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Genetics and Consequences of Crop Domestication

Sherry A. Flint-Garcia*

Agricultural Research Service, U.S. Department of Agriculture, 301 Curtis Hall, University of Missouri, Columbia, Missouri 65211, United States

ABSTRACT: Phenotypic variation has been manipulated by humans during crop domestication, which occurred primarily between 3000 and 10000 years ago in the various centers of origin around the world. The process of domestication has profound consequences on crops, where the domesticate has moderately reduced genetic diversity relative to the wild ancestor across the genome, and severely reduced diversity for genes targeted by domestication. The question that remains is whether reduction in genetic diversity has affected crop production today. A case study in maize (*Zea mays*) demonstrates the application of understanding relationships between genetic diversity and phenotypic diversity in the wild ancestor and the domesticate. As an outcrossing species, maize has tremendous genetic variation. The complementary combination of genome-wide association mapping (GWAS) approaches, large HapMap data sets, and germplasm resources is leading to important discoveries of the relationship between genetic diversity and phenotypic variation and the impact of domestication on trait variation.

KEYWORDS: *genetic diversity, artificial selection, maize, teosinte, breeding*

INTRODUCTION

The domestication and breeding histories of crop species have a profound influence on the diversity present in modern crops. An understanding of genetics and breeding concepts and methodologies and of domestication can help us manage the genetic resources that are available for the various crops and how to use this diversity for crop improvement. A series of vignettes on the major crop species are used to illustrate similarities and differences in domestication and breeding histories. A detailed discussion of maize illustrates the interrelationship between domestication and breeding history, genetic diversity, genetic analysis, and crop improvement.

GENETICS AND BREEDING

Introduction to Genetics. To have a meaningful discussion about genetics and breeding, one must be familiar with terminology commonly used in these disciplines. A *trait* is a genetically determined characteristic. The *genotype* is the genetic constitution (usually focused on a specific gene) of an individual organism, and an *allele* is a variant form of a gene. The *phenotype* is the set of observable characteristics (usually focused on a specific trait) of an individual. A familiar example from human genetics can be used to demonstrate the use of these terms. The human ABO blood type is a *trait* controlled by a single gene on chromosome 9. An individual with the blood type A *phenotype* will have one of two possible *genotypes*: A/A or A/O, where A, B, and O are the *alleles* for this gene. *Genetic variation* is a population genetics term used to describe allelic differences among individuals of the same species or a specific population. Following the example above, some isolated human populations have only the O/O genotype and thus have *no genetic variation* for the gene controlling ABO blood type.

Genetic variation can arise through a variety of mechanisms, resulting in changes in genotype and new alleles. Point mutations are changes to the base pairs, resulting in single-nucleotide polymorphisms (SNPs) and small insertions or deletions (InDels) of base pairs; both of these mutation types usually affect a single gene. Entire genes can be deleted or duplicated (gene loss or gain). Larger scale mutations occur at the chromosomal level, including deletions and duplications of chromosomal regions, whole chromosomes (aneuploidy), or entire genomes (polyploidy). In addition, recombination between homologous chromosomes results in the shuffling of genes during meiosis, resulting in new combinations of genes in the progeny. Transposable elements or "jumping genes" can completely disrupt gene function by landing within a gene and can cause other chromosomal aberrations. Each of these mutation types occurs at a different frequency within a species, and the frequency of each mutation type varies from species to species; for example, in maize, approximately 90 SNP mutations occur each meiosis.[1]

An individual's phenotype results from the combination of its genotype, the environment, and genotype by environment interactions. Heritability is the proportion of genetic variation relative to the total phenotypic variation within a population, ranging from 0 (purely environment) to 1 (purely genetic). In the human "nature versus nurture" debate, behavioral scientists often study twins to determine the relative contribution of genotype and environment to trait expression. When identical twins that share the same genotype are separated at birth, the effect of the environment can be determined. On the other hand, fraternal twins share the same gestational environment but can have very different genotypes. One would not expect ABO blood type or eye color to be influenced by the environment; thus, the genetic contribution to ABO blood group is stronger than the environment, indicating high heritability. Conversely, one would expect language to be

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more influenced by the environment than by genetics; thus, human language is a low-heritability trait. The vast majority of traits, especially in plants, are of intermediate heritability.

