Maize domestication and gene interaction

Michelle C Stitzer[1,2] and Jeffrey Ross-Ibarra[1,2,3]

[1]Department of Plant Sciences, University of California, Davis
[2]Center for Population Biology, University of California, Davis
[3]Genome Center, University of California, Davis

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mcstitzer@ucdavis.edu

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Abstract

The process of domestication presents a tractable system for following evolutionary change, as selective pressures shift, resulting in adaptation to the new ecological niche of cultivation. Perhaps the most detailed understanding of this process comes from *Zea mays*, where morphological, genetic, and genomic studies have elucidated the ancestry and selection that transformed a wild plant, the teosinte *Zea mays* subsp. *parviglumis*, into the domesticated maize *Zea mays* subsp. *mays*. These studies have identified five major morphological differences that distinguish these two subspecies, and careful genetic dissection of these phenotypes has assisted in understanding the underlying molecular genetic changes. But maize domestication was a consequence of more than just five genes, and regions throughout the genome contribute to this change. Their effects are contingent on genetic background, and the interactions between alleles and genes that give rise to phenotypes. This includes dominance relationships, epistatic interactions, and pleiotropic constraint, as well as how these variants are connected in gene networks. Together, we review the role of gene interactions in generating the dramatic phenotypic evolution seen in the transition from teosinte to maize.

Introduction

Zea mays subsp. *mays* is an important and widely-grown crop, but its survival is dependent on human cultivation. Although a cob of corn can contain hundreds of seeds, all are constrained to the cob. If all seeds germinate *in situ* they remain in close proximity, and seedling competition would inevitably impact fitness. Seeds are also available and apparent to bird and mammal predators, unprotected from their harsh digestive tracts. In spite of these characteristics that limit its survival in the wild, the maize plant, once noted as a 'man-made monstrosity' (Beadle, 1972), is well-adapted to the new ecological niche it has invaded.

Maize was domesticated from a teosinte — the wild grass (*Zea mays* subsp. *parviglumis*) — about 9000 years ago in the Balsas region of southwest Mexico (Matsuoka et al., 2002; Piperno et al., 2009), but the term 'teosinte' is used more broadly to refer to five species within the genus *Zea* (Iltis and Doebley, 1980; Doebley and Iltis, 1980). These species are highly adapted to their environment (Hufford et al., 2012a) and form large populations across much of Central America (Wilkes et al., 1967). The existence of both the wild ancestor and the domesticate growing in close proximity — the only difference being the ecological environment enacted by cultivation — makes the comparison between maize and teosinte useful for understanding evolution.

The initial stages of domestication are largely analogous to a plant encountering a new ecological niche. By regenerating and replanting seeds between generations, selective breeding and seed saving allow for adaptation to agronomic environments. The domestication process may shift selection pressures from biotic interactions like competition and colonization to traits of value for human consumption, like large non-dispersing seeds, reduced branching, and other nutritional and harvest-related phenotypes (Doebley et al., 2006). Byproducts of cultivation can also alter biotic interactions, for example by allowing pests to specialize on a domesticate (Bernal et al., 2017), or alter phenotypes less visible to conscious human selection, such as root architecture (Burton et al., 2013). For maize, these new selection pressures altered constraint on the genetic underpinnings of phenotypes.

Maize did not arise as a result of selection on only a few genes, although major effects enabled by a few genes were essential. Domestication required moving existing variation into a coherent genetic background, to allow many loci to contribute in total to dramatically different phenotypes. Although we can never perfectly reconstruct the combination of selective forces giving rise to modern maize, genetic and genomic tools now allow some insight into these processes. Gene interactions can limit the path which evolution takes, and can facilitate or impede rapid evolution. Maize domestication and comparison to teosinte provides a temporal and phenotypic context in which to understand both the origin and end point of selection. Here we review major domestication genes, highlight the role of gene interactions in the domestication of maize, show how these interactions have complicated attempts to achieve coherent results in understanding the inheritance of domestication phenotypes, and explain how epistasis can be leveraged by experimentalists to take advantage of natural diversity to understand maize biology and domestication.

Genetic basis of domestication

Maize domestication altered phenotypes

Maize has a female inflorescence so different from any wild plant that its origin was debated throughout the 20th century. Although early experimentalists observing and crossing maize and teosinte were assured of the ancestral state of teosinte (Harshberger, 1896; Collins and Kempton, 1920; Weatherwax, 1924) vocal criticism planted doubt in the minds of botanists throughout the middle of the 20th century (Mangelsdorf and Reeves, 1939; Mangelsdorf et al., 1974). At one extreme, the tripartite hypothesis proposed the ancestor of maize was an extinct popcorn, and that teosinte arose from crosses between corn and the related genus *Tripsacum*, with further crosses giving rise to the diversity of maize we observe today (Mangelsdorf and Reeves, 1939). The alternative teosinte hypothesis argued that teosinte was the direct ancestral form of maize (Beadle, 1939). These conflicting origins of maize triggered a debate that would not find resolution for over 50 years, when molecular methods and archaeological evidence vindicated teosinte, specifically *Zea mays* subsp. *parviglumis*, as the ancestor of maize (Matsuoka et al., 2002; Piperno et al., 2009; Bennetzen et al., 2001).

