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A COMMERCIAL BREEDING PERSPECTIVE OF MAIZE IMPROVEMENT FOR DROUGHT STRESS TOLERANCE

Abstract – As the most produced grain crop in the world, maize (*Zea mays*) is a cornerstone of the global agricultural economy. Technological innovations in molecular genetics, environmental characterization, and predictive breeding have continued to drive genetic gain in maize, even for target populations of environments with high heterogeneity of water availability. Environments prone to drought stress remain key targets where genetic gain must continue to maintain a resilient food supply. Here we review advances towards improving maize drought tolerance; the review focused on molecular and physiological mechanisms underpinning drought tolerance, and methodologies that improve prediction of the genotype by environment interactions under drought conditions.

Keywords: *Zea mays*, drought-tolerance, genotype-by-environment, physiology, genomic selection, GWAS

UMA PERSPECTIVA COMERCIAL DO MELHORAMENTO DE MILHO PARA TOLERÂNCIA À SECA

Resumo - O milho é o cereal mais produzido no mundo e um dos pilares da agricultura mundial. Inovações tecnológicas em genética molecular, caracterização ambiental e predições genômicas tem auxiliado na obtenção de ganhos genéticos contínuos na cultura do milho, mesmo em ambientes de seleção com elevada heterogeneidade na disponibilidade de água. Ambientes com predisposição ao estresse hídrico permanecem alvos principais nos quais o ganho genético deve continuar para manter o suprimento de alimentos. Neste artigo revisaremos o progresso no melhoramento de milho para tolerância à seca. Os mecanismos moleculares e fisiológicos que sustentam a tolerância à seca e metodologias que aprimoram a predição das interações entre genótipo e ambiente sob condições de seca são revisados.

Palavras-chave: *Zea mays*, tolerância a seca, genotype-by-environment, fisiologia, seleção genômica, GWAS

Maize is the largest grain crop in the world with an estimated 1,133.89 million metric tons produced in the 2020/2021 season worldwide (USDA, 2022), representing enormous socioeconomic importance for humanity. Maize is a critical source of food, feed, energy and derivatives with hundreds of applications in the industry. In Brazil, maize is the second most cultivated crop, with its largest use for feed, ethanol production and export. However, increasing environmental instability around the world, including in Brazil, has caused significant losses in maize yield production and poses risks to the resiliency of agricultural systems (Cunha et al., 2019).

Drought events have increased in frequency and intensity in several regions of the planet in recent decades, and drought is associated with the most serious global economic and social losses, affecting more people than any other natural disasters (Cunha et al., 2019). Because of this, selection of drought-tolerant genotypes with improved water use efficiency and production in these adverse environments is one of the most effective ways to improve the global productivity and stability of maize (Paterniani et al., 2015). Investments in maize breeding for drought stress tolerance is becoming more critical as the global climate continues to change, with increased temperatures, lower precipitation rates, and irregular distributions of rainfall, especially in the tropical and subtropical regions (Cairns & Prasanna, 2018). Crop growing regions consisting of environments where water limitation is ubiquitous but variable across planting dates, locations and/or years results in cyclic economic and social losses and represent a challenge to genetic progress for yield and other relevant traits achieved through plant breeding. If genotypes of variable levels of drought tolerance

are grown across a set of test environments that vary in the occurrence, timing and intensity of water stress, significant changes in the genotype relative performance between environments are expected to occur. This phenomenon, known as genotype-by-environment ($G \times E$) interaction, complicates the identification of superior genotypes, bringing a high level of uncertainty to the selection process (De la Vega & Chapman, 2006, 2010).

Several analytical approaches have been proposed to estimate the relative size of the $G \times E$ interactions encountered in a genotype-environment system and to describe their nature, repeatability and predictability, allowing to accommodate their effects through appropriate selection strategies aimed at exploiting broad and/or specific adaptation in maize (Löffler et al., 2005; Cooper et al., 2021). Similar methods demonstrated for sunflower can be most useful to inform decisions (De la Vega & Chapman, 2006, 2010). These methods allow: (1) separating noise-rich from pattern rich $G \times E$ variability; (2) grouping environments according to the manner they discriminate among genotypes; (3) grouping genotypes according to their relative responses to test environments; (4) describing the relationships between genotypes and environments; and (5) finding opportunities for exploiting indirect responses to selection (e.g., managed environments and putative traits). The separation of the $G \times E$ structure of multi-environment trials into repeatable (i.e., identified genotype-specific responses to known environmental drivers such as drought) and non-repeatable elements and the description of the first ones in terms of genotypic reaction norms across environmental groups (i.e., environment types) provide the insights to identify useful variability for water stress tolerance that could be exploited in plant breeding for adaptation

to drought-prone environments. The characterization of drought environments often includes the use of crop growth models, tools that consider all elements to calculate a water balance for the crop and that could be applied over the geographical region to characterize the target population of environments (TPE). Based on the soil water supply and demand, it is possible to quantify the frequencies of type and intensity of the drought environment, and thus provide clear target for selection to the breeders (Löffler et al., 2005; Harrison et al., 2014). Cooper and Messina (2021) show the link across methodologies starting from stability analyses to the use of gap analyses to enable the use of enviromics in plant breeding.

As a fundamentally biophysical and biochemical process, maize drought tolerance is a complex and dynamic process. Water scarcity affects several processes in plant growth and development, including interruption of cell expansion caused by decreased turgor, adjustments in the photosynthesis rate, stomata aperture and regulation of osmotic pressure - exchange of cellular gases, activation of antioxidative reaction mechanisms and accumulation of plant hormones (Cramer et al., 2011; Benešová et al., 2012). The combination of these processes convey drought tolerance to manifest as a quantitative trait controlled by many loci which are highly influenced by different environmental conditions, including temperature, precipitation, and soil status (Bänziger et al., 2004; Waraich et al., 2011). As such, achieving genetic gain for drought tolerance requires characterization of the target population of drought environments to ensure the environments in which selection decisions are made will enrich for adaptive traits, or that any biotechnological traits introduced are expected to impact the proper response. Here, we review relevant topics for improving drought

tolerance in maize, starting with genetic basis via associated genes and quantitative trait loci (QTL); to hormonal, and metabolic pathways; to physiological determinants; to methods for environmental characterization and GxE interactions for selection decisions; and finally, to the integration of these findings and concepts in commercial breeding programs.

