Review Article

Domesticative Selection for Low Prolificacy and High Harvestability and Mutability Led to Evolution of Modern Maize from Wild Teosinte: A Brief Review of the New Genetic, Genomic and Archaeological Evidence

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Maize/corn (*Zea mays* subspecies *mays*), the most productive cereal food crop was domesticated, progressively, 9000-4000 years ago in the Mexican and Amazonian regions of South America. Archaeological, genetic and genomic evidence shows that a genotype of teosinte (*Zea mays* subspecies *parviglumis*, the progenitor of maize), in which many desirable traits got recombined and made the plant produce plentiful of easily harvestable and directly consumable grains in a small number of cobs (low prolificacy), was selected and evolved into the modern maize crop. The selected genotype carried on its genome mutant alleles in at least 1000 genes; however, among them a small number of loci produced very large effects. The large effect alleles, identified to have led to maize domestication, are *teosinte branched1* (*tb1*), *teosinte glume architecture 1* (*tga1*), *grassy tillers* (*gt1*), *tassels replace uppers-ears 1* (*tru1*), *ramosa 1* (*ra1*), *zeafloricaula leafy 2* (*zfl2*), *zfl 1*, *zeaagamous-like 1* (*zagl1*), *shattering 1* (*sh1*) and *atr* (*ataxia telangiectasia* and *rad3* related). All the major effect alleles, except *atr*, being in transcription factor encoding genes, apparently the functions of their downstream genes determined the maize domestication traits. The downstream gene network of *tb1* has been partially catalogued. TB1 represses certain cell cycle genes, and activates *gt1*, *tru1* and *tga1*. TGA1 represses a small number of MADS-box transcription factor genes. ATR regulates DNA damage response mechanisms by activating the products of several downstream DNA repair proteins/enzymes. TB1 and GT1 activate the pathways for synthesis of abscisic acid and jasmonic acid, suppress that for gibberellins and reduce sugar levels and energy balance. The downstream network of *gt1* remains largely unknown and networks of *tb1* and *tga1* are not fully characterized. Need is emphasized for the analyses of all the maize loci that affected domestication via their mutagenesis (random and CRISPER systems directed), over-expression transgenesis and RNAi interference, and expression of the resulting variants in all the organs, under varying environments. Imperativeness of the information so gained in the directed improvement of agronomic features of maize and other parallelly domesticated cereals is pointed out.

Keywords: Maize domestication; Grassy Tillers 1; Ramosa 1; Shattering 1; Tassels Replace Upper-Ears 1; Teosinte Branched 1; Teosinte Glume Architecture 1; Zea Floricaula LEAFY 2; Ataxia Telangiectasia and RAD3 Related

Introduction

Maize (or modern maize, family Poaceae, tribe Andropogoneae; 2n = 20, genome size 2500 Mb; GC content 47.4%) is a staple crop, used as source of flour and oil, industrial raw materials such as syrup, ethanol and plastic and feed for livestock. In 2018, world's maize grain production was 1068 million tons,

26 million tons in India. Together with rice and wheat, maize meets ~ 70% of world's food consumption. With its genome carrying 35,000 protein coding genes, many more non-coding genes and 1,30,604 intact transposable elements, maize is serving as a model for breeding, genetics and genomics among crop plants (Wang *et al.*, 2016; Jiao *et al.*, 2017; Yang *et al.*, 2019).

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Modern maize was domesticated 9000-4000 years ago (ya) from teosinte; it now occupies a status of subspecies (*Zea mays* ssp. *mays*) distinctly morphologically diverged from the parental subspecies teosinte (*Zea mays* ssp. *parviglumis*). Modern maize and teosinte are members of the same species, because maize continues to carry many features of teosinte and can be crossed with it. Origin of maize in South America, from the wild populations of teosinte, involved progressive selection of naturally occurring morphological mutations of economic importance and their recombinants. Early domesticated maize differed from wild type teosinte, most importantly, in being unbranched, and bearing only a few large ears/cobs and on them disarticulatory naked grains.

Evolution of modern maize has been investigated intensively since the early studies of Manglesdorf and Reeves (1938) and Beadle (1939), using a variety of genetic- and genomic- procedures on the landraces of teosinte, landraces and accessions/ cultivars of maize and archaeological specimens of the evolving maize recovered in Americas. Several genes whose variant alleles were selected during teosinte/maize domestication have been identified, but many loci found associated with the domestication remain to be annotated. The timeframe and geographical areas of maize domestication have been largely elucidated. This review briefly illuminates the morphological traits that distinguish teosinte and maize, summarizes the archaeogenetic studies which define the times and geography of major domestication events and identifies a network of genes and loci whose mutant alleles got recombined and selected in domesticated maize and nucleotide content changes, as revealed by genetic and genomic studies. It also identifies subject areas of research deficit which need to be pursued in future.

Genetic Morphological Differences Between Wild Teosinte and Modern Maize that Decreased Prolificacy and Increased Harvestability in Maize

Both teosinte and maize are monoecious; they are interfertile and possess self-cum-cross pollinated reproductive system. The phenotype of modern maize differs from its teosinte parent in many traits, but five of these are of major importance whose selection made maize a high yielding grain crop. These relate to shoot architecture, fertility of spikelets, phyllotaxy and sturdiness of female inflorescence and nakedness

of kernels/grains/seeds. The differences for these characters between teosinte and maize are briefly described in the table 1 and depicted in the Fig. 1. The maize alleles that determine the domesticated traits are also identified in Table 1.

