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WHY ONTOGENY MATTERS DURING ADAPTATION: DEVELOPMENTAL NICHE CONSTRUCTION AND PLEIOTORPY ACROSS THE LIFE CYCLE IN *ARABIDOPSIS THALIANA*

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This case study of adaptation in *Arabidopsis thaliana* shows that natural selection on early life stages can be intense and can influence the evolution of subsequent traits. Two mechanisms contribute to this influence: pleiotropy across developmental stages and developmental niche construction. Examples are given of pleiotropy of environmentally cued development across life stages, and potential ways that pleiotropy can be relieved are discussed. In addition, this case study demonstrates how the timing of prior developmental transitions determines the seasonal environment experienced subsequently, and that such developmental niche construction alters phenotypic expression of subsequent traits, the expression of genetic variation of those traits, and natural selection on those traits and alleles associated with them. As such, developmental niche construction modifies pleiotropic relationships across the life cycle in ways that influence the dynamics of adaptation. Understanding the genetic basis of life-cycle variation therefore requires consideration of environmental effects on pleiotropy.

KEY WORDS: Colonization, gene duplication, genetic correlations, life history, niche construction, ontogeny, phenology, pleiotropy.

Natural selection occurs over the entire life cycle of an organism, and that life cycle unfolds within a sequence of seasonal environmental change. The timing of prior developmental transitions therefore determines the seasonal environment experienced by subsequent life stages. Moreover, selection at prior life stages alters the genetic environment against which subsequent life stages are selected, especially when pleiotropy is present such that genes regulating prior life stages also regulate subsequent stages. The precedence of expression of one life stage before another can therefore influence adaptation across the life cycle.

Niche construction refers to the ability of organisms to alter the environment they experience (Odling-Smee et al. 1996, 2003; Laland et al. 1999; Day et al. 2003). Niche construction through environmental cuing of development ("developmental niche construction") occurs when cued developmental transitions determine the environment experienced by subsequent life stages. Developmental niche construction influences not only exposure to seasonal environments of natural selection but also genetic expression. Because of genotype–environment interaction, niche construction can magnify or mask genetic differences. As such, it can also alter the magnitude of pleiotropy. Given the central role of pleiotropy and genetic correlations in adaptive dynamics, it is important to understand not only the genetic basis of pleiotropy but also its environmental basis. Developmental niche construction can be a major determinant of that environmental basis.

Using *Arabidopsis thaliana* as a case study, this review of research from our lab explores how natural selection on prior life stages can influence the evolution of subsequent life stages because of pleiotropy and because prior life stages determine the environment experienced subsequently via developmental niche

construction. We ask the following: (1) To what extent is selection on early life stages a selective filter? Regarding how prior life stages influence the genetic environment of subsequent stages, (2) what is the extent of pleiotropy in environmentally cued development across life stages, and what are some potential mechanisms to relieve pleiotropy across the life cycle? Regarding how prior life stages influence the ecological environment of subsequent stages, (3) how does environmentally cued development result in niche construction? Finally, (4) how does developmental niche construction influence adaptation and pleiotropy across the life cycle? This review shows that selection at early developmental stages—specifically the seed stage—can be an extremely strong, if frequently invisible, selective sieve. Such selection is expected to influence later life stages via extensive pleiotropy across life stages, which has been discovered recently, and because developmental niche construction alters the expression of allelic effects and natural selection on life-history alleles. Such niche construction can even modify pleiotropy across life stages to such an extent that a single gene acting early in life influences the entire life cycle. Thus, the ontogenetic context of selection has important consequences for predicting adaptive outcomes because of developmental niche construction and its effects on pleiotropy.

GENERAL PRINCIPLES: EVOLUTION OF PRIOR STAGES CAN INFLUENCE ADAPTATION AT LATER STAGES

Ramifying effects of prior natural selection on subsequent adaptation occur in three ways: reduction of population size, genetic linkage across life stages, and niche construction (Fig. 1).

First, in non-density-regulated populations, selective elimination of individuals can reduce population size, reducing the efficacy of natural selection and increasing the influence of random genetic drift (e.g., Wright 1931; Brussard 1974; Jensen and Bachtrog 2011). Thus, natural selection that occurs at prior stages via the elimination of maladapted individuals can impede adaptation at subsequent stages by reducing the size of the remaining population. A number of organisms produce abundant offspring, only a small proportion of which survive to establish. Impressive displays of pelagic larvae, insect eggs, or drifts of seeds are reduced to much more modest adult population sizes. If such reduction in juvenile population sizes is not random, but selective, then natural selection has great opportunity especially at early life stages.

Second, genetic linkage across life stages influences the dynamics of adaptation across the life cycle. When traits expressed early and later in development are genetically correlated, selection on early traits causes correlated selection on later traits (Lande 1979; Lande and Arnold 1983; Atchley 1984; Wagner 1988) in either an adaptive or maladaptive direction (Wagner 1995; Crespi 2000; Wagner et al. 2008). Genetic correlations can be caused by pleiotropy, physical linkage, or correlational selection and/or population structure that causes linkage disequilbrium. Pleiotropy is the most persistent cause of genetic correlations, because it does not degrade with recombination over successive generations, and has long been considered to be a major constraint on adaptive evolution (Fisher 1958; Barton 1990; Crespi 2000; Orr 2000; Griswold and Whitlock 2003). What is interesting here is that early traits are often exposed to selection before later traits, so that direct selection on early traits (and indirect selection on later traits) will occur before direct selection on later traits. This temporal component of direct versus indirect selection can make a difference when an episode of selection alters allele frequencies and consequently genetic variances.

Third, niche construction by prior life stages influences adaptation of subsequent stages. Niche construction occurs when attributes of organisms alter the environment that they experience (Odling-Smee et al. 1996, 2003; Laland et al. 1999; Day et al. 2003). It occurs through diverse mechanisms in both animals and plants, including direct environmental modification (building of structures such as nests, dams, etc.); addition or depletion of resources or secondary compounds; and habitat selection via mobility, modifications of morphology, or phenology. Because prior life stages can determine the environment experienced by subsequent stages, they can determine the phenotypic expression of later stages, the expression of genetic variation, and the environment of natural selection (Donohue 2005). Moreover, when niche construction influences the expression of genetic variation, it can make evolutionary responses to selection more sustained by releasing genetic variation under the evolved environment, or dampen evolutionary responses by masking genetic variation under the evolved environment (Donohue 2009). Niche construction by prior life stages therefore has the potential to influence genetic parameters and the evolutionary dynamics of subsequent stages.

The timing of biological events—frequently developmental events—is termed phenology. Environmentally cued phenology results in developmental transitions occurring only under specific environmental conditions. The timing of the development of prior stages therefore determines the seasonal environment experienced by later stages (Donohue 2003, 2005). As such, phenological cueing can be considered "developmental niche construction," a very general phenomenon that is likely to be manifest in any organism that develops in the wild under seasonally variable conditions in which the environment changes in a predictable manner over the course of development. For example, the timing of seed germination determines the seasonal conditions experienced by seedlings and adults; in insects, amphibians, and reptiles, the timing of hatch-out likewise sets the seasonal conditions experienced as adults.