The genetic basis of drought tolerance in maize

Genomic regions associated with drought tolerance in maize have been identified using linkage mapping, often performed in biparental populations or association panels as part of genome-wide association studies (GWAS). These approaches have been contributing to the rapid technological advances in maize breeding for drought tolerance (Zhu et al., 2016; Liu & Qin, 2021). In this section, QTL and major genes associated with drought tolerance will be discussed. Additionally, genomic regions associated with secondary drought-related traits will be presented to illustrate the complex architecture of drought tolerance in maize. Finally, limitations and applications of these findings will be highlighted considering different approaches focusing on maize breeding for drought tolerance.

QTL associated with drought-related traits have been widely identified in maize, including survival rate at seedling stage (Liu et al., 2013; Mao et al., 2015; Wang et al., 2016c), leaf rolling (Gao et al., 2019), leaf firing (McNellie et al., 2018), anthesis-silk interval (Wang et al., 2016a), flowering time (Wang et al., 2016a), and root traits (Li et al., 2018a). Studying a panel assembled by 367 inbred lines, Wang et al. (2016c) identified 42 candidate genes associated with drought tolerance in maize seedlings.

A natural genetic variation in *ZmVPP1* gene, which encodes a vacuolar-type H⁺ pyrophosphatase and is located close to the QTL peak, was highly associated with drought tolerance (Wang et al., 2016c). A 366-base pair (bp) insertion in the promoter region of the *ZmVPP1* gene, containing three MYB *cis* elements, conferred drought-inducible expression in drought-tolerant genotypes (Wang et al., 2016c). In addition, transgenic maize with enhanced *ZmVPP1* expression had improved drought tolerance (Wang et al., 2016c). Similarly, Mao et al. (2015) showed that an 82-bp miniature inverted-repeat transposable element (MITE) insertion in the promoter region of the *ZmNAC113* gene is significantly associated with drought tolerance in maize seedlings. The overexpression of *ZmNAC113* conveys drought tolerance in Arabidopsis and maize seedlings, improves water use efficiency, and enhances the expression of specific stress-associated genes (Mao et al., 2015).

Using comparative mapping, 13 PYRABACTIN RESISTANCE 1-like (PYL) family members were identified and cloned in maize (He et al., 2018). These genes, termed *ZmPYL1-13*, encode abscisic acid (ABA) receptors and play important roles in response to abiotic stresses (He et al., 2018). Combining phenotypic and genotypic data, He et al. (2018) identified that *ZmPYL8* and *ZmPYL12* genes had natural variants associated with drought tolerance. The main single nucleotide polymorphism (SNP) associated with drought tolerance in *ZmPYL12* was in the second exon and showed high linkage disequilibrium (LD) with another SNP located upstream. Tolerant alleles were identified in *ZmPYL12*, indicating causal alleles or in strong LD with them, while no tolerant alleles were identified in *ZmPYL8* (He et al., 2018). Overexpression of

ZmPYL8, *ZmPYL9* and *ZmPYL12* in Arabidopsis showed improved drought tolerance, indicating positive contributions of these genes under drought conditions (He et al., 2018). The expression of Clade A PP2C-A (PP2C-A) gene *ZmPP2C-A10*, which encodes a phosphatase that interacts with ZmPYL and other ABA receptors, is negatively correlated with drought tolerance in maize seedlings (Xiang et al., 2017). The overexpression of *ZmPP2C-A10* in maize plants repressed ABA responsive genes *ZmPP2C-A9*, *ZmNCED3* and *ZmABF2*, which are associated with drought tolerance (Mao et al., 2015), indicating its involvement in the ABA signaling (Xiang et al., 2017). A deletion in the promoter region of the *ZmPP2C-A10* gene, which involves an endoplasmic reticulum stress response element (ERSE), causes the loss of endoplasmic reticulum stress-induced expression and leads to improved drought tolerance (Xiang et al., 2017).

Dehydration Responsive Element Binding (DREB) proteins are considered major transcription factors controlling gene expression under stressful conditions in the ABA-independent pathway (Yamaguchi-Shinozaki & Shinozaki, 2006). Five DNA polymorphisms located in the promoter region of *ZmDREB2.7* gene were associated with different levels of drought tolerance in maize seedlings (Liu et al., 2013). The overexpression of *ZmDREB2.7* in Arabidopsis resulted in enhanced drought tolerance. In addition, a favorable allele of the *ZmDREB2.7* gene was identified conferring drought tolerance in tolerant maize lines (Liu et al., 2013). These results illustrate that, although considered a quantitative trait, there are major genes associated with drought tolerance either in ABA-dependent or ABA-independent pathways.

Several metabolic and physiological responses are involved in drought tolerance. However,

these physiological changes are not easily captured in a large set of genotypes. A GWAS using a panel of 318 maize inbred lines screened for 156,599 SNP revealed 63 loci associated with metabolic and physiological traits in different tissues/environments under well-watered and water stress conditions, with 23 loci highly responsive to water treatment (Zhang et al., 2016). Most of these loci seem to be involved in accumulation of carbohydrates and ABA-derived metabolites under drought stress, which has been suggested as a drought response in maize (Seki et al., 2007; Mohammadkhani & Heidari, 2008). The drought tolerance candidate gene *GRMZM2G041048*, which is located on chromosome five and encodes a F-box domain containing protein, was significantly associated with sucrose levels at 7 days after anthesis in ears under water stress condition (Zhang et al., 2016). F-box proteins such as FBA1 in wheat (An et al., 2019) and FBX176 in soybean (Yu et al., 2020) have been associated with drought tolerance.

Physiological indices such as leaf rolling and leaf firing or survival rate are commonly used for drought screening in the field. Five genomic regions controlling leaf rolling were identified in F_2 and $F_{2:3}$ maize populations involving the *abr11* Chang7-2 mutant background, which is sensitive to leaf rolling (Gao et al., 2019). The major QTL *qLRI4* located on chromosome four was fine mapped, and a 602-bp insertion was identified in the promoter region of the HD-Zip class IV gene *Zm00001d049443*, named as *ZmOCL5*, of *abr11* (Gao et al., 2019). This polymorphism was associated with leaf rolling in a F_2 population, as well as the insertion increased *ZmOCL5* expression (Gao et al., 2019). Assessing the biparental populations ‘B73 x CML103’ and ‘B73 x NC350’, in different vegetative stages, McNellie et al. (2018) identified three and four QTL associated with leaf firing, respectively. These QTL are located on chromosomes

one, two, and three in ‘B73 x CML103’ population, explaining up to 15.5% of the phenotypic variance, while QTL in ‘B73 x NC350’ population are located on chromosomes one, five, nine, and 10, accounting for 30.6% of the phenotypic variance (McNellie et al., 2018). The QTL located on chromosome one, found to be in common in both populations, explains 15.5% of the phenotypic variance for leaf firing in ‘B73 x CML103’ and 8.0% in ‘B73 x NC350’. In this region, the B73 allele is negatively associated with leaf firing. Considering that different leaf firing manifestations were not significantly correlated, and part of the QTL did not co-localize, McNellie et al. (2018) suggest that multiple pathways are involved in leaf firing control.