There are two broad types of traits: qualitative and quantitative. Qualitative traits have discrete phenotypic distributions and are generally controlled by one or a few genes. In contrast, quantitative traits have continuous phenotypic distributions and are controlled by several to many genes that interact with each other (epistasis) and with the environment (genotype × environment). An example of a qualitative trait is kernel color in maize, where a handful of genes determine whether the various layers of the seed are colored or colorless.[2,3] An example of a quantitative trait is native corn rootworm resistance, where many plant resistance genes interact with environmental factors including the soil conditions and insect pressure.[4]

Genetic variation and, hence, phenotypic variation within a population are subject to change. If a population is in Hardy–Weinberg equilibrium, the gene frequencies are balanced such that the progeny of the population will have the same allele and genotypic ratios as the parent population.[5] However, several forces that disturb the equilibrium can act on a population. Genetic drift is a change in the population's allele frequency resulting from a random variation in the distribution of alleles from one generation to the next. The effects of genetic drift are more pronounced in small populations, where rarer alleles can disappear from the population completely due to allele sampling, thus reducing overall genetic variation. Phenotypic selection, both natural and artificial, where survival and reproduction of certain individuals can confer an advantage over others within the population, can also result in rapid loss or fixation of alleles within a population. On the other hand, gene flow due to the migration of individuals between populations can increase genetic variation by bringing together alleles from each population.

Genotype to Phenotype. Most agronomic and evolutionarily important traits are quantitative in nature; that is, phenotypic variation for these traits is caused by a combination of segregation at multiple quantitative trait loci (QTL), the environment, and the interaction between genes and the environment.[6] A QTL is simply a region of the genome that controls a quantitative trait. The concept of a QTL can be somewhat vague; whereas one would hope that a single gene is responsible for the QTL, often QTLs consist of multiple linked genes.[7,8]

There are two common approaches to identifying the genes underlying QTL: linkage analysis and association analysis (also known as linkage disequilibrium mapping or association mapping). In linkage mapping, biparental populations are typically derived from parents that have opposing phenotypes for the trait of interest (e.g., resistant and susceptible for a disease), and a segregating population is derived by self-pollinating or backcrossing the F1.[8] The major limitation of linkage mapping is that the limited number of recombination events during the formation of the population results in low mapping resolution, often to 10 centiMorgan, corresponding to 10 million base pairs in many species.[9] Thus, the causative gene or genes are not likely to be identified in a single linkage mapping experiment. In addition to low resolution, linkage mapping surveys only two alleles in each population and, thus, presents a limited understanding of the genetic architecture of the quantitative trait. However, molecular markers flanking the QTL can be used in marker-assisted selection to transfer favorable alleles of the QTL from unadapted germplasm to elite germplasm.[10]

Association analysis, on the other hand, utilizes a population of unrelated individuals and exploits the thousands of generations of recombination that occurred since their descent from a common ancestor. The breakdown of linkage disequilibrium, or the correlation of polymorphisms within a region of the genome, due to the increased number of recombination events results in much higher mapping resolution, in some cases even allowing identification of the causative polymorphism within the causative gene. The limitation of association analysis depends on the species and germplasm.[11] Self-pollinating species tend to have much lower effective recombination rates and therefore larger blocks of linkage disequilibrium resulting in low mapping resolution; the opposite is true for out-crossing species. Diverse germplasm in out-crossing species suffers from a lack of statistical power due to low minor allele frequency (alleles are present in only a small number of lines) and/or population structure underlying the trait of interest.[12]

Plant Breeding. Plant breeding is the science, art, and business of improving plants for human benefit.[13] Modern traditional breeding consists of crossing two plants to produce genetic variation, followed by selection of progeny with desirable characteristics. Breeding is often done without knowledge of the genes controlling the trait(s) being selected. This earliest form of plant breeding is known as domestication (see following section), where plants were selected to be more productive, easier to harvest, or more aesthetically or gastronomically pleasing. Breeding continued for thousands of years, and by the end of the agricultural revolution that occurred in Europe in the 17th and 18th centuries, farmer breeders often had their favorite "family" or "heirloom" variety with its own set of characteristics that distinguished it from other varieties. After the discovery of inbreeding depression (the reduction in fitness as a result of breeding related individuals[14]) and heterosis (the F1 progeny of a cross between two diverse parents outperforms either parent for traits related to vigor and productivity[15]) in maize in the early 1900s,[16] modern breeding came into its own. In 1926, Pioneer Hi-Bred was founded as the first commercial hybrid seed company. Plant breeding continues today, using advances in molecular markers and biotechnology.