Fig. 1: Diagrammes and pictures of teosinte and maize plants and organs showing differences in plant and female inflorescence architectures and kernels (seeds). Female inflorescences (ears) and kernels are shown in yellow or brown colour and male inflorescences in blue colour. A, a plant of teosinte (*Zea mays* ssp. *parviglumis*); B, an ear of teosinte bearing 7 kernel containing fruitcases arranged in distichous phyllotaxy; C, a seed containing fruitcase of teosinte; D, longitudinally sectioned ear of teosinte in which a grain is seen enveloped inside the fruitcase consisting of glume and a part of rachis (cupule); E, a plant of maize (*Zea mays* ssp. *mays*); F, an ear/cob of maize; G, a seed of maize which is naturally devoid of any envelope; H, a transverse section of maize cob in which the central axis consisting of ear rachis (cupules) and glumes bears on the circumference 14 rows (7 ranks) of seeds; F and H, demonstrate polystichousphyllotaxy of maize cob

The teosinte plants are gigantic by being massively branched. Each node of the main stem bears a long lateral stem and the main and lateral stems are tipped by a tassel each. All nodes of lateral stems bear an ear, which may be simple or branched; altogether a teosinte plant has on it more than 100 ears. Like in all Andropogoneae species, teosinte ear bears pairs of spikelets on its rachis, however, one of

Table 1: Principal morphological differences between modern maize and wild teosinte, the parent from which maize evolved by domestication. The major genes/loci whose spontaneous mutant alleles underwent artificial selection and recombined during domestication are also identified

S. no.	Trait ^a	Phenotype in teosinte (<i>Zea mays</i> ssp <i>parviglumis</i>)	Phenotype in modern maize (<i>Zea mays</i> ssp. <i>mays</i>)	Gene(s)/ locus (loci) whose mutant alleles determine inheritance of maize phenotype	References
1	Shoot architecture	Main stem bears a number of lateral branches (tillers). Each branch is tipped by a tassel. Nodes on branches bear one or more ears (female inflorescences). There can be more than 100 ear inflorescences on a plant	Main stem has little tillering and is tipped by a tassel. One and rarely two upper nodes of stem form a branch each of which is tipped by an ear (cob)	Reduction in tillering results from apical dominance induced by the mutant form of <i>teosinte branching 1 (tb1)</i> gene whose expression is enhanced by insertion of <i>Hopscotch</i> transposable element 65 kb upstream of <i>tb1</i> ORF. Mutation in <i>grassy tillers1 (gt1)</i> gene reduces the number and increases the size of ear(s). Mutation in <i>tassels replace upper ears 1 (tru1)</i> gene controls bud dormancy and therefore aerial branch outgrowth. Expression of <i>tb1</i> , <i>tru1</i> and <i>gt1</i> is modulated by a number of genes which remain to be annotated	Doebley and Iltis 1980; Iltis and Doebley 1980; Doebley <i>et al.</i> 1995; Doebley <i>et al.</i> 1997; Dong <i>et al.</i> 2019; Studer and Doebley 2011 and 2017; Whipple <i>et al.</i> 2011; Wills <i>et al.</i> 2013 and 2018; Flint-Garcia 2017
2	Spikelet pairs on rachis in female inflorescence	One of the pair has aborted development, therefore only one spikelet forms seed	Both spikelets of the pair form a kernel (seed) each	The phenotype is controlled by <i>ramosa 1 (ra1)</i> ; other genes that are involved and are located on chromosomes 1, 2, 3, 4 and 10 remain to be annotated	Doebley and Stec 1991 and 1993; Doebley <i>et al.</i> 1995; Vollbrecht <i>et al.</i> 2005; Sigmon and Vollbrecht 2010
3	Phyllotaxy of female inflorescence	Succeeding nodes of rachis alternately bear a grain forming one spikelet (distichous phyllotaxy). The spike (ear) bears 5-12 grains; grains are small in size (one tenth of that of maize kernel)	Phyllotaxy is polystichous; it is whorled such that upto 10 ranks of spikelet pairs (or 20 grains) are formed simultaneously on ear because of collapse of internodes which become a part of the ear axis. There can be several hundred (< 800) kernels per cob	<i>Zea floricaula leafy 2 (zfl2)</i> , <i>zfl1</i> , <i>zea agamous-like (zagl 1)</i> , and several yet to be annotated genes located on chromosomes 1, 3, 4, 5, 9 and 10 are involved	Doebley and Stec 1991 and 1993; Bomblies and Doebley 2006; Briggs <i>et al.</i> 2007; Brown <i>et al.</i> 2011; Wills <i>et al.</i> 2013 and 2018
4	Sturdiness in female inflorescence	Inflorescence is fragile, rachis disarticulates on seed maturity releasing individual seed containing fruit cases	Inflorescence is sturdy, fully mature-dry kernels remain attached to cob since rachis has non-disarticulating nature	<i>Shattering 1</i> duplicates, including <i>sh1-1</i> , <i>sh1-5</i> , and <i>sh1-5.2</i> , are involved	Lin <i>et al.</i> 2012; Yang <i>et al.</i> 2016
5	Kernel(s)/ seed(s) naked or enclosed in fruitcase(s)	Each kernel is fully enclosed in a fruitcase comprised by a segment of rachis (cupule) and glume (bract). Fruitcase is hard because of lignification and silication	Kernels are exposed because cupule is reduced and glume is small and papery, and both glume and cupule are a part of cob's axis which is hard	<i>Teosinte Glume Architecture 1 (TGA1)</i> , itself positively regulated by <i>tb1</i> , is involved; it regulates many genes, including those determining the non-disarticulating rachis and polystichous phyllotaxy	Briggs <i>et al.</i> 2007; Preston <i>et al.</i> 2012; Wang <i>et al.</i> 2015; Studer <i>et al.</i> 2011, 2015 and 2017
6	Spontaneous mutation rate: high or low	Higher sensitivity to solar UV radiation due to low levels of repair of solar UV-radiation damage to DNA	Higher mutation rate due to errors in nucleotide excision repair of solar UV-damage to DNA	Mutated <i>ATR (Ataxia Telangiectasia and RAD3 Related)</i> protein gene, which is a regulator of DNA damage response, increases homologous recombination repair frequency and thereby induction of errors in DNA sequence	Wang <i>et al.</i> 2019; https://www.genecards.org/cgi-bin/carddisp.pl?gene=ATR