The identification of major genes and genomic regions associated with targeted traits will remain important for plant breeding. This section presented many genes and loci involved in different pathways that control or contribute to drought tolerance in maize. This is a crucial step to apply different molecular breeding approaches, including marker-assisted selection (MAS). However, there are several limitations to apply these findings in maize breeding for drought tolerance. First, the quantitative inheritance of drought tolerance, with many genes contributing to drought responses throughout the genome, makes MAS difficult. Second, there is strong interaction between QTL and environmental conditions. In addition, some of the QTL identified may be limited to a specific genetic background, usually those identified from biparental populations, due to marker association and low-resolution mapping (Campos et al., 2004). Third, although GWAS takes advantage of ancestral recombination to improve mapping resolution (Huang et al., 2014) and accesses more than two

alleles when compared to biparental mapping, there are minor alleles with limited power to detect. Fourth, loci identified by linkage mapping and GWAS must be tested in hybrids to verify their potential application for breeding. Once the effect of each locus is generally small, heterosis of grain yield and stress response could mask the effect of individual loci (Zhang et al., 2016). In this sense, these findings are applicable to improve specific secondary traits, such as leaf rolling, which might be selected using causal genes or strong QTL, not necessarily improving drought tolerance. The difficulty in working with individual genes is exposed by Simmons et al. (2021) who report that only 1% of the genes evaluated during 20 years of transgenic research manifested significant phenotypes under drought conditions. Different approaches must be considered to accelerate genetic gain for drought tolerance in a maize breeding program, including genome-wide prediction and selection.

The clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated nuclease protein (Cas) system has emerged as a valuable tool to unlock genetic knowledge and create novel products (Nuccio et al., 2021). In this context, Shi et al. (2017) reported that generation of maize lines carrying *ARGOS8* genome-edited variants, a negative regulator of ethylene responses, had elevated levels of *ARGOS8* transcripts compared to the native allele and they were detected in all tested tissues. The field study showed that *ARGOS8* variants increased grain yield by five bushels per acre under flowering stress conditions and had no yield loss under well-watered conditions when compared to the wild type (Shi et al., 2017). A complete understanding of the mechanisms involved in drought tolerance represents an important step to develop new maize varieties with outstanding performance under water-limited

conditions (Messina et al., 2020).

Transcriptomic and proteomic associations with plant drought response

The genetic mechanisms described above and the proteomic and metabolomic associated with plant response to water stress are complex and dependent on multiple factors. Plant growth regulators like ABA are small molecules known for modulating the expression of several defense signaling pathways triggered by either biotic and/or abiotic stresses; these can act independently or in association, and sometimes crosstalk between these signaling pathways is noted (Nakashima et al., 2014; Lim et al., 2015; Mona et al., 2017; Mahmood et al., 2019). ABA has been shown to be involved in the regulation of hundreds of proteins under water stress condition (Anderson et al., 2004; Du et al., 2012; Zhao et al., 2016; Zenda et al., 2018; Wang et al., 2019; Bharath et al., 2021).

Proteomic responses to drought in maize were studied considering drought stress by the application of polyethylene glycol in seedlings (Hu et al., 2015; Zhao et al., 2016; Xin et al., 2018; Pei et al., 2019), drought stress by withholding irrigation at seedling stage (Riccardi et al., 1998; Benešová et al., 2012; Zenda et al., 2018), repeated drought stress at seedling stage (Schulze et al., 2021), and drought stress at kernel filling (Yang et al., 2014; Wang et al., 2019; Dong et al., 2020). Investigation of drought induced protein abundance revealed major changes in the accumulation of ABA responsive proteins, proteins involved in ABA biosynthesis, photosynthesis, carbohydrate metabolism and water channels such as aquaporins (Yang et al., 2014; Xin et al., 2018; Zenda et al., 2018; Wang et al., 2019; Dong et al., 2020; Schulze et al., 2021).

Similarly, heat shock proteins (HSPs) play critical roles in response to water deficit stress and were found up-regulated in maize seedlings (Benešová et al., 2012; Xin et al., 2018; Zenda et al., 2018; Schulze et al., 2021) and kernels (Wang et al., 2019) upon drought stress. Several HSPs were shown to play a major role in the stabilization of protein structure and act as molecular chaperones, which participate in ATP dependent protein unfolding reaction and prevent denaturation during stress condition (Ghatak et al., 2017).

Photosynthesis becomes limited after frequent or long-term water deficits (Xin et al., 2018) and one important aspect for the plants to cope with drought stress is the recovery of photosynthesis (Wang et al., 2016c). Proteins involved in photosynthesis were differentially accumulated under water stress at the seedling stage in maize (Xin et al., 2018; Zenda et al., 2018; Pei et al., 2019; Schulze et al., 2021). Benešová et al. (2012) proposed that a less efficient synthesis of protective/detoxification proteins associated with drought tolerance are due to the inhibition of photosynthesis caused by hypersensitive early stomatal closure in a sensitive genotype. The most significantly enriched proteins in a drought tolerant genotype were associated with the photosynthesis antenna proteins pathway, suggesting that the drought-tolerance of maize inbred lines at the seedling stage was largely due to activated expression of photosynthesis proteins balancing light capture and utilization and improving non-photochemical quenching (Zenda et al., 2018). Photosynthesis pathway changes were also detected in a tolerant maize hybrid at the kernel filling stage (Dong et al., 2020).

Proteomic studies have revealed that nearly 20% of total drought-responsive proteins were

involved in carbohydrate and energy metabolism in leaves to cope with drought stress (Wang et al., 2016b). In maize, carbohydrate metabolism becomes limited at seedling stage after frequent or long-term water deficits (Xin et al., 2018), while drought stress at kernel filling decreased the remobilization of photosynthetic assimilates causing a reduction in ear growth, kernel filling, and size, with more pronounced occurrence in a susceptible line compared to a tolerant line (Wang et al., 2019). In seedlings, the abundance of most proteins known to be involved in carbohydrate metabolism gradually decreased as drought stress progressed, including enzymes involved in glycolysis, tricarboxylic acid cycle, and pentose phosphate pathway (Xin et al., 2018). Proteins of starch metabolism and proteins of sucrose biosynthesis were also found with significantly reduced abundance upon drought (Schulze et al., 2021).