Plant breeding is simply applying selection to decrease the frequency of unfavorable alleles (e.g., susceptibility to diseases and insects, susceptibility to drought, and unadaptedness) and increase the frequency of favorable alleles (e.g., increased yield, improved grain quality, and resistance to disease, insects, and environmental stresses). Breeding methodologies vary greatly between self-pollinating and cross-pollinating crops, especially in maize, where hybrid seed is produced, and have been described in more detail elsewhere[17−19] (see also Bregshello in this issue, DOI: 10.1021/jf305531j). However, in each case, effective breeding results in a change in the phenotypic mean of a population. Breeders select the "best" individuals from a population to form the following generation; as long as variation exists in the population, breeding by selection will continue to improve the population.

■ DOMESTICATION

All of the major crops around the world were domesticated from a wild progenitor species, primarily between 4000 and 10000 years ago.[20] Often there have been multiple rounds of

domestication and/or breeding, where the initial domestication event resulted in primitive landraces with an intermediate level of domestication and where modern plant breeding has resulted in varieties or cultivars that conform to the modern ideotype. The ideotype is the hypothetical ideal plant form that is thought to maximize genetic yield potential.[21] At each of these domestication and breeding steps, profound changes to the germplasm occurred, where the more domesticated germplasm pools have a narrower range of genotypic diversity.[22] In some cases the domesticates have broader phenotypic diversity as exemplified by the fruit shape, size, and color in tomato,[23,24] and in other cases cultivars have narrower phenotypic diversity relative to less domesticated landraces, as is the case in maize.[25,26]

The geographic region where domestication began and where most of a crop's genetic diversity resides is typically referred to as the crop's center of origin.[27] Although many "secondary centers of diversity" can be considered, there are six primary centers of origin around the world: China (soybean, rice, millet), Southeast Asia (banana, coconut, taro), the Fertile Crescent encompassing regions from Mesopotamia to the eastern Mediterranean to northern Egypt (barley, wheat, lentils, peas, chickpeas), sub-Saharan Africa (sorghum, pearl millet, cowpea, yam), Mesoamerica (corn, common bean, squash, sweet potato), and South America (potato, tomato, cassava, common bean, peanut). Germplasm banks have been assembled for all of the major crops by sampling the diversity present around the world, but in particular from the centers of origin, and accessions are readily available for most major crops.

Domesticates and their progenitor species generally differ by a suite of complex morphological, physiological, and genetic changes known as the domestication syndrome. The domesticated species often has a more robust plant structure, has lost natural seed dispersal (i.e., nonshattering), has lost seed dormancy, has synchronous flowering between the male and female organs, has larger fruits or grains, and has increased apical dominance (more determinate growth).[20] It has been hypothesized, and in many cases demonstrated, that the domesticates also have reduced physical and chemical defenses compared to their wild counterparts.[28−33] As early as 1859, Darwin observed that the modifications occurring during domestication have been of such magnitudes such that many domesticated crops cannot survive in the wild.[34,35]

In addition to phenotypic changes of the domestication syndrome, a species' genome also undergoes changes during domestication. During domestication, genetic variation across the genome is moderately reduced in the domesticate relative to the progenitor due to a genetic bottleneck associated with the sampling process; that is, only a small number of wild plants were chosen for domestication.[36] The relative loss of diversity varies greatly, depending on the species. Genes targeted by artificial selection during domestication and/or improvement have greatly reduced variation, as the combined effect of the population bottleneck and selection is much more severe.[37] The number of selected genes and the strength of selection is also variable between species. These reductions in genetic diversity affect the breeding and genetics of the domesticate as loci with greatly reduced variation are not able to contribute to phenotypic variation; they cannot be identified as QTL and cannot be used to improve the crops by breeding.

Domestication of Major Crop Species. A brief sketch of the domestication and breeding histories of various crop species is useful to demonstrate commonalities in the domestication syndrome across crops. Indeed, selection for nonshattering was a primary domestication trait in maize, rice, and wheat, although it appears that different genes were targeted by selection in each species.[38] However, each species also has unique aspects to its domestication and breeding history that make breeding and genetics studies in the modern crop challenging in its own right.

