Genotype-by-Environment Interaction and Plasticity: Exploring Genomic Responses of Plants to the Abiotic Environment

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Abstract

There is considerable interest in the occurrence and molecular mechanisms of phenotypic plasticity and genotype-by-environment interactions (G × E) in plant populations. The emergence of genomic tools, including quantitative trait locus (QTL) mapping and transcriptome studies, provides opportunities to identify G × E patterns and mechanisms across a diversity of phenotypes, species, and environments. We review progress in evaluating the presence and characterizing the mechanisms of G × E using genomic studies of abiotic responses in plants. Our review reveals that G × E is common, often caused by changes in the magnitude of genetic effects in response to the environment, and associated with diverse genetic factors and molecular variants. We illustrate this diversity with an examination of transcriptome studies and discussion of cloned genes underlying G × E. We discuss the caveats associated with existing studies and outline future directions for better understanding G × E and its impact on local adaptation and plant improvement.

INTRODUCTION

Reaction norm: the phenotypes expressed by a genotype under varied environmental conditions; represented graphically with environments on the *x*-axis and phenotype on the *y*-axis

Genotype-by-environment interaction (G × E): the effect of a locus that changes in magnitude or direction across environments

Plants are remarkable because of their ability to thrive despite their limited capacity to alter their surroundings. In particular, plants are exquisite in their ability to sense, respond to, and survive a variety of abiotic stresses (Bohnert et al. 1995). This is largely the result of acclimation to the environment through changes in physiology, metabolism, growth, and indeterminate development. These responses can be viewed as phenotypic plasticity—the ability of a single genotype to produce multiple phenotypes in response to the environment—and are often quantified and depicted as reaction norms (**Figure 1**). For example, plants exhibit striking morphological reactions to different light conditions, including the well-known shade avoidance pathway (Franklin & Whitelam 2005), and extensive aboveground architecture changes in response to nutrient limitation, competition, or damage (Tomlinson & O'Connor 2004). Similarly, plants display dynamic shifts in root growth architecture as they forage for nutrients and water resources in heterogeneous soil (Drew & Saker 1978). These outwardly apparent plastic responses are likely small in number when compared to the molecular, biochemical, and physiological changes that occur hidden from our eyes.

Many examples of phenotypic plasticity are clearly adaptive (e.g., shade avoidance) and may result in local adaptation. However, plastic responses can also be passive consequences of the resources available for growth and development. As such, neutral or maladaptive plasticity occurs and even adaptive plasticity involves costs and limits that may constrain evolution (Auld et al. 2010, De Witt et al. 1998, DeWitt & Scheiner 2004, van Kleunen & Fischer 2005). Theoretical and empirical studies of phenotypic plasticity have been a centerpiece of plant biology for decades. A number of reviews have focused on the field especially from an ecological and evolutionary perspective (Bradshaw 1965, De Witt et al. 1998, Des Marais & Juenger 2010, Pigliucci 2001, Scheiner 1993, Schlichting 1986). Here, we review recent advances in understanding natural genetic variation in plastic responses in plants using genetic and genomic tools.

Classic work by Clausen, Keck, and Heisey (reviewed by Nuñez-Farfán & Schlichting 2001) recognized the importance of genetic variation in plasticity in plants, though the significance of their work was not realized for several decades. Bradshaw (1965) was one of the first authors to recognize the importance of genetic variation in plasticity, measured as genotype-by-environment interaction (G × E), especially in an evolutionary context. His insight opened discussion about the

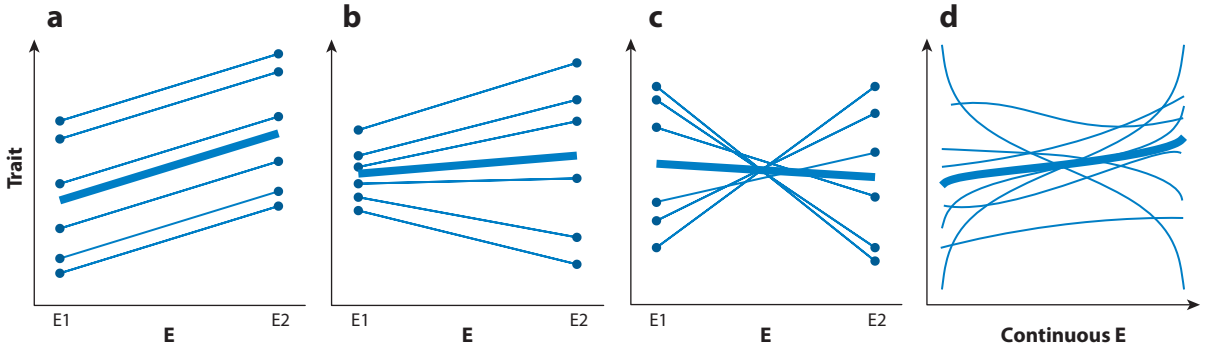

Figure 1

Reaction norm plots for various patterns of phenotypic plasticity. Thin lines correspond with the plastic response of a single genotype, whereas the single thick line represents the population average plasticity. The *x*-axis represents different environmental conditions and the *y*-axis represents the trait of interest; the series represents different genotypes. (*a*) Plasticity without genotype-by-environment interaction (G × E), (*b*) plasticity with variance-changing G × E, (*c*) plasticity with rank-changing G × E, and (*d*) plasticity and G × E with complex, continuous nonlinear functions.

mechanisms generating plasticity and the conditions that might favor or disfavor its evolution. Subsequently, a number of authors explored the conceptual importance of heterozygosity, allelic sensitivity, epistasis, and regulatory genes in the generation of plastic responses and their evolution (reviewed by Pigliucci 2001). Smith (1990) provided a plausible molecular model of plasticity by suggesting that duplicates from gene families may exhibit environment-specific expression allowing environmental sensitivity in key phenotypes. He emphasized the causal links between sensing of the environment with receptors, signal transduction pathways, and downstream molecular responses as critical aspects of any active adaptive response. These discussions culminated in debate about the existence of plasticity genes, their molecular basis, and the targets of selection leading to adaptive plasticity (Via 1993, Via et al. 1995).

Earlier work by Falconer (1952) and others took a different approach by framing the question in terms of pleiotropic effects of genes across environments. Falconer realized that a trait measured in two environments could be considered two different traits that were genetically correlated. In this framework, a perfect genetic correlation ($r_g = 1$) across environments would suggest that the same complement of genes control trait variation in both conditions: A positive correlation reveals consistent gene action, whereas a negative correlation suggests trade-offs or antagonistic gene action. Genetic correlations less than a value of 1, either positive or negative, suggest a mixture of common and unique genetic controls in each environment. Lack of correlation indicates novel genetic architecture across environments or a complex balance of positive and negative pleiotropic patterns at many loci. This perspective has played a guiding role in plant and animal breeding by integrating direct and indirect responses to selection across environmental conditions. Via & Lande (1985) extended this perspective with a theoretical model of the evolution of plasticity in natural populations. Additional theoretical work has linked reaction norm and genetic correlation perspectives (deJong 1985), been generalized to continuous environmental variation and function-valued traits (Gomulkiewicz & Kirkpatrick 1992, Stinchcombe et al. 2012), and introduced costs of plasticity (van Tienderen 1991) and aspects of population structure (Sultan & Spencer 2002). This rich theoretical framework has been critical in directing empirical work on phenotypic evolution, local adaptation, and breeding in plants.