Teosinte is largely indistinguishable from maize in vegetative parts of the plant, with the major evolutionary innovation of maize being its infructescence, or ear. Hence, early definition of major phenotypic differences between maize and teosinte focused on ear phenotypes, putatively controlled by 4-5 genes or blocks of genes (Beadle, 1939; Mangelsdorf and Reeves, 1939).
These distinguishing phenotypes are:

1. *Maize has paired spikelets, while teosinte has single spikelets.* In grasses, the spikelet is a short branch on which flowers are borne. Most grasses form many single spikelets along the

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inflorescence. But in the Andropogonae, a tribe of grasses that includes maize and teosinte, spikelets are paired in both female and male inflorescences (Wu et al., 2009; Kellogg, 2000). In teosinte, while there are paired spikelets in the tassel, in the ear only single spikelets are formed (Doebley et al., 1995b). The maize ear appears to regenerate the ancestral state of Andropogonae and reintroduce paired spikelets to the female inflorescence (Galinat, 1983, 1985). In teosinte, only one spikelet develops into a kernel and hardens into part of the fruitcase of teosinte seeds. In maize, each internode of the cob contains both spikelets, and each spikelet matures into a kernel. This phenotype is most observable during inflorescence development, when spikelet primordia initiate on the inflorescence meristem. The consequence of paired spikelets for maize is more mature pistillate flowers formed on the ear, and hence more seeds.

2. *Maize has at least four ranks to its ear ('polystichous'), while teosinte only has two ('distichous').* This is a consequence of phyllotaxy, in the initiation of new primordia on the inflorescence meristem. The vegetative phyllotaxy of maize and teosinte is distochous — only one leaf is initiated per whorl — leading to the alternating leaves characteristic of the adult plant (Jackson and Hake, 1999). In teosinte, this alternate initiation occurs along the inflorescence meristem as well, visible in the mature alternate triangular infructescence (Sundberg and Orr, 1990). In maize, the inflorescence is initiated spirally, with multiple ranks, playfully noted as less than the maximal 3/8 phylotactic fractions by one maize biologist who regularly inspected cobs of sweet corn after dinner (Bird, 1996). Multiple ranks of kernels also give rise to more kernels per ear in maize than teosinte.

3. *Maize has a non-disarticulating rachis, while the teosinte rachis disarticulates upon maturity.* The rachis is the inflorescence, representing the entirety of the ear in maize and teosinte. In teosinte, abscission layers form and divide the rachis into individual fruitcases, which fall apart and can then disperse. In maize, these abscission layers do not develop, and the rachis remains intact upon maturity, with kernels attached to the cob (Iltis, 2000; Chavez et al., 2012). This intact cob eases harvest, and makes the maize plant reliant on human intervention for seed dispersal.

4. *Maize has softer, smaller glumes, while the teosinte fruitcase is entirely enclosed by the outer glume of the spikelet.* Glumes are leaves that subtend a flower. Each glume is associated with a segment of the rachis, referred to as the cupule (Dorweiler and Doebley, 1997). In teosinte, together the glume and cupule fully enclose the kernel, and harden extensively at maturity. The teosinte cupulate fruitcase prevents predation, meaning teosinte seeds can pass unscathed through the digestive tract of birds and mammals (Wilkes et al., 1967). Maize glumes are reduced, and kernels are exposed once husk leaves are removed from the ear.

5. *Although the vegetative portion of the plant is largely homologous between maize and teosinte, maize has reduced axillary branching compared to teosinte.* Maize typically has shortened lateral branches at nodes near the top of the plant, tipped by ears, but little branching at lower nodes. In teosinte, upper lateral branches are elongated and tipped by tassels, while lower lateral branches elongate into basal tillers (Doebley et al., 1997). This is accomplished by both shortening of internodes and a reduction of branch initiation in maize. This branching difference affects the architecture of the plant, and reduces lateral branches into ears.

In total, these phenotypes represent the key morphological differences between maize and teosinte, used in their most recent taxonomic revision (Doebley and Iltis, 1980; Iltis and Doebley, 1980). A number of other traits distinguish maize and teosinte, many of which can be

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explained by the premature cessation of growth in axillary branches, leaves, and internodes (Doebley and Iltis, 1980). Although these phenotypes represent radical departures of maize from *Zea mays* subsp. *parviglumis*, both are classified as belonging to the species *Zea mays* following the biological species concept, as the two hybridize readily with no apparent loss of fertility.

