

The Genetics and Genomics of Plant Domestication

MICHAEL B. KANTAR, AMBER R. NASHOBA, JUSTIN E. ANDERSON, BENJAMIN K. BLACKMAN, AND LOREN H. RIESEBERG

This article attempts to summarize the current knowledge on plant domestication on the basis of recent genome sequencing. To this end, several topics are explored, including (a) domestication as a process, (b) the genetics of domestication, (c) the impact of domestication on plant genomes, and (d) how domestication studies may change in the future with new genomic information.

Keywords: evolution, genetics, plant biology, plant breeding

Food plants are a fundamental aspect of how people relate to their environment and how they experience culture. A primary goal cutting across the fields of plant genetics, evolutionary biology, and anthropology is to understand where, when, and how contemporary food plants were domesticated from their wild ancestors and modified for modern agriculture. In pursuing these goals, investigators are not only learning how traits that improve nutrition, yield, and ease of cultivation have changed, but they are also revealing important context about the origins of cultural traditions while yielding clues to the natural human lifestyle in prehistory. Recent advances in high throughput sequencing and computational techniques have fostered new approaches in studying the genetic and genomic changes that have accompanied plant domestication. In this article, we consider what these studies have taught us about the process of domestication, focusing on comparisons of crop plants and their wild progenitors. We first explore how domestication proceeds and the types of traits most often subject to change. Then, we consider how this process has pervasive impacts on the genes and genomic diversity of crop plants. We conclude with a discussion of promising future research areas enabled by technological and analytical advances in plant genomics, including large-scale germplasm resequencing and ancient DNA analyses.

Domestication as a process

Domestication is a well-studied process, beginning with Darwin's (1859) work describing how selection alters cultivated taxa (Gepts 2004, Meyer and Purugganan 2013). The process proceeds by several commonly observed steps that transition a wild organism to one that is more amenable to

human use—that is, a *domesticate*. These steps roughly consist of (a) wild harvesting; (b) conscious and unconscious selection to modify plant characteristics (e.g., architecture, flowering time, dormancy, size, and reduction of defensive structures); and (c) conscious selection of plant material for specific locations and uses with the plant generally losing the ability to survive without human care (Harlan 1992). Stemming from Darwin's initial examination of this selection-driven process as a model for how natural selection could occur, a major and productive research direction has emerged in the field of evolutionary biology that focuses on examining the power and details of evolution driven by directional selection (Meyer and Purugganan 2013).

Centers of origin. Early studies of where plant domestication first occurred were dominated by the *centers of origin* concept. This hypothesis, initially proposed by Alphonse de Candolle (1890) and later refined, expanded, and popularized by Nikolai Vavilov (1926), posits that domestication occurred in a few discrete “centers” and then expanded through human migration and/or trade. Initially, centers of origin were hypothesized on the basis of the resemblance and diversity of phenotypes in modern germplasm, archaeological remains of cultivated species, and their likely wild ancestors (Harris 1990). More recently, researchers have employed molecular phylogeographic and population genomic analyses, which use DNA-sequence diversity within and among lineages to infer patterns of ancestry and descent, and in doing so, they have refined earlier hypotheses and suggested new ones (Meyer and Purugganan 2013).

Recent genomic and archeological data suggest that the concepts of discrete centers of origin or diversity may

oversimplify the actual histories of cultivated species. In many cases, the evolution of crop plants has been a more complex and continuous process (Harlan 1971, Harris 1990), often characterized by multiple independent domestication events (*Hordeum vulgare*, barley; Morrell and Clegg 2007) in large or diffuse geographic regions (*Malus x domestica*, apple; Gross et al. 2014) that lack a defined center of origin (Armelagos and Harper 2005). Although limited in universality, these concepts nonetheless remain useful frameworks for (a) finding valuable variation for plant breeding; (b) studying how a species' diversity changes over time beyond its native range; and (c) determining the nature and extent of genotypic and phenotypic evolution in crops, especially as they are introduced to new environments. This last use illustrates another way in which domesticated crop diversity can be a fruitful means to study evolution by natural selection, because it provides context for understanding how adaptation to new environments has shaped crop genomes and has sometimes resulted in the evolution of partial or complete reproductive isolation.

Domestication syndrome. Investigators have searched for phenotypic characteristics common across crop plants (*domestication syndromes*) that may help illuminate agents of selection, as well as the order and pace of domestication. The domestication syndrome includes grain retention by loss of shattering (rice, barley, wheat, soybean), reduction of lateral branching (maize, sunflower), or flowering-time modification (small grains, sunflower, maize, soybean). These changes may facilitate harvest, increase yield, and alter the timing of the growing season, which can facilitate expansion of cultivation beyond the native range and adaptation to new environments. Because domestication is a process and trait differences accumulate over time, more recently or less intensively cultivated crops may exhibit different levels of expression of the domestication syndrome than the earliest and most intensively cultivated species (figure 1; supplemental tables S1 and S2). Since its conceptual introduction by Harlan and colleagues (1973), the domestication syndrome has been repeatedly emphasized in the literature, but its long centrality to the field may be at odds with its generalizability. The convergent evolution of similar traits under cultivation is pronounced in the crop plants with the most enduring and intensive levels of production, and domestication syndromes are not as prominent in minor crop plants showing different levels of domestication (Meyer et al. 2012).

Many authors have sought to determine how quickly domestication has proceeded, and archaeologists and geneticists have reached conflicting interpretations, often suggesting lengthy and rapid transitions, respectively (Gepts 2004). Distinguishing between these possible histories is important because the answer shapes how we understand the origins of agricultural practices and technology. Consequently, linking the length of time it took for such advances informs inferences about the rise and fall of civilizations. Multiple methods have been used to ask this question, including

forward-in-time simulations (Allaby et al. 2008), coalescent simulations (Gao and Innan 2008), and selection experiments (Hillman and Davies 1990), but clarifying the intricate and conflicted record remains challenging. For example, empirical studies have shown that it can take as little as 20 years to eliminate unwanted genetic variation and fix a single domestication trait such as nonshattering (Hillman and Davies 1990), but the archeological record shows that it took approximately 1000 years for the Neolithic package (farming, pottery, villages, obsidian) to emerge in the Fertile Crescent (Wilcox 1998) and that farming may have expanded at just approximately 1 kilometer per year (Ammerman and Cavalli-Sforza 1971).