Early studies of barley (*Hordeum vulgare*) suggested a single domestication event from *H. vulgare* ssp. *spontaneum* approximately 10500 years ago in the Fertile Crescent. However, a recent study suggests two independent domestication events, where wild barleys form two distinct geographical clusters.[39] The wild barleys from the western region of the Fertile Crescent contributed the majority of the diversity found in the European and American barley cultivars, whereas the wild barleys east of the Zagros Mountains contributed to the diversity of the Central Asian and Far Eastern cultivars. Two-row barley cultivars have lower protein and higher fermentable sugar content, desirable characteristics for malting and fermentation, whereas six-row barley cultivars tend to have higher protein content and are best suited for animal feed. The earliest target trait has been proposed to be nonshattering,[40] followed by a change from two- to six-rowed spikes[41] and selection for free threshing grains (naked seeds).[42]

Wheat (*Triticum* ssp.) has a very complex evolutionary history due to polyploidization and distinct market classes.[43] Approximately 500 000 years ago in the Fertile Crescent, two diploid progenitors, *Triticum urartu* (AA genome) and *Aegilops speltoides* (SS genome), hybridized to form the tetraploid species *Triticum dicoccoides* (AASS genome). This tetraploid species was domesticated approximately 10000 years ago, resulting in emmer wheat (*Triticum dicoccum*, AABB) and durum wheat (*Triticum turgidum*, AABB). The diploid einkorn wheat (*Triticum monococcum*, AA) was domesticated around the same time from *Triticum boeoticum* (AA). And finally, around 10000 years ago, a tetraploid species (AABB) hybridized with *Triticum tauschii* (DD genome) to form the two hexaploid wheat species *Triticum aestivum* (AABBDD) and *Triticum spelta* (AABBDD).[44] The primary domestication trait in wheat was nonshattering, with secondary traits being glume reduction to improve threshing, changes in plant architecture and in ear and kernel size, loss of seed dormancy, and lower grain protein and increased grain carbohydrate content.[45] Several domestication traits have been genetically mapped and/or characterized, including the *q* locus that confers free threshing,[46] the *hd* locus controlling photoperiod insensitivity, and the *br* locus controlling shattering.[47] Today, derivatives of many of these species are used for very specific purposes. For example, the hexaploid *T. aestivum* has been bred for high protein quality needed for breadmaking, breeding within tetraploid *T. turgidum* has resulted in durum wheat used to make pasta, and specialty markets are currently being developed for einkorn wheat as an alternative for people suffering from celiac disease. The multiple ploidy levels and distinct market classes are responsible for extensive population structure within wheat.[48−50]

The story of rice (*Oryza sativa*) domestication from its wild ancestor *Oryza rufipogon* is an example of the ever-changing face of science. There are five prominent groupings in modern rice cultivars: indica, aus, aromatic, and temperate and tropical japonica.[51] Until recently, it was believed that there were two independent domestication events that were responsible for the two major subgroups of rice, japonica (including aromatic) and

indica (including aus).[52] However, a recent study suggests that the initial domestication event occurred in China around 9000 years ago to create the japonica group, which then replaced more primitive domesticates in India about 4000 years ago.[53] Domestication was achieved by reducing shattering via a transcription factor that controls development of the abscission layer between the grain and the pedicle,[54] reducing seed dormancy via a regulatory gene controlling seed maturation,[55] increasing the number of grains per panicle,[56] and changing grain size and shape.[57]

Soybean (*Glycine max*) has undergone several rounds of domestication from *Glycine soja* beginning about 3000−5000 years ago in China, although the details of domestication are not clear.[58−61] A severe bottleneck occurred during domestication, resulting in Asian landraces containing only 50% of the genetic diversity and 19% of the rare alleles found in *G. soja*.[62] Approximately 80% of North American cultivar heritage can be traced back to the introduction of 17 founder landraces. Modern breeding transformed these founder landraces into elite cultivars, thereby reducing the genetic base of soybeans in the United States even further. Domestication traits in soybean include determinacy, increased seed size, modified flowering time, lighter seed color, and a nonshattering pod.[63,64] Several QTL have been mapped for many of these domestication traits;[65] however, to date, only determinate growth habit has been resolved to the gene level.[66,67]

