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Evolutionary processes from the perspective of flowering time diversity

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Summary

Although it is well appreciated that genetic studies of flowering time regulation have led to fundamental advances in the fields of molecular and developmental biology, the ways in which genetic studies of flowering time diversity have enriched the field of evolutionary biology have received less attention despite often being equally profound. Because flowering time is a complex, environmentally responsive trait that has critical impacts on plant fitness, crop yield, and reproductive isolation, research into the genetic architecture and molecular basis of its evolution continues to yield novel insights into our understanding of domestication, adaptation, and speciation. For instance, recent studies of flowering time variation have reconstructed how, when, and where polygenic evolution of phenotypic plasticity proceeded from standing variation and *de novo* mutations; shown how antagonistic pleiotropy and temporally varying selection maintain polymorphisms in natural populations; and provided important case studies of how assortative mating can evolve and facilitate speciation with gene flow. In addition, functional studies have built detailed regulatory networks for this trait in diverse taxa, leading to new knowledge about how and why developmental pathways are rewired and elaborated through evolutionary time.

Keywords: evolution, flowering time, adaptation, domestication, speciation, evo-devo, phenotypic plasticity, phenology

I. Introduction

Timing the initiation of reproductive development appropriately in the context of seasonally changing conditions is critical for fitness. In angiosperms, if flowering occurs too early, floral tissues may be damaged by late frosts, pollinators and other flowering conspecifics may not yet be abundant enough to ensure all ovules are fertilized, and plant size may constrain total flower production. If flowering occurs too late, a plant may encounter conditions unfavorable for seed maturation or dispersal, fail to set seed before dying in season-ending frosts or droughts, or leave offspring in poor growth environments.

As a consequence of these and other time-dependent factors that influence survival, fecundity, and gene flow, plants have evolved mechanisms to regulate their seasonal reproductive phenology—when flowering begins and ends—through internal timekeepers and environmental signals. Developmental plasticity of flowering time to environmental signals is particularly important in

temperate environments, as these mechanisms allow plants to sense changing signals highly predictive of growing season timing and actively adjust flowering accordingly. For instance, many plants require prolonged exposure to cold, or vernalization, for floral induction as this indicates the passage of winter and avoids mortality that would result from prematurely flowering in the fall (Bouché *et al*., 2017). In many annual plants, a permanent memory of winter is established through stable epigenetic silencing of factors that repress flowering, but in perennials, this silencing is not stable, allowing new vegetative growth that will flower in future years (Hyun *et al*., 2019).

Obligate or facultative flowering responses to photoperiod, a reliable indicator of calendar date compared to other environmental inputs, are also common adaptations to ensure the appropriate seasonal timing of reproduction. Photoperiod measurement is achieved by the circadian gating of light- or dark-inducible signaling mechanisms, such that only when days are above or below the required length is the flowering regulatory signal transmitted (Song *et al.*, 2015). Pathways involving epigenetic regulation have also been discovered that track plant age to prevent seedlings from flowering prematurely (Hyun *et al*., 2017). These pathways converge to regulate several floral inducers expressed in the shoot apical meristem and also a mobile hormonal signal known as florigen, which is encoded by homologs of the FLOWERING LOCUS T (FT) protein and moves from the leaf to the shoot apex to induce flowering (Andrés & Coupland, 2012).

Because the start and duration of the growing season vary across the landscape and between wild and agronomic environments, flowering time and its regulation by environmental cues are frequent targets of and contributors to evolutionary processes operating within and between species. Due to its agronomic importance, regulation of flowering time has received intensive study in model organisms and diverse crop species (Andrés & Coupland, 2012; Blackman, 2017). The highly detailed knowledge of developmental mechanisms produced by this immense body of work has facilitated abundant research into the genetic underpinnings of the processes of domestication, adaptation, and speciation and also allowed for comparisons at macroevolutionary scales that have informed our understanding of how developmental networks evolve. Here, we review how genetic studies of flowering time variation have advanced our understanding of these key evolutionary processes, with particular emphasis on recent work and on synthesizing findings across study systems. We conclude by highlighting areas where genetic studies of flowering time variation are poised to make major contributions to evolutionary biology in the future.

II. Domestication

The evolutionary transformation of wild plants into crops is a multi-stage process (Kantar *et al.*, 2017; Gaut *et al.*, 2018). During initial domestication, early farmers began managed cultivation of a species and consciously or unconsciously selected on harvest and yield traits. Next, cultivation spread from the center(s) of origin, and during this dispersion stage, adaptation to local environmental conditions was often essential. Finally, during modern improvement, breeders have further altered crops through artificial selection on natural variants or induced mutants. Flowering time and its environmental regulation have often been targets of selection during these processes, as altering these traits and their underlying pathways can impact critical components of yield including seasonal phenology, plant architecture, and developmental synchrony at harvest.

Here, we primarily focus on the evolution of flowering time during initial domestication and dispersion, as these stages share greatest similarity to evolutionary processes operating in natural populations (Purugganan & Fuller, 2009). We first take a trait-centric perspective, drawing on literature from diverse crops. In doing so, we aim to illustrate how flowering time evolves as a multifaceted phenotype comprised of genetically dissociable regulatory modules that integrate information from multiple seasonal cues and developmental timekeepers (Blackman, 2017). Then, we specifically describe how the evolution of photoperiodic flowering during maize dispersion provides a compelling case study of polygenic adaptation, as knowledge of causal variants reveals how evolution of this trait accumulated over space and time.

Evolving long-day annuals into crops by reducing photoperiod and vernalization responses

Many herbaceous annual species germinate in the fall and overwinter before flowering in the spring. In these taxa, vernalization is often required to relieve the repression of flowering established early in development, and long-day photoperiods activate floral inducers and/or relieve other repressors of those inducers. However, spring plantings are often favored in agriculture, and the pressure to flower quickly in the spring may be reduced or absent in an agronomic context depending on environmental conditions. Thus, substitutions that attenuate these inductive responses have been favored in some crops since delayed flowering can improve resource utilization and yield with extended growing seasons (Table 1).

For instance, many spring-sown varieties of barley (*Hordeum vulgare*) and einkorn wheat (diploid *Triticum monococcum*) differ from winter-sown varieties by regulatory mutations, missense substitutions, or even full deletions of *VRN2* (*VRN-H2*), a pseudo-response regulator (PRR; Yan *et al.*, 2004). Functional *VRN2* represses floral inducer expression until it is down-regulated by *VRN1*

(*VRN-H1*), a MADS-box transcription factor expressed in response prolonged cold. Therefore, spring varieties of these grains can flower without vernalization. Other spring einkorn wheat varieties carry deletion variants in the *VRN1* promoter (Yan *et al.*, 2003, 2004). Spring-sown barley varieties also segregate for a missense variant in another PRR, *Ppd-H1*, which delays flowering under long days by preventing induction of the *FT* homolog *HvFT1*. The frequency of the missense allele varies clinally such that non-responsive genotypes are more common at more northern latitudes, where mild summer conditions make for longer growing seasons (Turner *et al.*, 2005; Jones *et al.*, 2008).