To understand how adaptation of prior life stages influences adaption at subsequent stages, we need to know the intensity of

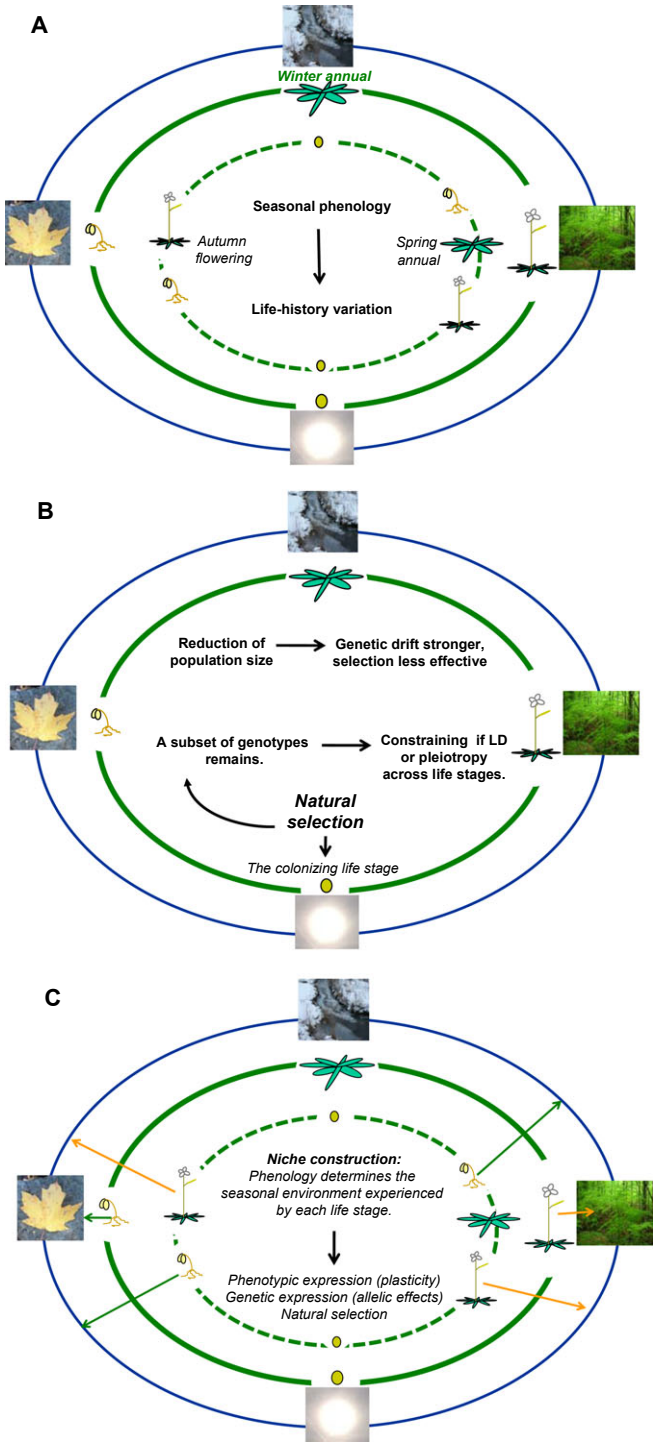

Figure 1. How might adaptation of prior life stages influence adaptation of subsequent life stages? (A) Development under natural seasonal conditions: the timing of developmental transitions over the course of the seasons determines the life history that is expressed. In winter annuals, seeds germinate in autumn and plants flower in spring. In spring annuals, seeds germination in spring and plants flower that same spring. In the autumn-flowering life cycle, seeds germinate in autumn, and plants flower that same autumn. (B) Demographic and genetic constraints of selection on prior life stages: natural selection on prior life stages can reduce population size at later stages, making drift stronger and selection less efficient. It also changes allele frequencies at genes under selection at early life stages. If those alleles exhibit linkage disequilbrium with alleles controlling later life stages (via population structure, physical linkage, or pleiotropy), selection at early stages can cause correlated selection at later stages. (C) Niche construction by prior life stages. The timing of the transition from one life stage to the next determines the seasonal environment experienced by the subsequent life stage (indicated by arrows). This environment can influence phenotypic expression, the expression of genetic variation, and natural selection on the subsequent life stage.

selection on prior stages, the degree of genetic correlations, and especially pleiotropy, across life stages, how prior life stages determine the environment experienced subsequently, and how that environment alters pleiotropy and thereby evolutionary dynamics.

PRIOR DEVELOPMENTAL STAGES AS A SELECTIVE FILTER

Early stages need to survive in order for subsequent stages even to be expressed. In plants, seeds are frequently the first to experience a novel environment after long-distance dispersal. As such, seeds can act as a selective filter. How intense is selection on this earliest stage, and does selective elimination at early life stages compromise adaptation at subsequent stages?

Studies in *A. thaliana* have found evidence of local adaptation and natural selection on seed properties—especially germination traits. Montesinos et al. (2012) found in glacial refugial populations on the Iberian Peninsula that populations from locations with hotter summers were more strongly induced into dormancy by hot temperature, which suggests dormancy is adaptive under conditions of summer drought. Molecular evidence for adaptation of dormancy was recently provided by Kronholm et al. (2012), who showed that alleles at a major dormancy locus, *Delay Of Germination 1* (*DOG1*), in European populations were distributed such that alleles associated with higher dormancy were found in more arid locations. Geographic variation in *DOG1* expression level is also consistent with a cline in dormancy, such that *DOG1* expression and seed dormancy are both higher in southern ecotypes (Chiang et al. 2011). Combined, these results suggest that dormancy is necessary to prevent germination before summer drought conditions, although this hypothesis has not been tested directly in the field in native populations.

Direct measures of natural selection on dormancy in diverse species verify that dormancy can be under strong natural selection (reviewed in Donohue et al. 2010). In *A. thaliana*, natural selection on the timing of germination was exceptionally strong (Donohue et al. 2005b), resulting in the near fixation within a single generation of alleles associated with delayed germination (Huang et al. 2010; Fig. 2). These alleles were linked to quantitative trait loci (QTLs) for dormancy, and were located near the genes *DOG1* and *DOG6* (*Delay Of Germination 6*, at present still unidentified; Alonso-Blanco et al. 2003; Bentsink et al. 2006, 2010). Thus, genetic variation associated with variation in germination timing can be depleted by selection extremely quickly, changing allele frequencies of the surviving population.

In this experiment, selection at the germination stage reduced sample sizes considerably, and selection on post-germination stages was much weaker than selection on germination (Donohue et al. 2005a). Moreover, the strength and mode of selection on post-germination traits depended on the timing of seed germination (see also Donohue 2001), as did the expression of quantitative-genetic variation for post-germination traits. The prior developmental transition of germination did alter selection and the expression of genetic variation on traits expressed subsequently, indicating that at least in this experimental colonization event, prior life stages can influence the evolutionary dynamics of subsequent life stages.

It is important to realize that strong selective sieves that alter adaptation of subsequent life stages can occur at any developmental stage. Thus, "prior" life stages with respect to natural selection need not be early stages developmentally. Selective elimination of maladapted genotypes at the colonizing stage is probably a frequent, if invisible, occurrence. Colonizing life stages, such as seeds as in the above example, would experience novel selective environment first, yet in other organisms larval stages, juveniles, or adults may be the colonizing life stage. Similarly, when environmental change occurs in situ via temporal environmental change, which life stage experiences a novel environmental challenge (and thereby intense natural selection) first depends on when the environmental challenge occurs within the life cycle. For instance, if climate change is expected to alter spring temperatures more than summer temperatures, then life stages occurring in spring (e.g., early life stages such as seedlings or larvae) would be exposed to the novel selective environment; but if summer drought is expected to be the major new environmental challenge, then more mature stages (e.g., vegetative or reproductive plants, pupae, metamorphic amphibians) would be the first to be exposed to novel selection. In novel environments or extreme climatic events, selection at any stage can occur episodically and with great intensity, as shown in taxa as diverse as plants, invertebrates, and birds (e.g., Bumpus 1898; Boag and Grant 1981; Seeley 1986; Brown and Brown 1998). When this occurs, selection occurring within a single generation on a particular life stage can cause correlated selection of subsequent stages, within and across generations, and can influence the evolutionary potential for adaptation at subsequent stages by leaving only a subset of genotypes available for natural selection to act on.