A more protracted domestication process may also have been a result of early farmers retaining wild-like variation for certain characteristics within the population and having different approaches to cultivating domesticates. For example, under some circumstances, a domestication syndrome trait such as shattering may have been partially maintained through traditional harvesting practices, in part, to ensure adequate reseeding (figure 2; Vennum 1988, DeHaan et al. 2016). The extent to which generalizations can be made from these data about the relative roles of *conscious* (intentional selection for a trait) or *unconscious selection* (selection that occurs because of technology or practice) is unclear for several reasons. Gaps in the archeological record can lead to inaccurate inference on the origin and spread of domesticates (Larson et al. 2014). Observed gene flow between crops and wild relatives may also lead to incorrect inferences of a protracted domestication history (Baute et al. 2015). Finally, the independent domestication goals of different cultures may have led to different ideotypes (ideal plant type) that are not largely recognized as domesticated, potentially leading to incorrect inferences of technological trajectories.

Clear and universal generalizations about the location and pace of the domestication process in plants may also be elusive because domestication does not conform to a singular process across species but instead may reflect a diversity of idiosyncratic processes influenced by species-specific biology, genetics, and cultural–historical contexts. This theme of selection both as an act of science and as a matter of art permeates the language of plant breeding, including phrases such as “the art of breeding” and “the breeder’s eye” (the ability to see a well-performing plant just by walking the field), with the latter often viewed to be as important as quantitative data (Bernardo 2014).

The genetics of domestication

Genetic studies of domestication permit insights into how humans can interact with and alter their environment over evolutionary timescales. In this context, plant breeding and domestication are akin to local adaptation in wild populations. As crop plants came to be cultivated in gardens and agricultural field environments and as they have been dispersed geographically to new areas, discrete populations became established from a relatively small number