Maize plants also respond to drought by an increase in aquaporin abundance, which is reverted upon rewatering of the plants. The increase in water channels may be interpreted to allow cells to take up more water into cells and thus overcome decreasing water potential in soils (Schulze et al., 2021). An obvious response of plants to drought would be to regulate the cellular water transport. In fact, aquaporins are among the most regulated transporters at the plasma membrane. Their abundance in the membrane is adjusted as well as their activity (Besserer et al., 2012).

Although genotypes display similar phenotypes in response to drought treatments, with some proteins found to accumulate in both, sensitive and tolerant genotypes, there are induced changes in proteome that are related to genotype-specific responses (Benešová et al., 2012; Yang et al., 2014;

Zenda et al., 2018; Pei et al., 2019; Wang et al., 2019; Dong et al., 2020; Schulze et al., 2021). Most of the comparisons detected higher number of differentially accumulated proteins (DAPs) in sensitive genotypes compared to tolerant genotypes (Benešová et al., 2012; Yang et al., 2014; Zenda et al., 2018; Wang et al., 2019; Schulze et al., 2021), indicating that sensitive and tolerant genotypes detected the extent of the same drought stress conditions differentially. Drought-tolerant genotypes might perceive the prevailing drought conditions as mild and then modulated fewer DAPs (Zenda et al., 2018) and show dampened response (Schulze et al., 2021), while sensitive genotypes perceive the same conditions as severe and modulated more abundant DAPs in response (Zenda et al., 2018), showing higher magnitude of responses and stronger phenotypes (Schulze et al., 2021). Zenda et al. (2018) and Wang et al. (2019) evaluated the proteomic profile of two maize inbred lines contrasting for drought tolerance, YE8112 (tolerant) and MO17 (susceptible), at the seedling and kernel filling stages, and identified contrasting protein levels between them at both stages. At the seedling stage a total of 721 DAPs were identified. Among these 721 proteins there was a set of 13 proteins that were only accumulated by YE8112 after drought treatment. The proteins with highest change in abundance level in YE8112 were associated with the photosynthesis antenna protein pathway, which is responsible for fast absorption and transference of light to the central site of chemical catalysis. Ability of YE8112 to better cope with water deficit can be attributed to a more efficient photosynthesis system, with appropriate balance between light and CO₂ capture and utilization, increase peroxidase activity, increased synthesis of proteins with detoxification role and enhanced chaperone stabilization of drought-

induced denaturation proteins. At the kernel filling stage, YE8112 specifically induced proteins mostly participated in pathways related to protein processing in the endoplasmic reticulum and tryptophan metabolism, whereas MO17-exclusive proteins were involved in starch and sucrose metabolism and oxidative phosphorylation pathways. Superior drought tolerance shown by YE8112 at kernel filling stage, compared to MO17, is attributed to its redox post-translational modifications and epigenetic regulation mechanisms, up regulation of HSPs, enriched energy metabolism and secondary metabolite biosynthesis, and up-regulation of seed storage proteins.

Similarly, transcriptomic and physiological analysis of two maize hybrids contrasting for drought tolerance revealed differentially encoded proteins and signaling pathways modulating response to water stress (Pei et al., 2019; Dong et al., 2020). More proteins were observed in the enriched pathways of the tolerant hybrid ND476 than in the sensitive hybrid ZX 978 and both hybrids diverged significantly in the pathway responses to drought stress. The drought tolerance of ND476 was attributed to oxidoreductase, peroxidase and hydrolytic enzyme activities to promote cell redox homeostasis maintenance, elevated expression of stress defense proteins, and reduced synthesis of redundant proteins to help plants preserve energy to fight drought stress (Dong et al., 2020). In parallel, the authors also evaluated the protein levels in the inbred lines and observed more up-regulated proteins in the drought-tolerant line (Qi319) than in the drought-sensitive line (Zheng58), while down-regulated proteins were more abundant in the Zhen58 than in Qi319. The identified proteins were related to photosynthesis, energy and metabolism, signaling pathways, protein synthesis and defense (Pei et al., 2019).

Morpho-physiological determinants of Genotype by Management in drought environments

Yield in field crops is determined by the harvested kernel number per unit land area and average kernel weight. Both traits vary across genotypes and environments in maize. Kernel number is the primary trait responsible for most yield variations (Early et al., 1967; Otegui, 1995; Chapman & Edmeades, 1999) due to the sensitivity of reproductive physiology to drought (Westgate & Boyer, 1985; Messina et al., 2019). Understanding and predicting the number of kernels per plant or per unit land area is critical for guiding maize breeding and crop management for yield improvement under drought environments where the frequency of stress around flowering time is a component of the TPE.

Kernel number has traditionally been modeled as a function of biomass accumulation at the reproductive structure bearing kernels (i.e., ears), and the reproductive efficiency by which this biomass is used for setting kernels (Fischer, 1985). This biomass accumulation in the ears depends on both total plant growth and biomass partitioning to reproductive structures (Echarte et al., 2004; Borrás & Vitantonio-Mazzini, 2018). Under drought stress conditions there is a general response of reduced plant growth. In maize there is substantial native genetic variation in yield tolerance to drought stress generating reductions in plant growth. Different trait combinations can explain genotype differential plant yield reductions under reduced plant growth by reduced water availability. These consider the relationship between plant growth and biomass partitioning to the reproductive structure bearing kernels during the flowering period (Figure 1A).

The first common effect of reduced water

availability is limited canopy growth. Plant growth is an integrative response and is commonly well captured by crop simulation models through its effect on canopy leaf expansion and light capture, or water capture and use. There are known traits that affect genotype plant growth under stressful situations that can be related to differential radiation use efficiency (Lindquist et al., 2005) or water use efficiency (Reyes et al., 2015). Root anatomy and morphology-related traits are described as key components of maize drought tolerance. Large cortical cells have been associated with deeper rooting, improved stomatal conductance, and higher CO₂ assimilation (Chimungu et al., 2014). In this sense, drought tolerance may be associated with a reduction in the metabolic cost of soil exploration. Maize recombinant inbred lines with few and long lateral roots showed substantially deeper rooting, higher leaf relative water content, and improved stomatal conductance compared to lines with numerous short roots (Zhan et al., 2015).