Molecular geneticists have studied G×E using the traditional tools of forward and reverse genetics and the evaluation of condition-dependent mutants. In the case of plant biology, G×E studies have often centered on efforts to construct models of important signaling pathways for key environmental interactions. For example, one of our best known molecular pathways in plants relates autonomous growth and development with temperature and light conditions to control the onset and timing of flowering (Kim et al. 2009). Similarly, exciting progress has been made in identifying components of the drought signaling pathway, including the recent discovery of ABA hormone receptors and their interaction with signaling transducers, drought inducible transcription factors, and a host of downstream responses (Cutler et al. 2010). In addition to mutant studies, molecular biologists made early use of microarray technologies to study plant gene expression responses to abiotic stress. These studies often identify thousands of transcripts that are either up- or down-regulated under stress conditions such as heat shock, cold acclimation, osmotic stress, or salt exposure (Kilian et al. 2007); they have been especially valuable for identifying complex regulatory networks from differentially expressed gene sets (Zou et al. 2011), generating hypotheses about important downstream responses (Battaglia et al. 2008), and identifying potential crosstalk and pleiotropy of responses across stresses (Yoshioka & Shinozaki 2009). Despite this progress, very little is known about natural variation in these genetic pathways or their role in adaptive plasticity in natural populations (Des Marais & Juenger 2010, Juenger 2013).

Many longstanding questions remain concerning plasticity. How common is G×E? What type of quantitative genetic architecture underlies G×E? What is the role of transcriptional

Genetic architecture: the genetic basis of a phenotype, including the number of genes, their allelic effects, and interactions among loci and the environment

Function-valued trait: any trait that varies as a function of another continuous predictor variable including environmental variation

Pleiotropy: the phenotypic effect of a gene on more than one characteristic of an organism

QUANTITATIVE GENETIC ANALYSES OF G × E

Many approaches have been used to explore G × E at the phenotypic level, though analyses based on linear models are predominant. Although familiar, limitations of the linear model approach include the prejudice of additive over interactive effects (Lewontin 1974, Wahlsten 1990), complexity in the various formulations and interpretation of parameters from factorial models (Fry 1992), implications of scale and transformation on testing and estimation (Lynch & Walsh 1998), and difficulties interpreting the cause of interaction when observed (Bowman 1972) (e.g., rank versus variance changing interaction). Linear mixed models based on maximum likelihood offer flexibility, including options to directly model heterogeneous variances, and the ability to test specific hypotheses concerning the across-environment correlation (Fry 2004, Littel et al. 1996). Graphical and regression approaches such as GGE biplots (Yan & Kang 2003), AMMI (Gauch & Zobel 1996), and joint (stability) regression (Eberhart & Russell 1996) are commonly used in the agricultural literature. Recent methods based on random regression (Schaefer & Jamrozik 2008) and genetic covariance functions (reviewed in Stinchcombe et al. 2012) are flexible and can model function-valued or complex responses to continuous environments (**Figure 1*d***). Similarly, multivariate mixed models may help elucidate global plasticity and G × E of trait sets (Robinson & Beckerman 2013). These latter methods are critical advances that will allow empirical efforts to better embrace the nature and frequency of environments and the dimensionality of plastic responses.

regulation of gene expression in plastic responses? How important are receptors, signaling pathways, or structural protein variation in generating adaptive plastic responses within species? How and when does genetic architecture constrain the evolution of plasticity? In this review, we begin by considering how patterns of trait expression across environments can reveal the genetic architecture of G × E. We survey empirical studies that have employed a quantitative genetic approach to identifying the loci that underlie plant responses to the environment. Summarizing these studies allows us to assess the frequency of different mechanisms of G × E. We next take a broader genomic approach by reviewing whole-genome transcriptional profiling studies coupled with experimental manipulations of the environment. These studies give an unbiased genome-wide view of how loci respond to environmental perturbation. Finally, we describe a small but growing number of studies that have identified the specific genes and nucleotide variants responsible for allele-specific responses to the environment. Many successful efforts to clone and characterize these genetic variants began as quantitative trait locus (QTL) mapping studies of traits expressing G × E; these examples therefore offer a powerful way to integrate molecular studies with classic quantitative genetic approaches for studying G × E.

Quantitative trait locus (QTL): a chromosome region that contains one or more sequence variants that affect a trait measured in an experimental population

Mixed models: statistical model of the general form $y = X\beta + Zu + e$, containing both fixed (β) and random (u) effects

QUANTITATIVE GENETICS AND G × E: GENETIC ARCHITECTURE

Quantitative studies of G × E often begin with a common garden experiment replicating germplasm (e.g., varieties, clones, genotypes) across different environmental conditions. These data are analyzed in a factorial ANOVA (analysis of variance) framework (see the sidebar, Quantitative Genetic Analyses of G × E) testing for constitutive differences among genotypes, environmental effects, and their interaction. G × Es are detected when there is genetic variation for responses to the environment that can be driven by changes in variance across the environments as well as rank changing of responses to the environment (**Figure 1**) (Falconer & Mackay 1996, Lynch & Walsh 1998). Although studies are often limited to pairs of discrete environments

QTL ANALYSES AND G × E

Paterson et al. (1991) reported one of the first evaluations of QTL × E with a simple comparison of QTLs detected with a tomato mapping population (*L. esculentum* × *L. cheesmanii*) grown at three study locations. The number of published studies and analytical methods for exploring QTL × E has since exploded (van Eeuwijk et al. 2010), especially in the agronomic literature. Many QTL mapping software packages implement tailored tests of QTL × E under an interval mapping framework, including several that incorporate sophisticated multiple QTL algorithms (e.g., multiQTL, QTLcartographer, GenStat, PLABqtl, R/qtl). An alternative strategy centers on deriving composite traits from breeding values of genotypes measured in multiple environments, such as the difference or ratio of response across the environment (Broman & Sen 2009). However, many questions remain concerning the construction of test statistics, adjustment for correlated features and relatedness in mapping designs, and control for multiple testing in QTL × E analyses. An especially promising approach stems from mixed model QTL mapping, as implemented in TAGQTL, GenStat, QTLrel, or PROC QTL. These methods allow researchers to fit a large family of QTLs and QTL × E models (recently reviewed by van Eeuwijk et al. 2010). In addition, new methods focused on mapping parameters derived from function-valued responses show promise for better characterizing QTL × E (Xiong et al. 2011).

(e.g., wet versus dry conditions), G × Es can involve complex interactions across a continuous distribution of complex environments (**Figure 1*d***).

The mechanisms underlying G × Es can be attributed to a number of different genetic architectures. A common interpretation of rank-changing G × E at the phenotypic level is the occurrence of genetic trade-offs through antagonistic pleiotropy. Here, an allele may additively increase the trait value in one environment while decreasing it in another. Such trade-offs can constrain responses to selection if the favored trait values are in the same direction in each environment. Alternatively, differential sensitivity occurs when the magnitude of the phenotypic effect of a gene depends on the environment. One can imagine an extreme case of differential sensitivity, often termed conditional neutrality, where an allele has a phenotypic effect in one environment, but no effect in another. One possible example of a conditional neutral gene is one whose expression is tightly regulated by an environment-specific promoter (e.g., transcriptional activation only under conditions of high light). All forms of differential sensitivity likely play critical roles in variance changing G × E. Finally, nonadditive effects—such as environment-specific dominance or epistasis, perhaps related to sensory perception and signal transduction—could lead to a diversity of G × E patterns at the phenotypic level. A critical aspect of these relationships is that rank-changing G × E at the phenotypic level does not require antagonistic pleiotropy and rather can result simply from a combination of allelic effects at many loci that exhibit differing degrees of differential sensitivity.