The exact details of tomato (*Solanum lycopersicum*) domestication are uncertain,[68] but most likely occurred in two phases, first in the Andes and more recently in Mexico.[69] The wild ancestor is proposed to be *Solanum pimpinellifolium*, which was initially domesticated in Peru or Ecuador, resulting in the weedy cherry tomato, *S. lycopersicum cerasiforme*. This wild cherry tomato then spread into Mexico, where it was further domesticated, resulting in early modern tomato cutivars. Domesticated tomato was brought to Europe by the conquistadors, or perhaps even Columbus, prior to its first description prior to 1544, and intense selection for fruit morphology followed in the 18th and 19th centuries. It is estimated that cultivated tomato contains only 5% of the genetic diversity present in wild relatives.[70] As the earliest domesticate was likely a cherry tomato, selection for increased fruit size and shape is undisputed.[24] However, other traits such as early flowering, growth habit, fruit color, and small seed size are also part of the domestication syndrome.[71] Tomato is considered to be a model system for genetic and evolutionary studies as several domestication QTL have been cloned and characterized.[23,72]

Common bean, *Phaseolus vulgaris*, is a very diverse crop species with a complex domestication and breeding history. Prior to domestication, the wild progenitor, *P. vulgaris*, is believed to have diverged into two major gene pools distributed in Mesoamerica and the Andes.[73] Two independent domestication events from these wild populations beginning about 4000 years ago[74] have led to present cultivar race structure.[75] It is estimated that 16% of the genome has been subjected to selection during domestication.[76] A recent molecular study confirmed earlier findings that there are five major genepools within wild beans (Mesoamerican−Mexican, Guatemalan, Colombian, Ecuadorian−northern Peruvian, and Andean−Argentina, Bolivia, and southern Peru) that correspond to geographic regions and that cultivated beans were more closely related to the Mesoamerican−Mexican and Andean−Argentina, Boliviam and southern Peru wild beans.[77]

Sunflower (*Helianthus annuus*) was domesticated from common sunflower (*H. annuus*) in a single domestication event about 4000 years ago in eastern North America,[78] in the region of western Kentucky or eastern Missouri. Cultivated sunflower is unbranched, produces a single large head, and has relatively large achenes (seeds), which are held on the plant until harvest, whereas common sunflower is branched along its entire stem, with each branch having numerous small heads and relatively small achenes that shatter when disturbed.[79] QTL have been identified for many of the domestication syndrome traits.[80] In addition, fatty acid synthesis pathways[81] and flowering time genes[82] were likely targets of selection during domestication.

A CASE STUDY OF MAIZE: WHAT CAN WE LEARN FROM MAIZE DIVERSITY USING BREEDING, GENETICS, AND GENOMICS?

Maize (*Z. mays*) is an important crop worldwide, both economically and nutritionally. Maize was grown on over 90 million acres and valued at $12 billion in the United States in 2011.[83] Maize is the third leading source of daily calories worldwide, after only wheat and rice.[84] Here maize is used as a case study to demonstrate the effect of domestication and breeding histories on crop germplasm, diversity, breeding, genetic, and genomic studies.

Maize Domestication, Genome, and Diversity. Maize was domesticated from teosinte (*Z. mays* ssp. *parviglumis*) in a single domestication event, approximately 9000 years ago in southern Mexico.[85] As primitive maize and more advanced maize was spread north and south across the Americas, it encountered new environments (e.g., humid regions with high disease pressure, dry plateaus, etc.) and was used for various purposes (e.g., ceremonies and rituals, food uses such as tortillas or hominy, etc.). Maize adapted to these new environments in the form known as landraces, that is, open-pollinated populations adapted to specific environments and/or human uses. Although each landrace has distinct genetic and morphological characteristics, there is often more diversity within a landrace than between landraces,[86] indicating their broad genetic base. By the time the New World was discovered by the Europeans, maize had spread from Mexico to Canada and Argentina and had become part of early American agriculture. Beginning at the end of the 18th century, breeders discovered they could create high-yielding maize by first creating inbred lines and then crossing the inbreds to form hybrids.[16] Thus, we often describe the germplasm pool in terms of teosinte, landraces, and inbred lines.

The B73 maize reference genome has recently been published,[87] summarizing over 100 years of maize research and formally bringing maize into the genomics era. B73 was chosen as the reference inbred for the genome project because of its importance in the history of hybrid breeding in the United States and for its role as a genetic stock. Maize's 10 chromosomes are the result of multiple polyploidization events, the most recent of which was a whole genome duplication event that occurred 5−12 million years ago.[88] The genome sequence project predicted approximately 32700 genes in B73, although the final number of genes will likely be higher, perhaps 40000 or more. Nearly 85% of the B73 genome sequence is annotated as transposable elements[89] or what was referred to until recently as "junk DNA".[90]

Whereas the B73 genome is very useful as a reference genome, B73 is only a single inbred line in an extremely diverse

species, where two randomly chosen inbred lines are more diverse than the difference between human and chimps.[91] Early estimates of diversity were based on small sample sizes, in terms of both number of loci and number of taxa examined. For example, a sequencing survey of 21 loci along chromosome 1 across 25 taxa (9 inbred lines and 16 landraces) indicated a high level of diversity, that is, one SNP every 104 bp.[91] A study of 94 microsatellite (or simple sequence repeat, SSR) loci across a large number of inbred lines revealed high diversity and the nature of population structure that exists in maize.[92] Because of the breeding history of corn, inbred lines have a distinct population structure including sweet corn, popcorn, stiff stalk, nonstiff stalk, and tropical/subtropical lines.

