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▶ To cite this version:

Yacine Djabali, Renaud Rincent, Marie-Laure Martin, Mélisande Blein-Nicolas. Drought plasticity QTLs specifically contribute to the genotype x water availability interaction in maize. 2023. hal-04002996v1

HAL Id: hal-04002996
https://hal.inrae.fr/hal-04002996v1

Preprint submitted on 23 Feb 2023 (v1), last revised 19 Oct 2023 (v2)

Drought plasticity QTLs specifically contribute to the genotype x water availability interaction in maize

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Abstract

Key message **Multi-environment genome wide association study of drought stability indices allow to detect QTLs specifically involved in the genotype x water availability interaction.**
Abstract Concerns regarding high maize yield losses due to increasing occurrences of drought events are growing, and breeders are still looking for molecular markers for drought tolerance. However, the genetic determinism of traits in response to drought is highly complex and identification of causal regions is a tremendous task. Here, we exploit the phenotypic data obtained from four experiments carried out on a phenotyping platform, where a diversity panel of 254 maize hybrids was grown under well-watered and water deficit conditions. To dissociate

drought effect from other environmental factors, we performed multi-environment genome-wide association study on steady-state means or drought plasticity indices computed for six ecophysiological traits. We identify 102 steady-state QTLs and 40 plasticity QTLs. Most of them were new compared to those obtained from a previous study on the same dataset. Our results show that plasticity QTLs cover genetic regions not identified by steady-state QTLs. Furthermore, for all traits, except one, plasticity QTLs are specifically involved in the genotype by water availability interaction, for which they explain between 60% and 100% of the variance. Altogether, steady-state and plasticity QTLs captured more than 75% of the genotype by water availability interaction variance, and allowed to find new genetic regions. Overall, our results demonstrate the importance of considering plasticity indices in multiple environments to decipher the genetic architecture of trait response to stress.

Keywords: drought response, phenotypic plasticity, GxE, GWAS, QTL, maize

Introduction

Maize, currently the leading cereal crop ahead of rice and wheat (FAOSTAT, 2022), is massively produced, traded and exported worldwide (Wu and Guclu, 2013; Erenstein et al, 2022). The major maize-producing countries are the United States, China and Brazil, with production exceeding seven hundred million tons per year since 2019 (FAOSTAT, 2022). This success is due not only to advances in agronomic practices and breeding, which have improved maize agronomic performance (Mazur et al, 1999; Balconi et al, 2007; Kelliher et al, 2019; Simmons et al, 2021), but also to the capacity of maize to adapt to a wide range of environments (Lanari, 1979; Rotili et al, 2019). Besides being the most widely produced crop in the world, maize also has a strong social and economic impact. As an easy and cheap source of calories and micro-nutrients, maize has become a staple food for many people, especially in Sub-Saharan countries. In developed countries, maize is also widely used in the starch industry and in the production of livestock products (Shiferaw et al, 2011; Ranum et al, 2014; Ekpa et al, 2018).

One of the principal threats to maize production is drought (Zipper et al, 2016; Daryanto et al, 2016; Song et al, 2020). Despite having a C4 metabolism, which ensures good water use efficiency (Crafts-Brandner and Salvucci, 2002), maize can be severely affected by water deficits (Salehi-Lisar and Bakhshayeshan-Agdam, 2016). The defense mechanisms that decrease water losses also reduce plant growth (Tardieu et al, 2017). For instance, the water loss / CO_2 absorption trade-off associated with stomata closure leads to a decrease in photosynthetic activity and biomass production, indirectly affecting grain yield (Efeoğlu et al, 2009; Wang et al, 2019; Song et al, 2019). Water deficit can also directly induce severe yield loss if it occurs during flowering and prevents silk development, an essential step for grain production (Sah et al, 2020). With climate change, drought scenarios are expected to occur more frequently in maize-producing regions (Seager et al, 2014; Cook et al, 2014; Gudmundsson and Seneviratne, 2016). Together with the increase in human population, this is a major concern for global food security (Harrison et al, 2014; Lobell et al, 2014; Meng et al, 2016). Drought tolerance is a highly integrated trait resulting from the combination of many genetically variable traits, such as water use, leaf growth and transpiration rate (Tardieu et al, 2014). Consequently, developing drought-tolerant maize varieties through breeding programs is a solution of choice to mitigate yield losses (Campos et al, 2004, 2006; Cooper et al, 2014). Aided by advances in genomics, genome-wide association studies (GWAS) are one of the most popular and powerful approaches for identifying genetic polymorphisms associated with inter-individual variations of traits of interest (Zhang et al, 2020; Zhao et al, 2022). These so-called quantitative trait loci (QTLs) are further used in breeding programs. However, detecting QTLs related to the genotype x water availability interaction is complex since drought tolerance strongly depends on the environmental conditions faced by the plants. When only a single experiment is conducted to study drought stress, it is impossible to dissociate the effect of water conditions from the effect of other environmental factors that may fluctuate between experiments. To tackle these confounding effects, it is necessary to carry out multi-environment trials (METs) (Boer et al, 2007; Rodrigues, 2018).