a: Modern maize and wild teosinte differ in a number of physiological traits, including that teosinte is a short day plant and its seeds enter dormancy, contrastingly maize flowering is photoperiod independent (Minow *et al.*, 2018) and maize seeds do not enter dormancy (Avendano Lopez *et al.*, 2011)

them aborts and only one develops into a seed. Thus on account of distichous phyllotaxis teosinte ear has up to a dozen kernels. Each kernel/grain is enveloped in silica and lignin containing hard fruitcase formed by glume and a part of rachis called cupule, much like a walnut or pistachio nut, which upon maturity drops from the inflorescence for dispersal. Grains/seeds of teosinte are difficult to harvest and consume by humans. Maize plants are single stemmed, main stem is tipped by a tassel. The axils of one or two leaves on the stem bear an ear each. When a maize plant has two ears, both ears mature nearly synchronously, making the cob harvesting convenient. Maize ear has polystichous or whorled phyllotaxy. Multiple spikelet pairs are formed on closely located ear nodes as if produced simultaneously. Thus an ear/cob of maize has up to 1000 seeds arranged in 2 to > 20 rows around hard central axis formed by ear axis (cupules) and glumes. The maize seeds are not enveloped and do not disarticulate from the cob spontaneously. The nakedness of grains make them directly usable. Briefly, in the domesticated maize, plants are smaller and easier to harvest than in teosinte. Selection for domestication (domesticative selection) led to larger grains and large ears but overall edible biomass did not change.

Time and Place of Teosinte Domestication into Modern Maize: Archaeogenomic Findings

Genomic studies on ancient cobs recovered as macro fossils and land races of two annual teosinte subspecies, namely *Zea mays* ssp. *parviglumis* and *Zea mays* ssp. *mexicana* (hereafter simply called as *parviglumis* and *mexicana*, respectively), and maize, and cultivars of maize have established (Matsuoka *et al.*, 2002; Zeder *et al.*, 2006; Piperno *et al.*, 2009 and 2014; Wang *et al.*, 2015; Ramos-Madriral *et al.*, 2016; Kistler *et al.*, 2018) that the origin of modern maize began with one domestication event from *parviglumis* in southwest Mexico. The so evolved proto-maize then spread to different parts of Mexico and South America and gradually evolved into modern maize. Fossilized proto-maize and maize cobs from the period 6250 to 4300 years BP have proved useful material in understanding the aspects of domestication process.

Morphology and dating of archaeological ears/cobs recovered in GuidaNaquitz cave in Oaxaca,

Mexico show that teosinte had been domesticated earlier than 6250 (6280-6210) ya (Piperno and Flannery 2001). Microsatellite genotyping based phylogenetic analysis on 193 maize accessions from all over Americas of the 500 years BP-period and 67 teosinte accessions from Mexico revealed that *parviglumis* and maize diverged 9188 years BP in Mexico. It was further concluded that the Balsas River Valley region (a lowland area) of Mexico, wherein *parviglumis* demonstrates maximum genetic variability, is the place of initial teosinte domestication event(s) exercised by the local nomadic farmers (Matsuoka *et al.*, 2002). Comparison of genomic sequences of a 5310 years old maize cob excavated in Tehuacan Valley in Mexico (located 450 kilometers northeast of Balsas River Valley) with those of 23 modern maize landraces and 15 *parviglumis* and 2 *mexicana* accessions showed that by 5300 years BP proto-maize carried the *tg1* allele of maize for soft and naked kernels, but the *zagl 1* allele, which determines the disarticulating ear character, was of *parviglumis* type. The cobs of this proto-maize were ≥ 2 cm long and carried 8 rows of kernels. The Tehuacan proto-maize was found to be more closely related to *parviglumis* than to *mexicana*, although there were signs of introgression with the latter. Both *parviglumis* and *mexicana* occur sympatrically in the lower and higher altitudes of Balsas River Valley. It is now known that maize obtained ~10% of its genetic content from *mexicana*. The slow pace of domestication in Mexico evidenced by macro-fossils has been attributed to low levels of natural back-crossing between proto-maize and *parviglumis* (Ramos-Madriral *et al.*, 2016; Lu *et al.*, 2019).