Quantitative trait locus mapping studies conducted in multiple environments provide empirical data that can be used to evaluate the relative importance of these mechanisms in generating G × E through standing genetic variation (see the sidebar, QTL Analyses and G × E). Specifically, the patterns of QTL additive effects across environments are representative of the underlying genetic architecture (**Figure 2**), including antagonistic pleiotropy, conditional neutrality, and differential sensitivity. This is a remarkably large field of research, especially when considering the agricultural crop literature addressing abiotic environments. Surprisingly, however, there has been no comprehensive review of this literature exploring the general patterns of QTL effects across environments (although see Collins et al. 2008, Lynch & Walsh 1998). Thus, we performed

Additive effect: the change in average phenotype produced by substituting an allele of one type for another

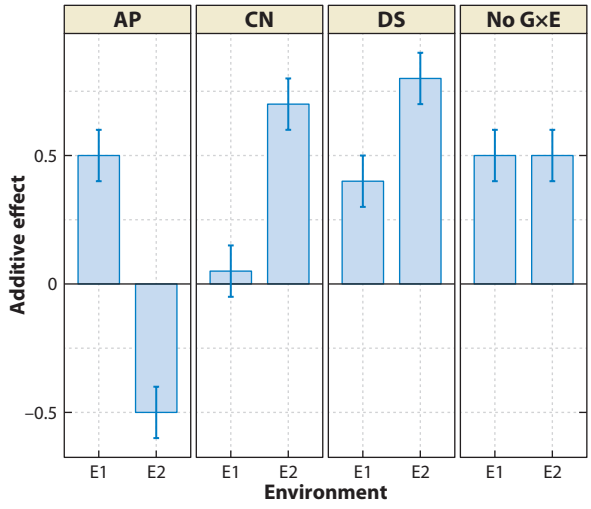

Figure 2

Patterns of quantitative trait loci additive effects for traits that show genotype-by-environment interactions (G × E) can fall into four main categories: (*a*) antagonistic pleiotropy (AP), the result of sign changing additive effects; (*b*) conditional neutrality (CN), additive effects limited to only specific environmental conditions; (*c*) differential sensitivity (DS), the result of changes in magnitude of additive effects; and (*d*) no G × E, no detectable change in additive effects across environments.

Supplemental Material

an exploratory review of the QTL literature to assess the following features of genetic architecture (see **Supplemental Text**; follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**): (*a*) the patterns of the number of QTLs associated with a given trait, (*b*) the patterns of additive effects within and between environments, and (*c*) the frequency of QTL-by-environment (QTL × E) interactions. In addition, we provide perspectives on the limitations of QTL data and explore general patterns of phenotypic plasticity.

We filtered nearly 700 QTL G × E studies to include only those studies that experimentally manipulated abiotic environments (e.g., by imposing an osmotic stress), reported environment-specific trait means, estimated additive effects of QTLs, performed statistical tests of significance, and localized QTLs by providing confidence intervals. Our filtering was motivated by concern for confounding with unknown experimental factors (e.g., management strategies, technician crews across space and time) and to focus our effort on a manageable number of abiotic stress responses. Only ∼4% of papers met our criterion after filtering; many studies centered on uncontrolled (random effect) environments, and a disappointing number of studies did not report basic descriptive or QTL statistics.

Limitations and Caveats of QTL Data

One fundamental problem with QTL data is censoring—only globally significant loci of sufficiently large effect are detected and reported. The majority of the studies we evaluated only report effect statistics for QTLs in environments where they met a significance threshold. Many authors interpret this pattern as strong support for a conditionally neutral genetic architecture when it may be due only to magnitude differences (differential sensitivity) and censoring at detection thresholds. Assuming censored QTLs fall below a detection threshold, we considered the additive effects in the censored environment as "zero" or null effects (for methods see **Supplemental Text**) and refer to them as environment-specific QTLs.

We report results from 37 studies (**Supplemental Table 1**) including over 900 QTL effects, multiple study designs (recombinant inbred line, RIL; second filial, F_2; backcross, BC; double haploid, DH; single seed descent lines, SSD; single segment substitution lines, SSSL), 11 species, a diversity of traits (collapsed into classes: germination, growth architecture, growth/size, metabolites/molecules, nutrient accumulation, phenology, physiology, and yield/fitness), and 6 environmental classes (damage, density, light/nutrient/water availability, osmotic stress, temperature, vernalization) (see **Supplemental Tables 2, 3**, and **4**). When possible, statistical conclusions are derived from linear mixed models including random "study" effects to account for structure and nonindependence of data reported from individual published experiments.

Most Traits Are Associated with Multiple QTLs

A central feature of genetic architecture is the number of genes controlling a polygenic trait, where the number of QTLs can be a proxy for the lower bound of this quantity (Mackay 2001). Our sample studies reported between 0 and 10 QTLs for a trait in an environment with a mean of 3.36 ± 2.03 SD (standard deviation) (modeled as a Poisson distribution: $\lambda = 3.36$) (see **Supplemental Figure 1**), suggesting that the majority of the traits in our database are moderately polygenic. Surprisingly, study designs, treatments, and trait classes did not contribute significantly to variation in the number of QTLs reported. In contrast, studies focused on natural species ($n = 16$) generally discovered a greater number of QTLs per environment (4.09 ± 1.76 SD) relative to crop species ($n = 21$) (2.91 ± 2.06 SD) ($\chi^2 = 7.94$, $df = 1$, $P = 0.005$).

Most QTLs Have Small Effects

A fundamental metric of quantitative genetics is the additive effect of a QTL. Here, we focus on the additive effect determined from inbred line crosses and experimental mapping populations as $a = (\bar{X}_{AA} - \bar{X}_{BB})/2$ (Falconer & Mackay 1996). Depending on the population design, it is also possible to estimate nonadditive genetic effects (e.g., dominance and epistasis), but here we restrict our focus to purely additive architecture. Many empirical studies report additive effects on the raw phenotypic scale for ease in biological interpretation (e.g., substituting QTL alleles would result in a 3-day increase in flowering time). Because phenotypes occur on different scales, additive effects are often standardized by the phenotypic SD. Alternatively, the QTL effect can be characterized by the proportion of the phenotypic variance explained by the QTL (e.g., PVE, R^2) in the experimental population in which it was discovered. However, surprisingly few studies (35% of QTLs from our survey) we examined provided trait SD, and many different metrics of percent variance explained were utilized. As such, we chose to standardize by the environmental trait means.

The distribution of standardized additive effects was L-shaped and well approximated by a gamma distribution (gamma: $k = 1.11$, $\theta = 0.09$; mean = 0.10 ± 0.11 SD) (see **Supplemental Figure 2**), suggesting that the majority of the QTLs in our database were of relatively small effect. This pattern is consistent with many other reviews, but should be interpreted as the true distribution with caution because of the known power limits and biases of QTL mapping (Beavis 1994). Variation in the pattern of additive effects was best explained by differences among trait classes ($\chi^2 = 71.73$, $df = 7$, $P = <0.0001$), where the range of largest standardized QTL effects spanned from 0.30 (nutrient accumulation) to 0.95 (growth/size).

G × E Is Common in QTL Studies

Our interest in G × E rests on how the additive effect architecture changes across environments. We graphically explored this pattern by plotting the standardized effect in a bivariate scatterplot

Figure 3

Biplot of quantitative trait locus additive effects from published data and standardized by the trait mean. Each *x*, *y* coordinate represents a comparison between an additive effect estimated in two environmental conditions plotted with the largest absolute additive effect on the *x*-axis. Above the *x*-axis shows differential sensitivity (DS), below the *x*-axis shows antagonistic pleiotropy (AP), and along the *x*-axis are environment-specific effects (censored or true conditional neutrality). Orange circles represent crop species, and blue diamonds represent natural species.

(**Figure 3**) with the largest effect plotted along the *x*-axis. In this presentation, QTLs that exhibit a sign change (antagonistic pleiotropy) fall below the origin, whereas QTLs that exhibit magnitude change (differential sensitivity) fall above the origin. Additionally, QTLs that exhibit effects specific to one environment and were censored in the contrasting environment (true conditional neutrality or censored differential sensitivity) are inferred along the *x*-axis (see **Supplemental Table 5**).