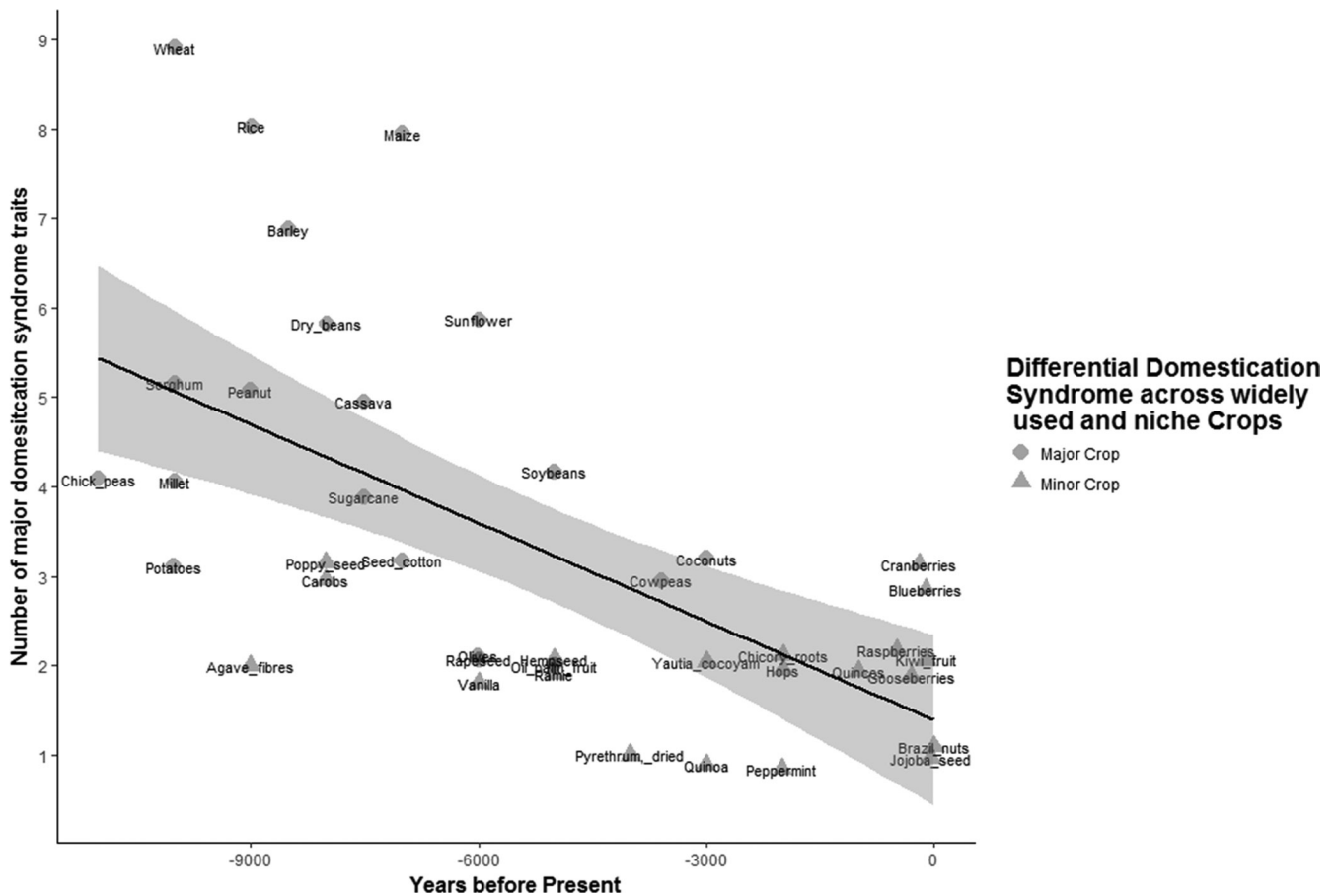


Figure 1. Using the FAO yield data to define the highest- and lowest-yielding major crops in the world (supplemental tables S1 and S2) and then surveying the literature to identify the major domestication phenotypes, we show the relationship between domestication time and the number of domestication traits. The shape indicates relative acreage based on FAO data. A slight jitter has been added to the data so that crop names do not overlap on the scatterplot. It becomes clear when examining a wide range of crops that differences in domestication stage are common and depend in part on the length of time under domesticated and cultivation extent, as well as on the crop's life history (e.g., generation time) and mating system. There is also a trend for older domesticates that have the classical domestication syndrome to be grown on larger acreages and to be more differentiated phenotypically relative to progenitors. There is also a trend for species with similar roles in the human diet (e.g., grasses) to share a similar number of domestication traits.

of founders (Ladizinsky 1985). Introduction to these novel agricultural ecosystems has driven unique adaptations relative to wild progenitors, as well as other genomic changes reflecting accompanying demographic transitions and gene flow. Thus, by characterizing patterns of change in genome sequence diversity, structure, and organization, as well as identifying causative genetic changes at individual loci, we can learn the molecular mechanisms and speed with which genetic and phenotypic responses to artificial selection occur, potentially shedding light on how cases of natural evolution proceed as well. In addition, because genomic patterns of diversity reflect histories of ancestry, migration, and change in population size, population genetic studies in extant and archaeological samples can also deepen our understanding of where crops were domesticated and how best to marshal genetic resources in cultivated and wild

germplasm for crop improvement. All of these efforts have been greatly accelerated and become even more rewarding thanks to the advent of high throughput sequencing technologies that have allowed rapid and cost-effective investigation at the levels of whole genomes.

The timing and location of domestication. To find information that will help date when and locate where agriculture started across the world, investigators have turned both to the archeological record and to the patterns of sequence diversity of genes that contributed to change in important domestication phenotypes. Because we know that the historical record is fragmented and incomplete, archaeological evidence provides a lower bound on how and where early domestication may have started (approximately 10 thousand–12 thousand years ago; Skoglund et al. 2010). However, evidence of wild