The domestication of proto-maize into modern maize proceeded in Mexico, as well as in parts of south America. Kistler *et al.* (2018) compared genomes of 40 maize landraces indigenous to south America, with those of 68 modern and 9 archaeological maize and 2 ancient *parviglumis*, published earlier. The study showed that proto-maize was under cultivation in southern Amazon region (present Brazil and Bolivia) 6500 ya. Cobs of 4300 ya maize recovered in El-Gigante Rockshelter in Honduras, located on southern side of Mexico, were bearing 10-14 rows of kernels, like in many maize land races (Kennet *et al.*, 2017). The archaeological references collated by Bush *et al.* (1989) and Kistler *et al.* (2018) indicate that the monophyletic proto-maize, developed

by selection of rare recombinants between teosinte plants carrying useful traits by Balsas River Valley farmers in Mexico 9000 ya, was being cultivated widely in Mexico and its produce had spread by trade southwards widely atleast 7500 ya onwards. While proto-maize genotypes of varying morphology were being cultivated in different areas of central and southwestern America, advanced recombinants of the agriculturally useful traits were being selected and fixed. This activity was especially prominent in the Amazon region where wild annual teosinte were largely absent. It appears that the modern maize like genotypes had emerged in several areas of south America by 4000 ya. Modern maize reached western north America (USA) ~ 3200 ya, eastern USA ~ 2100 ya and Canada ~ 700 ya (Janicke-Despres *et al.*, 2003; Kistler *et al.*, 2018; Stitzer and Ross-Ibarra 2018).

Discovery of Maize Alleles of Some Major Effect Genes whose Selection Reduced Branching, Increased Seed Size And Improved Harvestability

Modern maize and its ancestor *parviglumis* teosinte are highly diverged phenotypically and yet belong to the same species because of high gametophytic compatibility between them. Among the many differences between maize and teosinte, the five major morphological changes that led to their classification as distinct subspecies of *Zea mays* have been briefly described in the section 2 above with reference to Table 1. Since the work of Beadle (1939), a number of studies using a spectrum of genetic and genomic approaches, on genetically diverse maize and teosinte landraces/varieties from all over Americas, have revealed following as the genetic basis of sub-speciation. Maize evolved by selection of alleles with major effect at a small number of genes together with compatible allelic changes in moderate and small effect genes that interact with major effect genes/ alleles. Higher level of mutability in the proto-maize populations undergoing domestication had a deterministic role. The forward genetic studies of inheritance of domestication traits showed that each of the five morphological traits that distinguish maize from teosinte is determined by few to many genomic regions spread across all the 10 chromosomes. The comparative genomics studies that scanned the genomes of maize and teosinte variants, to identify the signatures of selection, showed that atleast 1000 genes (or 2-5% genome) were targeted by

domesticative selection (Doebley and Stec 1991 and 1993; Vigouroux *et al.*, 2002; Briggs *et al.* 2007; Hulfard *et al.*, 2012; Lemmon and Doebley 2014; Studor *et al.*, 2017). Whereas the selection was focussed on ear architecture, the correlated response led to change in plant architecture (Yang *et al.*, 2019). The lessons from hitherto genetic information on the large effect mutant alleles selected to attain the maize domestication traits are gene-wise summarized hereunder. The bulk of the downstream genes whose mutant alleles got selected for their compatible interaction with large effect mutant alleles remain to be elucidated.

Teosinte Branched 1, Grassy Tillers 1 and Tassels Replace Upper-Ears 1

In maize, suppression of prolificacy and formation of one or two large ears bearing bold kernels is determined by domestication (or domesticative) alleles of the genes *teosinte branched 1 (tb1)*, *grassy tillers 1 (gt1)* and *tassels replace upper-ears 1 (tru1)*. The gene *tb1*, located on chromosome 1, is one of the apical dominance regulators which suppresses lateral branching that could arise from outgrowth of axillary buds formed on the main stem. It encodes a cycloidea type class II TCP protein domain containing transcription factor that binds to promoters on account of its basic-helix-loop-helix structure (Kosugi and Ohashi 2002). There is overexpression of the TB1 protein from its maize allele because of insertion of a *Hopscotch* insertion (transposable) element 63 kb upstream of *tb1* start codon. The enhanced expression of TB1 in nodal plexus is the cause of inhibition of lateral branching in maize plants. There is evidence from the genomic studies that the maize allele at *tb1* mutated 28,000 ya (Studer *et al.* 2015). The gene *gt1* also contributes to apical dominance in maize and thus allows formation of only one or two ears per plant which bear heavy seeds. It functions downstream of *tb1*. The *gt1* gene located on the short arm of chromosome 1 encodes a homeodomain zipper transcription factor. The maize *gt1* allele has a 2.72 kb prolificacy (*prol 1.1*) sequence 7.5 kb upstream of its first codon that allows overexpression of *GT1* protein in maize plant's main stem nodes such that meristematic growth in large majority of them is inhibited. The maize *gt1* allele arose 13,000 ya (Wills *et al.*, 2013 and 2018). The gene *tru1*, located on the long arm of chromosome 3, which encodes an ankyrin

repeat domain protein containing a BTB/POZ motif, is activated by TB1 for ectopic expression in axillary branches. TRU1 inhibits axillary branch growth and promotes formation of female flowers (Dong *et al.* 2017).