METs are experiments carried out in multiple environments where a trait of interest is measured in each experiment. For example, in Millet et al (2016), yield was measured in 29 different fields representing multiple experiments with contrasting conditions. More complex METs can include paired conditions represented in several experiments. For example, in Prado et al (2018), stomatal conductance in maize was measured in four experiments, each with two different watering conditions (well-watered and water deficit). To detect QTLs of interest from METs, GWAS can be carried out for each experiment separately. Then, among all identified QTLs, some are selected for their contribution to the genetic effects using a modeling approach (Diouf et al, 2020) or because they are present in a specific set of experiments (Millet et al, 2016; Prado et al, 2018; Touzy et al, 2019; Hu et al, 2021). Another approach in METs with paired conditions is based on phenotypic plasticity, **i.e.** the variation in phenotype for a given genotype in response to different environmental conditions (Bradshaw, 1965). Plasticity indices can be computed for each trait with regression models as proposed by Finlay and Wilkinson (1963) or by computing the relative difference or ratio between two studied conditions (Peleg et al, 2009; Zhai et al, 2014; dos Santos Silva et al, 2021). Performing GWAS on plasticity indices then allows the detection of condition-responsive QTLs, hereafter called plasticity QTLs (Wang et al, 2013; Zhai et al, 2014; Ye et al, 2019). Recent studies in rice and wheat have shown that plasticity QTLs tend to be positioned near stress-responsive genes (Mai et al, 2021; Fatiukha et al, 2021) and that many of them do not overlap with the QTLs detected separately in each studied condition (Kusmec et al, 2017; Diouf et al, 2020).

In this study, we investigated the relative contribution of plasticity QTLs and QTLs detected separately under two watering conditions (hereafter called steady-state QTLs) to the genotype by water availability interaction for drought-related traits in maize. To this end, we analyzed previously published phenotypic data acquired for six ecophysiological traits and 254 maize genotypes grown under two watering conditions repeated in four independent experiments (Prado et al, 2018). Because the four experiments were conducted over three years and two seasons, high variations in vapor pressure deficit and light were observed between experiments (Prado et al, 2018) and were considered as fluctuating environmental effects. We show that plasticity QTLs do not overlap with steady-state QTLs and contribute specifically to the genotype by water availability interaction.

Methods

Description of the phenotypic and genomic data used

The phenotypic dataset used in this study was previously published by Prado et al (2018). This dataset consisted of six ecophysiological traits, namely biomass (Biom), leaf area (LA), transpiration rate (Transp), stomatal conductance (gs_max), water use (WU) and water use efficiency (WUE), measured on a diversity panel of maize hybrids obtained by crossing 254 dent lines selected for their restricted flowering window with a standard flint line (UH007). Three replicates of each hybrid were grown under two watering conditions (well-watered, WW, and water deficit, WD). This experimental design was replicated in four different experiments, defined as fluctuating environments, during three different years and two different seasons: spring 2012, spring 2013, spring 2016 and winter 2013. Plants were grown at the INRAE PhenoArch phenotyping platform located in France at Montpellier (Cabrera-Bosquet et al, 2016; Prado et al, 2018), with applied soil water potentials equal to -0.05 MPa for the WW condition and ranging from -0.3 to -0.6 MPa for the WD condition. For each trait, watering condition and experiment, the average of the three replicates was adjusted by taking into account the greenhouse spatial effect (hereafter called the genotypic mean), as described in Prado et al (2018).

