



Genomics of Developmental Plasticity in Animals

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Developmental plasticity refers to the property by which the same genotype produces distinct phenotypes depending on the environmental conditions under which development takes place. By allowing organisms to produce phenotypes adjusted to the conditions that adults will experience, developmental plasticity can provide the means to cope with environmental heterogeneity. Developmental plasticity can be adaptive and its evolution can be shaped by natural selection. It has also been suggested that developmental plasticity can facilitate adaptation and promote diversification. Here, we summarize current knowledge on the evolution of plasticity and on the impact of plasticity on adaptive evolution, and we identify recent advances and important open questions about the genomics of developmental plasticity in animals. We give special attention to studies using transcriptomics to identify genes whose expression changes across developmental environments and studies using genetic mapping to identify loci that contribute to variation in plasticity and can fuel its evolution.

Keywords: developmental plasticity, reaction norms, environmentally responsive genes, genomics of plasticity, plasticity variation

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ADAPTIVE DEVELOPMENTAL PLASTICITY

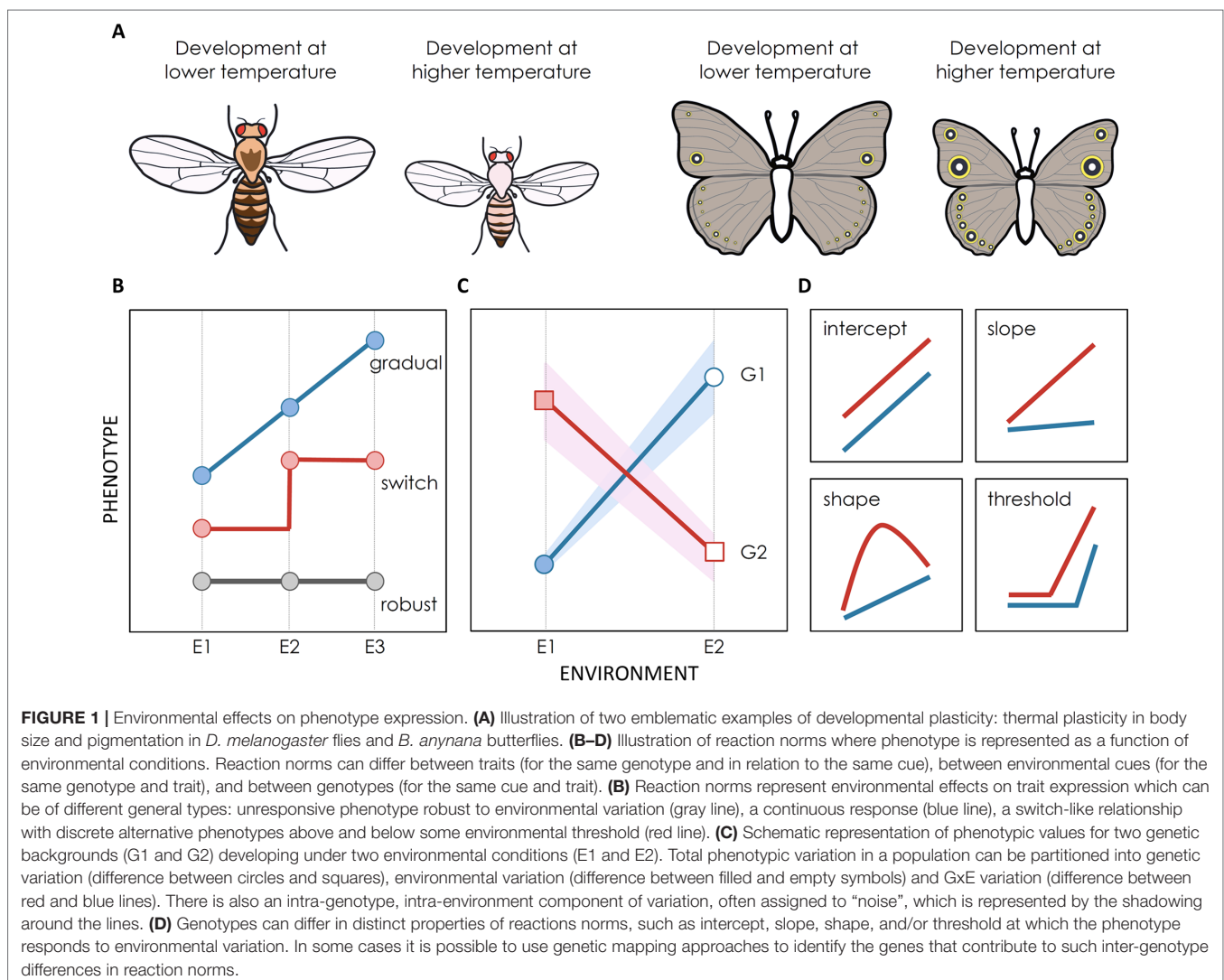
Phenotypic variation is the raw material for natural selection to drive adaptation and speciation. Studies on a variety of taxa have provided valuable insights into the molecular mechanisms that produce phenotypic variants and into the evolutionary forces and ecological conditions that shape phenotypic frequencies in populations (see Carroll, 2000; Stern, 2000; Whitehead and Crawford, 2006; Laland, 2015). We have accumulated detailed data of the genetic basis of variation for many adaptive traits (including morphology, pigmentation, behavior, and life histories) in relation to diverse selective agents (including communication, mating, and infection; e.g. Sasabe et al., 2007; Greenwood et al., 2011; Martins et al., 2014). Progress also includes studies that explore the role of environmental conditions as instructive agents that can affect the production, more than just the frequency, of phenotypic variants (Przybylo et al., 2000; Chakir et al., 2002; Gilbert and Epel, 2009; Torres-Dowdall et al., 2012; Day and McLeod, 2018; Fraimout et al., 2018; Sentis et al., 2018). This environmental regulation of phenotype expression, by which a genotype can produce different phenotypes depending on the external conditions experienced, is called phenotypic plasticity. During adulthood, environmentally induced phenotypes are often reversible, as is the case with rapid metabolic, physiological, or behavioral alterations (e.g. Oufiero and Whitlow, 2016; Abbey-Lee and Dingemans, 2019; Guzzo et al., 2019). In the case of developmental plasticity, external environmental cues influence