Ramosa 1

Maize cobs bear kernels in straight rows. This phenotype results from development and growth of both of the spikelets initiated on the nodes of maize ear. Selection of this domestication trait is related to mutations in the cis-regulatory region(s) of the domestication locus *ramosa 1* (*ra1*) gene located on chromosome 7. The selected mutation(s) permit increased expression of *ra1*, a C2H2 EPF-subclass zinc finger transcription factor, involved in the regulation of the genes determining female inflorescence architecture (Vollbrecht *et al.*, 2005; Sigmon and Vollbrecht 2010).

Zea Floricula Leafy 2 and Zea Agamous-Like 1

The architecture of maize cobs/ears underwent domesticative selection for high yield via high kernel/grain number. Spiral phyllotaxy in maize cobs allows 4-10 ranks and therefore 8-20 kernel row number. Among the candidate loci located on chromosomes 1, 2, 3, 4, 5, 9 and 10 that show signatures of selection in the determination of high kernel row number, two have been identified as the *zeafloricaula leafy 2* (*zfl2*) gene located on chromosome 2 and *zeaagamous-like 1* (*zagl1*) gene located on short arm of chromosome 1. Both specify transcription factors: the *zfl2* gene product is FLORICULA/LEAFY type of transcription factor and the product of *zagl1* gene is a MADS-box transcription factor. Both selected maize mutant alleles express the gene products at increased levels because the mutations occurred in their cis-regulatory regions (Doebley and Stec 1991 and 1993; Bomblies and Doebley 2006; Brown *et al.*, 2011; Wills *et al.*, 2013 and 2018). The maize alleles *zagl1* and *zfl2* have also been implicated in early flowering (Bomblies and Doebley 2006; Wills *et al.*, 2018).

Zea mays Shattering 1 Orthologues

Non-shattering of kernels from mature ears/cobs was also a strongly selected trait in maize domestication. Domestication process selected alleles of the YABBY

transcription factor coding *zm shattering 1-1* (*zmsh 1-1*) gene located on chromosome 1 and the orthologous *zmsh 1.5 -1* + *zmsh 1.5-2* genes located on chromosome 5 which underwent insertional mutations that disrupted their code (Lin *et al.*, 2012). There is some evidence that the loss-of-function allele got selected also for another YABBY class transcription factor gene *zmYAB2.1* located on chromosome 1, for the attainment of non-shattering phenotype in maize (Yang *et al.*, 2016)

Teosinte Glume Architecture 1

Maize domestication involved selection for its plant type that produced only a few cobs on which naked kernels got formed on the circumference of their hard-non-disarticulating central rachis, such that kernels got arranged in polystichous phyllotaxy on the rachis. The kernel containing 7-12 fruit cases of teosinte, formed by combination of hardened glume and cupule of spikelet, and the rachis bearing them were repurposed by domesticative selection into the central axis of cob in maize to bear many naked kernels of big size. A non-synonymous mutation in the exon 1 of *teosinte glume architecture 1* (*tgal1*) gene located on chromosome 4, selected during maize domestication, contributed to all the above mentioned useful traits of maize, including large size, shape and nakedness of kernels, sturdiness and spiral phyllotaxy of cob and reduction in lateral branching leading to formation of 1 or 2 cobs. The mutation changed the property of TGA1 protein from being a gene activator to that of a gene repressor. The maize TGA1 protein, a squamosal promoter-binding (SBP-Box) transcription factor, having undergone mutation acquired a property of forming stable dimers. No loss-of-function mutation is known in maize *tgal1* gene. The maize *tgal1* allele arose about 10,000 ya (Preston *et al.*, 2012; Wang *et al.*, 2012 and 2015).

The following salient-points emerge from the above catalogue of the major-effect maize domestication genes: *tb1*, *gt1*, *trul*, *ra1*, *zfl2*, *zagl1*, *sh1*, and *tgal1*. (i) All of the major effect domesticative alleles are in genes encoding transcription factors. (ii) The maize mutant alleles in *tb1*, *gt1*, *trul*, *zfl2* and *tgal1* have effect on seemingly unrelated phenotypes or are pleiotropic. (iii) The domesticative alleles in *tb1*, *gt1*, *ra1*, *zfl2* and *zagl1* increased the gene expression, mainly by use of cis elements present

in transposon inserted 5' to the gene's open reading frames. Thus a highly significant role of transposable elements, that comprise c. 85% of maize genome, is testified in the evolution of modern maize. (iv) A point/transversion mutation in maize *tga1* gene converted the product from being a gene activator into a gene repressor. (v) The transcription factor products of *sh1* genes became non-functional due to incorporation of loss-of-function mutation in their maize alleles. Altogether, it is clear that all the major effect domestication genes in maize produce their effect via the functions of downstream genes targeted by them. To understand the gene expression changes that mediate the phenotype of modern maize, it is imperative that the gene network of each of the above identified transcription factors genes be catalogued function-wise. Some progress that has been made in elucidation of the network of genes whose expression is controlled by *tb1* is summarized below.

Gene Network Targeted by the Maize *tb1* Allele

The maize allele of *tb1* gene selected during domestication is a master regulator that is known to control a cascade of transcription factors and certain cell cycle genes, that determine development and morphology of plant's shoot, root, female inflorescence, flower and seed, pleiotropically. In the course of domestication the multitude of transcription factors controlled by *tb1* or by gene(s) downstream of *tb1* also underwent mutant allele selection, for adaptation to genetic changes in their regulatory or interactive genes. The network of genes, thus far known to be interactive with the maize *tb1* allele (Studer *et al.* 2017; Dong *et al.* 2019) is diagrammed in Fig. 2.