The genomic dataset contained 977,459 SNPs obtained using a combination of a 50K Infinium HD Illumina array (Ganal et al, 2011), a 600K Axiom Affymetrix array (Unterseer et al, 2014) and 500K markers obtained by genotyping by sequencing (Negro et al, 2019). SNPs with a minor allele frequency (MAF) below 0.05 or a heterozygosity rate above 0.15 were filtered. Missing values were imputed by Beagles 3.1 (Browning and Browning, 2007). SNPs were mapped on the Zm00001d.2 gene models annotation of the B73 reference assembly (ZmB73_RefGen_v4) of the maize genome obtained from MaizeGDB (https://www.maizegdb.org/assembly#downloads).

Calculation of plasticity indices

The drought stability index DSI_{tg} as described in Bouslama and Schapaugh Jr. (1984) was calculated for each trait t and genotype g. It is defined as the ratio between the genotypic mean of a trait t for a genotype g under water deficit to the genotypic mean of the same trait for the same genotype under the well-watered condition.

Estimation of the genetic variances

For each trait, variances of genotype (G), genotype by fluctuating environment (*i.e.* the season and year combination) interaction (GxF), and genotype by water availability interaction (GxW), were estimated using a linear mixed model :

$$Y_{gwf} = \mu + E_{wf} + \underline{G_g} + \underline{(G \times W)_{gw}} + \underline{(G \times F)_{gf}} + \underline{\varepsilon_{gwf}} \tag{1}$$

where: Y_{gwf} is the genotypic mean of genotype g in the watering condition w and the fluctuating environment f; μ is the overall mean; E_{wf} is the fixed effect of the environment wf defined as the combination between the watering condition w and the fluctuating environment f; all underlined terms are independent random effects distributed following a Gaussian law.

Multi-environment GWAS

For each trait, multi-environment GWAS was performed by adding a fixed effect of the fluctuating environment in the single locus mixed model of Yu et al (2006) :

$$Y_{gf} = \mu + F_f + \alpha.X_g + \underline{G_g} + \underline{\varepsilon_{gf}} \tag{2}$$

where: Y_{gf} is the DSI or genotypic mean under WW or WD of genotype g in the fluctuating environment f; μ is the overall mean; F_f is the fixed effect of fluctuating environment f; α is the fixed effect of the SNP allelic dose X_g (coded as 0,1 and 2) for the genotype g; $G_g \sim \mathcal{N}(0, \sigma_g^2.K)$ is the random effect of genotype g, with K the kinship matrix computed with the whole set of SNPs except those located on the same chromosome as the tested SNP (Rincent et al, 2014), following the approach published by Astle and Balding (2009) and implemented in the R package *statgenGWAS*; $\varepsilon_{gf} \sim \mathcal{N}(0, \sigma^2.I_n)$

is the residual error. This model was run using the function *GWAS* of the R package *rrBLUP* (Endelman, 2011).

SNPs were considered to be significantly associated if their p-values were below 10^{-5}. SNPs less than 0.1 cM apart were clumped into QTLs and annotated following the most significant SNP.

QTLs associated with DSI were defined as plasticity QTLs while those associated with WW or WD genotypic means were defined as steady-state QTLs.

QTLs colocalization is defined by the overlap of the linkage disequilibrium (LD) windows of QTLs as described in Negro et al (2019). Genes associated with QTLs, *i.e.* genes located in QTL LD windows, were retrieved from the Zm00001d.2 gene models annotation .gff3 of the B73 reference assembly (https://www.maizegdb.org/assembly#downloads).

Estimation of the relevance of steady-state and plasticity QTLs

To assess the biological relevance of the detected steady-state and plasticity QTLs, we followed the approach previously described by van Eeuwijk et al (2010). A multi-environment mixed model was first fitted following Prado et al (2018) in order to estimate by the restricted maximum likelihood (REML) the variance components of random effects:

$$\begin{aligned} Y_{gwf} = \mu + E_{wf} + PC_g + (PC \times E)_{gwf} \\ + \underline{G_g} + \underline{(G \times W)_{gw}} + \underline{(G \times F)_{gf}} + \underline{\varepsilon_{gwf}} \end{aligned} \quad (3)$$

Here we consider the fixed effects of the genetic structure PC_g and its interaction with the fluctuating environment E_{wf}. PC_g are coordinates of genotype g projected onto principal component analysis axes built with the kinship matrix K. The number of axes used was chosen following the Kaiser criterion.