Phenotypic descriptions are often simplifications of complex morphologies, and as humans we introduce biases towards studying phenotypes the human senses can discern (Stebbins, 1950; Dobzhansky, 1937). But the repeatability of domestication syndromes across plants suggests some phenotypes distinguishing maize and teosinte — such as larger fruits or seeds, reduction of seed dispersal, and reduced branching— are systemically selected across domesticated crops (Hammer, 1984; Ross-Ibarra et al., 2007; Doebley et al., 2006). And in the case of artificial selection, human interpretation of differentiatable phenotypes is probably accurate, as domestication required observation by early farmers and identification of those phenotypes that mattered for domestication, which in turn required separation of maize and teosinte germplasm pools. These arguments suggest that the phenotypes described above are likely relevant for understanding the evolutionary genetics of maize domestication.

Inheritance of phenotypes

Building on these observed differences between taxa, numerous studies attempted to understand the genetic basis of this differentiation by crossing maize and teosinte to observe phenotypic distributions of these traits in their progeny. In large part these experiments led to murky conflictions, likely due to the use of diverse germplasm, differing quantification of phenotypes, and wide crosses that generated segregation distortion in observable offspring. Researchers used diverse species of teosinte including *Zea luxurians* (Collins and Kempton, 1920; Rogers, 1950a,b; Lambert and Leng, 1965) and *Zea mays* subsp. *mexicana* (Rogers, 1950a,b; Langham, 1940), and a variety of maize lines such as Tom Thumb popcorn (Collins and Kempton, 1920), a photoperiod insensitive maize inbred (Rogers, 1950a,b), maize 'of medium maturity' (Langham, 1940), and Hy2 (Langham, 1940). Given the high genetic diversity found today among major maize inbred lines (Bukowski et al., 2015; Chia et al., 2012), it is no wonder that crosses using different species found conflicting results. Even traits shown to be controlled by a single Mendelian locus in some studies, such as paired vs. single spikelets, were not consistently interpreted as such, often due to allelic differences among the lines used or perhaps due to a zeal for examples following rediscovery of Mendel's laws (Rhoades, 1984). For example, when crossing Durango teosinte (*Zea mays* subsp. *mexicana*) to Guarany maize (a Peruvian landrace, with extended vertical distance between cupules (Galinat, 1959)), single spikelets were observed in the F1, but when the same teosinte was crossed to North American maize (with relatively compressed distances between cupules), spikelets were paired (Mangelsdorf et al., 1974). And although Rogers (1950a) find multiple genes linked to spikelet pairing, they recover a locus on the same chromosome as that of Langham (1940) who considers it to be controlled by a single gene. About half of these studies classified the major differences between maize and teosinte as quantitative (Mangelsdorf, 1947; Rogers, 1950a,b; Collins and Kempton, 1920), the other half as Mendelian (Langham, 1940; Galinat, 1971, 1988). And while the original interpretation of both Mangelsdorf and Reeves (1939) and Beadle (1939) was that of four major genes or chromosomal regions of linked genes, many later investigations suggested almost every chromosome contributed to the domestication phenotype (Mangelsdorf, 1947; Rogers, 1950a,b). Together, these investigations highlighted that the key morphological differences between maize and teosinte are often oligogenic, that substantial genetic variation exists within both maize and teosinte, and that the genetic background a maize allele is found in can determine its effect on phenotype. But,

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even after observation of tens of thousands of plants across these experiments, the genetic basis of differentiation between maize and teosinte was still unclear, making it difficult to investigate how they evolved and how domesticators selected on them.

QTL based inquiry

While connecting the inheritance of individual phenotypes to their underlying genes was not possible, a straightforward alternative was to identify progeny of a F2 population resembling maize and teosinte parents (Beadle, 1972). In contrast to earlier crosses between maize and teosinte, Beadle (1972) selected 'primitive' maize varieties to avoid confusing genetic variation that was selected during the modern breeding of maize with changes due to domestication. He grew 15,000 plants of a cross between the maize race Chapalote and his most maize-like teosinte, the Chalco race of *Zea mays* subsp. *mexicana* (Wilkes, 2004) and observed that approximately 1 in 500 plants yielded ears looking like either the maize or teosinte parent (Beadle, 1972, 1980). This reduced the number of genes involved to between four and five, similar to that suggested by Langham (1940). It is notable, however that this observation inherently suggests some deviation from additive gene action — with four genes, 1 out of 256 plants should have been similar to each parent, and with five genes, 1 out of 1024.