The master transcription factor TB1, a class II TCP protein is expressed constitutively in maize because of the integration of Hopscotch transposable element upstream to its open reading frame. Thus TB1 expression occurs largely independent of the shade avoidance genetic apparatus that functions via phytochromes upstream of *tb1* gene. The TB1 protein of maize acts by binding to GGNCCC motifs in the promoter of its target genes. It has come to possess dual activity that of repressor for some genes and of activator for another class of genes. The molecular mechanism or cofactors, if any, that modulate the activity of TB1 as a repressor or an activator of genes remains to be determined.

Fig. 2: Network of the domesticated allele of the gene *tb1* (*teosinte branched 1*). The solid or broken red and green lines, respectively, indicate repression and activation of the gene activity under the control of *phy B* (*phytochrome B*), *tb1* miR156 (*microRNA 156*) and *gt1* (*grassy tillers 1*) and *tga1* (*teosinte glume architecture 1*). The solid lines mean that the nature of interaction has been proved to be direct. The genes regulated by *tb1* are: *pcna2* (*proliferating cell nuclear antigen 2*) and *prl* (*proliferata*) that encode cell cycle determining proteins; *etb1.2* (*enhancer of tb1.2*) a cis element of *Zm YAB2.1* (*Zea mays YABBY* transcription factor 2.1); *gt1* (*grassy tillers 1*) which encodes a homeodomain zipper transcription factor; *tru1* (*tassels replace upper ears1*) which encodes a BTB/POZ ankyrin repeat transcription factor; and *tga1*. The genes *tb1* and *gt1* activate biosynthesis of inhibitory phytohormones-jasmonic acid (JA) and abscisic acid (ABA) and repress biosynthesis of growth stimulatory hormones gibberellins (GA) and pathway(s) associated with sugar availability. Several MADS-box transcription factors, including *zag1* (*zeaagamous 1*), *zag2*, *zmm3* (*Zea mays MADS3*), *zmm19* and *ZmMADS2* are repressed by *tga1*. In addition of *tb1*, domestication process selected mutant alleles in *etb1.2*, *gt1*, *tru1*, *tga1*, and all the listed MADS-box genes/ loci. This figure is a modified version of the figure 5 of Studer *et al.* 2017 and figure 6 of Dong *et al.* 2019.

TB1 acts as the activator of several major effect genes: the *gt1*, *tga1*, and *tru1* genes (Studer *et al.*, 2017; Dong *et al.*, 2017). TB1 is an activator of its own gene. TB1 activity reinforces GT1 expression which involves *prol1.1* allele upstream of *gt1*. TB1 and GT1 reduce sugar levels, increase levels of abscisic acid and jasmonic acid and reduce the concentrations of gibberellic acid and thereby contain branching. TRU1, activated by TB1 is part of the

regulatory hub that makes tiller buds dormant (Dong *et al.*, 2017 and 2019). Thus the strongly expressed TB1 and GT1 functions suppress initiation of secondary ears on maize plants. TB1 serves as the direct activator of *tga1*, such that the downregulatory effect on *tga1* of miRNA156, the product of *CORNGRASS1* gene which decreases the abundance of *tga1* transcripts, is minimal. The TGA1 protein because of a transversion mutation in it strongly represses a number of MADS-box transcription factor genes. Perhaps many other genes, yet to be identified are regulated by TGA1. The MADS-box genes *zag1* (*zeaagamous homolog 1*), *zag2*, *zmm3* (*zea mays MADS3*), *zmm19* and *zmMADS2* have been shown to be repressed by TGA1. It is also known that the identified MADS-box genes have themselves undergone allelic changes to adapt to the repressive role of TGA1 in maize (Zhao *et al.* 2011). The roles of the MADS-box genes interactive with *tga1* gene remain to be revealed (Studer *et al.* 2017; and references therein).

TB1 protein represses the *ZmYAB2.1* (a YABBY class transcription factor) gene by acting at the *etb1.2* (enhancer of *tb1*) locus upstream to it. Further, the *ZmYAB2.1* gene underwent selection for a loss-of-function mutation during maize domestication. The two effects nullified the function of *ZmYAB2.1* in elongation of internode length in the female inflorescence, thus permitting closely packed spiral phyllotaxy of ear internodes in the cobs of modern maize. TB1 has also been found to reduce the expression of cell cycle genes *pcna2* (*proliferating cell nuclear antigen 2*) and *prl* (*prolifera*) by binding to their promoters. Both *pcna2* and *prl* are involved in the control of DNA replication in floral organs. These genes do not show evidence of allelic change under the selection pressure of maize domestication (Studer *et al.* 2017).

Functional cataloguing of all the downstream target genes of major effect maize genes is desirable for designing of improved genetic pathways for higher yields in maize and related Poaceae crops. A pathway for exploiting *tga1* and its orthologs to improve maize has been outlined (Wei *et al.*, 2018).

Metabolome Changes Associated with Teosinte to Maize Domestication

The domestication selection in teosinte led to

evolvment of maize in which the grain size increased, grains became non-shattering, inflorescence bearing the grains increased in size with more grains and plant became less branched. These phenotypic changes involved major changes in gene expression profile of the whole plant. Comparison of seedling metabolomes of maize vs teosinte has revealed that the domestication process led to correlated reshaping of the metabolome. A total of 461 metabolites showed divergence; the divergent metabolites were largely alkaloids, terpenoids and lipids (Xu *et al.* 2019). These findings are suggestive of genetic changes in chloroplast and mitochondrial genomes in addition to the nuclear genome.