Then, a multi-locus multi-environment mixed model (van Eeuwijk et al, 2010; Prado et al, 2018) was fitted by adding the fixed effects of the QTLs and QTLs by environment interaction in (3):

$$\begin{aligned} Y_{gwf} = \mu + E_{wf} + PC_g + PCQ_g + (PC \times E)_{gwf} + (PCQ \times E)_{gwf} \\ + \underline{G_g} + \underline{(G \times W)_{gw}} + \underline{(G \times F)_{gf}} + \underline{\varepsilon_{gwf}} \end{aligned} \quad (4)$$

where PCQ_g is the fixed effect of a given set of steady-state or plasticity QTLs. PCQ_g are coordinates of the genotype g projected onto principal component analysis axes built with a kinship matrix computed with a set of significant SNPs that describe the QTLs. The number of axes used was chosen following the Kaiser criterion.

Let r be one of the three random effects : G, GxF, and GxW. The proportion of variance γ_{qr} explained by a given set of SNPs q for the random effect r is defined by:

$$\gamma_{qr} = \frac{\Gamma_r - \Gamma_r^*}{\Gamma_r} \tag{5}$$

where: Γ_r is the variance component of the random effect r in (3) and Γ_{qr}^* is the variance component of the random effect r in (4).

Results

GxE interactions are driven more by fluctuating environment effects than by water availability

To evaluate the effects of the fluctuating environments, we calculated the Pearson correlation coefficients for each trait between the four experiments from the genotypic means in WD and WW as well as the DSIs (Fig. 1). This showed that measurements of the same trait in two different fluctuating environments are more distant from each other than measurements of different traits in the same fluctuating environment. This is even more apparent for DSIs (Fig. 1C) than for WW and WD genotypic means (Fig. 1A-B). This result highlights the importance of the effects of the fluctuating environments on the phenotypes of drought-related traits.

Fig. 1: Correlogram of Pearson's correlations obtained for (A) WW genotypic means, (B) WD genotypic means and (C) DSI between each pair of fluctuating environment x trait combinations.

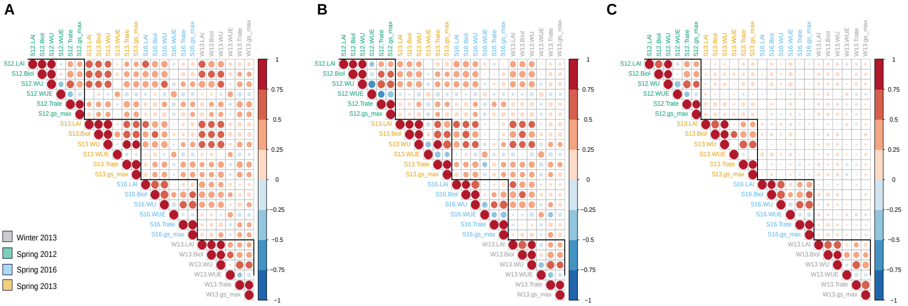
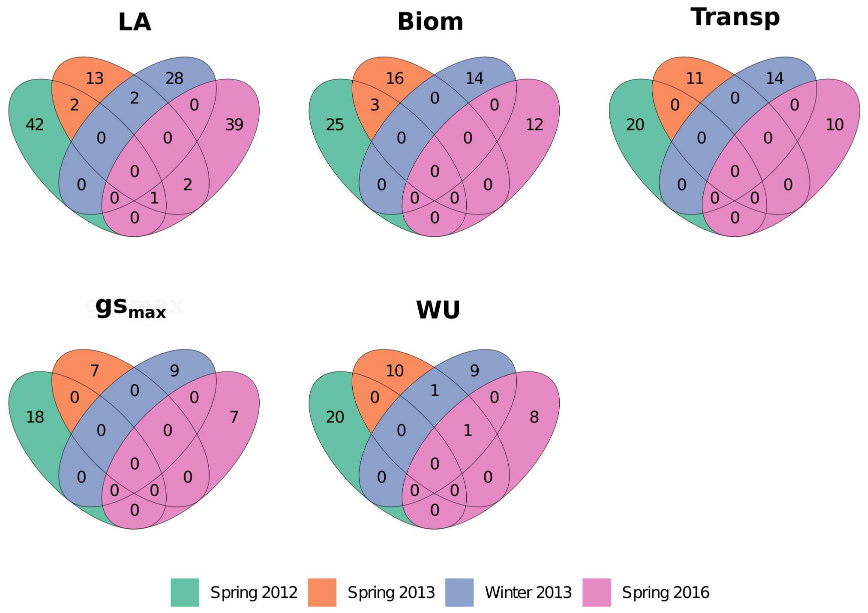


Table 1: Proportions of trait variance explained by the effects of the genotype, the GxF interaction and the GxW interaction, as calculated from (1).