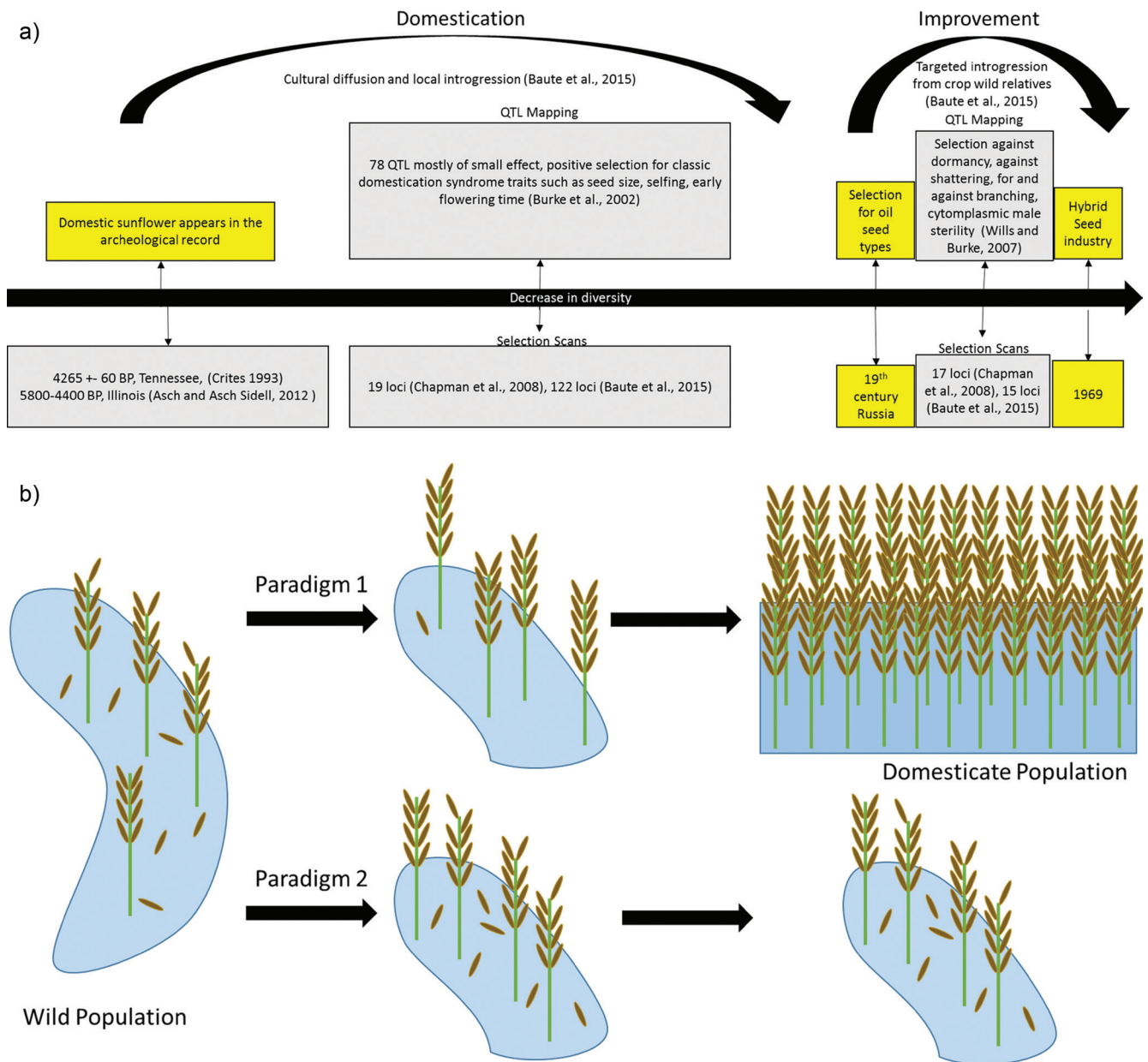


Figure 2. (a) In this figure, we show a relative timeline (in which domestication is shown to have taken much longer than improvement) of important archeological and genetic events in sunflower domestication history and the method of detection that was used to identify selection if applicable. The yellow boxes correspond to important historical events and the gray boxes to an empirical finding. Sunflower domestication occurred once, with all extant lineages tracing back to a single source population found in the eastern United States (Harter et al. 2004, Blackman et al. 2011). There is extensive linguistic, mineral, and cultural evidence suggesting a long history of sunflower farming in many different cultures (Rieseberg and Burke 2008, Blackman et al. 2011). During the sunflower cultivation history, different traits have been selected for during initial domestication and improvement (gray background). *Helianthus annuus* has a large species range and cross-fertility with many wild relatives that can provide novel genes for different local environments (Baute et al. 2015). This has led to many uses of wild relatives in sunflower breeding (Kantar et al. 2015), and these factors combined have helped maintain diversity within cultivated sunflower. **(b)** *Zizania palustris* L. (wild rice) has been harvested from naturally occurring stands for thousands of years (Johnson 1969). The Anishinaabe of North America have a strong cultural relationship with wild rice (Manoomin), a seed that is traditionally harvested from wild populations (Vennum 1998). Formal domestication in the classical sense (paradigm 1) commenced in the first half of the twentieth century, with efforts directed at “domestication-syndrome” traits, including reduced shattering (Oelke 1993). The differential treatment of this annual grass species by indigenous and nonnative peoples is exemplified by their approaches to shattering: The Anishinaabe harvesting practices maintained shattering (Paradigm 2) and used stem binding to retain some seed (Vennum 1998, Eule-Nashoba 2010), and the nonnative breeding efforts sought to reduce or eliminate shattering.

harvesting and plant use extends thousands of years further back (Richerson et al. 2001) and for nine independent areas of domestications worldwide (Harlan 1971, Smith 2006).

Constraints on the domestication process. Generalizations about the genetics of the domestication process have emerged. Arguably the most widespread consequence of domestication is a *genetic bottleneck*, in which the genetic variation of a population is reduced through a decrease in population size. Often, cultivated species show evidence of genetic bottlenecks during initial domestication, although the extent to which diversity is reduced may vary among crops. Then, additional bottlenecks may occur when the crops are traded from region to region and when crops are improved for specific uses (e.g., the breeding of sunflower lines specialized for oil versus edible seed production). In addition to the demographic effects of reduced breeding population size—that is, genetic drift (Ladizinsky 1985)—artificial selection also decreases genetic diversity in domesticated and improved plants through the removal of allelic variants of genes that confer characteristics undesirable for cultivation (Wright et al. 2005, Morrell and Clegg 2007, Allaby et al. 2008). The effects of genetic drift are, theoretically, distinguishable from those of selection because although drift results in a genome-wide reduction of diversity, selection should only reduce diversity within domestication-associated genomic regions. However, nonequilibrium demographic histories, such as those associated with domestication and breeding, can generate heterogeneous patterns of variation across the genome, potentially producing false positives in genome scans for selection (Excoffier 2004).

Decreases in diversity caused by bottlenecks and selection may be partially offset by *admixture*, or interbreeding between domesticates and local wild populations. Admixture often occurs as the geographic ranges of domesticates expand, potentially protracting the domestication period and complicating analyses of the timing and location of domestication (Larson et al. 2014). The importance of admixture depends on the length of the domestication period, the extent of range expansion, as well as the life history and mating system of the crop and its wild relatives. Genetic exchange can occur throughout the domestication process (Baute et al. 2015) and may represent an important impediment to domestication in some plant species, because a constant influx of wild alleles may swamp the strength of unconscious or conscious selection favoring differentiation in trait values amenable to cultivation. Indeed, the development of reproductive barriers is closely associated with successful domestications (Dempewolf et al. 2012), although it is not clear whether it is a cause or a consequence of domestication. Even after domestication, introgression of novel traits and genetic variation from wild relatives can shape crop genomes; wild relatives and primitive domesticates have often been used as source germplasm to breed in useful traits (Castañeda-Álvarez et al. 2016).

The genetic basis of domestication. Numerous ever-evolving techniques have been applied to detect and characterize the genetic basis of domestication, allowing more nuanced and complex interpretations of the domestication process to emerge. Figure 2 explores how genetic architecture and domestication paradigm influence how we interpret the genetics of domestication in a given species. The major methods for characterizing the genetic basis of domestication can be categorized into top-down and bottom-up approaches. *Top-down* methods start with phenotypic observations and then connect genotype to phenotype by genetic mapping in segregating populations generated from controlled crosses. *Bottom-up* techniques start with extant genetic variation and look for signatures of selection in the genome. Top-down genetic mapping approaches are best applied to obvious phenotypic differences in traits such as plant architecture or seed size. Just as Mendel approached his examination of varieties of peas and their diverse traits, the number and effect size of loci involved in these traits can be explored in the progeny of crosses between parents that differ for traits of interest. Unlike Mendel, however, researchers today can marshal the power of molecular markers to identify which regions of the genome that cosegregate with trait variation in the progeny. More recently, genome-wide association analyses have been completed using diverse germplasm, rather than in controlled crosses such as those described above, to map underlying causal variant(s) (Ross-Ibarra et al. 2007, Gepts 2014). Dissecting domestication traits down to their allelic basis can uncover the responsible variant, whether it be epigenetic or a genetic substitution, insertion, deletion, duplication, transposon activity, or chromosome rearrangement (Meyer and Purugganan 2013). Frequently, multiple loci are implicated as major contributors to domestication syndrome traits, and the same genomic regions harbor variation affecting multiple traits, indicating the involvement of pleiotropic genetic changes or the impact of closely linked variants with independent effects. The ability to detect these variants, as in any mapping population, depends on the genotyping depth, marker type, population size, and phenotyping accuracy, among other factors (Korte and Farlow 2013). Often, these studies have indicated that the domestication syndrome has a relatively simple genetic basis, with some individual loci making large contributions to the phenotypic differences between crop plants and their closest wild relatives.