developmental rates and/or trajectories and lead to changes in adult phenotypes that are often irreversible (reviewed by, e.g., Nijhout, 2003a; West-Eberhard, 2003; Beldade et al., 2011; Moczek et al., 2011; Edelaar et al., 2017; Klingenberg, 2019; **Figure 1**). The effects of environmental conditions can also affect the phenotype of future generations and this type of trans-generational plasticity is receiving increased attention (e.g. Gapp et al., 2014; Walsh et al., 2016; Heckwolf et al., 2018; Schulz et al., 2019; Fuxjäger et al., 2019). This review focuses on intra-generational developmental plasticity in animals, including an overview of its reciprocal effects on evolution (**Box 1**) and an emphasis on the genomic underpinnings of its regulation and of its evolution. A number of insightful reviews have provided a historical perspective of the concept and importance of plasticity and non-genetic inheritance in the study of evolution (e.g. DeWitt and Scheiner, 2004; Pigliucci, 2007; Bossdorf et al., 2008; Mesoudi et al., 2013; Deans et al., 2015; Nicoglou, 2015; Charlesworth et al., 2017; Futuyama, 2017; Svensson, 2018).

Inductive and Selective Environments

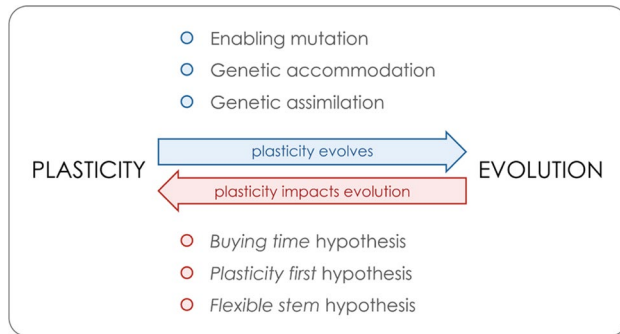
Developmental plasticity is pervasive in nature, with many environmental factors affecting the expression of different traits in a variety of species. Emblematic examples of developmental plasticity include temperature-dependent sex determination in reptiles (Merchant-Larios and Díaz-Hernández, 2013; Mitchell et al., 2018; Noble et al., 2018), nutrition-dependent caste determination in social insects (Maleszka, 2008; Smith et al., 2008), and density-dependent production of dispersing morphs in swarming locusts (Pener and Simpson, 2009; Ernst et al., 2015) and other insects (e.g. aphids; Braendle et al., 2006).