Traits	G	$G \times F$	$G \times W$	ε
LA	49.7	10.7	2.3	37.3
Biom	42	4	9.4	44.5
Transp	27.3	10.4	2.4	59.8
gs_max	20.6	9	3.6	66.8
WU	39.6	12.2	5.9	42.3
WUE	25.8	14.4	3.3	56.4

To further quantify the contribution of the fluctuating environments to genetic variance, we computed, for each trait, the proportion of the variance explained by the effects of genotype, GxF and GxW (Table 1). Globally, the most important effect was the genotype effect, which explained 20.6 - 49.7% of the trait variances. Variance explained by GxW was low (2.3 - 9.4%), and for all traits except biomass, it was 2.1 to 4.7 times lower than the variance explained by GxF. This result indicates that by conducting single-environment GWAS, the probability of detecting a fluctuating environment-responsive QTL is higher than that of detecting a water availability-responsive QTL. This result is supported by the fact that there is almost no overlap between the sets of QTLs detected by Prado et al (2018) in the four fluctuating environments (Fig. 2).

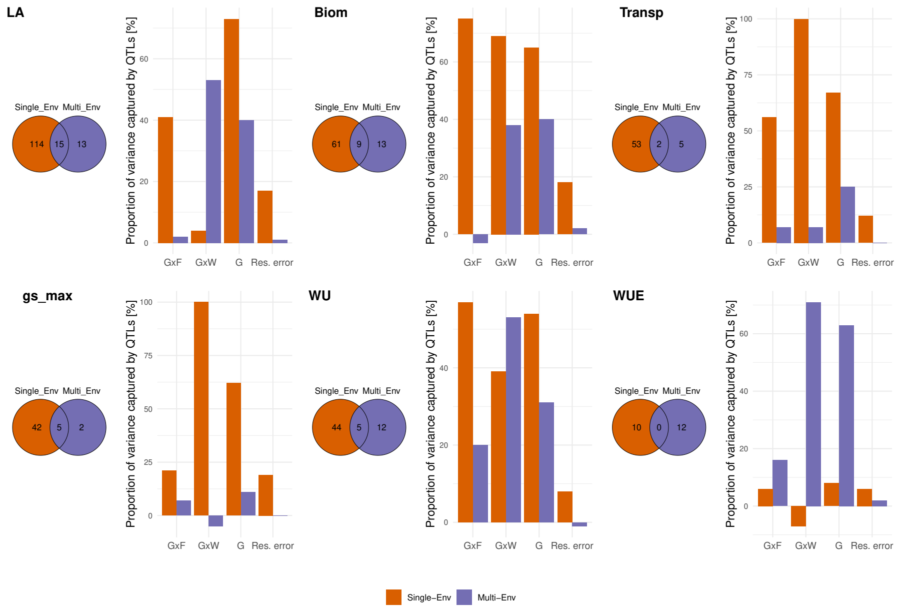
Fig. 2: Venn diagrams showing the overlap between the QTL sets detected by Prado et al (2018) in four fluctuating environments by using single-environment GWAS.



Multi-environment GWAS enhances the detection of water availability-responsive QTLs

To assess the effect of the fluctuating environment on QTL detection, we performed multi-environment GWAS on genotypic means. This allowed us to detect 102 steady-state QTLs, (60 in the WD condition and 42 in the WW condition) (Table S1), spanning 395 genes in total (Table S4). Compared to the steady-state QTLs previously obtained by single-environment GWAS with a p-value threshold of 10^{-5} (Prado et al, 2018), QTLs obtained by multi-environment GWAS were less numerous (2.9 to 7.9 times less for all traits except WUE) and were mainly new QTLs (see the Venn diagrams in Fig. 3). We then compared the contribution of all QTLs detected in the four single-environment GWAS *vs* those detected by multi-environment GWAS to the variations due to genotype, GxF and GxW (see bar plots in Fig. 3, Table S2). For three traits, (Biom, gs_max and Transp), the QTLs detected only by multi-environment GWAS contributed less to the variations due to genotype, GxF and GxW than the QTLs detected only by single-environmental GWAS. For gs_max and Transp, this may be explained by the fact that the number of multi-environment QTLs considered was very low compared to that of single-environment GWAS (2 and 5 *vs* 45 and 53, respectively). For the two traits LA and WU, the QTLs detected only by multi-environment GWAS contributed less to the variations due to genotype and GxF but much more to the variations due to GxW. Finally, for WUE, the QTLs detected only by multi-environment GWAS contributed more to the variations due to genotype, GxF and GxW. Overall, these results show that for half of the traits considered, multi-environment GWAS allowed to decrease the noise from the fluctuating environment and detect new QTLs that were more responsive to water availability than to the fluctuating environment.