In contrast, in winter varieties of wheat (polyploid *Triticum aestivum* ssp. *aestivum*), photoperiod response is fine-tuned among populations by copy number variants (CNVs) and allelic combinations of homeologs of *Ppd-H1* (Bentley *et al.*, 2013; Würschum *et al.*, 2015, 2018). Adding copies accelerates flowering under non-inductive short days, allowing southern European populations to initiate reproduction and grain filling earlier in the calendar year to escape end-of-season summer heat and drought. Quantitative variation in long-day response mediated by earlier flowering under non-inductive short days is also observed across cultivars of two domesticated legumes, pea (*Pisum sativum*) and lentil (*Lens culinaris*). In both cases, variants that produce frameshifts in orthologs of *EARLY FLOWERING 3* (*ELF3*), a component of the circadian clock, are responsible (Weller *et al.*, 2012)

Adapting short-day crops to shorter growing seasons by altering photoperiod response

Environments with short growing seasons or with long end-of-season photoperiods pose challenges for crops domesticated from short-day wild ancestors, as flowering too late risks mortality from early frosts prior to maturity. Therefore, for many such species, domestication or dispersal to higher latitudes or altitudes has selected for variants that abolish or reduce the strength of the short-day flowering response (Table 1). For instance, two recent elegant studies in tomato (*Solanum lycopersicum*) attribute the shift from a strong short-day response to early, nearly day-neutral flowering to allelic variation in *SELF PRUNING 5G* (*SPG5*), a paralog of the tomato *FT* ortholog *SINGLE FLOWER TRUSS* (*SFT*) (Soyk *et al.*, 2017; Zhang *et al.*, 2018). *SP5G* has evolved to function as a repressor of flowering in long days, but a 52-bp deletion in a 3' UTR enhancer region, which causes improper transcript termination rather than reduced transcript initiation, shows evidence of selection during domestication (Zhang *et al.*, 2018).

Recent evidence suggests that allelic variation in a *FT* homolog may also be responsible for the evolution of earlier flowering under non-inductive long days in day-neutral temperate cultivars of

sorghum (*Sorghum bicolor*; Cuevas *et al.*, 2016). Another example of mechanistic convergence is observed in temperate-adapted cultivars of short-day rice (*Oryza sativa*), where induction of early flowering under non-inductive photoperiod conditions occurs in a manner parallel to the barley and wheat examples above, i.e., through missense or null alleles in orthologs of the PRRs *VRN2* and *Ppd-H1* (Xue 2008, Yan 2013, Koo 2013). Finally, convergent evolution at the genetic level is also observed in legumes. In soybean (*Glycine max*) and independently in both domestications of common bean (*Phaseolus vulgaris*), loss-of function alleles in homologs of the light receptor *PHYTOCHROME A* have been implicated in the evolution of photoperiod insensitivity (Xu *et al.*, 2013; Jiang *et al.*, 2014; Weller *et al.*, 2019).

Polygenic evolution during range expansion

Since its initial domestication ~9000 years ago from short-day teosinte (*Zea mays ssp. parviglumis*), maize (*Z. mays L.*) spread from the tropical lowland Balsas River basin into temperate and higher latitude areas of North America where it faced many of the same climate-associated challenges as the crops discussed above (Swarts *et al.*, 2017). We give special focus to maize here because recent functional, quantitative genetic, population genomic, and archaeological DNA studies have together made exceptional progress in unraveling how this unfolded. Maize landraces vary from 35-120 days to flower. This variation is highly polygenic, involving thousands small effect polymorphisms (most alter flowering time by <1 day) that often also show population genomic signatures of latitudinal or altitudinal adaptation (Buckler *et al.*, 2009; Romero Navarro *et al.*, 2017). Many of these polymorphisms are in regions of low recombination, and recent work has determined that time to flowering and genome size are positively correlated, a pattern driven predominantly by variation in the number of large heterochromatin knobs (Bilinski *et al.*, 2018) and that highlights how chromosome-scale differences may influence adaptation (Fig. 1a). Even discounting SNPs whose association with flowering variation solely reflects linkage disequilibrium with these larger structural features, there are likely still hundreds of adaptive flowering time variants in maize.

Five genes contributed specifically to the reduction of short-day response as maize cultivation spread northward, and most causal variants are known. For instance, upstream of *ZNC8*, the maize *FT* homolog that promotes flowering under short days, a nucleotide substitution and a small deletion are each associated with higher gene expression and earlier flowering under long days (Fig. 2a; Guo *et al.*, 2018). The former is nearly fixed in maize landraces throughout the Americas and segregates within teosinte subspecies, suggesting an early sweep from standing variation. The latter is only

found on haplotypes with the early allele of the former, is at higher frequencies in northern landraces, and segregates only within *Z. mays ssp. mexicana*, consistent with adaptive introgression from this highland teosinte subspecies facilitating northward dispersion. Two genes—*ZmCCT9* and *ZmCCT10*—are PRRs homologous to *VRN2*, and loss-of-function alleles caused by transposable element (TE) insertions in their promoters are more frequent at higher latitudes. These alleles cannot repress their downstream target *ZCN8* (Hung *et al.*, 2012; Yang *et al.*, 2013; Huang *et al.*, 2018b). Likewise, a TE insertion at higher frequency in Northern populations disrupts the function of *Vgt1* (or *ZmRap2.7*), an AP2/ERF transcription factor that represses *ZCN8* expression in long days (Ducrocq *et al.*, 2008). All these insertions appear to have occurred *de novo* post-domestication; a molecular evolutionary analysis of the terminal repeats of the *ZmCCT9* and *ZmCCT10* TE insertions dated their origins to ~4645 and ~7269 years before present (ybp), respectively (Huang *et al.*, 2018b). The MADS-box transcription factor *ZmMADS69*, which promotes flowering by repressing *Vgt1*, also shows a signature of a selective sweep associated with domestication, but the causal variant(s) is unknown (Liang *et al.*, 2019).

This exciting composite, interdisciplinary body of research demonstrates how adaptive changes accreted throughout a regulatory network as selection drove the evolution of day-neutral flowering to short-day flowering during as maize cultivation spread northward. (Fig. 2b), yielding ample insight into evolutionary process and illustrating how evolutionary change during the dispersion stage of domestication could be highly similar to climate adaptation in wild populations. The common involvement of *de novo* TE insertions suggests that these mobile elements are potent sources of new adaptive loss-of-function variants. Furthermore, the combined involvement of standing variants and *de novo* post-domestication alleles in building multi-locus genotypes with temperate-adapted phenologies is consistent with the delayed expansion of maize agriculture out of the southwest United States for a couple millennia (Swarts *et al.*, 2017). Notably, a sample of archaeological maize cobs from that period (~1900 ybp) is fixed for all the early flowering variants except the *Vgt1* TE. However, counter to expectation, two Southern Mexican genomes dating to ~5000 ybp carry both *ZmCCT* TEs but have the late flowering *ZCN8* alleles (Guo *et al.*, 2018). Thus, a richer archaeological time series may reveal additional aspects of domestication and dispersion that other processes have obscured from modern genomes over time.

III. Adaptation

Natural selection improves the fit of organisms to their environments. However, the environment varies over space and time, and consequently, individual populations within species may diverge phenotypically as they adapt to their local habitats and may maintain trait variation across generations. Each of these adaptive processes may involve changes at few or many loci; be biased toward or away from particular genes or types of substitutions; and could result from several evolutionary mechanisms. Consequently, to know what underlying processes can and have occurred, it is essential to dissect the genetic architecture and/or molecular basis of adaptive trait variation and examine genotypic effects in natural environments.

Flowering time is a highly tractable model trait for examining these aspects of the adaptation process. Common garden studies have revealed that genetic clines in flowering time with elevation, latitude, or other climate parameters are common (e.g., Kollmann & Bañuelos, 2004; Stinchcombe *et al.*, 2004; Kawakami *et al.*, 2011; Van Dijk & Hautekèete, 2014), and shifts to rapid cycling life histories frequently accompany adaptation to environments with seasons abbreviated by terminal drought or seasons long enough to sustain multiple annual life history cycles (e.g., Donohue, 2002; Baduel *et al.*, 2016; Ferris *et al.*, 2017). The responsiveness of flowering to vernalization, photoperiod, and ambient temperature cues also varies in ways both similar and distinct to the patterns observed among geographically widespread crop species (Lempe *et al.*, 2005; Blackman *et al.*, 2011; Anderson *et al.*, 2011; Ream *et al.*, 2014; Kooyers *et al.*, 2015). Early progress in examining the genetics of flowering time diversity was dominated by work in the model plant *Arabidopsis thaliana* due to its experimental advantages. However, the development of new population genomic methods, the expansion of genomic resources, and the extension of functional tools to other species in the Brassicaceae, wild relatives of crop species, and several classic evolutionary systems now allow for genetic dissections approaching the scale of individual genes in these species too. Here, we consider how these studies and some additional relevant findings from work on crop landrace diversity inform our understanding of adaptive processes operating within and among populations.