Alternatively, the genetic basis of domestication can also be detected by bottom-up approaches that leverage population genetic analyses to detect putative signals of selection without an *a priori* consideration of related phenotypes (Gepts 2014). By not including a phenotypic component, these methods are inherently less biased toward the visible domestication syndrome traits (Ross-Ibarra et al. 2007); nevertheless, they are empirically limited by marker density, the detection of false positives, and sampling design (Tiffin and Ross-Ibarra 2014). Thus, considering the results of any single analysis as putative and confirming them by a secondary method elevate confidence in the findings. The

Table 1. A list of recent studies exploring the number of loci involved in the domestication and/or improvement process.

Crop	Domestication	Improvement	Accessions or method	Reference
African Rice	73 regions ($\pi_w:\pi_c$) or 24 regions (CLR)	–	Resequencing 20 cultivars (<i>Oryza glaberrima</i>) and 19 wild (<i>O. barthii</i>) accessions. Selection signals detected with $\pi_{wild}:\pi_{cultivar}$ and composite likelihood ratio tests.	Wang M et al. 2014
Carrot	“Identified local differentiation signals on chromosomes 2, 5, 6, 7, and 8”	–	Resequencing of 35 accessions (18 cultivated, 13 wild, and 4 other <i>Daucus</i> species). Domestication loci detected as F_{ST} outliers comparing eastern wild (5) and cultivated (6) accessions.	Iorizzo et al. 2016
Common Bean	930 windows in Mesoamerican and 750 in Andean or 1,835 candidate genes in Mesoamerican and 748 in Andean	–	Resequencing of 60 wild individuals and 100 landraces from Mesoamerican and Andean gene pools. The criteria to detect signals of selection required the window or gene to be in the top 90% of the pool's empirical distribution for both $\pi_{wild}:\pi_{landrace}$ ratios and F_{ST} values.	Schmutz et al. 2014
Cucumber	112 genomic regions	–	115 lines (13 wild, 103 cultivated) analyzed with deep resequencing. Selective sweeps detected as loci in top 5% of $\pi_{wild}:\pi_{cultivated}$ values and the top 5% of XP-CLR results.	Qi et al. 2013
Maize	484 loci	695 loci	Resequencing of 35 improved lines, 23 landraces and 17 wild relatives. Focused on top 10% of XP-CLR results.	Hufford et al. 2012
Maize	–	406 regions in US accessions, 399 in Ex-PVPs, and 397 in Chinese lines. (2.73%–3.08% of the genome)	Resequencing 278 temperate inbred lines detecting selection with composite likelihood ratio test and 1% cutoff.	Jiao et al. 2012
Rice	55 selective sweeps	–	Resequencing 446 wild and 1083 <i>indica</i> and <i>japonica</i> varieties. Genome-wide selection signals detected with $\pi_{wild}:\pi_{cultivated}$.	Huang et al. 2012
Rice	64 regions in <i>japonica</i> and 75 regions in <i>indica</i>	–	Resequencing 40 accessions and 10 wild progenitors. Signals of selection detected as regions of lower diversity ($1-\pi_{cult}:\pi_{wild}$) using 0.25% cutoff.	Xu et al. 2012
Sorghum	Many regions each encompassing many megabases	–	Resequencing of 971 accessions including wild, landraces, and landrace-conversion lines.	Morris et al. 2013
Soybean	121 loci	109 loci	302 accessions (62 wild, 130 landraces, 110 elite) with 11x NGS coverage and XP-CLR to detect selective sweeps.	Zhou et al. 2015
Sunflower	122 genes	15 genes	Transcriptome data from 38 genotypes of wild and cultivated (landrace and modern lines) <i>Helianthus annuus</i> (L.), 21 genotypes of <i>Helianthus petiolaris</i> (Nutt.) and 21 genotypes of <i>Helianthus argophyllus</i> were analyzed for F_{ST} outliers.	Baute et al. 2015
Wheat	–	21 regions in the spring wheat and 39 regions in the winter wheat	2994 accessions of hexaploid wheat including landraces and modern cultivars genotyped at 9000 gene associated SNPs. Evidence of selection detected with pair-wise haplotype sharing within populations and F_{ST} between populations.	Cavanagh et al. 2013

feasibility of these bottom-up approaches has increased with improvements in sequencing technology and reduction in genotyping cost and is now a common practice (table 1). Estimates of the number of loci under selection in the domestication process are wide ranging, from as few as 55 in one rice study (Huang et al. 2012) to as many as 484 loci in maize (Hufford et al. 2012). Despite the wide variation in these estimates, bottom-up approaches do imply a more complex genetic basis for domestication than that suggested by top-down studies. In part, this difference

emerges because bottom-up approaches detect loci underlying a larger fraction of selected traits (e.g., morphological, developmental, physiological, and biochemical), whereas only those associated with visible phenotypes are typically studied by top-down methods.