With the advent of high-throughput, next-generation sequencing technology, population genetics can truly be studied at the genome level. Haplotype maps, or HapMaps, are catalogs of common genetic variants within a species. The first-generation maize HapMap (HapMap_v1) project used methyl-sensitive restriction enzymes to sample gene-rich regions in 27 inbred lines and resulted in 1.6 million SNP/indels.[93] One interesting finding is that B73 captures only 70% of the SNPs from the whole set of 27 inbred lines, which validates the extensive noncollinearity, or violation of gene order (synteny) within a species, that was initially observed in small regions of the genome.[94,95] The HapMap_v1 analysis also identified hundreds of selective sweeps, where genetic diversity was less than expected. The second-generation Maize HapMap (HapMap_v2) project conducted whole-genome sequencing of random sheared DNA in 103 lines (60 inbred lines including those from HapMap_v1, 25 landraces, 19 wild relatives) and resulted in 55 million SNPs.[96] These SNPs are not simply background noise in unimportant regions of the genome. For example, 7.5% of genes carried variation that resulted in a predicted premature stop codon in at least one of the lines.[96] In another study, comparative genomic hybridization of a diverse panel of maize and teosinte revealed that over 10% of 30500 genes examined exhibited copy number variation (CNV) or presence/absence variation (PAV) relative to the B73 reference genome.[97] Many of the maize inbreds were missing 500−1000 genes relative to B73. Clearly, maize is an incredibly diverse species. Thus, an incredible amount of variation exists between any two inbred lines; for example, as many as 10 million SNPs differ between B73 and Mo17,[96] two inbreds that exemplify the genetics in a farmer's field.

All of these resources have been brought to bear on the study of domestication traits. George Beadle[98,99] proposed that there are five major genes that distinguish maize and teosinte. Indeed, exactly five QTL were detected for large-scale morphological differences between maize and teosinte.[100] With diligence and patience, researchers have pursued several of these QTL with great success. The tillering trait is largely controlled by *teosinte branched 1* (*tb1*), which acts as a repressor of organ growth and contributes to apical dominance by repressing lateral branch outgrowth.[101] The signature of selection was identified in the promoter region, 60 kb upstream from the start codon.[102] The maize allele conferring one main stalk with short, feminized lateral branches is caused by a retrotransposon insertion resulting in higher expression of the maize allele and thus stronger repression of tillering.[103] Another domestication QTL that has been resolved is *teosinte glume architecture 1* (*tga1*). Teosinte seeds are covered by a hardened fruitcase composed of lignified glumes, whereas maize kernels are "naked" on the ear. Although the components of the fruitcase are present in maize, their development is disrupted so that the kernels are not encased as in teosinte.[104] *Tga1* was fine mapped down to the founding member of the squamosa promoter binding protein (SPB) family of transcriptional regulators, and the causative lesion appears to be an amino acid change in the protein.[105]

The advent of genomic tools has likewise enhanced the study of domestication traits in maize. A resequencing study of 774 maize genes across 14 inbred lines revealed that 2−4% of the genes examined experienced artificial selection[106] which, extrapolated to 60000 genes in maize the genome, implies that as many as 1200 genes were targeted by domestication and/or breeding. Using the maize HapMap_v2 data set of genome-wide sequence data to compare the 55 million SNPs across 75 inbreds, landraces, and teosinte revealed that landraces retain 83% of the diversity of teosinte and that artificial selection was stronger during domestication than improvement by modern breeding efforts.[107] The same study found that at least 1000 genes experienced selection during domestication and/or breeding. Studies are ongoing to determine which genes and traits were most affected by artificial selection during domestication and breeding.