In the study of the regulation and evolution of developmental plasticity, it is often useful to distinguish between the environmental factor(s) that can induce changes in development, hereafter called inductive environmental cue(s), and the environmental factor(s) responsible for fitness differences between induced phenotypes, hereafter called the selective environment (**Figure 2A**). The relationship between inductive and selective environments is, in fact, of fundamental importance



BOX 1 | Reciprocal interactions between plasticity and evolution.

We illustrate the key aspects of the relationship **between plasticity and evolution**, whose reciprocal interactions are further discussed in the main text. On the one hand, plasticity is itself a heritable trait that is under selection and can evolve (blue arrow). Above the arrow, we list three of the genetic mechanisms relevant for the evolution of plasticity. On the other hand, plasticity has been proposed to impact adaptive evolution (red arrow). Below the arrow, we list three of the proposed non-mutually exclusive and partly overlapping hypotheses by which plasticity might positively impact adaptive evolution and diversification.



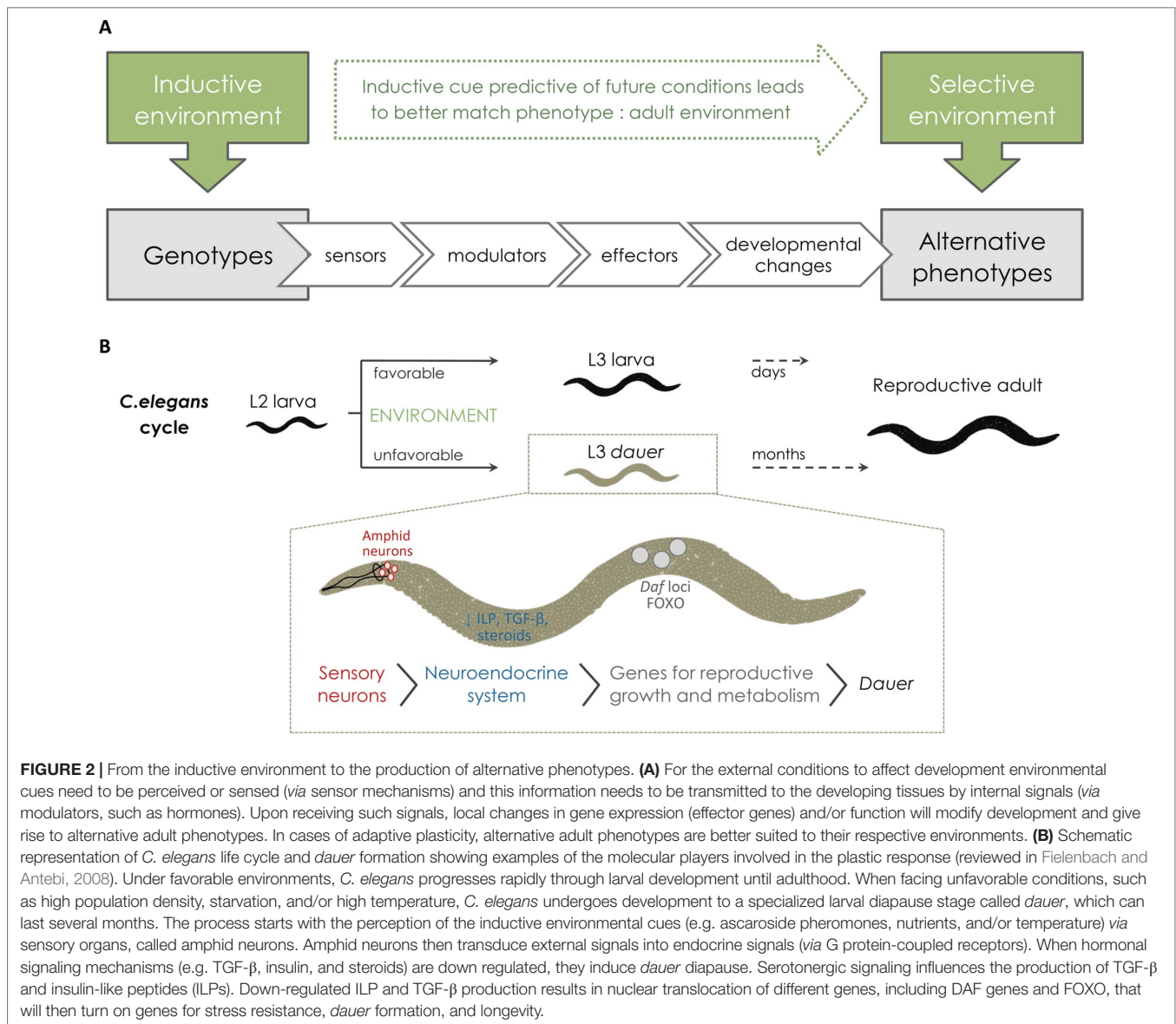
Enabling mutation refers to a genetic alteration conferring environmental sensitivity to a phenotype that was originally not plastic. This allows the expression of plasticity, which can thereafter be shaped by selection (e.g. Suzuki and Nijhout, 2006). Note that although such a mutation refers to the acquisition of plasticity from a non-plastic ancestral, it has been proposed that some level of plasticity is likely the ancestral condition for developmental processes (e.g. Newman and Müller, 2000; Nijhout, 2003a; Nijhout et al., 2017).