Only eight studies report the occurrence of antagonistic pleiotropy (22% of studies). Moreover, the number of QTLs with sign-changing additive effects are few and account for only 22 of the 1,525 QTL comparisons we evaluated (1.4% of QTL comparisons). Five of these cases are associated with tillering responses of rice to planting density (Liu et al. 2012) and five are from yield-related QTLs in *Arabidopsis thaliana* (Hausmann et al. 2005, Ungerer et al. 2003) and sorghum (Sabadin et al. 2012). In contrast, nearly every study reported environment-specific QTLs (92% of studies; either true conditionally neutral effects or censored), with 57% of QTLs lacking a significant effect in at least one study environment. Taken together, these data suggest, as a lower bound, that nearly 60% of QTLs exhibit G × E caused by antagonistic pleiotropy or environment-specific effects. Although the presence of G × E through antagonistic pleiotropy or environment specificity can be inferred from reported results, the pattern for QTLs exhibiting differential sensitivity is more ambiguous. Unfortunately, few studies test for QTL-by-environment interaction or report uncertainties of the estimated additive effects.

We further explored QTL-by-environment interactions by evaluating the absolute difference in the standardized additive effects across environments as a measure of "QTL effect plasticity." Interestingly, QTL effect plasticity was strongly influenced by the architecture of the G×E ($\chi^2 = 180.97$; $df = 2$; $P < 0.0001$). Although rare, antagonistically pleiotropic QTLs exhibited the greatest QTL effect plasticity, with a 3.2-fold increase in effect across environment relative to differentially sensitive QTLs. These patterns suggest that differential sensitivity, when it exists, can often be subtle. QTL effect plasticity also varied across trait classes ($\chi^2 = 118.02$; $df = 7$; $P < 0.0001$), with QTLs for germination and yield/fitness traits exhibiting a 4.3-fold greater effect plasticity than QTLs for metabolites/molecule production.

Patterns of Trait Plasticity

Although there is a large body of empirical literature associated with phenotypic plasticity, there has been little effort to explore patterns of trait plasticity at the population level with features of genetic architecture, trait characteristics, or environments. Are some phenotypes more or less plastic? Do certain environments elicit greater plastic responses? Is there a relationship between the QTL effect plasticity for a trait and the average plastic response in a population? We used our database to explore how population-level trait plasticity is associated with these factors, including QTL effect plasticity.

Variation in phenotypic plasticity was greatest among species ($\chi^2 = 4.06$, $df = 1$, $P = 0.04$) and trait classes ($\chi^2 = 82.36$, $df = 7$, $P < 0.0001$). On average, natural species exhibited greater plasticity than crop species (1.8-fold difference). This is perhaps not surprising given historical artificial selection for environmentally stable crops. In general, phenology traits were the least plastic and nutrient accumulation traits were the most plastic (1.3-fold difference) among all trait classes. Phenotypic plasticity varied across genetic architectures ($\chi^2 = 9.89$, $df = 2$, $P = 0.007$), with the greatest average plasticity being in traits that were associated with antagonistically pleiotropic QTLs and the least plasticity being in traits associated with differentially sensitive QTLs (1.6-fold difference). The most intriguing discovery was an interaction between genetic architecture classes (antagonistic pleiotropy, differential sensitivity, or environment-specific QTLs) and species classes (see **Supplemental Figure 3**; $\chi^2 = 13.66$, $df = 2$, $P = 0.001$). In crop species, traits associated with QTLs that exhibit antagonistic pleiotropy were the least plastic, whereas traits associated with environment-specific QTLs were the most plastic (2.6-fold difference). In contrast, the most plastic traits in natural species were associated with antagonistically pleiotropic QTLs and the least plastic traits were associated with differentially sensitive QTLs (2-fold difference). Finally, we used a random regression model to directly test for a relationship between trait plasticity and QTL effects plasticity. We found a strong global relationship between phenotypic and QTL plasticity ($\chi^2 = 339.55$, $df = 3$, $P < 0.0001$, $\beta = 0.18 \pm 0.04$).

Supplemental Material

Implications of Genetic Architecture and Patterns of Plasticity

Broadly interpreting QTL studies is fraught with challenges (Rockman 2012). Nevertheless, some of the patterns we observe are compelling and have interesting implications if representative of nature. As expected, traits exhibited a modest number of QTLs with a preponderance of small effect sizes across a diversity of crop and natural population studies. Importantly, G×E in standing polygenetic variation is appreciable as seen by frequent G×E at the phenotypic level (Fry 1996, Scheiner 1993, Windig et al. 2004) or when directly evaluating QTL×E, as reviewed here (**Figure 3**). Moreover, the phenomenon at the QTL level is dominated by changes in magnitude of effect rather than changes in sign. Surprisingly, we find a link between the type

of QTL × E architecture and the population-level pattern of trait plasticity. To our knowledge, there is no clear conceptual framework or expectation linking the underlying genetic basis of G × E and plasticity at the phenotypic level.

The common occurrence of rank-changing G × E suggests that genetic correlations measured across environments frequently differ from 1 ($r_{ge} \neq 1$ or -1), and as such are only rarely absolute constraints. The degree to which positive or negative genetic correlations of lesser extent will limit responses to selection depends on the direction of selection on traits relative to the genetic correlation (either reinforcing or antagonistic; Etterson & Shaw 2001), the frequencies of G × E effect architectures underlying the correlation (antagonistic pleiotropy, differential sensitivity, conditional neutrality), genetic variances in each environment, and the relative abundances of the environments in nature. In the special case of fitness components, or yield in agronomic settings, the pattern of QTL plasticity we report suggests that recombination could effectively generate individuals with high performance across environments by bringing together conditionally neutral alleles that lack trade-off. Interestingly, a number of field studies of local adaptation in natural populations have recently found evidence for the importance of conditionally neutral alleles for fitness (Anderson et al. 2013; Fournier-Level et al. 2011, 2013; Hall et al. 2010; Lowry et al. 2009), only weak trade-offs underlying local adaptation (Fry 1993, 1996; Hereford 2009), and suggest the importance of recombination as a limit to breeding in maize (Gore et al. 2009). Together, these patterns highlight the critical links between genetic architecture and recombination, either meiotic or through gene flow, in determining performance and local adaptation across heterogeneous environments (Kawecki & Ebert 2004).

THE MOLECULAR BASIS OF GENOTYPE-BY-ENVIRONMENT INTERACTION

Our review of the literature thus far has focused on plasticity and G × E in higher-order organismal traits. We turn next to an assessment of the molecular basis of these traits and their interaction with abiotic environments. This large body of literature allows two lines of inquiry. First, high-throughput genomic methods, particularly microarrays, have expanded G × E studies to allow a relatively unbiased view of genetic variation in plasticity at the genome-wide level. Second, the cloning and characterization of the molecular function of environmentally sensitive allelic variants gives insight on the origin, spread, and evolutionary processes shaping mutations that drive G × E.

Gene Expression Studies

Genome-wide assays of gene expression were rapidly adopted by molecular biologists focused on model or crop species, and public databases now host results from hundreds of studies and plant species identifying stress responsive genes [e.g., see Plexdb (Dash et al. 2012) or GeneInvestigator (Hruz et al. 2008) plant expression databases]. Many studies have subsequently asked how abiotic stress responsive gene expression is impacted by the mutation of particular genes, especially candidate transcription factors. For example, Vogel et al. (2005) discovered that 24% of the genes exhibiting cold-induced up-regulation in *A. thaliana* were also induced by overexpression of the transcription factor *CBF2* under warm conditions, suggesting *CBF2* as a major regulator of chilling-induced gene expression responses. A major achievement of these studies has been the identification of critical regulatory networks associated with cold acclimation (*CBF/DREB* regulon; Fowler et al. 2007), drought and salinity stress (*AREB/ABF* regulon; Fujita et al. 2005), and heat stress (*MBF1* regulon; Suzuki et al. 2008) as well as extensive crosstalk among pathways in plants

(Mittler & Blumwald 2010). However, only recently have studies begun to incorporate experimental designs that explore natural genetic variation in transcriptome responses to the environment.

