Yao et al., 2018; Liu et al., 2019).

Diversified Breeding Goals

Since the process of domestication of maize from its wild ancestors began several thousand years ago, yield has always been the central goal in breeding programs. In addition, there are now many new kinds of maize developed for specific purposes, the so-called “specialty corns,” such as silage corn, waxy corn, high-amylase corn, high-oil corn, high-quality-protein corn, sweet corn, and popcorn. The planting area of specialty corn has substantially increased since the early 20th century. For example, waxy corn was discovered in the 1900s in China, and its planting area now has reached ~800,000 hm² in China. Meanwhile, it has been reported that nearly 40% of maize produced in the United States is used to make ethanol for fuel (Ranum et al., 2014). These two observations reflect the increasingly diverse demands of maize breeding.

Based on the genomic changes during maize domestication and variations in positionally cloned maize genes that underlie QTLs for diverse traits, many traits are affected mainly by a limited number of genes. Taking the waxy endosperm trait as an example, mutation of only one gene (Wx) leads to an amylopectin content of nearly 100% in the endosperm (Sprague et al., 1943). Thus, it is possible that we could improve specific maize traits by manipulating only a handful of genes to meet modern demands for diverse maize types.

Reuse of Wild Relatives

It is estimated that maize retains 83% of the genetic diversity from its progenitor, Zea mays ssp. parviglumis (Hufford et al., 2012). This is actually a considerably higher proportion than found in analogous comparisons between other major crops and their wild species progenitors (Fernie et al., 2006), largely due to the fact that maize is an outcrossing species. Nevertheless, the teosintes represent important resources for pinpointing the genes/variants that are important for traits but have been lost during maize artificial selection (Li et al., 2019c; Tian et al., 2019). There are several ways to discover such genes/variants. First, traditional QTL mapping and positional cloning have been successfully used to clone genes within populations derived from crosses between maize and teosinte. For example, ZmCCT10 and ZmCCT9 were mapped and cloned using this method in a maize-teosinte BC2S2 population (Hung et al., 2012; Huang et al., 2018). Association mapping in a teosinte population has also been demonstrated to be a powerful approach by which to detect significant associations between genes and traits (Weber et al., 2007, 2008). However, these two studies performed candidate-gene-association analyses using <150 markers. It is expected that more loci, including some novel loci, would be detected by a GWAS with a much higher density of molecular markers. Recently, a k-mer-based association mapping method called association genetics with resistance gene-enrichment sequencing (AgRenSeq) was used to successfully discover and clone disease-resistance genes from crop wild relatives (Arora et al., 2019). Multi-omics data are also very powerful for identifying genes for traits (Liu et al., 2016; de Abreu E Lima et al., 2018; McLoughlin et al., 2018) The teosinte allele of cloned genes/variants could subsequently be directly applied in maize-breeding programs through introgression into modern elite maize lines.

An alternative possibility to rewilding maize would be to de novo domesticate teosinte, as was recently proposed by Fernie and Yan (2019), via either long-term backcrossing or short-term genome editing. The latter would require a successful transformation method for teosinte. As noted above, only a few hundred genes underwent selection during maize domestication. If we want to change only a few key traits to meet the aforementioned diverse breeding goals for maize, there may be as few as <100 genes that need to be edited. The resulting costs of this process—in terms of both time and money spent—will be greatly reduced relative to the previous process of human selection, which has already lasted for thousands of years.

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