The genetic architecture of flowering time adaptation

Many investigations have sought to characterize the number and effect sizes of loci that contribute to adaptive variation in flowering time segregating within single populations or among populations of a species. These studies contribute to ongoing dialogues about whether adaptation proceeds through allele frequency changes at many loci of small effect or few loci of major effect; whether and why we

see the same or different genes involved in convergent phenotypic evolution; and, thus together, how to model quantitative trait variation and how quick or how difficult adaptive evolution may be. Although an ever-growing number of individual studies have explored these questions in diverse species, a truly robust picture is as yet unavailable for most wild species for several methodological and biological reasons (Box 1). Nonetheless, when we look at some of the most comprehensive studies to date, different templates for the genetic architecture of flowering time adaptation have emerged.

For instance, when the genetics of flowering time variation was mapped in *A. thaliana* across 17 F_2 populations derived from 18 unique parent accessions and several additional recombinant inbred line (RIL) populations, the QTLs identified mostly map to allelic series at five major loci—including *FRIGIDA (FRI)*, *FLOWERING LOCUS C (FLC)* (and/or nearby *CONSTANS (CO*)), and two paralogs of *FLC* (*FLOWERING LOCUS M* and *MADS AFFECTING FLOWERING 2*), and *ERECTA*—plus rarer alleles at several other loci including *FT* (Salomé *et al.*, 2011). *FRI* is a positive regulator of *FLC*, which represses flowering until silenced by vernalization. *CO* is a positive regulator of *FT* in long days, and the two *FLC* paralogs are involved in the response of flowering time to ambient temperature. These results suggest that although the flowering time regulatory network is large and mutants in >300 genes affect flowering (Bouché *et al.*, 2016), adaptation may proceed primarily through large effect substitutions from a pool of allele diversity harbored at a few predictable "evolutionary hotspots", a pattern that may emerge because advantageous alleles with no or few negative pleiotropic effects arise more frequently at certain loci (Stern, 2013). Consistent with these patterns, seven additional *FLC* alleles that have sustained independent TE insertions are associated with reduced gene expression and earlier flowering (Lempe *et al.*, 2005; Quadrana *et al.*, 2016). Furthermore, natural variants that eliminate, attenuate, or otherwise alter the functions of *FRI*, *FLC,* and *CO* homologs have been implicated in the adaptive evolution of seasonal flowering in three other species (Yang *et al.*, 2018; Baduel *et al.*, 2018; Lee *et al.*, 2018) and between species (Kiefer *et al.*, 2017) in another genus in the Brassicaceae.

Other studies have called into question whether this major effect "hotspot" architecture is generalizable, however. For example, although initial association mapping by the 1001 Genomes Consortium detected just five flowering-time associated loci largely similar to those discussed above (Alonso-Blanco *et al.*, 2016), more in-depth analyses informed by eQTL analysis of the same set of accessions have detected ~40 additional loci harboring variants that that influence flowering time in *A. thaliana* (Zan & Carlborg, 2019). Moreover, another survey performed on the same dataset

yielded >80 genes with drought-associated, loss-of-function common variants that may alter flowering time (Monroe *et al.*, 2018), although more recent findings raise cautions about validating the pooled flowering time effects of large candidate genes sets with T-DNA insertion lines (Chong & Stinchcombe, 2019). As noted above, adaptive differentiation in flowering of maize landraces along altitude or latitude gradients may involve hundreds of genes (Romero Navarro *et al.*, 2017). In addition, bulked segregant analyses comparing allele frequencies of early and late flowering plants in three populations of the common monkeyflower, *Mimulus guttatus*, over multiple years detected tens to hundreds of single nucleotide polymorphisms (SNPs) or structural variants that contribute to adaptive variation within and between populations (Monnahan & Kelly, 2017; Troth *et al.*, 2018). However, many SNPs only affected flowering time in one of the populations and/or only in one growing season, a pattern reminiscent of several studies that have found flowering time QTL or variants mapped in growth chamber or greenhouse studies often do not affect flowering or fitness as anticipated in the field (Weinig *et al.*, 2002; Brachi *et al.*, 2010; Anderson *et al.*, 2011; Liu *et al.*, 2014). These results argue for an alternative model of flowering time adaptation where a myriad of loci throughout the various environmentally sensitive pathways of the flowering time regulatory network can harbor adaptive genetic variation, particularly when their gene-by-environment interactions are taken into account.

The disparate models--allelic series at few hotspots vs. highly polygenic--may emerge in part due to methodological differences (e.g., many fewer parental genotypes sampled by QTL mapping vs. GWAS or population genomics) or biological differences (e.g., highly selfing vs. highly outcrossing mating systems). Regardless, this important dichotomy signals that more expansive and comparable investigations of the genetics of adaptation in wild systems are needed. For instance, if adaptive evolution of flowering time is constrained to occur through repeated major effect substitutions at few loci, then adaptation to climate change may be constrained by a limited range of adaptive variants segregating in natural populations or involve long waiting times for the appearance of new advantageous variants. In contrast, if many genes can contribute ecologically equivalent allelic variation to flowering time adaptation and if loss-of-function mutations are often beneficial and occur frequently (e.g., following TE activation by environmental stress), the prospects for adaptation to climate change seem brighter.

Pleiotropy and fluctuating or spatially varying selection

Substantial inquiry has focused on balancing selection, the adaptive force that maintains polymorphism within a single population. Classic case studies have shown how heterozygote advantage and negative frequency dependent selection can sustain balanced polymorphisms (Box 2). Temporally varying selection, where the alleles and trait values favored in some generations are disfavored in other generations, is another important and potentially more pervasive evolutionary explanation. Because it is theoretically possible for an allele or multi-locus genotype with high geometric mean fitness across many generations to fix (thus eliminating any polymorphism) under fluctuating selective regimes however, antagonistic pleiotropy is often invoked as a critical requirement for maintaining balanced polymorphisms. In other words, alleles that confer high relative fitness in some years may suffer a fitness trade-off in other years either due to their direct effects on the trait that makes them sometimes favorable or indirectly through impacts on other traits.

Recent multi-year field studies of flowering time variation in *M. guttatus* have now affirmed that these conditions are indeed met in wild populations. For instance, one GWAS on a diversity panel derived from a single population first identified 24 pleiotropic SNPs associated with both delayed flowering and increased plant size in the greenhouse (Troth *et al.*, 2018). Then, by tracking them over three field seasons, the investigators found this set of “large and slow” alleles was maladaptive in shorter, drier seasons, when an early terminal drought leads to mortality before flowering or seed set, but favored in longer, wetter seasons because plants with delayed flowering grew larger and produced more, larger flowers, giving them higher fecundity.

Likewise, CNVs of *RLG1a*, a tRNA ligase, have been associated with both flowering time and plant size in *M. guttatus* (Fig. 1b; Nelson *et al.*, 2019). Individual alleles have one to three, or, rarely, an extreme number (>250) of copies, and all alleles segregate following single locus expectations. Carriers of the 3-copy allele have delayed flowering and larger size relative to 1-copy allele homozygotes, while extreme-copy allele carriers flower earlier but are of similar size to the 1-copy allele homozygotes. Consistent with the findings for “large and slow” SNPs, the 3-copy allele carriers were most fit due to a female fecundity advantage in a year with a long spring. Conversely, the 1-copy homozygotes and the extreme allele carriers had highest survival and seed set in years with an early drought. Since larger plant size is likely a direct developmental consequence of delayed flowering, the “large and slow” alleles and the 3-copy CNV of *RLG1a* have (or tag causal variants that have) pleiotropic and antagonistic effects in different seasons, and these trade-offs maintain the polymorphisms.