With an eye towards understanding the genetic basis of these traits, Doebley and Stec (1991) repeated this exact cross, phenotyping approximately 250 F2 progeny for domestication related traits and genotyping them using newly developed molecular markers. They identified 58 genomic regions associated with their 12 phenotypes, spread across all 10 chromosomes; most of these, however, were within 5 large regions on chromosomes 1, 2, 3, 4, and 5. Some phenotypes were controlled by large effect loci, like a single locus on chromosome 2 that explained 77.5% of the phenotypic variance for the number of rows of kernels per ear. But the majority of associated regions explained less than 10% of variation, consistent with a more oligogenic or even polygenic architecture. These researchers extended this work by crossing the presumed direct ancestor of maize, the annual teosinte *Zea mays* subsp. *parviglumis* and the maize race Reventador. Doebley and Stec (1993) largely recapitulated their previous results, and identified 50 associations, including some loci only associated in one of their two populations. Clearly loci that frequently show conditional associations are unlikely to be the key differences between maize and teosinte. Both studies, however, agreed that these five genomic regions on chromosomes 1, 2, 3, 4, and 5 disproportionately control the phenotypic differences between maize and teosinte, including over 70% of the loci explaining more than 10% of phenotypic variance in any trait (Doebley and Stec, 1991, 1993). This overrepresentation was later validated in a larger experiment using backcross progeny of *Zea mays* subsp. *parviglumis* and the inbred line W22 (Briggs et al., 2007), in which 64% of large effect loci were located to these regions.

Foreseeably, these five regions contain major effect loci that differentiate maize and teosinte. Further research has succeeded in cloning the genes underlying some of these QTL, enabling in some cases identification of the specific mutation underlying phenotypic differences between maize and teosinte. These regions can be envisioned in much the same way as the original traits used to differentiate the taxa.

They are:

1. *The paired spikelets of maize are associated with variants on chromosome 1 and 3 across multiple crosses of maize and teosinte.* Over half of phenotypic variation in paired spikelets can be explained by these two loci (Doebley and Stec, 1991, 1993), but the interval covers most of chromosome 1 and may represent multiple QTL (Doebley and Stec, 1993). These

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QTL are both epistatic and pleiotropic (Doebley et al., 1995a), with altered allelic effects in maize versus teosinte backgrounds, and impacting many other traits like plant architecture. Other loci are associated with paired versus single spikelets, notably those on chromosomes 2, 4, and 10 (Doebley and Stec, 1991, 1993). Some genes underlying spikelet formation are known from developmental genetic screens (*ra1*, chromosome 7; *ra2*, chromosome 3; *ra3*, chromosome 7) (Vollbrecht et al., 2005; McSteen, 2006), but these do not fall into the QTL intervals identified in these crosses. Presumably, these genes are members of pathways involving genes in these QTL, as *ra1* controls the switch to inflorescence determinacy that occurs with the production of spikelet pairs (Vollbrecht et al., 2005), and shows evidence of selection during domestication (Sigmon and Vollbrecht, 2010). A more promising locus is *tasselseed6*, which is found on chromosome 1, and mutants of which have been shown to delay spikelet meristem development(Irish, 1997; Chuck et al., 2007); to our knowledge, however, this locus has not been investigated as a domestication candidate. Fine-mapping the loci distinguishing paired and single spikelets is complicated by difficulty in phenotyping paired spikelets, as their appearance can be difficult to identify given the variable inflorescence phyllotaxies (Galinat, 1988), common to many of the maize parents.

2. *The two ranks of the teosinte ear are largely controlled by the gene zfl2 (Bomblies and Doebley, 2006).* This gene is responsible for reproductive identity, forming multiple ranks along the inflorescence meristem. *zfl2* is found within the QTL on chromosome 2, within a QTL interval that explains 36-77.5% of phenotypic variance for the number of rows of cupules (Doebley and Stec, 1991, 1993), and also has a small pleiotropic effect on other key ear traits of glume induration and disarticulation (Doebley and Stec, 1991, 1993). Of note, this QTL is not recovered in a backcross of *Zea mays* subsp. *parviglumis* to inbred maize (Briggs et al., 2007), further complicating the interpretation of this major effect gene. There are additional QTL on chromosomes 1, 3, 4, 5, 9, and 10 that modify this phenotype (Doebley and Stec, 1991, 1993; Briggs et al., 2007), including a paralog, *zfl1*, on chromosome 10 (Briggs et al., 2007).

3. *The disarticulating rachis of the teosinte ear has been recalcitrant to genetic identification.* This trait was ascribed to various loci that explained high amounts of phenotypic variation in crosses using different teosinte parents (Doebley and Stec, 1991, 1993), but association mapping within teosinte identifies *zagl1* as a potential candidate (Weber et al., 2008) in a region that explains 25.8% of variation in one maize cross (Doebley and Stec, 1991). *zagl1*, a MADS box transcription factor, is associated with ear size and has pleiotropic effects on flowering time (Wills et al., 2017).