A common experimental design focuses on a small sample of genotypes replicated across two or more environments and the quantification of transcripts detectable in a target tissue. The first studies taking this approach were largely from animal and microbial systems (e.g., fruit flies, worms, yeast) and reported extensive expression plasticity and appreciable transcript heritability (Gibson 2006, Gibson & Weir 2005, Hodgins-Davis & Townsend 2009, Stamatoyannopoulos 2004). For example, Zhou et al. (2012) discovered that ~15% of the expressed fruit fly transcripts exhibited plasticity in response to 20 differing lab environments. Ayroles et al. (2009) reported significant genetic variation in transcript abundance for over 68% of expressed transcripts in a set of 40 inbred fruit fly lines. The genome-wide aspect of these studies allows an evaluation of pattern in the degree of genetic variation and plasticity. For instance, Ayroles et al. (2009) found that the genetically variable transcriptome of *Drosophila melanogaster* was clustered into a small number of modules and that high-heritability transcripts were enriched for genes involved in responses to the environment.

In plants, the majority of studies have focused on crops and plant material central to breeding programs. For example, Kawasaki et al. (2001) studied the expression responses of salt tolerant and susceptible landraces of rice and discovered hundreds of transcripts exhibiting differential timing and abundance of expression under salinity treatments. Although relatively common, these studies rarely identify the cause of G × E because of many direct and indirect expression responses, but do occasionally point to plausible molecular pathways or biological processes. Recently, Des Marais et al. (2012) published a comprehensive study of *A. thaliana* responses to soil drying in a sampling of spring and winter annual accessions. Here, natural genotypes were exposed to a manipulation mimicking an ecologically realistic progressive drought. Notable levels of G, E, and G × E were detected. In the spring annual accession sample, 41.8% of the genes were genetically variable (G), 32.4% of genes responded to soil drying (E), and 21% of genes exhibited G × E at a false-discovery rate of 5% (**Figure 4**). Although the overlap between spring and winter accessions was high, many life-history-specific patterns were detected.

Data sets such as these are treasure troves for exploring patterns of functional genetic variation. For example, enrichment tests can be used to ask whether gene lists associated with plasticity or G × E are related to particular functional categories of genes, transcription factor binding sites in promoters, or patterns of nucleotide diversity. In Des Marais et al. (2012), genetic decomposition of the response to soil drying revealed that much of the G × E could be explained by only a few axes in principal components analysis (PCA) space. This result implies strong genetic structure in expression responses to soil drying, possibly through genetic variation in key drought-related transcriptional regulators. Similar expression results have been reported for responses to drought in sunflower (Rengel et al. 2012) and cold acclimation (Hannah et al. 2006), heat stress (Swindell et al. 2007), and elevated CO_2 in *A. thaliana* (Li et al. 2008). Natural variation in protein expression has also been observed in response to temperature (Tonsor et al. 2008). A novel study by Richards et al. (2012) explored the temporal pattern of gene expression in two *A. thaliana* accessions grown under natural field conditions. As with many studies, the authors found substantial expression divergence with 14% of the detected transcripts differentially expressed between accessions over the sampled time periods.

Expression QTL Studies

Genome-wide transcriptome studies provide entry into the genomic response of organisms to the environment. However, they do not specifically address the nature of the genetic effects leading

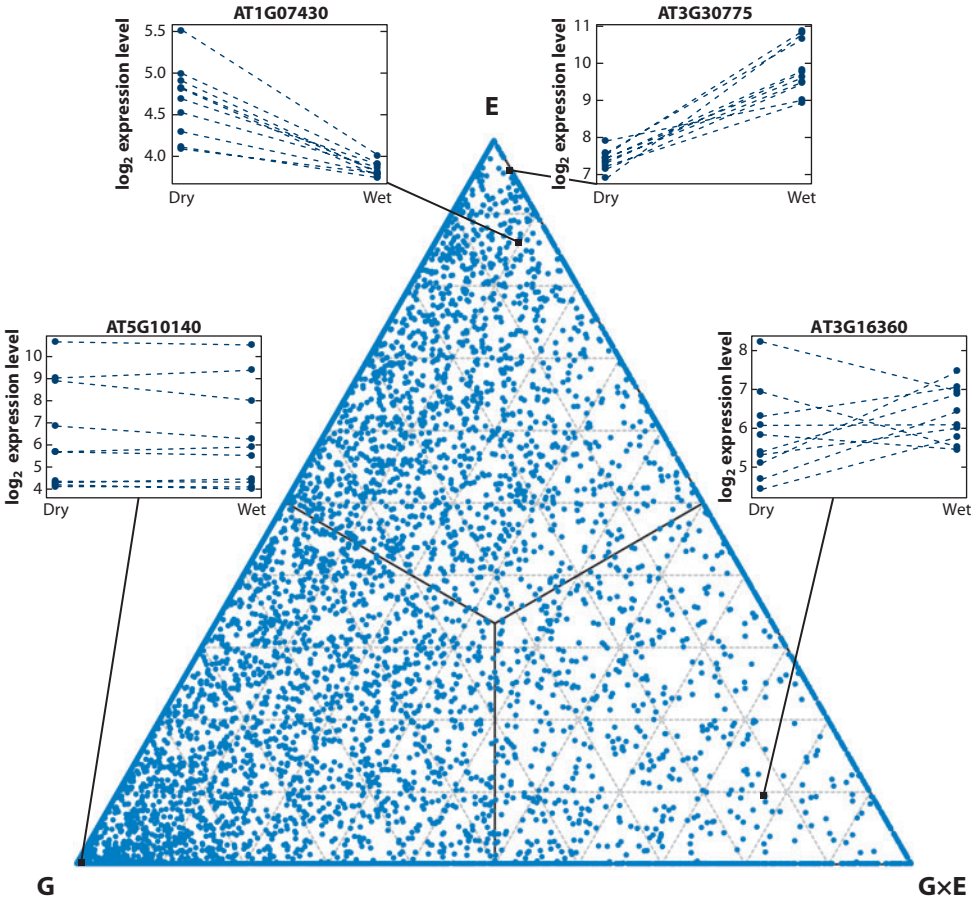

Figure 4

Ternary plot representing the genetic (G), environmental (E), and genotype-by-environment interaction (G×E) variance components (summing to 1, excluding residual variance) impacting gene expression responses to soil drying in *Arabidopsis thaliana* from Des Marais et al. (2012). The study is based on ten inbred spring annual accessions grown under control and drought-stressed conditions. Here, we plot 11,485 genes with variance components that sum to at least 25% of the total variance ($V_G+V_E+V_{G\times E}+V_{Res}$). A point at the center of the plot corresponds to a gene with expression equally impacted by G, E, and G×E, whereas a point at a vertex is dominated by a single factor. Insets: Reaction norm plots depicting $\log_2$ expression measures for representative transcripts: AT5G10140, Flowering Locus C; AT3G30775, Proline Dehydrogenase; AT1G07430, highly-ABA induced; AT3G16360, Histidine Phosphotransmitter 4.

to G×E as in traditional linkage analyses. One promising method is to link these approaches in expression QTL (eQTL) studies that consider transcript abundance as a trait in conventional linkage mapping (Kliebenstein 2009). These studies allow us to infer the effect size, dominance, and the genomic location of loci responsible for variation in transcript abundance. eQTL studies in plants find many transcript heritabilities exceeding 0.50 and that transcripts are influenced by both additive and nonadditive effects (Cubillos et al. 2012, Druka et al. 2010, West et al. 2007). Although many transcripts appear to be controlled by *cis*-eQTLs, *trans*-eQTLs are often detected and can occur in so-called hot spots influencing hundreds to thousands of genes across the genome. In a recent review, Cubillos et al. (2012) suggest that as much as 70% of the eQTLs detected in

***cis*-eQTL:** an expression QTL that maps to the location of the parent gene that produces the target mRNA

maize (Swanson-Wagner et al. 2009), rice (Wang et al. 2010), and *Brassica rapa* (Hammond et al. 2011) are *trans*-acting loci and that many of these cluster nonrandomly into genomic hot spots. The frequency and identification of *trans*- hot spots is still contentious (Breitling et al. 2008) and strongly dependent on statistical power, but their presence suggests that regulatory loci of large pleiotropic effect may play important roles in standing expression variability.