The two larger scale studies described above[106,107] indicate that approximately 1000 genes were affected by artificial selection. These genes have little or no variation in modern maize inbreds, yet these genes were critical to the transformation of teosinte to primitive maize and then into modern maize. These genes will not be identified in maize × maize QTL studies and cannot contribute to crop improvement by traditional breeding methods as there is no variation remaining in maize. In these cases, one must "go shopping" for variation in these genes to study their biological role in the plant and their potential for crop improvement. The North Central Region Plant Introduction Station currently houses 211 *parviglumis* accessions, 8573 maize landrace accessions, 2882 maize inbreds, and many populations of intermediate levels of inbreeding (http://www.ars-grin.gov search conducted on October 23, 2012). This germplasm collection represents a very important resource for breeding, as well as genetic and genomic studies, especially in the search for novel variation not present in modern maize varieties.

Although both selection studies above indicate that 2−4% of maize genes experienced selection, these studies also reveal that the vast majority of genes (96−98%) are neutral genes that were not affected by artificial selection. Thus, whereas the domestication and plant breeding bottlenecks reduced variation in inbreds compared to landraces compared to teosinte, high levels of diversity still exist for most genes in modern inbred lines. Thus, for most traits, inbred × inbred populations are still useful for breeding and genetic studies. However, one must still be willing to explore the range of diversity present in maize inbreds.

Diversity-Based Resources for Maize. Several publicly available resources have been or are being developed for the analysis of genetic diversity in maize. To utilize the range of diversity present in inbred lines, many association panels have been developed to take advantage of ancestral recombination events for high-resolution QTL mapping. Among these are the original panels of 102 and 302 inbred lines,[12,108,109] the 627 inbred lines with restricted range of flowering time representing the Wisconsin Diversity panel,[110] the 151 inbred lines primarily from China,[111] 71 inbred lines developed in Germany,[112] 375 inbred lines from Europe and America,[113] 75 proprietary

commercial inbred lines,[114] and 245 tropical and subtropical maize inbred lines from CIMMYT in Mexico.[115] Each of these panels has its own advantages and disadvantages in terms of adaptedness to the target environment, genetic diversity, resolution, population structure, linkage disequilibrium, etc.[116]

Many traits have been dissected using association analysis including flowering time, kernel composition, and primary and secondary metabolism.[109,110,112−115,117−123] Whereas QTL mapping resolution is high, power is often quite low due to allele frequency imbalances within the population.

Nested association mapping (NAM) was developed to overcome the low power issues of association mapping. Nested association mapping combines the historic recombination events of an association mapping panel with recent recombination events of linkage mapping populations, resulting in high mapping resolution and high statistical power for improved quantitative trait dissection.[124,125] Solely on the basis of genetic diversity, 25 inbred lines were chosen from the 302 inbred line panel[12] that, when combined with B73 and Mo17, would maximize genetic diversity. These 25 NAM founders were crossed to B73, and a population of 200 recombinant inbred lines (RILs) was derived from each of the 25 F1s.

NAM has been used to dissect traits by joint linkage QTL mapping[117,126−129] as well as genome wide association mapping (GWAS).[117,127−130] For example, joint linkage analysis in NAM indicated that 22 QTL control kernel oil content.[117] The largest oil QTL was on chromosome six, and colocalized with a previously characterized oil synthesis gene, *acyl-CoA:diacylglycerol acyltransferase* (*DGAT1-2*).[131] In the 2008 study, a high-oil line (19% oil) was crossed to a line with standard oil content (~3.5% oil), and the authors determined that the high allele was caused by a 3 bp indel that resulted in a phenylalanine insertion in the end of the protein. In the 2012 study, GWAS in NAM and the 302 association panel identified five polymorphisms within the *DGAT1-2* coding region that associated with oil content and formed three distinct haplotypes that correlated well with the allelic effects from the joint linkage analysis. Interestingly, however, the high oil allele from Tzi8, a tropical inbred from Nigeria, had a B73 haplotype throughout the entire *DGAT1-2* coding region, indicating that there are other causative sites beyond those that have been described. Fine mapping studies are underway to determine the nature of the Tzi8 allele.