Notably, these *M. guttatus* alleles also vary in frequency among populations (Troth *et al.*, 2018), indicating that antagonistic pleiotropy may also contribute to local adaptation to spatially-varying selective pressures. Characterization of non-functional and functional *FRI* alleles in *A. thaliana* has revealed that this likely explains why functional *FRI* alleles are associated with drier habitats on average than non-functional *FRI* alleles. However, unlike the *M. guttatus* cases, the pleiotropy results from different downstream impacts of the polymorphism in different environments (Lovell *et al.*, 2013). Non-functional *FRI* alleles promote drought escape through rapid growth and early flowering. However, they also compromise water use efficiency because they cannot activate proline synthesis under drought stress through an *FLC*-dependent pathway, preventing drought tolerance.

These results lend evolutionary weight that reinforces the need to be mindful of evidence that mutants or natural variants in so-called flowering time genes often impact diverse other developmental and physiological traits (e.g., Pin & Nilsson, 2012; Ortiz-Marchena *et al.*, 2014; Auge *et al.*, 2019). Also, although pleiotropy is generally viewed negatively as a source of trade-offs or as a brake on the rate of adaptive evolution, it need not always be so. When an allele confers multiple favorable phenotypic effects, known as synergistic pleiotropy, then the overall selection coefficient will be larger, potentially facilitating divergence in the face of gene flow. For instance, recent work suggests that synergistic pleiotropy of alleles of *TWIN SISTER OF FT* (*TSF*), which affect reproductive phenology but also impact branch number and the height:rosette diameter ratio in the field, can promote rapid divergence even at the microhabitat scale within populations of *A. thaliana* (Frachon *et al.*, 2017).

The molecular basis of flowering time adaptation

Another major question in this field is whether the adaptation process has predictable substitution biases (Stern & Orgogozo, 2009). Essentially, do certain mutation types preferentially contribute to adaptive evolution? One prominent hypothesis is that adaptation will be biased toward evolution through *cis*-regulatory changes since their effects can be restricted to particular tissues, developmental stages, or environments in contrast to coding sequence changes that may have pleiotropic impacts whenever a protein is expressed (Stern, 2000). Several meta-analyses supported this hypothesis, but others have argued that summarizing trends observed across traits and across all plants and animals, obscures important variation in the magnitude and heterogeneity of substitution biases (Streisfeld & Rausher, 2011). A large sample of causal natural variants affecting

flowering time and its environmental regulation provides a strong trait-specific dataset to address this problem. Most of these variants have been discovered in *A. thaliana* or other brassicas, but ever-improving resources in other plant groups should reduce this taxonomic bias going forward.

Coding, *cis*-regulatory, and CNVs all contribute to variation among natural populations, and all of these alleles eliminate or attenuate gene function, consistent with the bias that many more mutations will have loss-of-function rather than gain-of-function effects (Table 2). One notable trend is that coding variants, whether deletion or missense alleles, are associated with the losses of responses to environmental cues more often than *cis*-regulatory alleles. Many such mutations in *FLC* and *FRI* abolish vernalization response in the Brassicaceae. Likewise, a missense mutation segregating in *Brachypodium distachyon* compromises the function of an *FT* paralog (Woods *et al.*, 2019). Expression of this paralog under short days is required to confer competency for floral induction when long days are experienced subsequently.

In contrast, *cis*-regulatory variants are more enriched among polymorphisms causing quantitative variation in flowering time or its environmental responsiveness. For instance, in both *A. thaliana* and *Capsella rubella*, a series of regulatory alleles of *FLC* are differentially sensitive to vernalization cues, with different alleles requiring different durations of cold exposure to be silenced and thus promote flowering (Coustham *et al.*, 2012; Li *et al.*, 2014, 2015; Yang *et al.*, 2018). In both *Arabidopsis arenosa* and *A. thaliana*, variants with more tandem repeats in the *CO* promoter flower later likely because they have an additional binding site for *CYCLING DOF FACTOR 1*, a repressor of *CO* expression (Fig. 1c; Rosas *et al.*, 2014; Baduel *et al.*, 2018). Convergent evolution involving the same repeat array may reflect a bias toward mutations that occur at higher rates, as much as a fixation bias for specific, limited allelic effects.

Together, these trends suggest that substitution biases in the type of mutations contributing to natural variation for this trait reflect the qualitative vs. quantitative nature of the favored trait variation more so than pleiotropy. Only examining SNP variation, a common GWAS approach, may often be insufficient. Insertion-deletion, CNVs, and even more complex rearrangements (e.g., chimeric variation in tandem-duplicates of *MAF2*, Rosloski *et al.*, 2010) commonly cause phenotypic variation (Table 1; Fig. 1). Because these variant types arise by different mutational processes and impact local recombination rates, nearby SNPs may be ineffective in tagging them well by linkage disequilibrium (Schrider & Hahn, 2010).

IV. Speciation

The evolution of flowering time is often highlighted as a potentially important contributor to the emergence of new plant species. As populations diverge in seasonal reproductive phenology, plants will more often be fertilized by pollen from their own population than by pollen from other populations, and this assortative mating constitutes a barrier to gene flow. Indeed, this process can confound GWAS and gene-environment association analysis, as variants causing flowering time divergence come to co-vary with population structure (e.g., Larsson *et al.*, 2013; Tyler *et al.*, 2016). Additional prezygotic and extrinsic postzygotic isolation results when flowering time divergence is driven by local adaptation or the timing of flowering of interpopulation hybrids reduces fitness relative to parental genotypes. Such processes fit with the mode of speciation known as ecological speciation, where reproductive isolation arises as a direct or indirect byproduct of divergent selection (Schluter, 2009), and flowering time can be considered a so-called "magic trait" since its adaptive genetic divergence leads automatically to increased assortative mating (Taylor & Friesen, 2017).

Some of the earliest computer simulation models of speciation explored these possibilities, revealing how plastic differences in flowering time can facilitate speciation of adjacent, or parapatric, populations and how reinforcing selection can drive further flowering time divergence when interpopulation species hybrids form (Crosby, 1970; Stam, 1983; Dijk & Bijlsma, 1994). Consistent with these predictions, several empirical studies have found that flowering time differences contribute considerably to reproductive isolation between ecotypes or incipient species (e.g., Runquist *et al.*, 2014; Sedeek *et al.*, 2014; Ferris *et al.*, 2017). Sympatric speciation theory shows that disjunct genetic clusters can emerge from a single, finite population on short evolutionary timescales even through non-selective processes when ample genetic variation for flowering time exists and individual plants flower for only brief periods over a long flowering season (Devaux & Lande, 2008). In addition, shifts in phenology may aid establishment of nascent polyploid species (Ramsey, 2011). Despite these conceptual advances and observations and also despite our detailed understanding of flowering time regulation, flowering time genes hardly contribute to the "speciation genes" literature (Rieseberg & Blackman, 2010). Nonetheless, several recent genetic studies have yielded results that bear upon predictions of verbal or analytical models of the speciation process.

Speciation with gene flow

If flowering time differences do arise due to divergent selection and cause assortative mating that helps maintain phenotypic differentiation between species in sympatry, the causal flowering time loci should also remain differentiated even while divergence is eroded throughout most of the genome.

Recent work in the monkeyflower species pair of *M. guttatus* and *M. nasutus* has explored this possibility. These species are often found in sympatry and despite observed natural hybridization, they remain largely morphologically and developmentally distinguishable (Martin & Willis, 2007; Kenney & Sweigart, 2016). *M. guttatus* is an outcrosser and bee-pollinated, while *M. nasutus* is a predominant selfer.