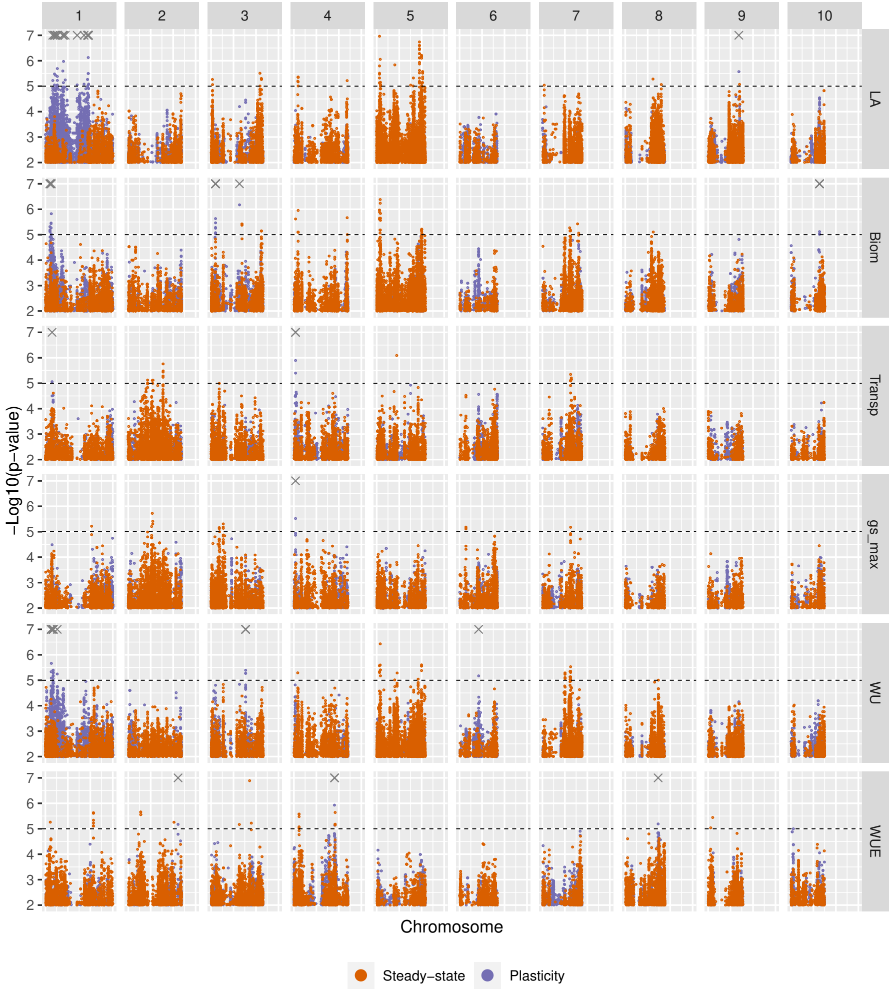
Fig. 3: Comparison between steady-state QTLs detected by single-environment and multi-environment GWAS. The Venn diagrams show the overlap between the two QTL sets. The barplots show the proportions of variance of the genetic, GxF interaction and GxW interaction effects that were captured by a given QTL set, as computed from (3) and (4). A QTL is characterized as a couple identifier-associated trait.