The number of loci segregating for beneficial variants greatly affects the efficiency with which selection can act. As interest in diversifying food systems and domesticating new species has expanded recently, the ability to define the minimum number of loci needed to select for domestication to

be able to create realistic timelines for *de novo* domestication has great practical value. A recent simulation study suggests that the early cultivation and domestication process may have an upper limit of only 50 to 100 loci under selection (Allaby et al. 2016) because each individual and successive selective sweep comes at a cost to total genetic diversity. The remaining diversity is an important source of variation for ongoing adaptation to changing farming practices, biotic, and abiotic pressures. A bottleneck would leave a population ill equipped to respond to changing conditions or to purge deleterious mutations, potentially leading to a collapse. Empirical results from recent bottom-up studies in many crops are roughly comparable to the simulation estimate (table 1). When differences are observed they may be rooted in methodology (e.g., differences in statistical stringency among studies) but may also arise because of important biological attributes, including high levels of standing variation, weaker population bottlenecks through domestication, or regular gene flow from adjacent populations.

Complications in identifying “domestication loci.” The observation that certain combinations of trait changes are common to the most widely cultivated crops raises the question of whether such phenotypic convergence is accompanied by genotypic convergence. In other words, do the same mutations, genes, and/or genetic pathways underlie the repeated evolution of the same trait changes in diverse crop species (Morrell et al. 2012, Meyer and Purugganan 2013)? However, the ability to detect domestication loci depends in part on the ages of the underlying mutations (Innan and Kim 2008). Old mutations already drifting neutrally at moderate frequencies in the wild progenitor population can become beneficial in the context of cultivation, and selection under domestication can rapidly drive them to high frequency. These “soft sweeps” are difficult to detect because of their occurrence on multiple genomic backgrounds (Gepts 2014). New mutations are often initially much more likely to be lost to drift because of their rarity than to be established by selection. Thus, it has been predicted that novel mutations for domestication syndrome traits may be more likely to establish in inbreeding crop species because they are more likely to occur in homozygous genotypes, whereas adaptation in outcrossing crops is more likely to be based on standing variation that does not suffer such high likelihood of loss by chance (Allaby et al. 2016). Exploring the evolutionary history of the specific variants responsible for domestication syndrome traits can help elucidate further questions, such as where domestication occurred, how many times, and which geographic direction agriculture spread. For instance, the presence of a flowering gene variant at low frequency in wild populations of Eastern North American *Helianthus annuus* as well as modern cultivars provided further support that this region was the source of the single domestication of this species (Blackman et al. 2011).

Histories of genome duplication, genomic rearrangements, and gene duplication can further complicate the

search for domestication loci. Whole genome duplications are pervasive in the ancestry of angiosperms and in crop evolution. In fact, there is a much higher prevalence of polyploidy among major domestic crop species than among general plant species (Salman-Minkov et al. 2016). Many side effects of polyploidization can prove beneficial through the domestication process. Genome duplication can serve as a postzygotic barrier reducing gene flow with a progenitor (Rieseberg and Willis 2007). The increase in the number of genes and/or alleles can capture and maintain the genetic diversity of progenitors even through population bottlenecks. The increase in genetic redundancy can also act as a buffer against the accumulation of deleterious mutations and relax the constraints on gene duplicates offering an opportunity for new gene interactions (Gepts and Papa 2002).

Peering into the past with archeological DNA (aDNA). Recent technological advances in sequencing in archaeology have led to the ability to explore preserved individuals from multiple sites closer to the time of domestication of different species (Fordyce et al. 2013). Initial studies revealed that ancient individuals are more similar to extant landraces than to elite material (Mascher et al. 2016, Ramos-Madriral et al. 2016). Other studies have used archeological sites along trade routes to establish the timing of when new crops were introduced to regions (da Fonseca et al. 2015). The ability to identify the genetic variation at a snapshot in time allows for an unprecedented level of direct hypothesis testing about the rate of genetic change and timing of crop adoption.

The impact of domestication on plant genomes

The demographic effects often associated with domestication (e.g., decreased effective population size, decreased diversity, and change in mating system), as well as directed selection for particular traits, may have dramatic impacts on genomic architecture. For example, demographic changes will reduce the efficiency of purifying selection (Beissinger et al. 2016), decrease effective recombination rates, and create conditions that facilitate a phenomenon known as *allele surfing*, in which alleles that are not beneficial but coincidentally exist in individuals with important domestication alleles rise in allele frequency as well. Although there is also evidence of large-scale chromosomal structural changes (Yang et al. 2012), changes in transposable-element content (Chia et al. 2012), and changes in copy-number variation (Wang Y et al. 2015), here, the focus will be on the hypothesized increase in the number of putatively deleterious mutations fixed or segregating within the genomes of cultivated taxa. Many authors have termed this the “cost of domestication” (e.g., Liu et al. 2017); however, there has been disagreement on whether this mutational load is a cost that actually decreases fitness in domesticates.

Estimating *genetic load*, a term referring to the accumulation of nonlethal deleterious alleles in a population that lead to a reduction in fitness (i.e., yield or quality in crops), is difficult. The absolute impacts of lethal mutations cause them

to be quickly removed from the population (Charlesworth 2012), whereas beneficial mutations will rapidly rise in frequency within the population (Robertson 1960). However, because many mutations are only mildly deleterious, they may persist for many generations, similar to mutations that have no effect on fitness (Fay et al. 2001). The selective sweeps characteristic of domestication frequently lead to the *fixation* (i.e., present in all individuals in a population) of large genomic regions because meiotic recombination events are only so frequent, leading neighboring genetic content to “hitchhike” along with the targeted desirable domestication regions (figure 3). These hitchhiking mutations may have small deleterious effects that recombination and selection around the domestication loci may only be able to pare away naturally over long evolutionary timescales (e.g., rice; Lu et al. 2006). In addition, demographic bottlenecks can frustrate elimination of these variants from populations.