Both species must experience a minimum critical photoperiod for floral induction, but *M. nasutus* can flower under shorter day lengths and thus earlier in the season than *M. guttatus*, (Fishman *et al.*, 2014). In the field, the temporal isolation caused at least in part by this change in photoperiodic regulation has been estimated to account for anywhere from ~4% to ~90% reduction in hybrid seed production relative to random mating, depending on the site and the direction of gene flow. Because the flowering period of F_1 hybrids overlaps more with *M. guttatus*, introgression of *M. nasutus* alleles into *M. guttatus* is observed more often than the reverse (Martin & Willis, 2007). Genetic mapping reveals that two major effect QTL almost entirely explain the difference in critical photoperiod between the species (Fishman *et al.*, 2014). Consistent with a contribution to reproductive isolation in sympatry, the allelic diversity at one of these loci shows reduced introgression and is more differentiated between the species compared to the rest of the genome (Kenney & Sweigart, 2016).

Although this *Mimulus* example likely involved a fully allopatric phase at some point in the past, temporal isolation is of central importance in the best-known example of sympatric speciation in plants. Two palm species that evolved from a common ancestor on small, highly remote Lord Howe Island are primarily reproductively isolated by differences in soil type preference and flowering time. Temporal isolation through flowering displacement is 80% or 97% depending on the direction of gene flow (Hipperson *et al.*, 2016). Although some of this displacement is due to developmental plasticity that may have helped kickstart assortative mating by soil type (Gavrilets & Vose, 2007; Devaux & Lande, 2008), genetic differentiation also contributes to the species difference. Through differential expression analysis, selective sweep analysis, and functional tests of *A. thaliana* homologs, investigators have identified several candidate genes for this differentiation, including a homolog of the known flowering time regulator *FPA* (Dunning *et al.*, 2016). Because several of these genes are annotated with other functions that could respond to divergent selection on different soil types, it is tempting to speculate that synergistic pleiotropy may have facilitated both adaptive divergence and assortative mating, fitting the “magic trait” model under which sympatric speciation is most likely to

succeed (Servedio *et al.*, 2011). Expanded genomic resources for the *Howea* palms and functional studies in phylogenetically closer species may lend more credence to this possibility in the future.

Allopolyploidy and gene interactions

When a new polyploid individual evolves, it does so in sympatry with its progenitor(s) of lower ploidy. Consequently, to establish a new polyploid species, it must overcome being mated to extinction by its neighbors of different ploidy, a problem known as minority cytotype exclusion (Oswald & Nuismer, 2011). If temporal isolation is a direct consequence of the polyploidy event, then a new polyploid species is more likely to establish. Investigations into the control of flowering time in the allopolyploid *Arabidopsis suecica*, derived from *A. arenosa* and *A. thaliana*, demonstrate a mechanism by which such an immediate flowering displacement may emerge upon polyploidy (Wang *et al.*, 2006). The *A. thaliana* genome contributes a strong functional *FLC* allele and a non-functional *FRI* allele. Conversely, the *A. arenosa* genome contributes a weak *FLC* allele and a strong *FRI* allele. Hence, in the natural and newly synthesized allopolyploids, these two strong alleles interact epistatically such that *AaFRI* transactivates *AtFLC*, and the resulting high expression of *FLC* delays flowering relative to either diploid progenitor (Fig. 3).

IV. Evolution of developmental networks

Gene regulatory networks coordinate the complex orchestration of gene functions so that cells grow, divide, and adopt particular fates in a spatial-, temporal-, and environment-specific manner during development. By understanding why and how these networks become rewired or co-opted over time, we can learn how novel developmental programs evolve at both micro- and macroevolutionary scales. In addition, comparative studies of the networks regulating homologous traits in species that shared a common ancestor millions to hundreds of millions of years ago can reveal when gene functions are highly conserved; when circuit logic is conserved even if the specific proteins, RNAs, or *cis*-regulatory elements turnover, a process known as developmental system drift (Box 2); and how independent solutions to the same developmental problem can be reached entirely convergently. Finally, determining how network structures have evolved to confer robustness to genetic or environmental variability also has critical applications in conservation and agriculture.

By describing networks in multiple species to a level of mechanistic complexity that often yields important new insights into the fundamentals of gene regulation, flowering time research has repeatedly made seminal contributions to understanding these processes. For instance, early work

comparing the *GIGANTEA-CO-FT* regulatory circuit between *A. thaliana* and rice was among the first studies to demonstrate how the transcriptional relationships between homologous genes have been rewired to confer opposite behavior (*i.e.*, long-day vs. short-day response; Hayama *et al.*, 2003). Several recent papers have reviewed which aspects of flowering time regulation are conserved or differ among major study systems (Andrés & Coupland, 2012; Song *et al.*, 2015; Bouché *et al.*, 2017). Therefore, we narrow our focus here to recent examples that illustrate particular conceptual advances achieved or supported through evolutionary developmental studies.

Versatility in gene networks facilitates life history evolution

The perennial brassica *Arabis alpina* has emerged as a powerful model system for examining how homologs of flowering time genes known from *A. thaliana* process information from internal and external timekeepers differently, resulting in its distinct life history (Fig. 4). *PERPETUAL FLOWERING1* (*PEP1*) is the *A. alpina* ortholog of *FLC,* and like *FLC*, it represses flowering unless the plant experiences sufficient vernalization. However, unlike *FLC*, which remains fully silenced post-vernalization, *PEP1* expression reverts to high levels in warm conditions and represses flowering in the meristems of young vegetative branches that will continue to grow and not flower until after the next winter. *PEP2*, orthologous to *APETALA 2* (*AP2*), is required to activate *PEP1* after vernalization (Lazaro *et al.*, 2019). The competency of *A. alpina* meristems to respond to vernalization cues is age-dependent; the expression of a small RNA, *miR156*, declines over developmental time and, in doing so, de-represses expression of *SQUAMOSA PROMOTER BINDING PROTEIN-LIKE 15* (*SPL15*), a promoter of flowering (Xu *et al.*, 2016; Hyun *et al.*, 2019). Age-dependent interactions between *PEP2* and another small RNA *miR172* also regulate axillary meristem competency independent of *SPL15* (Bergonzi *et al.*, 2013; Lazaro *et al.*, 2019)

SPL15 expression is also repressed by *PEP1* without vernalization and following reversion under warm conditions. Thus, *SPL15* integrates signals that confer competency so that axillary meristems that are too young and/or have not experienced cold do not produce flowers in *A. alpina* (Hyun *et al.*, 2019). In contrast, all meristems in *A. thaliana* are able to flower under warm, long days post-vernalization regardless of age because *FLC* is stably repressed, allowing *FT* induction to promote floral initiation. Congener and annual *Arabis montbretiana* also flowers in post-vernalization, warm days by this mechanism because *AmFLC* is also stably repressed by vernalization. The same is true for a near isogenic line carrying *AmFLC* rather than *PEP1* in an otherwise *A. alpina* background and when *AmFLC* is transformed into *A. alpina pep1* mutants. Since *cis*-regulatory

variants can quantitatively alter the duration of cold necessary for stable *FLC* repression (Coustham *et al.*, 2012; Li *et al.*, 2014, 2015; Yang *et al.*, 2018), it is easy to conceive how natural selection could quickly modulate this capacity and shift the relative influence and redundancy of the age, vernalization, and photoperiod pathways for floral induction, driving evolutionary transitions in life history strategies while still preserving individual pathway structure.

Extensive turnover and convergence in developmental networks

When we observe homologous phenotypes preserved across species separated by long evolutionary timescales, it is easy to assume that the regulatory interactions that structure the underlying developmental networks are also conserved. However, through either adaptive or neutral processes, developmental system drift frequently transpires (True & Haag, 2001). This process is the evolutionary equivalent of treading water. The underlying developmental mechanisms churn with change over time often without yielding a noticeable impact at higher scales of phenotypic organization due to the robustness of the system, leaving the overall impression of conservation. Indeed, ample empirical work in animal and fungal taxa has found, for instance, that the transcription factor binding sites can turnover rapidly even as gene expression levels remain conserved (e.g., Borneman *et al.*, 2007; Schmidt *et al.*, 2010; Berthelot *et al.*, 2018).