Other traits commonly referenced to understand differential hybrid responses to water stress are related to genotypic differences in plant biomass partitioning during flowering (Figure 1B). This is usually pronounced when comparing new vs. old genotypes. In maize, the reproductive structure where kernels are set is an axillary ear located at the middle of the plant. This structure is not dominant and has poor biomass allocation under conditions of reduced plant growth. Whenever plant growth is reduced by limited water or nutrients, ear growth is reduced not only because the entire plant is accumulating less biomass but also because the proportion of the total biomass that is effectively allocated at the ear level is further reduced (Figure 1B). This non-constant biomass partitioning to the

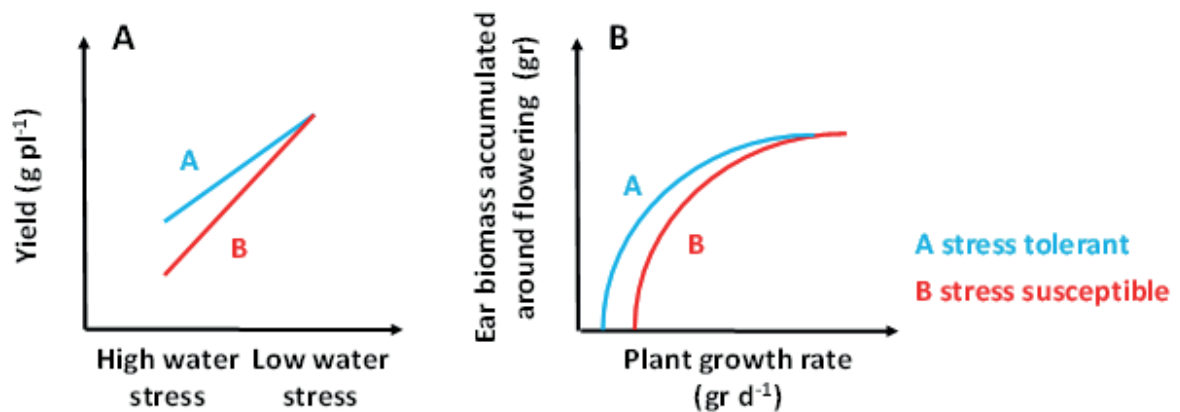


Figure 1 – Theoretical description of the physiological base of drought tolerance associated with reproductive biomass partitioning differences during flowering between a stress tolerant (Hyb A, light blue) and a stress susceptible hybrid (Hyb B, red). Figure 1A describes the genotype by water environment interaction for yield, and Figure 1B describes the expected differences in biomass partitioning to the ears around flowering.

ear during the seed set period is unique to maize, as other crops like wheat, sorghum, or soybean show relatively constant partitioning values (Miralles & Slafer, 1998; Van Oosterom & Hammer, 2008; Rotundo et al., 2012). Hormonal plant growth regulators affecting plant biomass distribution or male sterility genes affecting tassel growth (Loussaert et al., 2017) can be effective in reducing competition between developing reproductive organs and improving ear growth and kernel set under limited plant growth environments.

A third set of traits that provide additional genotype tolerance to stressful situations is plant to plant variability. The non-constant curvilinear nature of maize plant biomass allocation at the ear level during flowering has important consequences, especially when coupled with the normally observed plant to plant growth differences within canopies. At low plant growth environments non-uniform canopies tend to have large proportions of barren plants when compared to more uniform ones, severely affecting

yield.

Similar kernel numbers can be attained by optimizing different trait combinations, especially when considering all traits show ample genetic diversity in maize. A modeling study conducted with Pioneer genetics in the US showed that ear size at silking (a measure of reproductive resilience) is a major contributor to improved performance under drought (Figure 2, yellow area) (Messina et al., 2011; Cooper et al., 2014b; Messina et al., 2019). This is associated with silk appearance under conditions of water deficit and is referred as reproductive resilience in Figure 2. In contrast, in the absence of water deficit and ample nutrient availability, plant canopy size, leaf N concentration, and radiation use efficiency are major determinants of yield potential through radiation capture and transformation efficiency (Figure 2). At intermediate levels of productivity, which encompass most production environments, yield determination is dependent upon multiple traits including water saving by limited transpiration and their interactions

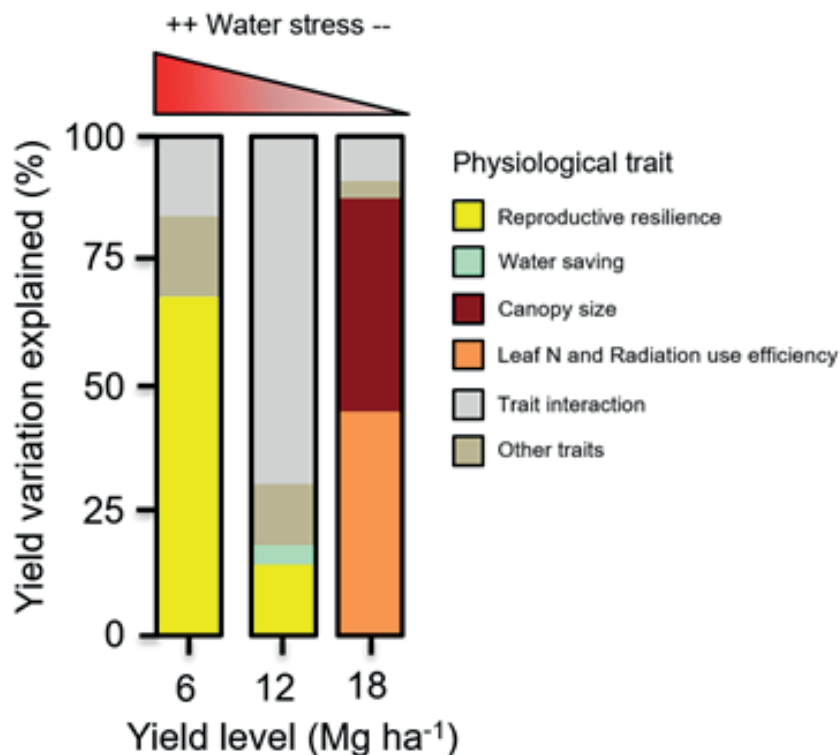


Figure 2 – Relative weight of physiological traits explaining yield variation in low and high yield environments associated with different levels of water stress. Redrawn from Messina et al. (2020).