There are many methods currently available to detect mildly detrimental mutations and potentially remove them from domesticated populations. These methods have been facilitated by advances in DNA-sequencing technology that allow researchers to inexpensively examine many individuals of a crop species rather than the small samples feasible with earlier methods. Low-cost data as well as new algorithms and statistical tests permit estimation of genome-wide and region-specific proportions of putatively deleterious mutations and of their potential effects in a given genotype relative to other individuals within a species and to closely related species, such as Provean (Choi and Chan 2015), Polyphen (Adzhubei et al. 2010), SIFT (Kumar et al. 2009), and likelihood ratio tests (Chun and Fay 2009). Generally, these methods test whether mutations lead to major-effect amino-acid substitutions while accounting for how constrained the residue is based on the gene’s evolutionary history.

Empirical evidence from rice (Nabholz et al. 2014, Liu et al. 2017), maize (Mezmouk and Ross-Ibarra 2014), barley (Kono et al. 2016), soybean (Kono et al. 2016), and sunflower (Renaut and Rieseberg 2015) have documented an increased number of nonsynonymous mutations in domesticated taxa relative to their wild progenitors and an increased number of predicted deleterious mutations in regions of low recombination (centromeric regions and regions around selective sweeps). This brings up general questions about how selection should be employed in breeding programs. For example, should breeders select for positive traits or against lines with higher estimated mutational load, and should selection be different in primitive domesticates versus elite lines? There is potential to use this information to reduce load through the implementation of various selection regimes such as marker-assisted selection, marker-assisted recurrent selection, genome editing, and genomic selection. It is also unclear to what extent these selection regimes would differentially affect annual, perennial, and clonal species. Different breeding strategies may work better in different species (i.e., genomic selection in annual species but genome editing in clonal species).

Domestication redux

Although domestication has served as an important model for biology for a century and half, it remains an active and central process for those who are students of evolution, speciation, and plant breeding. Groundbreaking discoveries, fresh perspectives, and novel technologies continue to provide additional twists and insights on this classic theme. The continued exploration of the specific underlying genes and genetic consequences of domestication, leveraging new resources, and new views on old crops will no doubt prove fruitful for years to come.

Domestication and speciation. As we discussed previously, the domestication of plants and animals has been used as evidence for evolution by natural selection (Darwin 1859), as well as a window for the study of evolutionary processes (e.g., Hancock 2012). However, domestication studies have had surprisingly little impact on our understanding of speciation, and speciation theory has almost never been used to inform our understanding of domestication. Domestication provides a view of the very earliest stages of speciation, and contemporary interactions between crops and their wild relatives offer a means to study the evolutionary consequences of hybridization (Ellstrand 2003). In addition, reproductive isolation itself may be a key domestication trait that facilitates domestication by reducing gene flow between crops and their wild progenitors (Dempewolf et al. 2012). However, this may be best investigated in species with long domestication histories; many newer domesticates or domesticates with long generation times (e.g., woody perennials) lack substantial barriers to gene flow.

Two outstanding questions about speciation include (1) which reproductive barriers evolve early in the speciation process and (2) whether hybrid incompatibilities frequently arise as a byproduct of divergent selection. Domestication provides a useful system for addressing both questions because domesticated plants are of recent origin, the selective pressures used to create them are well understood, and 75% of the world’s most important crops exhibit one or more reproductive barriers from their wild progenitor (Dempewolf et al. 2012). Also, domesticated species frequently hybridize with their wild relatives (Ellstrand 2003). Because the resulting hybrids typically exhibit reduced fitness but not full inviability, crop–wild hybrid zones may provide an opportunity to determine the conditions that favor *reinforcement*, the process by which natural selection directly favors the evolution of increased reproductive isolation.

The identification and characterization of genes and mutations that underlie reproductive isolation have also attracted much attention recently because like domestication genes, “speciation genes” may also reveal a great deal about evolutionary processes (Blackman 2016). The cloning and characterization of such speciation genes have been facilitated by the expansion of genome sequences and functional tools available for crop plants. Rice in particular has become a workhorse for identifying genes underlying hybrid