To our knowledge, only one comparative transcription-factor binding site study examining taxa of considerable evolutionary distance has been reported in plants. Mateos *et al.* (2017) compared the binding of *A. thaliana FLC* and its *A. alpina* ortholog *PEP1* to their respective organism's genomes through chromatin immunoprecipitation and high-throughput sequencing. Consistent with the extensive turnover observed in other taxa, only 28 of 204 bound genes (14%) shared direct target sequences in both species and only eleven more genes were commonly bound by both orthologs but at species-specific binding sites. Flowering time genes, as expected, were over-represented among the conserved targets. Interestingly though, both transcription factors directly bind and upregulate genes annotated as cold-responsive, but target almost entirely non-overlapping gene sets. Thus, these transcription factors serve at least two common functions, flowering and cold-response regulation, but for cold-response, there is a pattern potentially consistent with developmental system drift, assuming the *FLC* ortholog in the common ancestor of these two species also served this function. That is, an orthologous upstream regulator has maintained its functional role, yet has evolved to target a similar but not directly orthologous set of genes to produce a homologous trait.

Pathways may also misleadingly appear conserved between distant taxa due to convergent evolution. Homologous genes may gain a similar or the same role in a regulatory network multiple times independently, whether anew or reversing a previous loss along an evolutionary lineage. The regulation of *FT* homologs by *CO* homologs has emerged as one major case study of such high evolutionary lability (Ballerini & Kramer, 2011). Homologs of *CO* act as photoperiod-dependent regulators of *FT* homologs throughout the Brassicaceae and in rice, potato (*Solanum tuberosum*), sorghum, barley, strawberry (*Fragaria vesca*) and possibly soybean (Hayama *et al.*, 2003; Wu *et al.*, 2014; Yang *et al.*, 2014; Mulki & Korff, 2016; Abelenda *et al.*, 2016; Kurokura *et al.*, 2017), though in some cases the regulation is partially or entirely indirect. However, substantial evidence in legumes (pea and *Medicago truncatula*), morning glory (*Ipomoea nil)*, and poplar (*Populus* spp.) suggests that *CO* orthologs are not upstream regulators of *FT* in these species (Hayama *et al.*, 2007; Hsu *et al.*, 2012; Wong *et al.*, 2014; Ridge *et al.*, 2016). Thus, *FT*-regulatory function appears to have been repeatedly evolutionary lost, gained, or both throughout the angiosperms. One gain of this function by *CO* likely occurred through coding and *cis*-regulatory changes following gene duplication near the origin of the Brassicaceae, as the sole *CO* homolog in the Cleomaceae, the sister clade to the Brassicaceae, functions similar to *COL1* and *COL2*, two *CO* paralogs that have circadian functions but do not impact photoperiodic flowering in *A. thaliana* (Simon *et al.*, 2015). Finally, in a particularly striking instance of convergent evolution, two independently transcribed genes, each of which encodes one of the two major protein functional domains found in *CO*, physically interact to regulate *FT* paralogs in sugar beet in a photoperiod-dependent manner (Dally *et al.*, 2018).

That different clades have independently evolved aspects of their photoperiod pathways is not surprising. Different taxonomic groups have adapted to colonize and thrive in temperate regions much more recently than they shared common ancestors. These independent histories of adaptation have also been invoked to explain the involvement of different phytochromes in photoperiod regulation and the complete lack of homology between the vernalization pathways of the temperate brassicas and grasses, for example (Chen *et al.*, 2014; Woods *et al.*, 2014). What is surprising is that *CO* homologs are repeatedly recruited or disconnected somehow. One explanation for this pattern may be that *CO* homologs have a strongly conserved function in photoperiodic regulation of another fundamental function like carbohydrate metabolism (Serrano *et al.*, 2009; Ortiz-Marchena *et al.*, 2014), and thus they are predisposed to be co-opted for novel photoperiodic adaptations. Because *CO* promotes transcription both by directly binding DNA and as a co-activator (Blackman & Michaels, 2010), *CO* homologs may also have more routes to gain new functions compared to other gene

families. Lastly, because photoperiodic flowering often involves multiple mechanisms acting together to repress flowering in non-inductive photoperiods and promote flowering in inductive photoperiods, and since several other pathways converge at *FT* transcriptional regulation, the *CO-FT* regulatory relationship may be especially prone to loss through developmental system drift when rendered redundant or irrelevant by shifts in control elsewhere in the network.

Network elaboration through gene duplication

Gene duplication is a prominent driver of developmental system drift and convergence, as different members of gene families with similar functional capacities may swap in and out of pathways in diverging taxa over time. In addition, gene family expansion has long been postulated to be an important, potent source of evolutionary novelty in gene networks. On arrival, new gene duplicates are often partially or wholly functionally redundant to the ancestral gene copy. They may bind to the same *cis*-regulatory sequences, interact with the same protein complexes, or process the same metabolic compounds. Consequently, until the redundancy of young duplicate pairs is fully resolved through loss of one copy or subfunctionalization, new duplicates are well positioned to evolve new cooperative or competitive interactions with the ancestral gene copy or other paralogs that elaborate gene networks.

To our knowledge, studies of recent lineage-specific duplicates of *FT* were the first to demonstrate the mettle of this theory empirically. In particular, young *FT-like* genes in several species have evolved anti-florigenic regulatory activities, likely by competing with *FT* for partners in the florigen activating complex in the shoot apical meristem. This mechanism was first suggested by findings in sunflower (Blackman *et al.*, 2010). A frameshift allele of a recently duplicated, meristem-expressed *FT* copy rose to high frequency during sunflower domestication, and this allele acts in a dominant negative manner by interfering with the capacity of a different *FT* paralog to promote flowering in an *A. thaliana ft* mutant background. In tobacco, several recently duplicated *FT* paralogs that act to delay flowering have mobile transcripts and are capable of binding the tobacco *FD* paralog, lending support to the hypothesis that they inhibit *FT* function through competition for activation complex partners (Harig *et al.*, 2012; Huang *et al.*, 2018a). An *FT* paralog in soybean (*GmFT1a*) may similarly antagonize the action of florigenic *FT* paralogs (Liu *et al.*, 2018). Additional evidence that developmental networks may be adaptively elaborated through novel antagonistic protein interactions between young duplicates and ancestral paralogous copies has now emerged in other systems (e.g., Charrier *et al.*, 2012; Dennis *et al.*, 2012).

In several other cases, lineage-specific *FT* duplicates have evolved to antagonize the canonical *FT* paralog's function not by competing for protein interactions but instead by repressing its transcription. This mode of evolved antagonism was first discovered in sugar beet (Pin *et al.*, 2010), and subsequent studies of *FT* paralogs that suppress photoperiod-induced responses in onion (*Allium cepa* L.) and tomato have described similar mechanisms of action (Lee *et al.*, 2013; Soyk *et al.*, 2017). The evolution of lineage-specific *FT* homologs also illustrates how gene duplication can facilitate the evolution of novelty through co-option. *FT* paralogs distinct from those that function in the environmental regulation of flowering have evolved to act as photoperiod-specific regulators of bulb and tuber formation in onion and potato, respectively (Navarro *et al.*, 2011; Lee *et al.*, 2013).

V. Conclusions and future directions

Our goal has been to highlight how investigating the genetics of flowering time diversity has enriched our understanding of fundamental evolutionary processes. Several discoveries summarized above reveal how diverse types of variants have repeatedly altered the pathways that regulate the developmental plasticity of flowering time as the seasonal phenologies of populations or crops have adapted to local climate variation. Many examples of convergent genetic evolution are noted, indicating that "evolutionary hotspots" often harbor adaptive genetic variation in this trait. However, additional studies in *Arabidopsis*, maize and *Mimulus* suggest that polygenic adaptation may also be common, particularly if standing variation within populations is characterized by antagonistic pleiotropy across years or locations. Recent case studies also illustrate how flowering time facilitates ecological speciation with gene flow and polyploid speciation. Finally, comparisons of regulatory pathways among distant taxa have found extensive rewiring through turnover and convergence at several hierarchical scales and demonstrated how gene duplications foster developmental network innovation through multiple mechanisms.