***trans*-eQTL:** an expression QTL that maps far away from the genomic location of the parent gene that produces the target mRNA

A logical extension of this approach is to evaluate the occurrence and pattern of eQTLs as expressed across environmental variation. What fraction of eQTLs is environmentally sensitive and do these effects underlie G×E for important performance phenotypes? eQTL analyses in yeast and animal systems offer a tantalizing first look. Generally, *cis*-acting eQTLs explain more transcript variation than *trans*-acting eQTLs, although in yeast and *Caenorhabditis elegans* these *trans*-acting eQTLs are more often associated with expression G×E (Li et al. 2006, Smith & Kruglyak 2008). In yeast, approximately 40% of detected eQTLs are associated with G×E, a fraction comparable to what we estimated in our QTL review above.

In plants, there have been only a handful of studies manipulating abiotic conditions and quantifying transcripts in mapping populations. Hazen et al. (2005) measured transcript abundances in rice plants exposed to drought stress using susceptible and tolerant parental lines and double-haploid progeny. Similarly, Street et al. (2006) studied drought responses in a *Populus deltoides* F_2 mapping population to test for colocalization of differentially expressed genes with drought-related QTLs. Although not explicitly eQTL studies, both studies identify candidates that could underlie G×E responses to abiotic stress. To our knowledge, the only formal eQTL study in plants involving an abiotic manipulation was published by Hammond et al. (2011). This study focused on *Brassica rapa* leaf tissue from plants grown under two levels of phosphorus (P) availability. Their study identified considerable transcript heritability and over 3,226 transcripts responsive to P. In total, Hammond et al. (2011) report 14,257 physically mapped eQTLs exhibiting a predominance of *cis-e*QTL effects. However, they also report several notable hot spots including a striking region associated with over 1,311 eQTLs that exhibited enrichment for genes involved in P metabolism. Unfortunately, the authors do not present formal tests of G×E nor do they discuss the impact of P availability on the QTL additive effects.

The coming years will see an abundance of plant eQTL studies conducted under a variety of conditions. An exciting advance will come from the use of next-generation sequencing technologies for both genotyping and transcriptome analyses; these efforts should greatly improve data quality and experimental sample sizes. It will be crucial that these studies are well-replicated, contrast realistic environments in a controlled manner, and formally test for eQTL×E. QTL studies that integrate expression, metabolite, physiology, and fitness measures may finally allow mapping of genotype to ecologically meaningful phenotype and will hopefully help to better illuminate G×E across biological levels of organization.

Cloning Genes Exhibiting G×E

In order to understand the origin, spread, and evolutionary processes impacting G×E we need to identify the specific genes that control G×E phenotypes and the mutational variants that define functionally distinct alleles. Identifying these genes will allow us to ask whether certain types of genes (e.g., those coding for environmental sensors, biosynthetic enzymes, or regulatory proteins), characteristics of genes (e.g., those with paralogs, or complex *cis*-regulatory control), types of mutation (coding/noncoding, those induced by transposable elements, etc.), and molecular mechanisms (condition-dependent epistasis, gene expression, enzymatic activity) are more often drivers of G×E. Identifying genes exhibiting G×E will also allow comparative analyses across lineages and tests for parallel and convergent evolution in responses to the environment. **Table 1** reports a partial list of such genes identified to date.

Table 1 Examples of cloned genes driving genotype-by-environment interactions in plant abiotic traits

Gene	Trait	Gene type	Species	Polymorphism	Molecular architecture	Effect architecture	Reference
CBF2	Cold tolerance	Transcription factor	*A. thaliana*	Promoter deletion	Expression	DS	(Alonso-Blanco et al. 2005)
P5CS1	Osmotic stress	Biosynthetic enzyme	*A. thaliana*	Splice variant	Protein amount	DS	(Kesari et al. 2012)
CRY2	Photoperiod	Photoreceptor	*A. thaliana*	Amino acid sub	Protein stability	DS	(El-Din El-Assal et al. 2001)
FT	Photoperiod/ vernalization	Protein binding	Several	Promoter polymorphism	Expression	DS	(Kojima et al. 2002, Lin et al. 2000, Schwartz et al. 2009, Yan et al. 2006)
FT	Photoperiod	Protein binding	*H. annus*	Frame shift	Expression	DS or CN	(Blackman et al. 2010)
PPD1	Photoperiod	2-component signaller	*Triticum* spp	Promoter deletion	Expression	DS	(Beales et al. 2007)
PPD1	Photoperiod	2-component signaller	*H. vulgare*	Coding	Protein-protein interaction	DS	(Turner et al. 2005)
CO (Hd1)	Photoperiod	Transcription factor	*O. sativa*	Coding, intron 1	Truncated protein, expression	AP	(Lin et al. 2000, Yano et al. 2000)
BRX	Root growth	Transcription factor	*A. thaliana*	Nonsense mutation	Protein activity	DS	(Gujas et al. 2012, Shindo et al. 2008)
PHYA	Seedling emergence	Photoreceptor	*A. thaliana*	Amino acid sub	Protein stability	DS	(Maloof et al. 2001)
PHYB	Seedling emergence	Photoreceptor	*A. thaliana*	Amino acid sub	Protein-protein interaction (inferred)	DS	(Filiault et al. 2008)
PHYC	Light sensitivity/ photoperiod	Photoreceptor	*A. thaliana*	Multiple	Reduced function	DS	(Balasubramanian et al. 2006)
SUB1A	Submergence tolerance	Transcription factor	*O. sativa*	Presence/ absence	Presence/ absence	DS	(Fukao et al. 2011, Xu et al. 2006)
APR2	Sulfate accumulation	Reductase	*A. thaliana*	Amino acid sub	Enzyme activity	DS	(Loudet et al. 2007)
FRIGIDA	Vernalization	Transcription factor	*A. thaliana*	Deletion	Presence/ absence	DS	(Johanson et al. 2000)
FLC	Vernalization	Transcription factor	*A. thaliana*	Splice variant, intron polymorphism	Partial loss of function	DS	(Caicedo et al. 2004)
RAS1	Salt tolerance	Transcription factor	*A. thaliana*	Nonsense mutation	Loss of function	DS or CN	(Ren et al. 2010)

Abbreviations: DS, differential sensitivity; CN, conditional neutrality; AP, antagonistic pleiotropy.

Many cloned G × E genes have been identified through a combination of QTL, fine-mapping, and candidate gene strategies. Confirmation that a gene is causal for a G × E phenotype requires a complementation test. In molecular genetic analysis, stable transgenic complementation is regarded as the gold standard for evidence of causality, though such approaches are not universally applicable. First, reliable protocols for introducing heterologous DNA into the genome are unavailable for many species and still challenging in many crops. Second, variation in trait expression is often caused by the genomic point of transgene insertion and ectopic or misexpression of the construct (Peach & Velten 1991). This technical hurdle is particularly acute when effect sizes are small, when a phenotype of interest is caused by subtle expression differences, or when alleles are incompletely dominant. As an alternative, candidate confirmation can be achieved by crossing the two (or more) alleles under study to a common mutant line to assess differential quantitative complementation across environments (Mackay 2001). Perhaps owing to these challenges, most studies reporting cloned G × E genes involve dramatic life-history differences among genotypes of a small number of model or crop species. Because the fitness effects of many of these mutations have not been studied explicitly, the following discussion of trait architecture (e.g., antagonistic pleiotropy, conditional neutrality) refers only to trait values, not fitness or yield.