Prospects of Deploying Polymorphisms at *Zmtb1* and *Zmtga1* Genes and theirs Orthologs to Cause Agronomic Improvement in Cereals

The archaeological, genetic and genomic studies have indicated that the process of domestication has been largely parallel in the cereals, including maize, rice wheat, barley, sorghum and pearl millet. The artificial selection exercised by early farmers (12,000-4,000 ya) on the wild parental subspecies/species of cereal crops was for the presence of the following kinds of domesticative traits: less vegetative growth and improved prolificacy (small number of grain-rich inflorescences), naked bold grains that did not disarticulate from the inflorescence spontaneously, and easiness in the harvesting of grain bearing inflorescences and in separation of grains from inflorescences (Salamini *et al.*, 2002; Paterson *et al.*, 2003; Fuller *et al.*, 2014; Schilling *et al.*, 2018). In maize, selection of the useful traits amounted to selection of recombinants carrying naturally induced mutant *Zmtb1* and *Zmtga1* alleles, which imparted large majority of the desirable traits (Flint-Garcia 2017). There is evidence that genes orthologous to *Zmtb1* and *Zmtga1* are carried in multiple copies in cereals. For example, in addition to *Zmtb1*, *BRANCH ANGLE DEFECTIVE 1 (BAD1)* is the other cycloidea type class II TCP domain gene identified and characterized in maize (Bai *et al.* 2012). This class of genes characterized in rice are *OsTB1* and *PROLIFERATING CELL FACTOR 1 (OsPCF1)* and (*OsPCF2*) (Kosugi and Ohashi 1997; Nicolas and Cubas 2016). There are 30 orthologs of *Zmtga1* in maize and 16 orthologs of these in rice (Martin-Trillo and Cubas 2010). The *tb1* and *tga1* orthologs are

transcription factors that regulate a large number of downstream genes. However, there is need for intensification of studies which will characterize genes interactive with *tb1* and *tga1* orthologs. This information is pre-requisite for directed improvement in cereals for traits such as plant and inflorescence size, upright leaves, tillering, flowering time and grain size, shape and yield. Table 2 summarizes agronomically improved phenotypes of strains of certain cereals in which *Zm tb1* and *Zmtga1* orthologs are over- or under-expressed or have in them loss-of-function mutations.

Increased expression of *Zm tb1* or its orthologs *Ta TB1* and *Os TB1* in rice reduces tillering. Reduction in tillering also occurs in wheat and rice plants that hyper-express *Zm tb1* (Lewis *et al.* 2008; Choi *et al.*, 2012). Over-expression of *Ta TB1* induces production of axillary spikelets in spikes of wheat (Dixon *et al.* 2018). Loss-of-function of *Zm tb1* ortholog *INTERMEDIUM-C* and/or *zmgt1* ortholog *VRS1*, makes barley spikes six rowed. Increased expression of *Zmtga1* ortholog *OsSPL13* makes rice grains longer and increases grain yield. Yield of rice grains is also increased when *Zmtga1* orthologs *OsSPL14* and *OsSPL16* are overexpressed; in these plants tillering is reduced.

There appear to be immense possibilities of causing agronomic improvement in cereals, by knowledgeable tailoring of the *Zm tb1* and *Zmtga1* orthologs and the genes regulated by them.

**Domestication Diversified
Genomes of Crops from those of
their Wild Type Parents**

A comparison of more than 8.8 million

Table 2: Phenotypic effect of hyper- or hypo-expression or loss-of-function of orthologs of maize (*Zea mays* ssp. *mays*) *teosinte branched 1 (tb1)*, *teosinte glume architecture 1 (tga1)*, *grassy tillers 1 (gt1)* and *tassels replace upper-ears 1 (tru1)* genes in cereals other than maize

S.no.	Maize gene	Heterogous cereal species	Ortholog of maize gene	Phenotypic effect	References
1	<i>Zm tb1</i>	<i>Triticum aestivum</i> (wheat)	<i>Ta TB1</i>	Hyper-expression reduces tillering and stimulates production of axillary spikelets on inflorescence	Dixon <i>et al.</i> , 2018
2		<i>Oryza sativa</i> (rice)	<i>Os TB1</i>	Decreased expression increases tiller number and increased expression reduces tillering and panicle number	Choi <i>et al.</i> , 2012
3		<i>Hordeum vulgare</i> (barley)	<i>INTERMEDIUM-C(Hv TB1)</i>	Loss-of-function plants produce inflorescences bearing six rows of spikelets	Ramsay <i>et al.</i> , 2011
4		<i>Pennisetum glaucum</i> (pearl millet)	<i>Pg tb1</i>	The alleles <i>Zm tb1</i> and <i>Pg tb1</i> have analogous phenotypic effects	Ramigereaun <i>et al.</i> 2011
5	<i>Zm tga 1</i>	<i>Oryza sativa</i> (rice)	<i>Os SPL16 /Os GW8</i>	Over-expressing plants are dwarfer, have accelerated flowering, bear panicles with lesser branching, have higher grain yield and the grains produced are broader; loss-of-function plants produce slender grains of better quality	Wang <i>et al.</i> 2012
6			<i>Os SPL14</i>	Increased expression is associated with less tillering, profuse panicle branching and higher grain yield	Miura <i>et al.</i> 2010
7			<i>Os SPL13</i>	Hyper-expression enhances grain length and overall grain yield	Si <i>et al.</i> 2016
8	<i>Zm gt1</i>	<i>Hordeum vulgare</i> (barley)	<i>Hv VRS1 (Six-Rowed Spike 1)</i>	Loss-of-function mutants produce six-rowed inflorescences	Komatsuda <i>et al.</i> 2007
9	<i>Zm tru1</i>		<i>Hv CUL 4 (UNICULM-4)</i>	Loss-of-function mutants are ligule-less and demonstrate decreased branching and tillering ^a	Tavakol <i>et al.</i> 2015