Plasticity QTLs specifically contribute to the GxW interaction

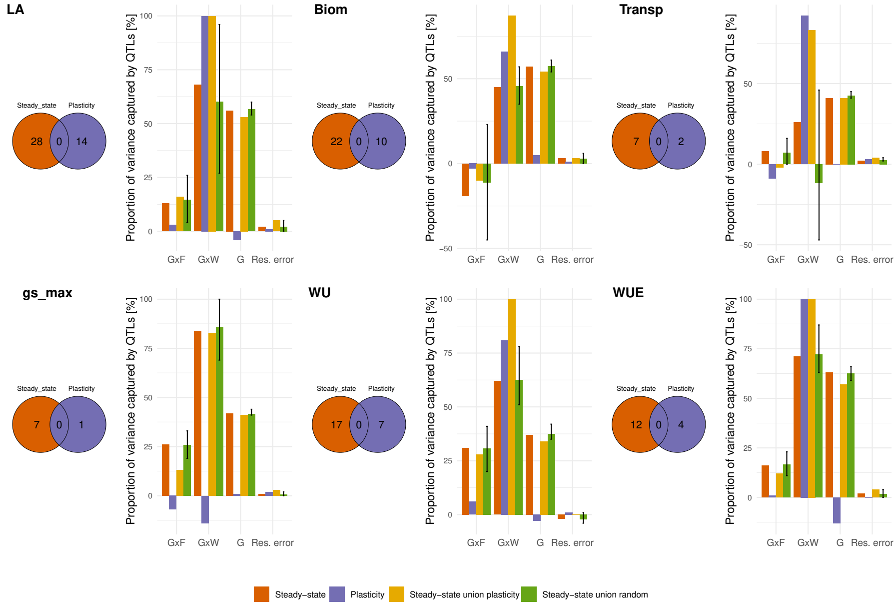
Using multi-environmental GWAS, we identified 40 plasticity QTLs from DSIs (Table S1), none of which overlapped with the 102 steady-state QTLs (see the Venn diagrams in Fig. 5). These plasticity QTLs are highlighted on the Manhattan plots shown in Fig. 4 and cover 240 genes (Table S4).

Fig. 4: Manhattan plots showing the results of the multi-environmental GWAS performed for each trait. Only the SNPs with -log10(p-value) lower than 2 are shown. The SNPs tested for their association to WW and WD genotypic means are depicted in orange and those tested for their association to DSIs are depicted in blue. Dashed black lines correspond to the QTL detection threshold. Grey crosses indicate the position of detected plasticity QTLs.



For all traits, plasticity QTLs were 2 to 7 times less numerous than steady-state QTLs and contributed weakly to the variance due genetic and GxF effects (Fig. 5 and Table S3). However, for all the traits except gs_max, for which only one plasticity QTL was detected, plasticity QTLs strongly contributed to the variance due to GxW effects (60 - 100%). Steady-state QTLs mainly contributed to the variance due to GxW effects in four traits (LA, gs_max, WU and WUE), as well as to the effects of genotype and GxF. For all the traits except gs_max, plasticity QTLs contributed more to the GxW effect than steady-state QTLs. To evaluate to what extent plasticity QTLs were complementary to steady-state QTLs, we considered jointly plasticity and steady state QTLs and compared their biological relevance to a control set of QTLs comprising steady-state and randomly selected QTLs (Fig. 5). For all the traits except gs_max, steady-state and plasticity QTLs jointly contributed more to the GxW effect than steady-state plus randomly selected QTLs. Altogether, these results show that plasticity QTLs are good candidates for understanding the genetic architecture of the GxW interaction.

Fig. 5: Comparison between steady-state and plasticity QTLs detected from multi-environment GWAS. The barplots show the proportions of variance of the genetic, GxF interaction and GxW interaction effects that were captured by a given QTL set, as computed from (3) and (4). For each trait, 1000 steady-state plus random QTL sets were constituted with steady-state QTLs and n SNPs randomly selected among the total number of SNPs available (977,459) in order to control over-fitting. With n the number of plasticity QTLs detected for the trait. A QTL is characterized as a couple identifier-associated trait.



Discussion

Plants being sessile, they are continuously exposed to variable and potentially harsh environmental conditions that can cause biotic or abiotic stress. In crops, the ability to resist or tolerate such stresses is of great importance to maintain productivity without resorting to inputs. Here, we investigated the genetic bases of the drought response in maize using a MET approach. The objective of our study was to estimate the extent to which plasticity QTLs contribute to the GxW effect on drought-related traits in maize compared to steady-state QTLs.

Even though the experiments were carried out in a greenhouse with well-controlled watering conditions, the meteorological conditions outside the greenhouse were different from one experiment to the other. We took these different meteorological conditions into account, which allowed us to decompose the GxE interaction into GxW and GxF. We showed that the GxE interactions observed in the data were driven more by environmental fluctuations than by water availability. This may explain the low overlap between the sets of QTLs from each experiment (Prado et al, 2018).