4. *Although many ear traits differ between maize and teosinte, the most dramatic one observable in F2 crosses is that of glume induration, controlled by the gene tga1.* The maize allele of *tga1* inhibits secondary sexual traits in the female flower, preventing glume induration (Preston et al., 2012). A nonsynonymous mutation in exon 1 of *tga1* alters dimerization of the protein, affecting its stability and preventing activation of downstream targets (Wang et al., 2015). The chromosome 4 QTL that *tga1* is found within explains between 27-62.4% of phenotypic variation for glume hardness (Doebley and Stec, 1991, 1993; Briggs et al., 2007). Additionally, this gene appears to have pleiotropic impacts on disarticulation, lateral branch length, the pedicilate spikelet, and phyllotaxy (Wang et al., 2015).

5. *Aside from ear traits, the clearest morphological difference between maize and teosinte is plant architecture, for which Doebley et al. (1995a) first identified tb1 as the major locus.* The QTL region *tb1* is found within explains 35.9% of variation in tillering; the number of

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basal branches (Doebley and Stec, 1991). Later efforts identified the precise causal muation: rather than a change in the coding sequence of the gene, a transposable element insertion 65 kb upstream of the gene appears to enhance expression of *tb1* (Studer et al., 2011). This increased expression represses lateral branching, allowing the primary lateral inflorescence to compress into a female structure. The locus is allelic to a maize mutant that generates a branched, tillered phenotype (Burnham, 1959), and other loci within the QTL are pleiotropic for ear architecture traits (Studer and Doebley, 2011).

Non-additivity of domestication genes

Dominance, or interaction between alleles at a single locus, affects the exposure of an allele to selection. Although dominance modifiers can evolve, the recessivity of new mutations seems to be a general feature (Orr, 1991). Dominance is informative as to how selection could act on new mutations, and relevant to thinking about the visibility of segregating variation to selection.

In *Zea mays*, the dominance of a given allele can differ based on the genetic background it is found in. When QTL carrying a maize allele from chromosomes 1 or 3 were introgressed into a teosinte background, the maize allele was on average recessive to the teosinte allele (Doebley et al., 1995a). But when teosinte alleles at these loci were introgressed into a maize background, the maize allele was partially dominant to the teosinte allele, as it was when segregating in a F2 population (Doebley et al., 1995a).

Dominance of maize alleles in a teosinte background could generate a conflict, as if a maize-like phenotype arises in teosinte, it may be detrimental to plant fitness. As the alleles we today denote 'maize' initially arose in a largely teosinte background, this alteration to domestication related phenotypes may have been softened by their recessivity (Doebley et al., 1995a). Indeed, for these two QTL, dominance of maize alleles increases when the other locus is fixed for the maize allele and the remainder of the genetic background is teosinte (Doebley et al., 1995a). Together, these suggest that while mutations at these loci may have initially been recessive, their dominance may have increased as multiple maize alleles increased in frequency in genetic backgrounds of plants ancestral to maize.

In a maize background, the teosinte allele of *tga1* decreases grain quality, due to restriction of the growth of the kernel by hardened glumes, leading to cracking and susceptibility to pathogens (Dorweiler et al., 1993). But this would not be the genetic background a newly arising mutation sees, and the effect of the maize *tga1* allele in a teosinte background is less detrimental. Although ears of such a plant are shorter, they are still protected within husks until harvest (Dorweiler et al., 1993), and although mature kernels are exposed to pests, cultivation practices can abrogate the danger. This phenotype of the maize allele in a teosinte background could allow visual identification of heterozygotes (Wang et al., 2005) and seeds retained on an ear long enough to be dispersed, and could have allowed rapid selection — both conscious and unconscious.

Beyond single loci, the phenotypic means in F2's of maize x teosinte crosses and backcrosses of teosinte to maize deviate towards the teosinte parent (Doebley and Stec, 1993; Doebley et al., 1990, 1995a; Lambert and Leng, 1965). While some of these results could be due to epistasis, it nonetheless suggests that for a substantial portion of the genetic background, the teosinte allele is dominant in a teosinte background — most similar to the genomic environment an allele would be selected in.

Another way to consider dominance is through the molecular phenotype of gene expression. In allele-specific expression studies of crosses between maize and teosinte, although genes with *cis* effects on expression do not deviate from expectations for dominance, in genes showing *trans* effects,

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the maize allele is more commonly dominant to the teosinte allele in ear and leaf tissue (Lemmon et al., 2014). In addition, maize alleles of candidate domestication genes are more highly expressed than teosinte alleles (Hufford et al., 2012b; Swanson-Wagner et al., 2012; Lemmon et al., 2014; Wang et al., 2017). This dominance of expression may reflect selection for robustness of expression in the face of differing environmental conditions, assuring fitness under cultivation (Doebley et al., 1995a).