A future challenge that is becoming increasingly more feasible is to identify loci under natural selection at different life stages, and to quantify changes in allele frequencies caused by stage-specific selection. Such studies can be conducted within the context of colonization dynamics or different scenarios of environmental change, and can thereby determine which life stages are under the most intense natural selection, which experience the greatest changes in allele frequencies, and whether those alleles also influence phenotypes and fitness at subsequent life stages.

PLEIOTROPY ACROSS LIFE STAGES

How strongly selection at prior stages constrains adaptation at subsequent life stages depends on how quickly allele frequencies change in response to selection (which can be extremely rapid,

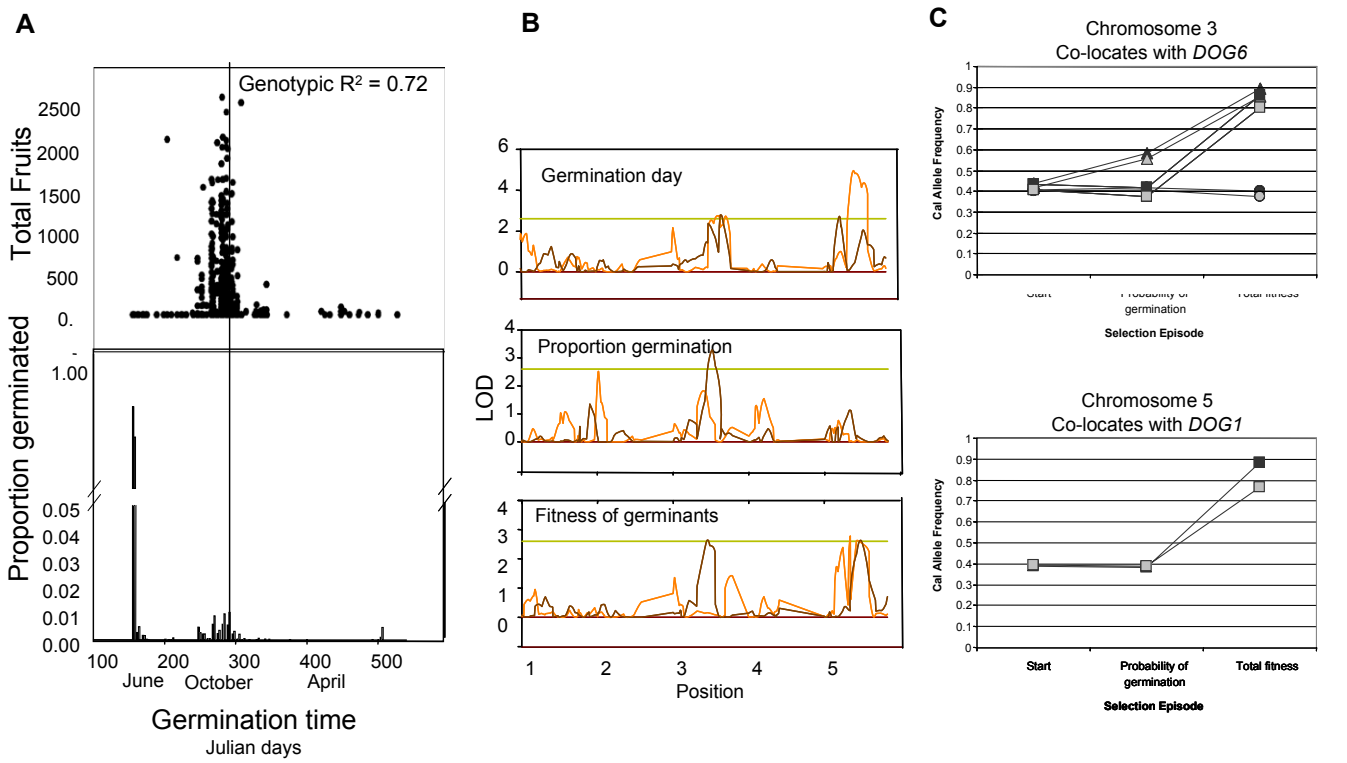

Figure 2. **Intense stabilizing natural selection on germination timing caused alleles associated with germination timing to approach fixation within a single generation. Results are from Donohue et al. (2005b; seeds dispersed in Kentucky during June). (A) The lower panel shows the proportion of seeds that were dispersed in the field (the y-axis) that germinated over the course of the experiment (the x-axis). The upper panel shows the number of siliques produced by seeds that germinated at the time indicated in the lower panel. Genotypic R^2 is the proportion of variance in fitness among recombinant inbred genotypes that was explained by germination timing. (B) Results of QTL analysis of germination timing (upper), proportion of seeds that germinated (middle), and total lifetime fitness measured as the number of siliques (lower). Logarithm of the odds (LOD) scores show the strength of the relationship between the marker at each position along the five chromosomes of *Arabidopsis thaliana* (the x-axis) and the phenotype. LOD scores are shown for seeds matured under short days (dark line) and long days (pale line), although results did not differ significantly between these treatments. The horizontal line indicates the threshold significance LOD score. QTLs for germination timing and germination proportion colocated with QTLs for fitness. C, change in allele frequency of markers associated with germination timing throughout the course of the experiment. Starting allele frequencies of dispersed seeds were below 0.5, and this frequency did not change for seeds that germinated. After selection on those germinants, allele frequencies approached fixation. Upper panel is for the QTL on Chromosome 3, which colocated with the known dormancy QTL called *Delay Of Germination 6* (*DOG6*). Lower panel is for the QTL on Chromosome 5, which colocated with the known dormancy QTL called *Delay Of Germination 1* (*DOG1*). Figures adapted from Donohue et al. (2005b) and Huang et al. (2010).**

as the above example shows), how tightly correlated they are to traits at subsequent stages, and how quickly such genetic correlations degrade with recombination. Of the different contributions to genetic correlations, pleiotropy is the most enduring. Understanding pleiotropy across life stages is therefore crucial for predicting ramifying consequences of natural selection at prior life stages.

Pleiotropy across life stages is expected, because the same trait may be expressed over the course of development, and different developmental transitions may require similar signaling and resource mobilization pathways. Recent work has provided evidence that environmentally cued developmental transitions that occur at different life stages share genes and genetic pathways (or at least portions of them). Among the best-studied examples in this regard in plants are genes involved in the regulation of flowering and seed germination.

Increasing evidence is accruing that genes involved in the environmental regulation of the transition to flowering are also involved in seed germination. These include genes in the pathways that sense photoperiod and light quality, temperature, and winter chilling. One of the best known examples are the phytochromes—plant photoreceptors that perceive red and far-red light—that are involved in germination, shade-avoidance responses such as elongation, and the regulation of flowering in response to photoperiod and light quality (Casal and Sanchez 1998; Casal et al. 2003). In the Brassicaceae, which includes *A. thaliana*, phytochrome apoproteins are encoded by five genes

that differ in both coding and regulatory sequences (Sharrock and Quail 1989; Clack et al. 1994; Mathews and Sharrock 1997), and most plant families have multiple phytochrome copies. The diversification of phytochrome copies and their involvement in multiple developmental transitions has been the subject of extensive study and numerous reviews (e.g., Casal and Sanchez 1998; Casal et al. 2003), and the phytochromes are one of the best examples of how one process of environmental cuing—light-quality perception—has been applied to regulate development across the life cycle. Despite the duplication and diversification of phytochrome genes, a given phytochrome can regulate both flowering and germination, thereby exhibiting pleiotropy.