a, This phenotype is inverse of loss-of-function *tru1* mutants in maize

single nucleotide polymorphisms (SNPs) segregating in 17 accessions of *parviglumis* and 23 land races and 60 cultivars of maize (Wang *et al.*, 2019) has revealed the following two highly important features of domesticative evolution of maize from teosinte, that may be common to domestication of other crops.

Enrichment of Genome with AT-Nucleotides

The genic and non-genic regions of all the chromosomes became AT enriched in maize as compared to teosinte. AT-enrichment was more pronounced in the non-genic segments of genome, such as in pericentromeric regions and transposable elements [which comprise 85% of the maize genome; bulk of them retrotransposons (>50%), SanMaguel and Vitte 2009]. Segments of genome rich in methylated CG underwent especially high level of AT enrichment. Such intensified genomic divergence between teosinte and maize has been attributed to high mutability (via gene sequence change and transposon/ retrotransposon mutagenesis) trait of maize populations undergoing domesticative selection. The high mutability trait resulted from increase in the errors in repair of DNA damage caused by natural exposure to solar UV-radiation, particularly UV-B radiation. Haploid pollen is a highly sensitive target of UV-B radiation; in them transposons are known to get activated (Walbot 1999). The average AT content of major maize transposons is 52% (SanMaguel and Vitte 2009). The selection of GC → AT mutations, in gene and non-gene DNA sequences genome-wide, led to enormous savings in energy, since production of GC base pairs requires much more energy than synthesis of AT base pairs (Ussery *et al.* 2009). It is observed that the saved energy, via AT enrichment of genome and low prolificative morphology, positively correlates with the observed high harvestability of maize versus teosinte.

Selection of Mutants in ATR Genes Led to Higher Mutability

Genome wide association studies (GWAS) on the SNPs in the above mentioned 100 accessions (Wang *et al.* 2019) led to the finding that mutant alleles in *ATR* genes have been responsible for the high mutation rate in maize populations as compared to mutation rate in bulk of *parviglumis* populations. The *ATR* (*Ataxia telangiectasia* and *RAD3 related*, a serine/

threonine kinase) gene is known to regulate DNA damage response mechanisms by activating downstream gene products, including those involved in nucleotide excision repair (NER) (Hu *et al.*, 2016). The *ATR* polymorphism observed in modern maize also existed in certain wild populations of teosinte. It is suggested that *ATR* mutant alleles were selected by early farmers, unknowingly, when they correlatively selected large effect mutant alleles in *tb1* and/or *gt1* plants based on morphology.

Parallelism has been noted between domestication of maize and soybean crops, in terms of AT enrichment of genome via the activity of *ATR* mutations selected during domestication (Wang *et al.*, 2019). Since AT-enrichment saves energy, that is required to increase the yield of crops, high GC → AT mutability via errors in repair of UV-damage may be a common feature of domestication process, which is a special kind of evolution dependent on artificial selection of a network of genes which together determine the traits of low prolificacy and high harvestability.

Concluding Remarks

Domestication in maize involved selection of polymorphism in at least 1000 (~1400) loci distributed over its 10 chromosomes. Thus far some major effect domesticating alleles have been identified and characterized. All of these (*tb1*, *tg1*, *tr1*, *gt1*, *ra1*, *zfl1*, *zfl2*, *zag1* and *sh1* duplicates) have been found to encode transcription factors. Only a few of these large effect domesticating genes have been investigated for their downstream genes whose functions are responsible for the phenotype of domesticated maize. For example, some progress has been made in cataloguing of the networks of *tb1*, *gt1* and *tg1* genes. However, there is need to characterize the entire network of 1000 or so loci/genes which underwent domesticating selection, by use of the available genetic-cum-genomic approaches. Each of the domesticating loci needs to undergo organ- and environment-wise expression, in its domesticating form and following incorporation of loss-of-function mutations and introduction of RNA interferences and over-expressing polymorphisms. There is also need to characterize the metabolome changes in different plant organs that have been associated with domestication.

Corresponding genetic-cum-genomic studies have also been in progress in other cereals, especially rice, wheat and sorghum, and a high degree of parallelism has been observed between the domesticating processes of cereals. Effects of the over-expressing domesticating maize genes should also be studied in heterologous cereals and vice-versa. The material and knowledge so gained will allow directed agronomic improvement in maize and cereals for gain in grain yield and produce of high quality.

Domestication of teosinte into maize has been found to have been driven by high mutability trait acquired via mutations in *ATR* genes. Transposon mutagenesis was most likely involved. These mutagenic mechanisms may have been responsible

for the polymorphism observed at <1000 loci for domesticative genes in maize and for AT enrichment of entire maize genome, in comparison to teosinte. There is need to investigate whether enhanced spontaneous mutagenesis and AT-enrichment of genome have been among the features associated with domestication of cereals in general.

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