Across all of these allelic interactions, there is an effect of genetic background. Indeed, dominance relationships shift when alleles are segregating in a F2, a teosinte backcross, or a maize backcross (Briggs et al., 2007; Doebley et al., 1995a; Doust et al., 2014), suggesting that interactions among loci — perhaps many loci — likely affect the evolutionary outcome of domestication.

Domestication involved many loci

While the handful of regions discussed above can have large phenotypic effects, it clearly takes more than five genes to make a maize plant. Indeed, Briggs et al. (2007) find that only 14 of their 314 identified QTL explain more than 10% of a trait, and it seems clear that many additional loci that were selected during domestication have yet to be identified. Mangelsdorf et al. (1974) attempted to reconstruct a teosinte phenotype by moving the four major segments he identified from teosinte into a single maize inbred line. Unsurprisingly, this did not work, instead generating a plant indistinguishable from maize. However, selective breeding of a teosinte plant with maize ancestry rapidly turned a teosinte-looking phenotype to maize in as little as 18 years (Weatherwax, 1924; COLLINS, 1925), suggesting that, given many loci, the background is sufficient for selection to act on gene interactions. There are voluminous combinations of other genes spread across all 10 chromosomes of maize, and many interact in developmental and physiological pathways. In large crossing experiments only approximately 50% of total phenotypic variation in all traits could be explained by all identified QTL (Briggs et al., 2007), leaving a large amount of unexplained variance, attributable to environmental differences, epistatic relationships, or small QTL statistically unobservable with the experimental design.

In contrast to QTL approaches which have tried to identify the genetic basis of specific phenotypes, a number of population genetic studies have sought to simply scan the genomes of maize and teosinte for signs of natural selection. Analyses of microsatellite diversity (Vigouroux et al., 2002, 2005) and sequence data from hundreds of individual loci in teosinte and inbred maize lines (Wright et al., 2005) both suggested that 2-5% of the genome had been targeted by selection. Whole-genome resequencing of teosinte and traditional maize landraces found a similar proportion of the genome affected by selection, and identified 484 regions of the genome as outliers, each likely representing a gene under selection during domestication (Hufford et al., 2012b). These selection scans can identify loci beyond those underlying morphological differences associated with domestication but may yet be important for fitness, such as loci involved in response to biotic or abiotic environments. Together, these studies suggest that a substantial proportion of the maize genome has been selected during domestication. To fully understand the ways in which evolution has shaped the genetic basis of traits in maize, we need to consider not only the genes involved, but the interactions amongst genes, and their interaction with the environment.

Epistasis

Epistasis occurs when the effects of an allele at one locus are altered by the presence of an allele at another locus. Epistasis can be envisioned in two ways. Statistical epistasis refers to deviations from

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additive relationships in a model (Fisher, 1918), while biological epistasis describes the interaction of gene products *in vivo* (Bateson, 1909). It can be difficult to distinguish the two with experimental data, because, for example, a locus exhibiting biological epistasis will show no statistical epistasis if the experimental population lacks variation for one interacting gene partner.

In maize, statistical epistasis is rarely observed in QTL analyses (Stuber et al., 1992; Edwards et al., 1987; Briggs et al., 2007) or genome-wide scans in panels of inbred maize (Wallace et al., 2014), but is more commonly found when individual cloned QTL are placed into different isogenic backgrounds (Doebley et al., 1995a; Studer and Doebley, 2011; Weber et al., 2008). One explanation for these differences is a lack of genetic variation — the genetic bottleneck arising from maize domestication altered allele frequencies throughout the genome (Eyre-Walker et al., 1998; Tenaillon et al., 2004; Wright et al., 2005), and modern maize often lacks phenotypic variation for relevant traits (Briggs et al., 2007; Xu et al., 2017). Consistent with this argument, statistical epistasis is identified with comparable ease in QTL populations that include a teosinte parent (Weber et al., 2008).

While insufficient variation at the loci involved is likely at least partly responsible for discrepencies among studies, the design of mapping populations can also dramatically impact the power to detect different forms of epistasis. Because of the large number of potential combinations and the need to control for genetic background, very large experimental populations are needed to test for statistical epistasis, and often only the strongest effects can be identified. Indeed, by phenotyping seven times more progeny than earlier mapping studies of maize and teosinte, Briggs et al. (2007) revealed 29 two-locus epistatic interactions, although only one was found in both environments studied. In addition to sample size, the kinds of crosses made will determine what allelic variation is present with which to detect epistasis. For example, in an F2 between maize and teosinte, the combined additive and epistatic effects of two QTL, on chromosomes 1 and 3, explain 60% of variation in paired vs. single spikelets (Doebley et al., 1995a), but when these regions are introduced to a teosinte background via backcrossing, they explain only 7.3% of variation in this phenotype. This suggests numerous other genes in the genetic background interact to generate this phenotype, and supports earlier experiments that found different numbers of loci controlling the trait in progeny from different crosses (Langham, 1940; Szabó and Burr, 1996).