Future efforts to identify the molecular basis of flowering time diversity will undoubtedly continue to advance the field of evolutionary biology. Current technologies for rapidly and cheaply generating heaps of population and functional genomic data are now often readily transferable across systems or applicable to archaeological and herbarium samples. Genome editing tools hold great promise for confirming gene and allele functions in a broader range of taxa. A point underscored by several studies reviewed above, however, is that there remains no substitute for multi-year, multi-site field studies for understanding how alleles function to produce trait variation and interact with selection in native environments. Bridging all these approaches is increasingly important

if we hope to predict how quickly and fully the flowering time diversity segregating within species will foster adaptation to non-analog combinations of seasonal cues and selective agents in future climates.

As new mechanisms of flowering time plasticity to drought, nutrient stress, ambient CO_2, and soil microbiota become better described, genetic investigations of their diversity should reveal how pleiotropic or modular adaptive variation affecting these responses can be (Blackman, 2017). Comparative study of these pathways may be particularly critical for learning how unique life histories like gregarious flowering or masting evolve (Peng *et al.*, 2013; Kobayashi *et al.*, 2013). Another area where flowering time is particularly poised to contribute is evolutionary epigenetics. Epi-allelic variation in flowering can be generated artificially (Cortijo *et al.*, 2014) but flowering epi-alleles adaptive in the wild remain undescribed. Given past theoretical findings, it is also tempting to speculate how epi-alleles for flowering could kickstart speciation, a possibility with precedence in postzygotic incompatibilities (Blevins *et al.*, 2017). Furthermore, comparisons of flowering time evolution in selfing and outcrossing species will illuminate how mating system influences the genetic architecture of adaptation and the reliance of adaptation on *de novo* mutations vs. standing variation (Glémin & Ronfort, 2013). Finally, more phylogenetically structured sets of network analyses are needed to determine which network properties promote developmental system drift and whether the exploration of genotypic space that occurs by this process fosters the origin of novel functions.

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Box 1: Connecting Genotype to Phenotype

Most studies reviewed here identified allelic variation affecting flowering time starting with either quantitative trait locus (QTL) mapping or a genome wide association study (GWAS). QTL mapping tests for linkage between genetic markers and trait variation in controlled crosses derived from a limited number of parents. QTL detection power and mapping precision depend on marker density, population size, and the number of generations of recombination since the initial cross. In many species, QTL mapping has been limited to one or two biparental crosses, sampling too few genotypes to yield a population- or species-wide picture of a trait's genetic architecture. Moreover, the challenging work to go from broad genomic intervals to causal variants is never completed for most QTLs.

GWAS overcomes some of these limitations. Hundreds of genotypes are sequenced, sampling much more diversity and many generations of recombination that have eroded trait-marker associations except at the causal polymorphism and the most tightly linked variants. Power to detect marker effects depends on the sample size of each genotypic class, and consequently, GWAS is most powerful for detecting common, large-effect alleles. Population structure and kinship must be controlled for to reduce false positives. Even with whole genome re-sequencing data, coverage is often too low to include copy-number or presence-absence variants, and many studies ignore haplotype and insertion-deletion information, complicating candidate gene and causal variant identification.

Neither of these approaches reveals whether allelic variation was shaped by past adaptive processes. Population genomic analyses are needed to infer selective sweeps or test for associations between allele frequency and environmental variation. Conversely, while population genomics studies on their own may highlight adaptive variation at homologs of flowering regulators (e.g., Keller *et al.*, 2012; Pyhäjärvi *et al.*, 2013), additional work remains necessary to connect sequence and flowering time variation, as these genes often regulate additional traits.

Box 2 - Glossary

Artificial selection: Human-imposed selection for desired phenotypes and the maintenance of those phenotypes in the population.

Convergent evolution: Repeated origin of similar phenotypes in independent evolutionary lineages.

Balanced polymorphism: Multiple alleles at a single locus are actively maintained by selection over many generations within a population.

Antagonistic pleiotropy: Allelic variation at a single locus where different alleles have the highest relative fitness in different environments.

Synergistic pleiotropy: Allelic variation at a single locus that confers beneficial effects through multiple phenotypes.

Ecological speciation: Reproductive isolation evolves as a by-product of divergent selection acting on populations adapting to different environments

Developmental system drift: Divergence through time of gene regulatory networks governing the development of a homologous trait even as the phenotype itself remains conserved

Figure Legends

Figure 1

Case studies at three scales illustrate how change in DNA copy number is associated with variation in phenology. (a) In maize, decreasing genome size and heterochromatin knob count with elevation is correlated with earlier flowering. Larger genome sizes are associated with slower cell production rates and thus likely slower developmental progress toward flowering. Data adapted from Bilinski *et al.* 2018. (b) In *M. guttatus*, copy number variation in a tRNA ligase is associated with variation in flowering time, and the relative fitness of these alleles differs across years. Data adapted from Nelson *et al.* 2019. (c) In *A. thaliana*, copy number variation in a cis-regulatory element in the *CO* promoter causes changes in flowering time and interacts with the presence/absence of a functional FRI allele. Data adapted from Rosas *et al*. 2014.

Figure 2

Polygenic adaptation during maize domestication and dispersion. (a) Regulatory relationships of genes involved in the evolution of photoperiodic flowering during maize domestication and dispersion. (b) A *cis*-regulatory allele of *ZCN8* (dark blue) became common as maize was domesticated and initially dispersed beyond the Balsas River basin (yellow star). Next, an additional variant in *ZCN8* and variants affecting *Vgt1*, *ZmCCT9*, *ZmCCT10* and *ZmMADS69* (light blue) allowed for further northward expansion of maize cultivation in North America.

Figure 3

Epistatic interactions between sub-genomes affect flowering following polyploidy. In allopolyploid *Arabidopsis suecica*, a functional vernalization pathway is restored through interactions between gene copies from both the *A. arenosa* and *A. thaliana* parental genomes. The strong *AaFRI* allele transactivates the strong *AtFLC* alleles to repress flowering unless plants experience sufficient vernalization.

Figure 4

Rewiring of flowering time regulatory pathways accounts for differences between annual and perennial life histories. (a) In the perennial *Arabis alpina*, cold exposure (blue interactions) and aging (green interactions) are both required to promote floral induction. (b) In *Arabidopsis thaliana*, long

1211 days (orange interactions) can promote flowering independently of cold exposure (blue interactions)
1212 and aging (green interactions).

Table 1. Flowering Time Genes Contributing to Crop Domestication and Dispersion

Phenotypic effect	Species	Common Name	Gene	Variant(s)	Reference(s)
Reduced photoperiod and vernalization response in long-day crops	*Hordeum vulgare*	Barley	*VRN2-H2*	deletion	(Yan *et al.*, 2004)
	Hordeum vulgare	Barley	*Ppd-H1*	coding sequence mutation	(Turner *et al.*, 2005)
	Triticum monococcum	Einkorn Wheat	*VRN2*	deletion; coding sequence mutation	(Yan *et al.*, 2004)
	Triticum monococcum	Einkorn Wheat	*VRN1*	5' cis-regulatory variation	(Yan *et al.*, 2003, 2004)
	Triticum aestivum ssp. aestivum	Winter Wheat	*Ppd-H1*	copy number variation; homeolog combinations	(Bentley *et al.*, 2013; Würschum *et al.*, 2015, 2018)
	Pisum sativum	Pea	*ELF3*	coding sequence mutation	(Weller *et al.*, 2012)
	Lens culinaris	Lentil	*ELF3*	coding sequence mutation	(Weller *et al.*, 2012)
Changes in photoperiod requirements in short-day crops	*Solanum lycopersicum*	Tomato	*SP5G*	3' UTR cis-regulatory variation	(Soyk *et al.*, 2017; Zhang *et al.*, 2018)
	Sorghum bicolor	Sorghum	*FT*	5' cis-regulatory variation	(Cuevas *et al.*, 2016)
	Glycine max	Soybean	*FT2c*	TE insertion in intron	(Wu *et al.*, 2017)
	Helianthus annuus	Sunflower	*HaFT1*	coding sequence mutation	(Blackman *et al.*, 2010)
	Zea mays L.	Maize	*ZCN8*	5' cis-regulatory variation	(Guo *et al.*, 2018)
	Zea mays L.	Maize	*Vgt1*	TE insertion in coding region, coding sequence mutation	(Ducrocq *et al.*, 2008)
	Zea mays L.	Maize	*ZmMADS69*	unknown	(Liang *et al.*, 2019)
	Zea mays L.	Maize	*ZmCCT9*	TE insertion in 5' regulatory region	(Huang *et al.*, 2018b)
	Zea mays L.	Maize	*ZmCCT10*	TE insertion in 5' regulatory region	(Hung *et al.*, 2012; Yang *et al.*, 2013)