Although maize inbreds contain an incredible amount of genetic diversity relative to other crop species, a subset of genes is nearly invariant in inbred lines due to directional selection and genetic bottlenecks associated with domestication and/or plant breeding. Therefore, variation for these genes must be reintroduced from landraces and/or teosinte (as discussed below). To this end, a set of introgression lines (ILs) is being developed from 10 *parviglumis* accessions in the B73 background. Maize and teosinte readily hybridize, both in the wild and in the nursery, given short daylength conditions as teosinte is photoperiod sensitive. The F1 hybrids are still photoperiod sensitive and result in highly tillered plants with long lateral branches. Short days tend to alleviate these photoperiod effects, resulting in moderately tillered plants and more compact growth habits. The F1 hybrids were backcrossed with B73 four times and then selfed to fix the introgressed teosinte regions. The resulting 887 near-isogenic lines (NILs) are approximately 97% B73, but each NIL has a different part of the genome from teosinte.

The development and characterization of the teosinte NILs is still underway, but they are already being used in a number of ways. The first is to answer empirical questions about the ~1000 genes that were targeted during maize domestication. What do these selected genes do? What traits were targeted by artificial selection during domestication/breeding? Are selected genes important to agriculture today? By combining phenotypic analysis of the NILs with genome-wide selection studies,[107] we can begin to answer some of these questions.

A second application of the teosinte NILs is QTL mapping of agronomically relevant traits that were also targeted during domestication and fine mapping to determine the gene(s) underlying the QTL. Several yield component traits and kernel composition traits were likely targeted during domestication, for example, kernel row number, seed weight, and kernel starch content. Preliminary QTL analyses of kernel row number and seed weight in the teosinte NIL populations indicate several QTLs with alleles with much larger allelic effects than those identified in NAM.[130]

A third and much more applied use for the teosinte NILs is to reintroduce variation into modern maize in a more targeted fashion. The biological hypothesis of domestication is that a loss of genetic variation results in a loss of phenotypic variation and that adding genetic variation restores phenotypic variation. This is a very testable hypothesis. However, a breeding hypothesis is that we can improve modern traits by reintroducing variation from teosinte. For example, an early population genetics study of six starch synthesis genes indicated that three exhibited signs of selection, that is, reduced genetic variation.[132] Reintroduction of diversity for these genes may result in increased or altered starch. Similarly, other kernel traits appear to be targets of selection including seed weight and other composition traits.[133] Future plans for the teosinte NILs include investigating kernel composition (i.e., starch, protein, and oil) and examining the teosinte alleles for DGAT1-2, the gene underlying the chromosome 6 QTL controlling oil content in NAM.[117]

CONCLUSIONS

It is clear that selection during domestication and plant breeding has reduced genetic variation in all crop species. Therefore, novel variation can be introduced from wild relatives and/or intermediate landraces, and some proportion of this novel variation will be useful in crop improvement by either traditional breeding methods or biotechnology. For example, several disease-resistance genes have been identified in wild tomato, *S. pimpinellifolium*,[134,135] and transferred into modern cultivars.[136] Of course, wild relatives and landraces have potentially useful variation for any trait and, thus, could contribute to increased production, reduction of inputs such as fertilizers and pesticides, increased tolerance abiotic stress, and improved nutrition.

Given that useful variation exists and that the useful alleles can be transferred into modern cultivars, native (non-transgenic) genetic variation can be used in breeding programs in three ways: independent of biotechnology, in conjunction with biotechnology, and via biotechnology. (1) Native variation crossed into modern cultivars from wild relatives via traditional breeding methods offers an alternative to genetically modified (GM) crops in countries where GM crops are not accepted. (2) Native genetic variation could provide alternate modes of action for resistance to insects and diseases which, when pyramided with transgenic events, could prolong the longevity

of existing GM products. For example, corn root worm has evolved resistance to multiple Bt transgenic events.[137−139] Identification and incorporation of native host plant resistance genes for corn rootworm resistance could slow the rate at which that insects tolerate commercial transgenic events. (3) Native variation can be used as a donor for biotechnology in crop improvement. Often, useful variation is linked to negative variation in wild/landrace donor germplasm, where selection for the useful variation can lead to a poorly adapted or low-yielding product (i.e., "linkage drag"). The use of transgenic approaches allows the separation of the useful variation from the negative variation, thus mitigating the effects of linkage drag. By using molecular biology tools, transgenic events can also increase the expression of native alleles, making them more effective.

Needless to say, plant geneticists and breeders need to continue their efforts to identify and utilize variation from wild and landrace germplasm. Success in this area of research will require a long-term commitment to exploring diverse germplasm.

AUTHOR INFORMATION

Corresponding Author

*E-mail: Sherry.Flint-Garcia@ars.usda.gov. Phone: (573) 884-0116. Fax: (573) 884-7850.

Notes

The authors declare no competing financial interest.

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