Compared to single-environment GWAS, multi-environment GWAS allowed to better fit the ecophysiological traits related to drought response: residual errors and GxF interactions were both smaller in multi-environment GWAS than in single-environment GWAS. In addition, the newly detected QTLs captured a larger part of the GxW variability for LA, WU and WUE. For the three other traits (Biom, Transp and gs_max), results are more mitigated: the number of newly detected QTLs was small compared to the several dozens of QTLs detected by the single-environment GWAS, which already explained a large part of the GxW interaction. Overall, by performing multi-environment GWAS, we multiplied individual observations and thereby increased the power to detect QTLs across environments (Cantor et al, 2010; Thomas, 2010). These results are consistent with those of Benaouda et al (2022), who showed that four multi-environment QTLs explained 20.6% of the heading time variance in wheat compared to 9.5% for the six single-environment QTLs detected by Langer et al (2014).

In this study, we also explored the gain provided by performing GWAS on plasticity indices for dissecting the genetic architecture of trait response to drought. We identified 40 plasticity QTLs and highlighted 38 genetic regions that differed from those associated with the steady-state QTLs. The results obtained with the multi-locus multi-environment model showed that plasticity QTLs specifically captured the variance of the GxW interaction. By comparison, steady-state QTLs not only captured the variance of the GxW interaction, but also a large part of the genetic variance and, to a lesser extent, part of the variance of the GxF interaction. These results indicate that, for the ecophysiological traits studied, the genetic control of phenotypic plasticity in response to drought does not completely overlap with that of the genetic control of the phenotypic mean. Similar results were previously observed in maize (Kusmec et al, 2017), tomato (Diouf et al, 2020) and cassava (dos Santos Silva et al, 2021). This indicates that the study of both steady-state and plasticity QTLs are required for understanding the genetic architecture of environment-responsive traits.

The complementarity of steady-state and plasticity QTLs can also help dissect the genetic basis of phenotypic plasticity. Three genetic models have been proposed to explain phenotypic plasticity (Scheiner, 1993; Via et al, 1995). First, the over-dominance model assumes that phenotypic plasticity is related to the number of heterozygous loci (Gillespie and Turelli, 1989). Second, the allelic-sensitivity model considers that the environment affects the allelic effect of the genetic factors that determine a trait. Third, the gene-regulatory model assumes that phenotypic plasticity results from epistatic interactions between structural and regulatory alleles. This last model implies that the genetic control of phenotypic plasticity is independent of the phenotypic mean. Our results favor the gene-regulatory model: first, the candidate genes that underlie the two types of QTLs are different; second, we have shown that plasticity QTLs are specifically involved in the GxW interaction.

In conclusion, considering both plasticity in response to drought and environmental fluctuations could allow us to gain a more precise understanding of the genetic control of traits in response to water stress. In the short term, our perspective is to go deeper into the functional annotation of the genes associated with the steady-state and plasticity QTLs. By comparing the two gene lists against gene regulatory databases, a strong result in favor of the gene-regulatory model would be to find that genes associated with the plasticity QTLs are regulators of genes associated with the steady-state QTLs. These findings may shed further light on the genetic regulatory system underlying the response of plants to stress.

Supplementary information. The datasets analysed during the current study are available from previous studies see Data availability on Declarations section.

The scripts used to conduct the analyses presented here are available upon request from corresponding authors see Code availability on Declarations section.

Acknowledgments. We thank Claude Welcker for the time he dedicated to helpful discussions about this work. We thank Santiago Alvarez Prado for giving us further information on the multi-environment multi-locus mixed models.

Fundings. This work and IPS2 have benefited from the support of the LabEx Saclay Plant Sciences-SPS (reference n° ANR-17-EUR-0007, EUR SPS-GSR). This work benefits also from two French State grants from INRAE and C-Land (reference n° ANR-16-CONV-0003) managed by the French National Research Agency under the "Investissements d'avenir" program integrated into France 2030 (reference n° ANR-11-IDEX-0003-02). The data analyzed in this work were produced during the Amaizing project (reference n° ANR-10-BTBR-01) managed by the French National Research Agency under the "Investissements d'avenir".

Declarations

Competing interests. The authors have no relevant financial or non-financial interests to disclose.

Consent to participate. Not applicable

Consent for publication. Not applicable

Data availability. The genotyping datasets analysed during the current study are publised in Negro et al (2019)
The phenomics dataset analysed during the current study is publised in Prado et al (2018)

Code availability. The scripts used to conduct the analyses presented here are available upon request from the corresponding authors.

Authors' contributions. MBN and MLM defined the research project. YD carried out the analyses. RR, MBN and MLM supervised the work. YD wrote the manuscript and MNB, RR and MLM revised and approved it.

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