During the transition to flowering, phytochromes act through the pathway regulating the biological clock. Genes in the clock pathway have now been shown to be involved in germination (Salome et al. 2008; Penfield and Hall 2009). Genes in other flowering pathways have also been implicated in germination, including the "autonomous pathway" that regulates flowering responses to various environmental factors such as nutrients and ambient temperature (Jiang et al. 2012), and the "vernalization pathway" that regulates flowering responses to chilling (Liu et al. 2011). It therefore appears that genes involved in environmental sensing and the regulation of developmental transitions in response to environmental inputs operate at multiple stages across the life cycle.

Downstream of genetic pathways of environmental perception are the genes that integrate these environmental cues to regulate developmental transitions. A major floral integrator in *A. thaliana* is *Flowering Locus C* (*FLC*), a MADS-box transcriptional factor that integrates cues from the autonomous and vernalization pathways as well as the gene *FRIGIDA* (Sung and Amasino 2004; Michaels et al. 2005; Shindo et al. 2005). Vernalization (chilling) stimulates flowering by epigenetically silencing *FLC* via chromatin remodeling (Michaels and Amasino 1999, 2001; Shindo et al. 2006). Natural allelic variants of *FLC* are associated with natural variation in flowering time, and variation in *FLC* expression predicts geographic variation in flowering time (Caicedo et al. 2004; Shindo et al. 2006). Therefore, *FLC* expression is hypothesized to be subject to geographically variable natural selection via its effect on flowering time.

Chiang et al. (2009) showed that *FLC* also regulates seed germination (Fig. 3). Natural and transgenic alleles with higher *FLC* expression exhibited higher germination percentages, especially at cool temperature and under autumn field conditions. *FLC* expression cycles in a manner that predicts dormancy state in seeds under field conditions (Footitt et al. 2011), and *FLC* expression at the rosette stage (Shindo et al. 2006) is significantly positively associated with natural variation in germination at cool temperature (Chiang et al. 2009). A recent GWAS also identified *FLC* as a QTL for germination (Atwell et al. 2010). Therefore, the integrator *FLC* pleiotropically regulates both flowering and germination.

One important question is how extensive is the pleiotropy across flowering and germination pathways. Although environmental sensing pathways seem to be shared across life stages, and the major integrator of these pathways—*FLC*—is also shared, how much of the downstream *FLC*-flowering pathway is also employed to regulate germination? In the flowering pathway, *FLC* represses the genes *FT* and *SOC1*, causing low expression of *AP1* and consequently inhibiting flowering (Fig. 3; Mandel and Yanofsky 1995; Ausin et al. 2005; Helliwell et al 2006). Chiang et al. (2009) found evidence of a shared pathway between flowering and germination. Mutants of *FT*, *SOC1*, and *AP1* mutants all showed significantly higher germination at cool temperature compared to the wild type, and *AP1*, *FT*, and *SOC1* were downregulated in a high-*FLC*-expressing NIL late during silique development compared to its weak *FLC* background L*er*. This is precisely what is expected if these components of the *FLC* flowering pathway are also involved in germination regulation. *FLC* regulation of germination subsequently occurs through the pathway of ABA degradation and GA synthesis (Chiang et al. 2009), the major hormones that promote dormancy and germination, respectively.

In sum, shared pathways of flowering and germination occur, with genes involved in environmentally cued development shared across life stages, and with *FLC*-mediation of germination acting through *FT*, *SOC1*, and *AP1* and subsequently through hormonal pathways. Identifying where the pathways of flowering and germination regulation diverge would contribute significantly to our understanding of the genetic basis of pleiotropy and the importance of pleiotropy as a constraint on adaptive phenotypic expression across the life cycle.

The association between *FLC* variation and germination revises our expectations of natural selection on *FLC* and our interpretation of the geographic distribution of *FLC* variation. In a recent field study that compared germination, flowering, and fitness of lines with different *FLC* alleles, Chiang et al. (2012) found that NILs containing alleles with high *FLC* expression had higher germination proportions, but these lines did not differ in flowering time or in fitness after the germination stage. Therefore, geographic patterns of the distribution of *FLC* alleles may be just as likely, if not more likely, to be determined by selection acting at the seed stage as the flowering stage. Under conditions in which *FLC* does influence flowering time, selection on germination is expected to influence flowering time expressed by the remaining population. Such hypotheses could be tested with field studies of diverse *FLC* alleles conducted across a geographic range, starting with the seed stage.

This example suggests some interesting avenues for future research on the genetic basis and adaptive consequences of