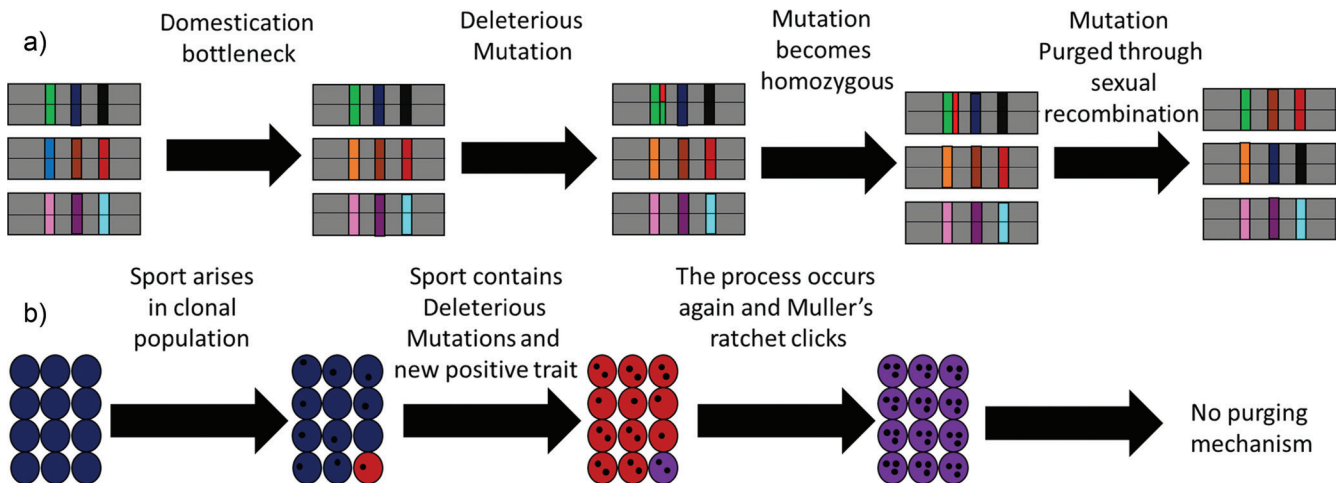


Figure 3. Genetic load in crops. Whether a crop plant is inbreeding, outbreeding, or clonal affects the ability of selection to remove deleterious mutations. (a) Sexual crops have the ability to purge genetic load through recombination. Self-pollinated crops remove deleterious mutations faster (recessive deleterious mutations are more likely to become homozygous and detectable by selection in selfing lineages and therefore purged more quickly) than cross-pollinated crops do. The bars represent different loci, and each bar color represents different alleles. (b) The tendency of mildly deleterious mutations to accumulate may be of greatest concern for clonally propagated crops. In such taxa, the somatic mutation rate appears to be high (Bobiwash et al. 2013), resulting in an overall higher per-generation deleterious mutation rate. Moreover, these mutations cannot be efficiently purged in the absence of sexual reproduction and thus may be fixed by genetic drift, increasing the total number of fixed deleterious mutations as was proposed by Muller (1964). This process has important implications for the breeding and production of perennial or clonal crops. The colored circles represent clonal lineages, and the black dots represent fixed deleterious mutations. In some instances, cultivars have been maintained for hundreds of years for their flavor profiles despite less-than-desirable yields, but a more sustainable practice would be to limit clone age. Genomic tools may make it possible to determine the ancestry of such clones and replicate their origins from fit ancestral genotypes or more quickly breed valuable genetic variants away from deleterious genetic backgrounds.

inviability and sterility (e.g., Yamagata et al. 2010). This work has contributed to the key observation that disease-resistance genes may commonly underlie hybrid inviability and also demonstrated that hybrid sterility can evolve through repeated substitution at a single locus. Further population genomic analyses of speciation genes and linked regions are likely to provide new insights into the relationship between domestication and reproductive isolation. For example, such analyses could provide information on whether the mutation(s) responsible for hybrid incompatibilities arose prior to domestication or during the domestication process, how quickly they became established, and the mechanism(s) (divergent selection, genetic conflict, etc.) responsible for their spread.

Exploration of abandoned crops. Many crops have come in and gone out of favor over the centuries, and germplasm is often lost leading to a disjointed domestication process. The current ease of genome sequencing coupled with the ability to explore aDNA allows for a simpler path toward exploring or even reviving abandoned crops. This relies on the ability to define appropriate domestication-syndrome suites for species and a better theoretical understanding of the expectation of the architecture of these traits. One example

of an abandoned crop is marshelder (*Iva annua*), an annual herbaceous member of the Asteraceae family and part of the Eastern North American crop complex (Smith and Yarnell 2009). This species was a domesticated part of the regional indigenous diet from $3,450 \pm 150$ BP (Smith 2006) until approximately 700 BP (Yarnell 1978), when it was likely supplanted by maize (*Zea mays*), beans (*Phaseolus vulgare*), and squash (*Cucurbita moschata*) prior to European arrival. The domesticated form of marshelder is now extinct, which is regrettable because the nutritional characteristics of this wild plant are exceptional relative to modern crops (Asch DL and Asch NB 1978). It may now be possible to examine the genetics of the domestication-syndrome traits in many ancient crops with targeted resequencing of known domestication genes already associated with specific traits in extant and archeological sequencing. Advances in aDNA recovery and historic climate modeling may also provide opportunities to see how crop allele frequencies have changed with respect to prehistoric climates. Data from these kinds of analyses may reveal whether the genes and/or genomic regions that contributed to domestication in these extinct crops are similar to those of successful crops or whether they differ in some way that might have contributed to abandonment. In addition, quantitative genetics approaches could

be used to examine whether modern wild populations are constrained by genetic correlations among domestication traits and whether those correlations may have led to crop abandonment.

Conclusions

The study of domestication continues to be a fruitful area of study in which the debates about the length of time, type and intensity of selection, and pattern of genetic architecture required for this process are ongoing. Specific traits, such as nonshattering, have been postulated to reach fixation in as few as 20 years (Hillman and Davies 1990). This idea and other recent work have suggested that with conscious selection for domestication phenotypes, domestication can be greatly accelerated (DeHaan et al. 2016). There are new resources for studies of selection and local adaptation that were once limited to model systems and are now readily transferable to many crop species. Historical efforts to collect and preserve wild relatives, landraces, and cultivated varieties have bolstered the world's public genebanks, and the onset of low-cost sequencing and global interest in these genetic collections have initiated a transition from long-term storage facilities to active exploration. For many crop species, the world's genebanks are now genotyped or fully sequenced. Within the next few years, thousands of crop wild relatives, landraces, and modern cultivars will be genotyped and available to the public scientific community. Although the focus of these efforts will be to enable plant breeders, these resources will be equally useful for studies of mutation, population genetics, genome evolution, and diversity in crop wild relatives. These data and techniques provide an opportunity to test alternative hypotheses regarding selection during domestication and their genomic consequences in side-by-side comparisons. Comparing modern and traditional breeding methods also opens the path to the domestication of new plant material that may fit new ecological and economic niches.

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Supplemental material

Supplementary data are available at *BIOSCI* online.

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Michael B. Kantar (kant0063@umn.edu) is affiliated with the Department of Tropical Plant and Soil Sciences at the University of Hawaii at Manoa, in Honolulu. Amber R. Nashoba is affiliated with the University of Alaska Anchorage. Justin E. Anderson is affiliated with the Department of Molecular Genetics and Physiology of Plants at Ruhr University Bochum, in Germany. Benjamin K. Blackman is with the Department of Plant and Microbial Biology at the University of California, Berkeley. Loren H. Rieseberg is affiliated with the Biodiversity Research Centre and Department of Botany at the University of British Columbia, in Vancouver, Canada.