During domestication, epistatic variation may be converted to additive variation as alleles fix at one or more of a set of interacting loci. But during intermediate phases after an allele arises but before selection fixes it, epistasis may alter the efficacy of selection. This can be seen in the interaction between QTL on chromosomes 1 and 3. When the frequency of the maize allele of the chromosome 1 QTL is low, the chromosome 3 QTL has little effect on the the proportion of branches terminated by male inflorescences, a teosinte-like trait (Doebley et al., 1995a). But when the chromosome 1 allele containing *tb1* increases in frequency, the ability to select on its interacting partner on chromsome 3 increases, as this epistatic variance increases at intermediate allele frequencies (Goodnight, 2004). With both teosinte alleles in a maize background, terminal inforescences are 90% male, but by simply substituting either QTL, this proportion is reduced to 21% with a teosinte allele only at chromosome 1, and 0.5% with a teosinte allele only at chromosme 3 (Lukens and Doebley, 1999). The main candidate gene in the chromsome 1 QTL, *tb1*, is fixed for the maize allele in all studies from early archaeological maize samples (Jaenicke-Despres et al., 2003; Vallebueno-Estrada et al., 2016), and the 'maize' allele is segregating in extant teosinte populations (Studer et al., 2011). This provides a temporal range for selection to act. The recent characterization of a candidate gene, *tru1*, within the chromosome 3 QTL (Dong et al., 2017) may allow finer scale temporal tracking of allele frequencies and the role of selection on epistatic partners. Altogether, this suggests that both the phenotypes presented to selection and

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the response to selection is dependent on other loci in the genome. In fact, biological epistasis may be common, with limited statistical capability to detect, as much of the shade avoidance pathway downstream of *tb1* has been shown to be targets of selection (Studer et al., 2017), but are not detected in screens capable of detecting statistical epistasis. Together, despite the fact that few of these loci have shown evidence of statistical epistasis in mapping studies, there is evidence for epistasis — both statistical and biological — contributing to domestication.

In total, these epistatic effects and effects of genetic background may alter the course of selection on phenotypes. If buffered by their interaction with other genes, maize alleles could have been maintained in wild populations of teosinte, while minimizing their effect on phenotype or fitness. Indeed, a number of experiments in teosinte have demonstrated the existence of such cryptic variation for maize-like traits (Lauter and Doebley, 2002; Weber et al., 2007, 2008; Vann et al., 2015). The introduction of new variation — via new mutations or hybridization between populations — could then release cryptic epistatic variation, generating novel phenotypes (Doebley et al., 1995a).

Pleiotropy

Plants are constructed of phytomers, repeated units of leaf, stem, and bud. The genes involved in generating these phytomers thus can be readily pleiotropic via development, having an effect on phenotypes that may appear at first glance distinct. In light of the phytomer, it is not entirely surprising that pleiotropic loci explain correlation in developmental traits of ear and tassel (Brown et al., 2011), flowering time in male and female flowers (Buckler et al., 2009), or leaf length and flower length (Tian et al., 2011). But pleiotropic loci extend even beyond the phytomer, as QTL involved in tassel and ear development are also classified as flowering time genes (Xu et al., 2017). In many such studies, it is not yet clear how many genes contribute to the observed pleiotropy, as efforts to fine-map individual QTL can split effects within the region into multiple heritable loci (Lemmon and Doebley, 2014).

Pleiotropy can constrain evolution, altering the response to selection. For example, the maize allele at *zfl2*, is implicated not only in the spiral ear phyllotaxy that generates increased kernel number but also a number of traits including earlier flowering (Bomblies and Doebley, 2006). In such a case, stabilizing selection on flowering time might limit the response to directional selection for increased kernel number.

Perhaps because of this kind of constraint, the only mutation thought to have arisen *de novo* and rapidly fixed during domestication is the nonsynonymous substitution in *tga1*. While the *tga1* ortholog in rice has pleiotropic effects on inflorescences and vegetative structures (Preston et al., 2012; Wang et al., 2015), *tga1* is expressed only in the maize ear, likely a result of gene duplication and subsequent subfunctionalization (Preston et al., 2012; Wang et al., 2015). The paralogous locus, not1, retains expression profiles like those in other grasses (Wang et al., 2011, 2012), suggesting that in maize, the effects of the maize allele of *tga1* are limited to the fruitcase itself, freeing it from constraints on selection due to pleiotropic effects elsewhere in the plant.