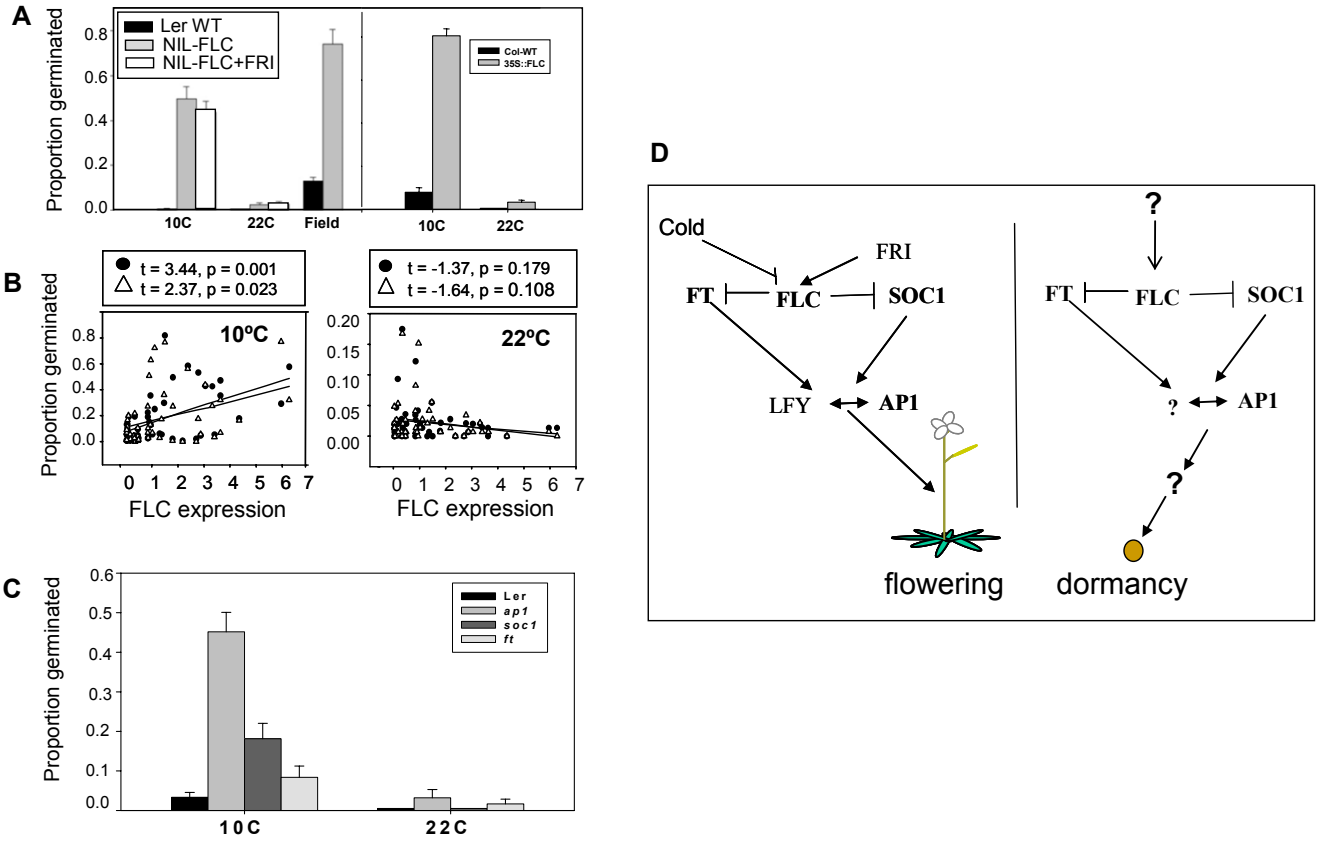

Figure 3. ***Flowering Locus C* (*FLC*) pleiotropically regulates flowering and germination. (A) Lines with higher *FLC* expression (NIL-FLC and NIL-FLC+FRI) had higher germination than the low-expressing background (Ler-WT) at low temperature (10°C) but not higher temperature (22°C). They also had higher germination in the autumn in the field (NIL-FLC+FRI was not used in the field). A transgenic line with *FLC* overexpression (35S::FLC) also had higher germination at low but not high temperature, causally implicating *FLC* in germination. NIL-FLC, near isogenic line on the Landsberg *erecta* background, with the Cvi allele of FLC introgressed; NIL-FLC+FRI, near isogenic line on the Landsberg *erecta* background, with the Sf2 alleles of *FLC* and *FRI* introgressed. (B) Natural variation in *FLC* expression at the rosette stage, estimated by Shindo et al. (2005), is correlated with germination proportion at low (10°C) but not higher (22°C) temperature. Each dot represents the mean of a given ecotype. Circles indicate that seeds used in germination assays were matured in short days; triangles indicate seeds were matured in long days. The *t*-statistic indicates the strength of the linear relationship between *FLC* expression and germination. (C) Knockouts of genes immediately downstream of FLC in the flowering pathway have higher germination at low (10°C) but not higher (22°C) temperature, revealing parallel pathways of *FLC* regulation of flowering and dormancy. (D) The *FLC*-flowering pathway and inferred *FLC*-germination pathway. Both pathways share common components immediately downstream of *FLC*. We do not know the point at which the pathways diverge farther downstream, nor whether *FLC* is regulated in the same manner during dormancy induction as it is prior to flowering. Figures adapted from Chiang et al. (2009).**

pleiotropy across the life cycle. Given that different life stages likely have different environmental tolerances, one expects that different life-stage transitions would be cued differently by environmental inputs, yet environmental sensing pathways are shared across life stages at least in the example provided here. To what extent are pathways of developmental regulation shared across life stages, and at what point do they diverge? Does pleiotropy occur primarily upstream in environmental sensing pathways; do different life stages use different environmental inputs but shared integrators; does divergence occur primarily downstream of environmental integration? Understanding the extent of pleiotropy across the life cycle and the pathways involved would lead to more precise predictions about how particular alleles are likely to influence fitness and at what life stage, which environmental factors are likely to impose the most intense selection on them, and as a consequence how particular alleles are expected to perform under different environmental scenarios across a geographic range.

NICHE CONSTRUCTION: THE SEASONAL CONTEXT OF DEVELOPMENT

Prior developmental transitions determine the seasonal environment experienced by subsequent life stages, resulting in developmental niche construction. Germination, for example, determines

the seasonal environment experienced by post-germination traits, and this can influence the adaptation of post-germination traits (reviewed in Donohue et al. 2010). In *A. thaliana*, the timing of germination influenced natural selection on flowering time and the expression of genetic variation for flowering time, as discussed earlier. This finding accords with a model of Wilczek et al. (2009), who showed a strong dependence of flowering time on germination time; the timing of germination determined the temperature experienced by rosettes, such that early germination resulted in permissive conditions for autumn flowering, but germination that was delayed even slightly resulted in rosettes experiencing conditions that delayed flowering until spring. What is interesting about this result is that the effects of germination on flowering occur entirely through changes in the environmental conditions experienced by developing rosettes after germination.

Similarly, the timing of flowering influences germination via maternal environmental effects, another general manifestation of developmental niche construction. The timing of flowering determines both the seasonal conditions during seed maturation on the maternal plant and the seasonal conditions experienced by seeds immediately after dispersal.

In *A. thaliana*, maternal temperature effects on germination are strong, such that cool seed-maturation temperature induces strong dormancy and delayed germination (Chiang et al. 2012). These maternal effects on germination ramify across the life cycle (Fig. 5). For a genotype with high dormancy, seed maturation under warm temperatures and dispersal in the spring induced the typical winter-annual life history, with germination in the autumn. In contrast, seed maturation under cool conditions and dispersal in the autumn induced a spring-annual life history, with germination in the spring. Thus, developmental niche construction acting via maternal environmental effects altered the basic life history that was expressed by this genotype, determining whether a winter annual or spring annual life history was expressed.

Maternal effects also altered the expression of allelic variation for genes involved with germination. For example, seed-maturation temperature altered which phytochrome contributed most to germination under field conditions (Donohue et al. 2012). When seeds were matured under warm temperature, *phyA* and *phyE* null plants had the most strongly reduced germination, but when seeds were matured under cool temperature, *phyB* nulls had the most reduced germination. Allelic differences of the gene *DOG1* also depended on maternal effects via both dispersal season and seed-maturation temperature (Fig. 5; Chiang et al. 2012). As an extreme contrast, cool seed-maturation temperature masked effects of *DOG1* allelic variation of June-dispersed seeds, but for autumn-dispersed seeds, cool seed-maturation temperature magnified the effect of the *DOG1* allele so that the high-expressing allele actually had a different life history, germinating in spring instead of autumn.

Because maternal effects influenced the expression of allelic differences, they also influenced natural selection on those alleles. In the case of the phytochromes, selection against *phyA* and *phyE* nulls via their effects on germination occurred for seeds matured under warm conditions but not cool conditions (Donohue et al. 2012). Selection against *phyA* existed even when matured under cool conditions, but not through changes in germination. Thus, maternal effects can alter which life stage that a given gene regulates is subject to natural selection.

Regarding selection on *DOG1* alleles, maternal effects actually imposed balancing selection (Chiang et al. 2012). When seeds were matured under warm conditions and dispersed in spring, delayed germination was favored such that the high-expressing *DOG1* allele had higher fitness. When seeds were matured under cool conditions and dispersed in autumn, accelerated germination was advantageous, so the low-expressing *DOG1* allele was favored.

These results show that developmental niche construction via maternal environmental effects can alter germination timing, the expression of genetic variation for germination timing, and natural selection on specific alleles associated with germination. Therefore, just as germination timing can influence adaptation of post-germination traits such as flowering time, flowering time can influence adaptation of germination. It is important to realize that early developmental stages can be influenced by adult stages in the previous generation. For this reason, adaptive processes need to be considered within the context of the sequence of trait expression both within and across generations.

This example suggests that developmental niche construction is likely to be common and to influence not only selection but also the expression of genetic effects. It would be interesting to know how generally and how precisely the environmental cueing of development determines exposure to important environmental factors in other organisms, and to quantify the degree to which that importance stems from effects on selection or from effects on genetic expression. With such information, we can begin to identify genes involved in controlling exposure to particular environmental factors and make predictions about their adaptive consequences.

THE GENETIC BASIS OF DEVELOPMENTAL NICHE CONSTRUCTION AND PLEIOTROPY ACROSS THE LIFE CYCLE

The genetic basis of environmentally cued development is the genetic basis of developmental niche construction. Organisms must restrict developmental transitions to particular combinations of environmental conditions to match particular life stages to the environmental conditions to which they are adapted. To match a given developmental stage to the appropriate seasonal environment requires precise cuing to multiple environmental

factors simultaneously. What are some potential genetic mechanisms whereby organisms accomplish such precise environmental cuing?