	Oryza sativa	Rice	*PRR37*	coding sequence mutation	(Koo *et al.*, 2013)
	Oryza sativa	Rice	*Ghd7*	deletion; coding sequence mutation	(Xue *et al.*, 2008; Yan *et al.*, 2013)
	Glycine max	Soybean	*PHYA*	deletion; coding sequence mutation	(Xu *et al.*, 2013; Jiang *et al.*, 2014)
	Phaseolus vulgaris	Common bean	*PHYA3*	coding sequence mutation	(Weller *et al.*, 2019)

Table 2. Flowering Time Genes Contributing to Natural Variation among Wild Populations[1]

Phenotypic Effect	Species	Gene	Substitution Type[2]	Reference(s)
Loss of Vernalization Response	*Arabidopsis thaliana*	*FRI*	Coding (20)	(Johanson *et al.*, 2000; Shindo *et al.*, 2005; Strange *et al.*, 2011)
	Arabis alpina	*PEP1*	Coding (4), Regulatory (1)	(Albani *et al.*, 2012)
	Capsella rubella	*FLC*	Regulatory (2), Coding (1)[3]	(Guo *et al.*, 2012; Yang *et al.*, 2018)
	Boechera stricta	*FLC*	Coding (1)	(Lee *et al.*, 2018)
	Arabidopsis arenosa	*FLC*	Coding (2)	(Baduel *et al.*, 2018)
Varying Duration of Cold Required for Vernalization	*Arabidopsis thaliana*	*FLC*	Regulatory (5)	(Coustham *et al.*, 2012; Li *et al.*, 2014, 2015)
Varying Sensitivity to Ambient Temperature	*Arabidopsis thaliana*	*FLM*	Regulatory (8)	(Lutz *et al.*, 2015, 2017)
Loss of Short-Day Vernalization Response	*Brachypodium distachyon*	*FTL9*	Coding (2)	(Woods *et al.*, 2019)
Early Flowering in Short Days	*Arabidopsis thaliana*	*FT*	Regulatory (2)	(Bao *et al.*, 2019)
	Arabidopsis thaliana	*MAF2*	Coding (1)	(Rosloski *et al.*, 2010)
	Arabidopsis thaliana	*SVP*	Coding (1)	(Méndez-Vigo *et al.*, 2013)
	Arabidopsis thaliana	*PHYC*	Coding (2)[3]	(Balasubramanian *et al.*, 2006)
Early Flowering in Long Days	*Arabidopsis thaliana*	*CO*	Regulatory (3)[3]	(Rosas *et al.*, 2014)
	Arabidopsis arenosa	*CO*	Regulatory (2)	(Baduel *et al.*, 2018)
	Arabidopsis thaliana	*FLC*	Regulatory (7)	(Lempe *et al.*, 2005; Quadrana *et al.*, 2016)
	Arabidopsis thaliana	*FRL1*	Coding (1)[3]	(Schläppi, 2006)

	Arabidopsis thaliana	*FRL2*	Coding (1)[3]	(Schläppi, 2006)
Early Flowering in Constant Light	*Arabidopsis thaliana*	*PHYD*	Coding (1)[3]	(Aukerman *et al.*, 1997)

[1]Only genes where flowering time function has been experimentally verified are listed. [2]Number of independent allelic variants discovered by type is given in parentheses. [3]One or more of the allelic variants has only been observed in one accession.

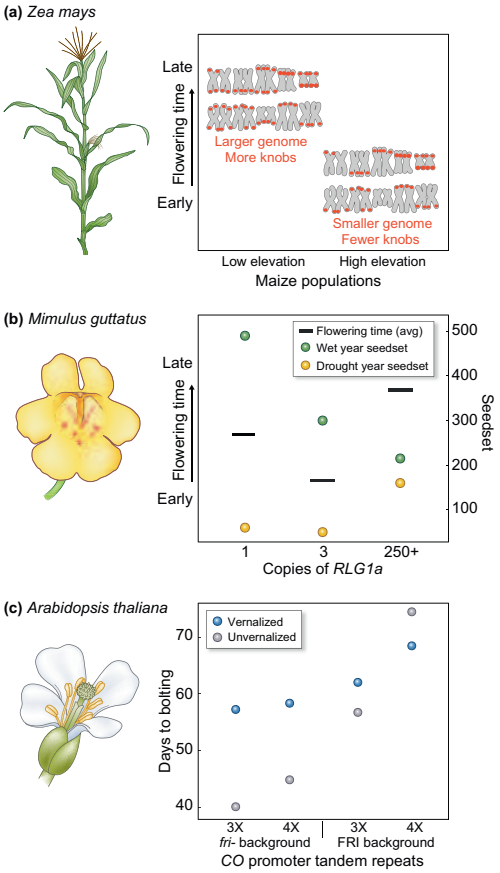

Figure 1

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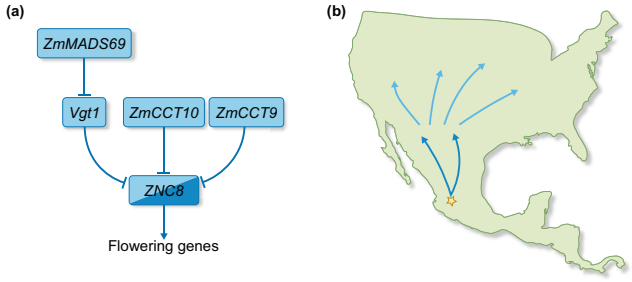

Figure 2

Tansley Review 30442

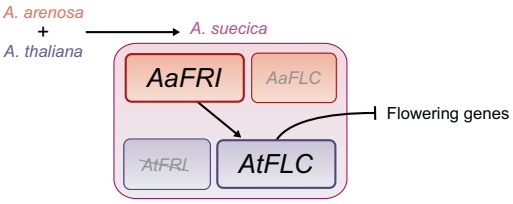

Figure 3

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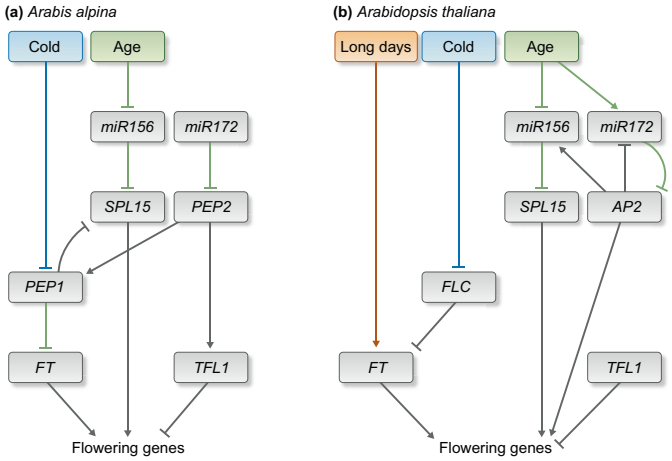

Figure 4

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