It has long been noted that many of the loci that differentiate maize and teosinte are pleiotropic (Beadle, 1939; Mangelsdorf and Reeves, 1939; Langham, 1940; Collins and Kempton, 1920), but recent dissection of the regulatory architecture by which *tb1* affects phenotypes shows a direct role for epistasis and pleiotropy. *tb1* is pleiotropic across many traits — apical dominance, length of lateral branches, growth of leaves on the lateral branches, pedicillate spikelet development, and root architecture (Hubbard et al., 2002; Gaudin et al., 2014). As a transcription factor, *tb1* binds to many regions of the genome. It directly regulates *tga1*, by binding its promoter, and is also intimately linked to the cell cycle, as it represses two cell cycle genes (pcna2, prl) (Studer et al.,

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2017). Beyond *tb1*, other loci within the QTL region on 1L found by multiple studies (Doebley and Stec, 1991, 1993; Briggs et al., 2007) contribute to ear morphology (Studer and Doebley, 2011), suggesting pleiotropy is common.

Gene networks of domestication alleles

Although genetic isolation of spontaneous maize mutants has been one of the most useful features of maize as a model (Nannas and Dawe, 2015; Strable and Scanlon, 2009), relating phenotypes from such studies to natural variation can sometimes be misleading. Spontaneous mutant phenotypes that make a maize plant look more like teosinte are common (e.g. *sos1* (Doebley et al., 1995b), *ba1* (Gallavotti et al., 2004), *tru1* (Dong et al., 2017), *tu1* (Wingen et al., 2012), *cg1* (Chuck et al., 2007)). Upon detailed analyses, however, while many of these generate similar phenotypes, they do not show population genetic signatures of selection during domestication and lack functional differentiation between the maize and teosinte alleles. This suggests a general redundancy in generating phenotypes, potentially by impacting different stages in pathways or positions in networks. This is not to say there is no value in determining the genetic basis of these mutants, indeed, *tb1* was identified first as a spontaneous maize mutant (Burnham, 1959), from a population that did not have recent teosinte introgression (Doebley and Stec, 1991).

Efforts to unite these loci into pathways and networks have elucidated the targets of selection. In contrast to the largely background specific effects of many maize alleles, *tb1* remains robust to genetic background — so much so that tillering was not phenotyped in F2 crosses beyond initial work by Doebley and Stec (1991). That *tb1* was so routinely implicated in differences between maize and teosinte may simply be due to the fact that it has an effect in every population tested because it is near the top of the shade avoidance pathway (Studer et al., 2017). This means that phenotypic effects can be amplified and fine-tuned through downstream targets. Additionally, these downstream targets of *tb1* show signatures of selection (Studer et al., 2017), suggesting further constraint on the entire pathway. That few of these downstream targets showing selection signatures have been identified as spontaneous mutants may provide insight into their essentiality to the plant, robust to alteration.

Consistent with intensified effects within regulatory networks, MADS box transcription factors are overrepresented as showing evidence of selection during domestication (Zhao et al., 2011). And although *tga1* is regulated by *tb1*, it generates a developmental program within the ear with many pleiotropic outcomes limited in morphological scope, from the shape of the rachis to changes in lignification and silica deposition in the glume and rachis (Doebley, 1996; Dorweiler and Doebley, 1997), acting as a transcriptional regulator (Wang et al., 2015). Together, these suggest a role for selection during domestication on alleles that have visible phenotypic outcomes by being amplified through pathways and networks, often intensified by dominance and epistasis.

Conclusion

Historically, hypotheses about the genetic architecture of maize domestication have varied between two extremes — a few large-effect loci (Mangelsdorf and Reeves, 1939; Beadle, 1939), to extremely polygenic (Iltis, 1983). Mapping of loci involved has tempered these two extremes, identifying hundreds of QTL (Briggs et al., 2007) or genes (Wright et al., 2005; Hufford et al., 2012b), but also identifying large effect loci that explain the majority of variation for some traits. In order to understand the function of an allele, biologists often restrict study to the genetic backgrounds in

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which the allele is most penetrant and expressive. Termed 'breeding dissection' (Wilkes, 2004), this essentially erases the background noise of polygenicity by isolating key loci in restricted genetic backgrounds to study them. But careful genetic dissection has also shown that epistasis and pleiotropy play significant roles in effecting the phenotypes on which selection can act, and may help explain contrasting results from investigations of single loci and those of broader mapping studies. The novel selective pressure of maize domestication generated conditions amenable to understanding how evolution works when selective optima shift. And careful genetic analyses of these phenotypes have revealed that genic interactions, at the level of dominance, epistasis, and pleiotropy played an important role in the evolution of the maize phenotype.

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Author Contributions

M.C.S and J.R.-I. planned and designed the research and wrote the manuscript.

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