The precise environmental cueing of a single developmental transition: a role for redundancy

Organisms must balance the need to restrict developmental transitions to occur under permissive conditions with the risk that overly strict environmental requirements could prevent development altogether. Frequently, certain environmental conditions can be permissive, provided they occur with complementary environmental conditions. For example, warm, wet conditions might be permissive, but warm, dry conditions may not. Preventing development in all warm conditions might be overly restrictive and prevent development even under favorable conditions. How do organisms modulate their development to occur under the widest range of permissive conditions? First, this requires mechanisms that restrict development from proceeding unless certain combinations of conditions are met; second, it requires mechanisms that permit development to proceed under any suitable combination of environmental conditions.

Environmental requirements for development to proceed can be imposed by environment-dependent gene expression, environment-dependent gene function, or both (West-Eberhard 2003; Bossdorf et al. 2008). Environment-dependent gene expression occurs via several mechanisms, including the interaction between specific transcription factors and particular *cis*-regulatory elements, and chromatin remodeling via methylation or histone modification (reviewed in Aubin-Horth and Renn 2009; Donohue 2012). Posttranscriptional regulation occurs via RNA processing in ways that affect the RNA sequence that is transcribed (alternative splicing) as well as the probability that it is transcribed (via RNA stability determined by interactions with small- or microRNAs; West-Eberhard 2003; Matzke et al 2009). Finally, gene products themselves may be environmentally sensitive, with temperature-dependent kinetic activity or stability, environmentally supplied substrates, or changes in conformation of environmental sensors as in the case of the phytochromes mentioned earlier. Much remains to be discovered concerning the extent of environmental regulation of each of these processes.

Adding together such environmental requirements, either for a single gene or for several genes throughout a developmental pathway, can impose increasingly more restrictive conditions for development to proceed. Each step of regulation imposes a conditional probability of the developmental process occurring, and the final probability is the multiplicative probability of each condition. Combinations of environmental requirements insure that the developmental process occurs only under specific combinations of conditions.

Such combinatorial requirements may effectively restrict development to very specific combinations of conditions, but they do not provide a mechanism whereby more than one combination of environmental factors permit the developmental process. This can be achieved, however, when multiple (environmentally sensitive) pathways contribute to the same developmental process. Each pathway may have its own restrictive combination of environmental requirements, but the developmental process itself can occur under all the appropriate combinations permitted by each of the pathways. Perhaps the most intuitive mechanism that produces such parallel, or redundant, pathways is gene duplication, whereby multiple copies of a given gene contribute to the same developmental process, but each does so under different combinations of environmental conditions.

The duplicated phytochromes offer an example. Although different phytochrome copies contribute to different developmental processes, as mentioned earlier, multiple phytochromes also contribute to the same developmental transition of germination (Heschel et al. 2007, 2008; Donohue et al. 2008). All the phytochromes contribute to germination under some conditions, but the contribution of each phytochrome depends on the particular light (Shinomura et al. 1994; Poppe and Schafer 1997; Shinomura 1997; Ritchie and Gilroy 1998; Hennig et al. 2001, 2002; Koornneef et al. 2002; Holdsworth et al. 2008) and temperature (Heschel et al. 2007, 2008; Donohue et al. 2008) experienced by seeds. In the low-dormancy background line in which these studies have been conducted, germination occurs across a wide range of temperature and light conditions, with different phytochromes promoting germination under different conditions. Natural populations have more restrictive germination conditions, and extensive natural variation has been reported for temperature- and light-dependent germination as well as for phytochrome haplotype. A recent GWAS (Atwell et al. 2010) identified *PHYB* and *PHYD* as QTLs for germination under 22°C and 10°C, respectively.

The specificity of conditions under which each phytochrome contributes to germination is the outcome of differences in gene expression (Quail 1994; Somers and Quail 1995; Goosey et al. 1997; Sharrock and Clack 2002) and differences in environmental sensitivities of their gene products (Kendrick and Spruit 1977; Shinomura et al. 1996; Braslavsky et al. 1997; Clough and Vierstra 1997; Elich and Chory 1997; Casal and Sanchez 1998; Eichenberg et al. 2000). The precise mechanisms whereby different phytochromes contribute to germination under different conditions are not yet known, however. The signal transduction pathway appears to be shared across phytochromes (Oh et al. 2004, 2006, 2009; Penfield et al. 2005), and this pathway subsequently regulates synthesis of and sensitivity to bioactive gibberellins (GA)—important stimulants for germination (Yamaguchi and Kamiya 2000; Holdsworth et al. 2008; Yamaguchi 2008). Even though all phytochromes may act through the same transduction pathway, it

is possible that environmental dependencies of downstream pathway components also contribute to the specificities of particular phytochromes. That is, if a specific phytochrome and a specific downstream gene are both expressed/bioactive under conditions in which the other phytochromes are not, and that downstream component has additional environmental requirements, then its interacting phytochrome would contribute to the final outcome only under those combinations of environmental conditions.

Determining how the architecture of environmental dependencies in signal transduction pathways is translated into environment-dependent phenotypic outcomes will require more study. In the case of the duplicated phytochromes, it is clear that large portions of the signal transduction pathways are conserved while the phytochromes themselves have diverged. Learning where, throughout signal transduction pathways, diversification in environmental sensitivities occurs will provide insights into how organisms are able to regulate their development in response to complex and temporally variable conditions.

Gene duplication, such as the duplicated phytochromes, provides a mechanism whereby a given developmental process can proceed under multiple specific combinations of environmental conditions. How generally gene duplication contributes to the environmental regulation of development is not well known. Evidence exists in diverse taxa for diversification in the regulation of expression of gene copies, which is consistent with divergence in environment-dependent expression of gene copies, although it may also reflect divergence of spatial expression or the evolution of dosage in general (Haberer et al. 2004; Li et al. 2005; Ganko et al. 2007; Edger and Pires 2009; Qian et al. 2010). A small number of examples suggest that diversification of gene copies influences responses to environmental conditions (Goldman et al. 2006; Liu and Adams 2007; Hanada et al. 2008; Zou et al. 2009). Future studies of the diversification of gene expression of duplicated gene copies would be especially interesting if they specifically investigated environment-dependent gene expression coupled with environment-dependent gene activity. This sort of redundancy of environmentally cued developmental pathways, whether through gene duplication or other mechanisms, can therefore restrict development to appropriate environmental conditions, but provide a range of permissive conditions and consequently not be overly restrictive.

It remains to be tested in a general manner the degree to which this sort of genetic redundancy influences the range of environmental conditions under which development can proceed. Comparative studies of taxa with different levels of redundancy, including gene duplication, could be used to ask: How does the degree of redundancy in developmental pathways influence niche specialization (narrow conditions permitting successful development) versus generalist strategies (wide range)? What combination of conditional gene expression and redundancy leads to the optimal environmental range of development? Experimental manipulations of gene expression could directly test how conditional gene expression of specific genes in response to specific environmental cues influences the range of conditions under which development proceeds in an adaptive manner.

Relieving pleiotropy

The above two examples of *FLC*-mediated germination and flowering and phytochrome-mediated development suggest different solutions to the constraint of pleiotropy. Gene duplication, or duplication of genetic pathways more generally, and stage-specific gene expression have the potential to relieve pleiotropy caused by a single gene regulating more than one developmental stage (Fig. 4).

Clearly, pleiotropy can be relieved by gene duplication: literally converting one gene into two or more genes. In the example of duplicated phytochromes, it has been shown that the different phytochrome copies are expressed differentially at different life stages and in different tissues (Quail 1994; Somers and Quail 1995). Thus, diversification of stage/tissue-dependent expression and gene-product activity of duplicated gene copies can result in each copy evolving more specialized function for its specific life stage. Gene duplication has been shown to relieve pleiotropic constraints in anthocyanin pathways, suggesting that it may be a general process whereby adaptively significant pleiotropy can be relieved (Des Marias and Rausher 2008).