Transgenic complementation: genetic engineering experiments to test the function of alternative alleles in a homogeneous genetic background

Quantitative complementation tests (QCT): an approach to infer the causal role of a candidate gene based on comparison of QTL effects in crosses to mutant and wild-type candidate gene backgrounds

Cloned Genes Reveal the Molecular Biology Underlying G × E: Case Studies

Natural plant populations display a wide range of flowering time behaviors (Nordborg & Bergelson 1999). These phenotypes have long been interpreted as cases of local adaptation, wherein natural selection optimized flowering time to ensure growth and reproduction during optimal conditions. Not surprisingly, plants have evolved complex regulatory systems to control phenology, driven largely by environmental cues such as photoperiod, temperature, and circadian signals (Kim et al. 2009). Because there are excellent examples of G × E for flowering time in several plant systems, a brief introduction to the general pathway is helpful.

The precise molecular components, and their interactions, have been studied most closely in *A. thaliana* in which a protein encoded by *FT* serves as the integration point for multiple environmental and cellular cues. FT acts as a florigen and directly signals for the activation of developmental genes that specify meristem identity. Expression of FT is repressed by Flowering Locus C (FLC), a transcription factor that itself is repressed by a transcriptional regulator Frigida (FRI) (Johanson et al. 2000, Michaels & Amasino 1999) and through epigenetic mechanisms (Heo & Sung 2011). The expression of FRI, in turn, is repressed by prolonged cold exposure. Prolonged cold, then, leads to upregulation of FT, which signals for the transition to flowering. Expression of FT is also promoted by CONSTANS (CO), which is responsive to signals arising from light and circadian cues.

Early work on rapid-flowering genotypes in *A. thaliana*—those that transition to flowering in the absence of a prolonged cold signal—identified several loss-of-function (LOF) alleles at the *FRI* and *FLC* loci. There are multiple, apparently independent, LOF *FRI* and *FLC* alleles segregating in nature. Some of these alleles result from missing *cis*-regulatory sites, whereas in others there are nonsense amino acid mutations or the gene sequence itself has been deleted (Gazzani et al. 2003). Nonfunctional or weak *FLC* alleles are caused by point and large insertion mutations in intron 1, which contains the binding site for FRI and other transcriptional activators (Caicedo et al. 2004, Gazzani et al. 2003, Sheldon et al. 2002). Here, then, is a case where the genotype (presence or absence of functional *FRI* or *FLC*) and environment (temperature) interact to generate differential sensitivity for flowering time.

Functional variation at *FT* also has a large effect on flowering in natural populations. Differential sensitivity to long-day (LD) length conditions in *A. thaliana* is driven, in part, by promoter polymorphism in *FT*, which leads to expression differences in LD but not short-day

(SD) conditions (Schwartz et al. 2009). Presumably, this expression variant affects binding by FLC to the *FT* promoter. Expression differences caused by promoter polymorphism are also found in wheat *FT* (*VRN3*) (Yan et al. 2006), leading to differential sensitivity to LD cues. Promoter variation in the rice ortholog of *FT*, *Hd3a*, also leads to expression differences but causes opposite responses in SD and LD conditions, suggesting a case of antagonistic pleiotropy for this trait (Kojima et al. 2002, Lin et al. 2000).

Wild populations of sunflower (*Helianthus annus*) flower more quickly under SD, whereas domesticated varieties flower more quickly under LD. The genetic basis of this difference is the photoperiod-dependent response of paralogs of *FT* (Blackman et al. 2010). The domesticated allele of *HaFT1* contains a frame-shifting mutation that results in a polypeptide that is 17 amino acids longer than the wild allele. Although both *HaFT1* alleles are expressed under LD and SD, a second unlinked *FT* paralog (*HaFT4*, which stimulates flowering, like the *A. thaliana FT*) is expressed only under LD. The domesticated long-form *HaFT1* acts as a dominant negative suppressor of *HaFT4* and thereby delays flowering in plants with the domesticated *HaFT1* allele. Here, G × E is affected via an environmentally insensitive allelic variant that modifies function at a second, environmentally sensitive locus, a fascinating case of environment-dependent molecular epistasis.

Several natural variants affecting seedling emergence and flowering time have been identified in the light receptor proteins of *A. thaliana*. All of these studies represent differential sensitivity to the light environment and do not involve differences in transcriptional regulation of the causal genes. In most *A. thaliana* accessions, the blue-light receptor CRY2 is quickly degraded by light, thus preventing it from signaling downstream effectors of flowering. CRY2 in the Cape Verde Islands (CVI) accession contains a single protein-stabilizing amino acid substitution that causes the protein to resist degradation by light and therefore continues to activate downstream genes (El-Din El-Assal et al. 2001). The net result is early flowering under short days; most *A. thaliana* accessions flower most quickly under long days. A similar situation is seen in the *A. thaliana* far-red light receptor PHY-A, which is generally expressed in the dark and signals for hypocotyl elongation associated with seedling emergence through the soil surface. PHY-A is rapidly degraded when the seedling emerges to light and subsequently switches to photoautotrophic growth. Maloof and colleagues identified a single naturally occurring amino acid substitution in a conserved residue causing increased protein stability and reduced degradation in the light (Maloof et al. 2001). The red-light receptor PHY-B also has a natural amino acid variant affecting seedling elongation under variable light conditions, in this case owing to modified protein-protein interaction (Filiault et al. 2008). SD flowering in the Fr-2 accession is caused, in part, by a nonsense substitution creating a premature stop codon in the red-light receptor PHY-C. A survey of geographically diverse genotypes suggests that functional variation at PHY-C drives variation in SD flowering across a latitudinal cline (Balasubramanian et al. 2006).

Interestingly, a number of physiological studies have documented strong negative genetic correlations between flowering time and measures of gas exchange physiology, including whole-plant water-use efficiency (WUE), in *A. thaliana* (Christman et al. 2008, Juenger et al. 2005, McKay et al. 2003). Early flowering accessions exhibit low WUE and late flowering accessions display high WUE, possibly as a result of antagonistic pleiotropy at genes of major effect (Lovell et al. 2013, McKay et al. 2003).

Several examples of G × E for cellular responses to soil and water availability have also been identified. Brevis Radix (BRX) is an *A. thaliana* transcription factor involved in the hormonal control of root elongation (Mouchel et al. 2004). Natural mutations in the coding sequence of BRX lead to hypofunctional protein, allowing plants to grow on acidic soils via a complex mechanism involving hyperactive proton pumps (Gujas et al. 2012). Because BRX is also essential for normal root elongation, these acid-tolerant genotypes have generally shorter root systems. Interestingly,

this results in a possible trade-off for fitness because the shorter root systems of hypomorphic BRX plants perform poorly in high-competition environments, perhaps owing to competition for limited soil resources (Shindo et al. 2008).

Although most rice (*Oryza sativa*) varieties cannot tolerate complete submergence, cultivated rice is often grown in fields prone to heavy flooding. Flooded rice plants elongate their stems and senesce leaves and, thus, have poor yield if they survive receding floodwaters. The *Sub1A* gene encodes a transcription factor that suppresses this elongation response, maintains sugar reserves, and activates scavenging pathways that reduce cellular damage following re-exposure to atmospheric oxygen (Xu et al. 2006). Most natural and cultivated rice varieties lack this gene entirely and rarely survive prolonged flooding. In *O. sativa* varieties with the *Sub1A* gene, only alleles with submergence-induced expression confer high flooding tolerance (Xu et al. 2006). Interestingly, functional Sub1A expression also confers higher drought and osmotic stress tolerance (Fukao et al. 2011), possibly suggesting that this allele evolved in climates with unpredictable but occasionally heavy rainfall. Because Sub1A does not appear to have deleterious effects in the absence of drought or flooding stress (e.g., exhibits conditional neutrality for yield), the locus has been widely introgressed into elite rice cultivars throughout Southeast Asia (Bailey-Serres et al. 2010). This is an outstanding example of the critical importance of G×E effect architecture in the breeding of abiotic stress tolerance crops.