(gray area, Figure 2) (Messina et al., 2015). The suite of traits determining drought tolerance are different to the ones determining yield potential therefore understanding the trade-off between these two suites of traits is critical to increase crop resilience without limiting productivity when environmental conditions are suitable to explore higher yields.

In TPEs where terminal drought or water deficits are ubiquitous, such as in the region of Mato Grosso in Brazil, and the western US corn belt, water limitation can affect kernel weights and yield. Under these conditions, management and genotype are tuned to manage the water balance for the crop to complete the growth cycle. Traits conducive to affect growth such as plant size and limited-transpiration

(Choudhary et al., 2013) can be targets for selection to improve drought tolerance (Cooper et al., 2014a; Messina et al., 2015). Because the traits are affected by temperature (Shekoofa et al., 2016; Rotundo et al., 2019) and regulate growth and water use, they can lead to genotype by environment interactions that are not evident to predict. Modeling approaches are necessary to integrate this knowledge and inform selection decisions (e.g., Messina et al., 2011; Cooper et al., 2014b, 2020, 2021).

Predictive breeding for maize drought tolerance

The decreasing costs of DNA sequencing and the availability of informative markers led to a major shift in the scale of quantitative genetics

(Washburn et al., 2020), allowing the implementation of genomic prediction and selection in breeding programs. In genomic prediction, thousands of markers are fitted simultaneously to estimate the genetic value of individuals to predict their phenotypes (Meuwissen et al., 2001). This strategy of predicting genome-wide effects to obtain accurate breeding values for individuals allowed for the acceleration of genetic gain per breeding cycle in traits with low heritability and complex genetic architectures (Heffner et al., 2009; Voss-Fels et al., 2019), and offers the opportunity to reduce the breeding interval cycle to at least half the conventional time and produces lines that, in hybrid combinations, significantly increase grain yield performance over commercial checks (Crossa et al., 2017).

Whole genomic prediction (WGP) has been deployed in the development of drought-tolerant maize worldwide, including private and public seed companies (Cooper et al., 2014a, 2014b; Crossa et al., 2014, 2017; Messina et al., 2020). This technology has been used to predict the performance of untested maize single-cross hybrids for drought tolerance in multi-environment trials, with genomic selection using additive and additive plus dominance models (Dias et al., 2018). Genomic prediction was also conducted in the Drought Tolerant Maize for Africa panel of 300 tropical and subtropical maize inbred lines tested under drought stress in Mexico, Kenya, Thailand, Zimbabwe and India to reveal the genetic architecture of grain yield and flowering time under well-watered and drought-stress conditions (Yuan et al., 2019) and in maize subtropical lines assessed for drought in India (Shikha et al., 2017).

In genomic prediction, two types of information are used: high density genome wide markers and phenotypic data on the traits of interest

from the target population of genotypes (TPG) evaluated in the TPE. TPG are evaluated in multi-environment trials (MET) for obtaining phenotypic data on yield and other traits in a sample of environments taken to represent the TPE (Figure 3). An estimation set or training population containing both genotypic and phenotypic data is used to create models of genotypic effects and to estimate the breeding values for individuals (Jannink et al., 2010). These models are then used to predict the breeding values for new individuals for which genotypic information exists (Meuwissen et al., 2001). Prediction accuracy is dependent on trait heritability, population size, population structure, marker density (Liu et al., 2018) and relies heavily on the relationship between the training population and the individuals being predicted (Crossa et al., 2017). Additionally, predictive ability is affected by the similarity between the environments comprising the estimation set and target prediction environments due to GxE and genotype by environment by management (GxExM) interactions. Accounting for these interactions when using genomic predictions for drought results in higher correlations between predicted and observed values (Messina et al., 2018).

In a traditional way, drought breakouts considering the locations of the MET classified as drought stress or locations from managed stress environments (MSE) are used for collecting phenotypic data for training datasets (Figure 3). Precision phenotyping in MSE enables the breeders to expose genetic variation of adaptive traits by managing irrigation. The timing and intensity of water deficit is critical to expose variation in traits conducive to expose variation for traits that maintain growth, affect kernel set and kernel

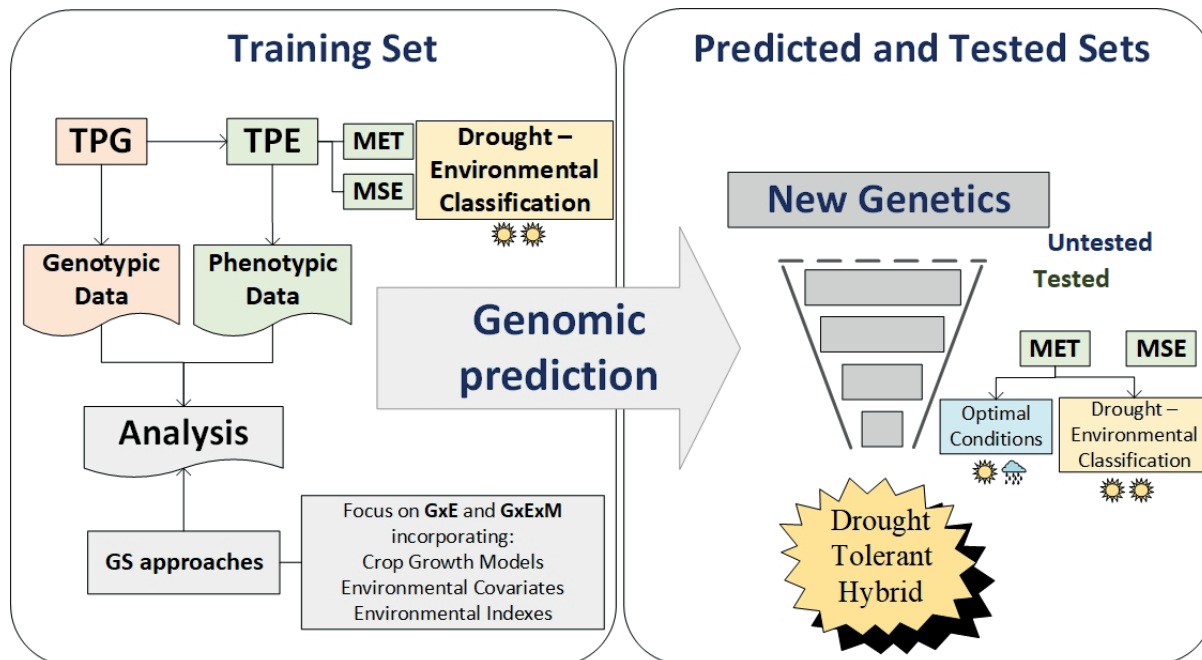


Figure 3 – Predictive breeding scheme focusing on commercial release of drought-tolerant hybrids. TPG, target population of genotypes; TPE, target population of environments; MET, multi-environment trials; MSE, managed stress environments; GS, genomic selection; GxE, genotype by environment interaction; GxExM, genotype by environment by management interaction.

weights. A major requirement to perform MSE is a rain-free dry season, where water stress is applied by managing irrigation. Precise phenotyping methods and the ability to reduce or isolate any interference of external variables from the experiments can significantly improve data accuracy, enhancing the success of a breeding program.