Although gene duplication seems a satisfying solution to genetic constraints, more evidence concerning the evolutionary sequence of specialization of gene copies is desirable. In addition to assessing whether gene copies are specialized to a particular developmental stage (subfunctionalization), one can ask whether taxa with fewer gene copies have more pleiotropically constrained development (stronger genetic correlations across life stages) and whether more developmental functions (regulation of more stages) are added with duplication events. To answer these questions requires assessing the degree of pleiotropy—the diversity of gene copy function across development—in taxa with different copy number and within a phylogenetic context. Specifically, quantifying copy number, functional diversity of gene copies, and developmental phenotypes, including the strength of genetic correlations across life stages, in taxa of known phylogenetic relationships would provide information on the temporal patterns of the evolution of gene duplication, phenotypes, and their relationship to one another. Pleiotropy needs to be the object of study.

Another possibility for the relief of pleiotropy is environmental specificity of stage-specific expression. Regulatory elements exist that induce gene expression at specific developmental stages. If stage-specific and environment-specific regulatory elements can be coupled, then it may be possible for

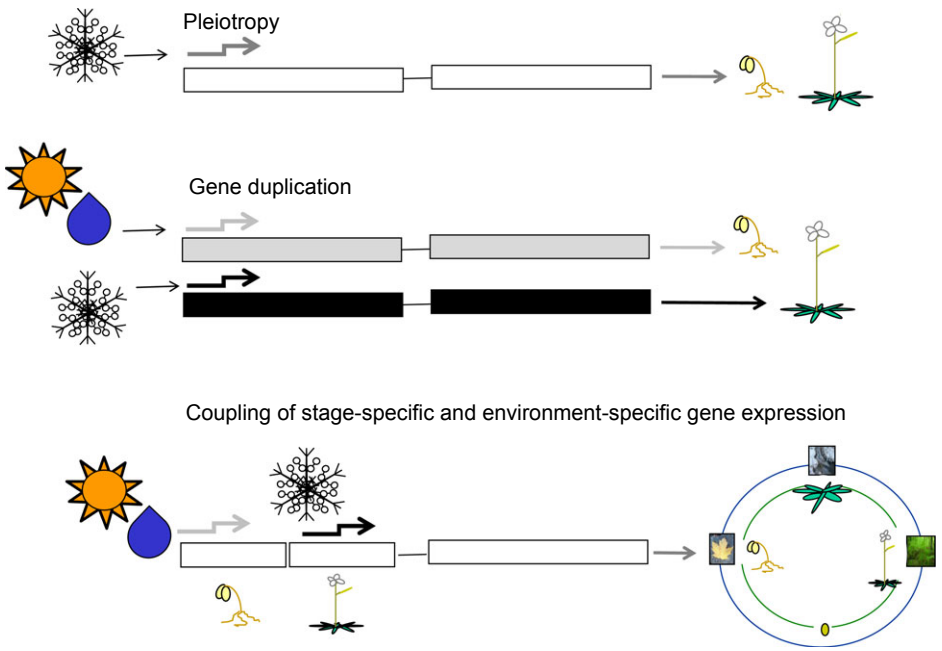

Figure 4. **Relieving pleiotropy. (A) Pleiotropy occurs when one gene controls more than one trait. If that gene is expressed at cold temperature (snowflake), the product will contribute to both traits (germination and flowering in this example) under cold conditions. (B) Gene duplication relieves pleiotropy when gene copies diverge, such that each copy controls a different trait. If environment-dependent expression of the gene copies also diverges, then one copy will contribute to a trait under one set of conditions, whereas the other contributes to a different trait under different conditions. (C) Constraints of pleiotropy can be weakened if trait/stage-specific regulatory elements can be coupled with environment-dependent regulatory elements, such that the different stages have different environmental sensitivities. If such coupling of regulatory elements can occur, then different developmental transitions (germination and flowering) can be triggered in response to different environmental conditions.**

each developmental stage to express independent environmental regulation. In this manner, different developmental stages may evolve their own adaptive environment-dependent expression profiles. Thus, an important question regarding gene regulation is whether environmental sensitivities of a given gene differ across life stages. If so, then the evolution of *cis*-regulatory elements has the potential to relieve pleiotropy across developmental stages.

To test this hypothesis requires first determining the extent to which gene expression at a specific life stage alters phenotypes across the life cycle. Second, if effects of stage-specific expression are confined to a given stage, are the patterns of expression of a given gene genetically correlated across life stages? For instance, *FLC* expression at the rosette stage was significantly correlated with seed germination (Chiang et al. 2009; Fig. 3). We do not know whether that relationship exists because of persistent effects of *FLC* expression at the rosette stage, or because gene expression is correlated between the rosette and seed-maturation stage. Manipulations of gene expression and measurements of genetic correlations of stage-specific expression are necessary to distinguish these possibilities. Finally, does each stage have its unique environmental profiles of expression? For example, does seed-specific expression occur primarily at low temperature whereas rosette-specific expression occurs primarily at high temperature, or do both stages exhibit high expression at low temperature?

Understanding mechanisms of pleiotropy across life stages, and mechanisms whereby pleiotropy can be relieved, is relevant for understanding adaptive developmental trajectories. Environment-dependent gene expression is likely to be central to adaptive ontogeny. For duplicated genes that have diversified with respect to the stage or tissue of gene expression, the evolution of independent environmental sensitivities across stages can occur through evolutionary changes in the expression profiles of each gene. For single genes that are expressed at different stages throughout development, however, the question is how independent are the environmental specificities of gene expression at different life stages.

Niche construction and environmentally induced pleiotropy

With developmental niche construction, genes that regulate developmental timing determine the seasonal conditions of subsequent development, which in turn can affect the expression of subsequent plastic phenotypes. Hence, allelic effects of early developmental genes can potentially ramify across the life cycle,