Many plants respond to water deficit and dehydration by adjusting their leaf osmotic potential and by synthesizing molecules that protect cells from dehydration damage. Inducible biosynthesis of the amino acid proline is thought to be involved in osmotic and redox regulation under stress. Kesari et al. (2012) identified abundant natural variation in *A. thaliana* proline content in response to low water potential. The genetic basis of this functional variation was shown to be a naturally occurring splice variant in a key proline biosynthetic enzyme, Δ^1-pyrroline-5-carboxylate synthase (P5CS1), that results in lower protein abundance and thus lower proline induction. The frequency of this splice variant, and the abundance of proline accumulation in response to low water potential, is correlated with several climate variables across the native range of *A. thaliana*. Moreover, the presence of an elevated ratio of nonsynonymous to synonymous substitutions, extended haplotype structure, and elevated F_{ST} all suggest that diversifying natural selection may have shaped the history of P5CS1, perhaps leading to local adaptation through differential sensitivity.

G×E in enzyme function has also been observed at the *adenosine 5′-phosphosulfate reductase* (*APR2*) locus, which encodes an isoform of a sulfate reduction enzyme. A single amino acid substitution observed in the *A. thaliana* Sha accession creates a significantly lower-functioning enzyme and causes much higher accumulation of sulfate in vegetative tissue (Loudet et al. 2007). Here, genetic variation only affects the trait in low-nitrogen environments because APR2 is expressed at sufficient levels in high-nitrogen environments to compensate for the poor enzymatic function of the Sha allele.

G×E is Caused by Diverse Genes and Molecular Variants

Although there are too few examples of cloned G×E genes to broadly generalize, several themes are evident. The first theme, echoing findings at the whole-transcriptome level, is that many different kinds of genes are involved in G×E. Earlier workers speculated that G×E might be driven by variation in proteins that were directly responsible for sensing environmental cues or in their direct signal transducers; such genes are important drivers of G×E, but many other types of genes play a role as well. The second general theme is that many kinds of mutation underlie G×E. A third generalization is that many mutations driving G×E appear to be rare and/or result in loss of or reduced function, though reliance on QTLs and candidate gene approaches has

undoubtedly created an incomplete picture. The limited power of QTL studies to detect small-effect and epistatically interacting genes, plus the incredibly time-consuming prospect of fine-mapping and cloning genes, means that only the largest effect mutants for a few charismatic traits have been cloned. For example, the repeated identification of orthologs of FT as a key component of flowering time variation may reflect phylogenetic conservation in this essential pathway, or it may reflect the tendency of researchers to invest in the most obvious and largest-effect loci.

PERSPECTIVES

Plants are remarkable in their ability to respond to the environment. A longstanding challenge in plant biology has been to better understand the proximate and ultimate mechanisms behind these responses. Our review suggests that G × E is common at both the QTL and gene expression levels and is primarily driven by differential sensitivity of alleles. At the molecular level, a variety of natural variants and mechanisms have been implicated including nonsynonymous changes in receptor proteins (PhyB, Cry2), loss-of-function mutations in transcriptional repressors (FRI, FLC), splicing variants in biosynthetic enzymes (P5CS1), and gene duplication in transcription factors (Sub1A) to name but a few. Nevertheless, additional studies are still needed to clarify the relative importance of different types of genes, mutations, and molecular mechanisms in G × E.

One interpretation of our survey is that antagonistic pleiotropy across environments may be a relatively rare driver of G × E with potential implications for local adaptation and breeding; however, this is perhaps an oversimplified view given the limited dimensionality of the experimental work to date. The vast majority of the studies we reviewed contrast simple pairs of manipulated environments, and our summary was restricted to a trait-by-trait evaluation. Moreover, the vast majority of QTL and expression studies focus on linear models and additive effects, investigate relatively few traits, and may be underpowered. Intriguingly, our examples of cloned QTLs more frequently implicated trade-offs and complexity, including the observation of pleiotropic traits (e.g., flowering time and WUE; FLC and FRI), sign changes across environments (e.g., acid soil versus competition; BRX), or environmentally dependent molecular epistasis (HaFT1 and HaFT4). Different patterns may arise with more realistic environmental gradients, with statistical models allowing for epistasis, or through detailed exploration of the impact of phenotypic plasticity for sets of functionally related traits. Multidimensional analyses of data from genomic screens of transcript, protein, or metabolite profiles may thus provide some of the first insights into the integrated structure of plastic responses and a better understanding of constraints (Walsh & Blows 2009).

SUMMARY POINTS

1. Genomic studies of natural variation point to the frequent occurrence of G × E for a variety of quantitative phenotypes.
2. The predominant genetic architecture underlying G × E is differential sensitivity. However, a rigorous evaluation of the prevalence of effect architectures is hampered by statistical issues, problems with data reporting, and inconsistencies in analysis methods. We encourage researchers to conscientiously report information relevant to G × E (e.g., QTL confidence intervals, standard errors of effects, effect estimates in all environments, and descriptive statistics for each trait); this will permit future meta-analyses that provide better insight into broad patterns of G × E.

3. Our analysis uncovered a striking relationship between the magnitude of QTL × E for a trait, which we call QTL effect plasticity, and the overall plasticity of that trait. Highly plastic traits are associated with QTLs that exhibit greater G × E. The evolutionary importance of this pattern is unknown, but perhaps suggests an intrinsic relationship between mechanisms generating variation at both the genetic and phenotypic levels.
4. Genome-wide transcriptome and eQTL studies provide an exciting avenue for studying a large number of phenotypes and evaluating the role of *cis* and *trans* mechanisms in G × E, although plant studies are still rare. Especially promising are tests for the occurrence of master regulators or G × E hot spots and enrichment analyses comparing particular pathways, gene classes, or molecular functions across environments.
5. Cloning G × E QTLs is challenging, and currently only a handful of published studies are based on rigorous validation. These studies report a surprising diversity of genes and functions underlying G × E. The most prominent patterns include the apparent preponderance of loss-of-function mutations, amino-acid changes in receptors, and several indications of antagonistic trade-off.

FUTURE DIRECTIONS

1. Local adaptation can be viewed as fitness G × E across habitats. Cloning genes involved in local adaptation is technically challenging but will be exceedingly valuable for moving the field forward. These efforts will provide much needed insight into the molecular causes of G × E as well as enable population genetic analyses of alleles of known function across relevant spatial, environmental, and temporal scales. Inferring the genome-wide occurrence of alternative effect architectures based on allele frequency changes and response to natural selection in the field is an especially promising approach (for an example, see Anderson et al. 2013).
2. Future studies should consider the influence and impact of mating system and population structure on effect architecture, G × E, and local adaptation. For example, one might expect conditionally neutral/beneficial alleles to easily spread and become fixed in outcrossers because of high gene flow, whereas antagonistically pleiotropic alleles may remain spatially restricted and polymorphic because of fitness trade-offs (Anderson et al. 2013, Colautti et al. 2012). This phenomenon could be one explanation for the high degree of differential sensitivity detected in our review, which focused predominantly on selfing model systems and crops.
3. Costs of phenotypic plasticity are often envisioned, but their mechanistic origin is largely unknown. Functional studies of cloned G × E genes, especially those involved in local adaptation, should help to determine the prevalence of genetically variable costs when they occur and possibly provide insight into strategies to minimize costs in agronomic settings.

4. Adaptive phenotypic plasticity involves accurate detection and assessment of environmental cues, often allowing for the prediction of future conditions. The resulting physiological priming and acclimation is poorly understood in plants, but may involve epigenetic-based integration and memory of signals from receptors and signaling cascades. Epigenetic modifications such as DNA methylation, chromatin modification, and chromatin remodeling may play a role in this critical phenomenon and are as yet unstudied in most natural systems.
5. There is a growing concern for the ability of plants to adapt to rapidly changing climate conditions, both in terms of the conservation of natural populations and the continued success of crop yields. Landscape genetics and climate association mapping methods will likely become important tools for understanding evolution in these changing environments. Incorporating a firm notion of G × E and plasticity in these analyses should help better determine the role of adaptive plasticity in the evolution of the abiotic niche.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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