Additional approaches to account for environmental variation include models that integrate dynamic crop physiological growth models into genomic prediction as a link function (Technow et al., 2015; Cooper et al., 2016; Messina et al., 2018, 2020), models that use environmental covariance structures (Jarquín et al., 2014; Heslot et al., 2015),

and models that incorporate environmental indices (Li et al., 2018b). Black-box machine learned models have also been applied to predict G×E interactions (Montesinos-López et al., 2018; Washburn et al., 2020).

Generally, these approaches all recognize that the genetic state of the plant (represented by markers) are being integrated with respect to their spatiotemporal environment to generate a phenotype of interest. In this sense, nonlinear dynamic models represent the closest conceptual approximation of this system, and these dynamic models essentially represent data compression; that is, how a given genotype will respond in a wide range of temporally

varying environments is compressed into marker effects or genotype effects regulating the genetic parameters of the model. This concept is particularly relevant for applications like breeding for drought tolerance where significant GxExM is anticipated (Cooper et al., 2020). A proof-of-concept study for integrating Crop Growth Models with WGP (CGM-WGP) through Approximate Bayesian Computation allowed the incorporation of CGMs directly into the estimation of whole genome marker effects in WGP (Technow et al., 2015). The CGM-WGP methodology was applied to an empirical maize drought MET data set and positive prediction accuracy was achieved. However, new areas for further research to improve prediction accuracy and to advance the CGM-WGP for a broader range of situations in plant breeding, were identified (Cooper et al., 2016). Later, the CGM-WGP methodology was improved, and using both synthetic and experimental data from a maize drought breeding program, there were realized advantages in prediction accuracy for yield, in both the water limited and the not water limited environments relative to the reference method BayesA (Messina et al., 2018; Diepenbrock et al., 2021).

Future developments of genomic prediction strategies that integrate environmental variation will likely advance via spatiotemporal modeling approaches, including techniques such as proximal and remote phenotyping, enviromics, data assimilation, and combining both knowledge-based modeling with algorithmic learning. These approaches will enable both more accurate prediction of GxE as well as better environmental characterization of environments in the training or estimation set relative to the distribution of the TPE.

Commercial release of drought-tolerant hybrids

In collaboration with public and private institutions, CIMMYT has been engaged in developing drought-tolerant (DT) maize varieties in sub-Saharan Africa, Asia, and Latin America. Increased genetic gain in grain yield under stress environments and intensive engagement with seed companies have been considered key components to provide maize varieties adapted to changing climate environments (Cairns & Prasanna, 2018). Seed companies have been releasing DT hybrids to provide protection against occasional drought stress in areas where maize has traditionally been grown and to enhance the viability of the crop in areas prone to drought stress (Adee et al., 2016). There are three DT maize hybrid technologies being used in the market: Pioneer Optimum AQUAmax[®], Syngenta Artesian[®], and Bayer DroughtGard[®]. The first two technologies were promoted as achieving drought tolerance through traditional breeding. The DroughtGard[®] technology was promoted as conferring drought tolerance through both traditional plant breeding and the introduction of a transgenic trait (Adee et al., 2016). The transgenic trait relies on a gene from the soil bacterium *Bacillus subtilis* which encodes a protein termed cold shock protein B (McFadden et al., 2019).

Comparing DT Optimum AQUAmax[®] and DroughtGard[®] versus non-DT maize hybrids, Adee et al. (2016) illustrated a yield advantage of the DT hybrids positively correlated with the environment evapotranspiration (ET) and vapor pressure deficit (VPD). DT hybrids yielded 5 to 7% more than non-DT hybrids in high and medium ET environments (>430mm ET), corresponding to seasonal VPD greater than 1200 Pa (Adee et al., 2016). The environmental index analysis confirmed that DT

hybrids were superior in stressful environments, with yield advantage of DT hybrids more pronounced as yield dropped below 10.8 Mg ha⁻¹ and averaged as much as 0.6–1 Mg ha⁻¹ at the low yield range (Adee et al., 2016). Drought-tolerant technologies can offer a degree of buffering against drought stress by minimizing yield reduction, but also maintaining a comparable yield potential in high yielding environments (Adee et al., 2016).

A wide range of efforts such as the use of multiple drought-specific environments, precision phenotyping, key genomics technologies, high number of molecular markers available across the whole maize genome, and efficient and specific genetic predictions are crucial to launch superior DT hybrids, such as Optimum AQUAmax® (AQ) products (Cooper et al., 2014a). Drought experiments must have acceptable levels of uniformity, low coefficient of variation and repeatability to generate reliable data and effective predictions to be aligned to the requirements of a successful breeding program. Also, DT or AQ hybrids must be tested in well-watered target regions to consolidate as a responsive hybrid with high productivity and desirable agronomic traits at both scenarios, thus, reducing the incidence of the problematic GxE interaction and improving yield stability (Cooper et al., 2014a). In fact, several stress and non-stress environments must be utilized as targeted locations during all stages of the breeding program. Combining all these techniques will result in long term genetic gain for yield on both, limited and well-watered conditions. The launch of these improved hybrids combined with superior agronomic practices can generate significant yield gain on-farm level (Cooper et al., 2014a, 2020).

In the US, the first year of commercialization of AQ maize hybrids was in 2011. Since then, the

average area of the US corn-belt planted with DT maize hybrids grew quickly to over 20% of the total area. In drought prone areas in the western US corn-belt, the land allocated to DT maize reached 39 % or more (Figure 4), as documented for the states of Nebraska and Kansas (McFadden et al., 2019). Over thousands of comparisons and environments in contrasting geographies, AQ maize yielded 37 g m⁻² more than non-AQ maize when exposed to drought stress conditions. Yield improvement under drought increased with planting density to at least 6.9 pl m⁻², where the yield difference was 50 g m⁻² (Gaffney et al., 2015).