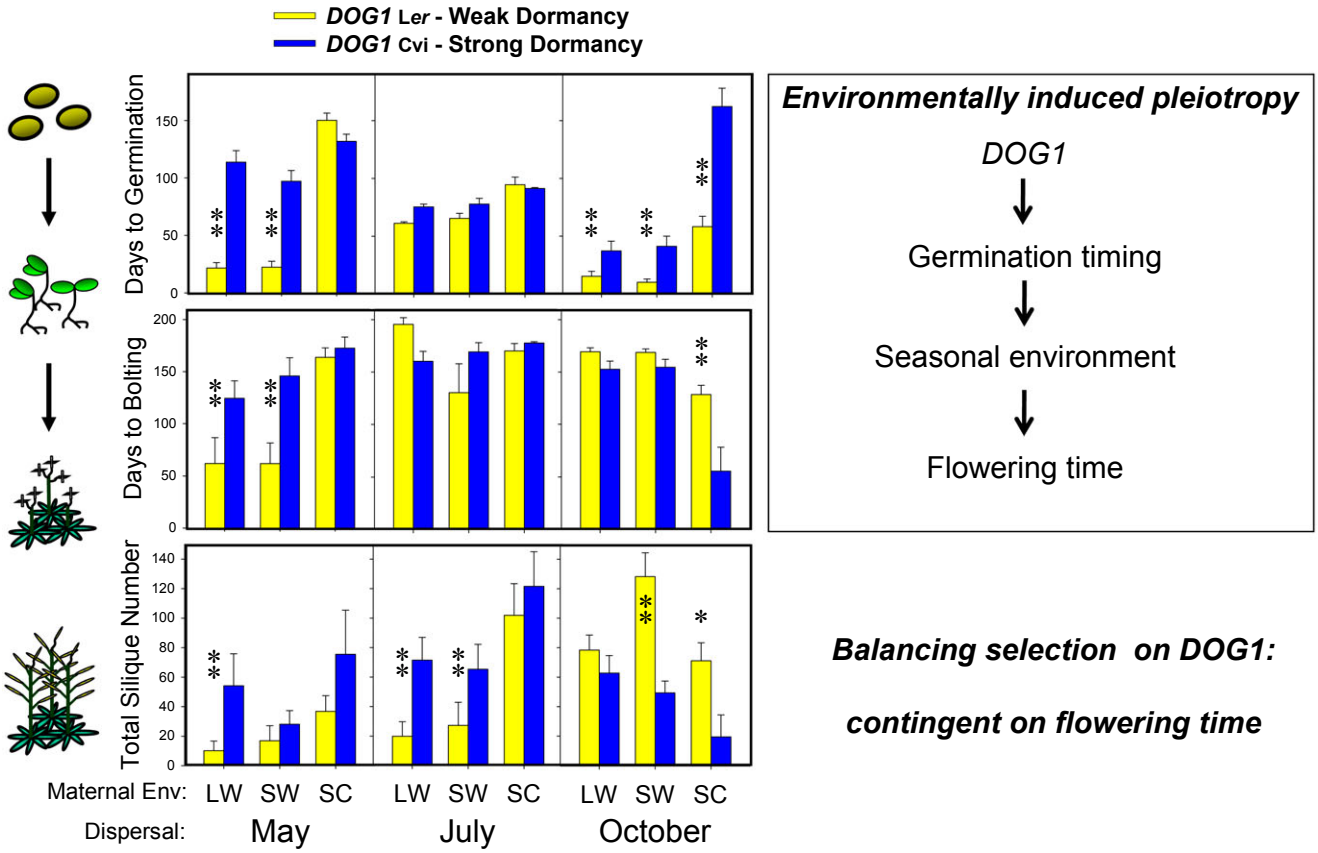

Figure 5. Environmentally induced pleiotropy. Upper: The dormancy gene *Delay Of Germination 1* (*DOG1*) influenced germination timing; the high *DOG1*-expressing allele (near isogeneic line, *DOG1*-L*er*, which has the Cvi allele of *DOG1* introgressed into the L*er* background) had delayed germination compared to the low-expressing allele (*DOG1*-Ler, the Landsberg *erecta* background). Its effect depended on flowering and dispersal conditions. Middle: *DOG1* also influenced flowering time through its effects on germination time, which determined the seasonal flowering cues experienced by rosettes. Lower: *DOG1* alleles influenced fitness. Flowering and dispersal conditions imposed balancing selection on *DOG1* alleles, favoring high *DOG1* expression when seeds were dispersed in spring or summer but low-*DOG1* expression when seeds were dispersed in autumn. Therefore, flowering time can influence selection on dormancy genes. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Figure adapted from Chiang et al. (2012).

such that one gene affects multiple traits. This ramification of the effects of developmental-timing genes can be considered to be environmentally induced pleiotropy.

As an example of such environmentally induced pleiotropy, in *Arabidopsis thaliana* growing under naturally seasonal environments in the field, a single locus acting early in development altered the entire life cycle (Fig. 5; Chiang et al. 2012). The dormancy locus *DOG1* influenced germination time, flowering time, and overall life cycle, demonstrating strong pleiotropy across the life cycle.

DOG1 influenced post-germination traits through its effects on germination timing (Chiang et al. 2012). Specifically, the high-expressing *DOG1* allele delayed the germination of spring-dispersed seeds until the autumn, which slowed growth and delayed flowering until spring, yielding a winter-annual life history. In autumn-dispersed seeds, the delay of germination until spring-time caused greatly accelerated flowering of spring germinants, as they were induced to flower by the long days of spring, soon after germination, resulting in a spring-annual life history. Thus, by determining the timing of germination, *DOG1* also determined the seasonal cues experienced by young rosettes, which in turn determined when those rosettes would flower and what life history would result.

For any organism developing in the wild, developmental-timing genes can have cascading pleiotropic effects on subsequent phenotypes because they determine the seasonal conditions of subsequent development, which in turn influence the expression of seasonally plastic phenotypes. This dynamic also operates across generations, such that maternal developmental timing has cascading effects on their progeny. This dynamic of environmentally induced pleiotropy is likely to be common for many organisms in the wild, and its potential ubiquity suggests

that pleiotropy may be underestimated under laboratory conditions. Thus, the temporal sequence of development under natural conditions can fundamentally alter allelic effects of developmental genes and patterns of natural selection on life-history loci.

This example emphasizes how important it is to allow the inclusion of environmental effects when quantifying the genetic effects of specific loci. In this case, the gene that influences flowering time in the field most was a dormancy locus, and similarly, flowering time influenced germination phenology as much as genetic variation at a major dormancy gene. Such environmentally induced pleiotropy occurs through developmental niche construction in seasonally variable environments. Studies that successfully identify loci under selection would gain much insight by characterizing phenotypic and fitness effects of those loci under natural conditions; without that, some of the strongest effects of those loci may not even be detected.

Conclusion

This case study shows that early life stages can be under intense natural selection, and allele frequencies at individual loci can change as a consequence of a single selective episode. These same loci can pleiotropically influence subsequent life stages, in large part because of developmental niche construction: a gene influences the timing of a life-stage transition, which determines the environment experienced subsequently, which in turn influences subsequent phenotypes. These are not subtle effects. The magnitude of environmental effects via such niche construction is as large as, or larger than, genetic effects of known causative genes in the examples provided here. Thus, pleiotropy, and selection on pleiotropic loci, is fundamentally altered by niche construction.

The examples here identify pleiotropy as an especially interesting focus of study when one considers the critical interactions between genetic loci and ecological environments, whereby genetically based traits influence the environment that organisms experience, and that environment alters genetic expression. First, as the field of ecological genetics becomes increasingly more proficient at identifying loci under natural selection, it will be interesting to determine how quickly allele frequencies at these loci change in response to natural selection, and at what point in the life cycle natural selection induces significant allele-frequency changes. This information would next allow tests of whether alleles that change in frequency in response to selection at prior life stages also influence phenotypes at subsequent life stages (within or across generations); that is, are these loci pleiotropic across the life cycle? To accurately characterize such pleiotropy, it is important that such tests be conducted under natural conditions, to allow for the realistic environmental interactions that can magnify or mask pleiotropy caused by genotype–environment interaction; quantifying environmentally induced pleiotropy within and across generations will provide important insights into how specific alleles are actually selected under ecologically realistic conditions, the life stage at which important selection occurs, and the environmental factors that impose selection on them. In addition to learning the environmental basis of pleiotropy, a number of interesting questions remain about the genetic basis of pleiotropy across environmentally sensitive life stages and how it is maintained or disrupted over evolutionary time. Describing the extent of pleiotropy across entire pathways and identifying when genetic pathways diverge is of value. Whether pleiotropy is more likely in upstream portions of pathways that involve environmental sensing, for example, or whether different life stages have different environmental perception but share regulatory integrators would be of great interest for interpreting how different life stages would respond to altered environmental inputs. The fundamental question of how a single gene can regulate environmental responses of very different developmental stages, that likely have different environment-dependent viabilities, suggests that analysis of regulatory factors could be informative; do genes have stage-specific environmental responses? If so, can it relieve pleiotropy across the life cycle? Whether genetic redundancy, and gene duplication as a particular example of redundancy, effectively relieves pleiotropy also merits more study, and comparative approaches could be especially interesting. To understand adaptation of life cycles requires analysis of how pleiotropy across the life cycle influences adaptive trajectories as well as how pleiotropy itself is modified by the ecological environments experienced by organisms.

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