Messina et al. (2020) showed that dedicated efforts towards drought breeding and, consequently, the launch of AQ hybrids led to a genetic gain in yield rate of 1.0-1.6% yr⁻¹ in recent years under drought stress, which is higher than 0.7 % yr⁻¹ genetic gain prior reported (Cooper et al., 2014a). Messina et al. (2020) also mentioned that the genetic gain for yield under well-watered environments, in the set of hybrids evaluated in their study, was similar to previous estimations (Cooper et al., 2014b) showing that the gain under limited water did not penalty under optimal water conditions.

Under favorable water conditions, hybrids extracted water from 0 to 1.0 m profile. In a situation where water availability reduces to 50% of evapotranspiration requirement, the DT hybrid AQ P1151AM extracted soil water from 0 to 1.6 m during kernel filling (Zhao et al., 2018). Similar results were described with the AQ hybrid P0876HR (Mounce et al., 2016). Zhao et al. (2018) showed that AQ P1151AM had higher yield compared to other hybrids under drought conditions. In addition, AQ P1151AM always had the lowest evapotranspiration rate, promoting the highest water use efficiency,

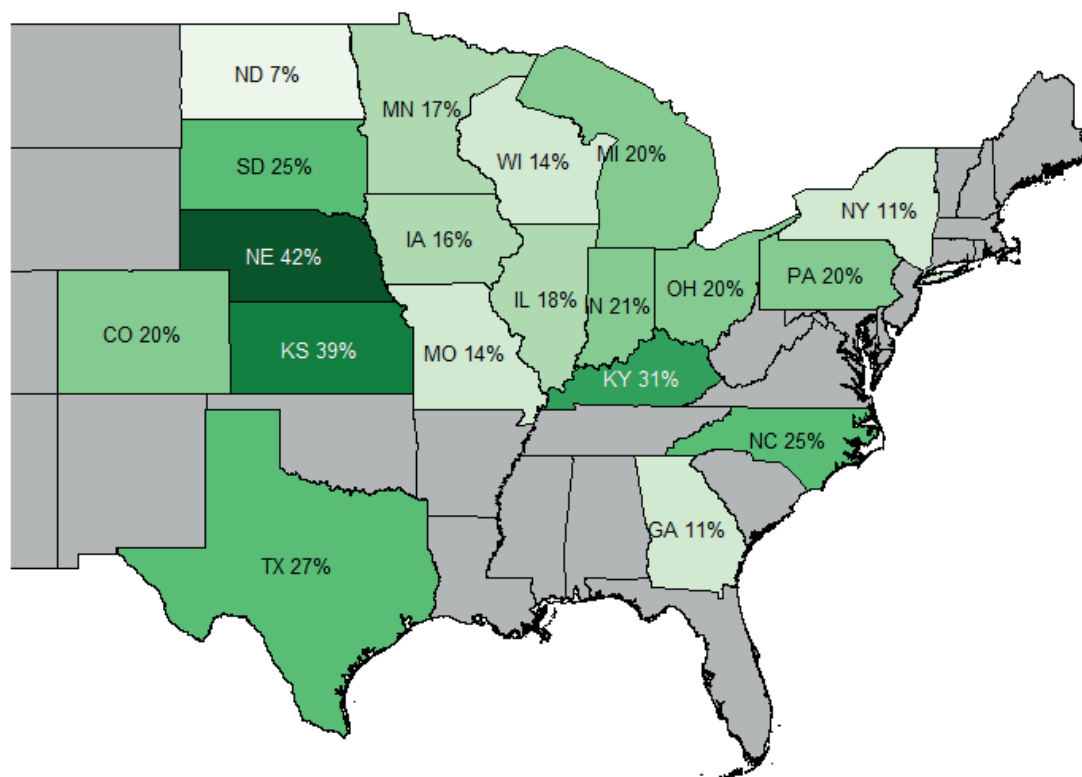


Figure 4 – Percent of each US State maize acreage planted with drought-tolerant (DT) hybrids in 2016. Source: McFadden et al. (2019).

which remains the main objective of maize breeding programs focused on water stress environments. Hao et al. (2015) found that the AQ hybrids P1151AM and P1564HR expressed 19.1% higher yield compared to conventional hybrids and up to 20.0 % greater water use efficiency in limited water environments, which became more efficient as drought stress increases. The same path was observed for yield, where AQ hybrids had higher performance under more severe water stress demonstrating that proper selection under drought environments can improve yield and water use efficient for that type of scenario (Hao et al., 2015).

Recently, Corteva Agriscience™ has decided

to bring the AQ technology to support farmers in Brazil. In April 2021, the technology was released in Brazil by the Pioneer seed brand. The first hybrid launched was P3845VYHR, which yielded 9882 kg ha⁻¹ against 9216 kg ha⁻¹ of the main competitors, with 75% of wins on a 2019 and 2020 basis considering 1140 comparisons. Under kernel filling drought stress in MS and MT states, P3845VYHR yielded 4794 kg ha⁻¹ versus 4362 kg ha⁻¹ of the main competitors, based on 2020 data with 20 comparisons. In summary, this hybrid showed high yield in overall analyses and a gain of 432 kg ha⁻¹ compared to the competitors under drought stress conditions at the kernel filling stage (Pioneer Sementes, 2021).

On the other hand, it is important to highlight that DT hybrids are not a guarantee of high yield performance under drought conditions by itself, regardless of the environmental conditions and agronomic decisions. There are several factors, which are specific to each hybrid, that will optimize its performance under drought conditions. One of these factors is hybrid positioning based on maturity, which represents an alternative way to prevent or diminish losses caused by water scarcity. Early maturity and/or early flowering hybrids tend to be less affected or even escape from drought at late stages by completing life-cycle prior the occurrence of drought. A combination of different maturities and mechanisms of drought tolerance are crucial to mitigate the risks of cropping in drought prone areas.

Final considerations

Climate change and population growth are driving demand for increased maize productivity and resilience, motivating the technological innovations necessary to meet this demand in an ecologically sustainable manner. Improved drought tolerance is a key trait to achieve these goals, and the research and commercial community have leveraged a wide variety of tools to explain the genetic and molecular basis of drought tolerance and accelerate the selection of superior germplasm. With the use of these technologies, the plant breeding community continues to achieve genetic gain in drought environments without penalties in non-stress conditions and improve the productivity of maize production systems.

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