Genetic accommodation refers to the process by which selection shapes the properties and/or magnitude of a plastic response (West-Eberhard, 2003; West-Eberhard, 2005; Crispo, 2007). Such changes in plasticity have been shown to occur under artificial and natural selection and include the evolution of both increased and decreased plasticity (e.g. Gomez-Mestre and Buchholz, 2006; Suzuki and Nijhout, 2006; Ledon-Rettig et al., 2008; Kulkarni et al., 2017).

Genetic assimilation refers to the process of genetic accommodation by which there is the fixation of what were previously environmentally induced phenotypes. This process is believed to have been involved **in the transition from polyphenisms to polymorphisms** and sustain a mechanism by which plasticity can promote phenotypic diversification (e.g. Schlichting and Wund, 2014; Ehrenreich and Pfennig, 2016; Schneider and Meyer, 2017). The **“buying time” hypothesis** suggests that when colonizing a new habitat or facing environmental perturbation, a “plastic population” can first adjust to the new conditions by expressing **distinct plastic phenotypes and thereby persist enough time for new mutations to happen and fuel adaptive evolution** (e.g. Chevin and Lande, 2009; Corl et al., 2018; Pennisi, 2018). As discussed in the main text, there is a rationale and specific examples why plasticity might hurt rather than help in the face of new environmental conditions (e.g. Langerhans and Dewitt, 2002; Ghalambor et al., 2007; Oostra et al., 2018). The **“plasticity first” hypothesis** proposes that plasticity can initiate and accelerate the rate of phenotypic change in that **plastic adaptive phenotypes can emerge earlier and faster than phenotypic changes due to genetic mutation**. Under this model, multiple initial alternative phenotypes generated by developmental plasticity can become genetically fixed by genetic assimilation (e.g. Levis and Pfennig, 2016; Levis and Pfennig, 2018). The **“flexible stem” hypothesis** relies on the exact same idea but focuses explicitly on plasticity **in ancestral species/populations facilitating phylogenetic diversification**. This will occur in cases where plasticity produced alternative phenotypes in sister lineages that were later on fixed by genetic assimilation (West-Eberhard, 2003; Wund et al., 2008; Schneider and Meyer, 2017).

for the evolution of plasticity (Nijhout, 2003a). In some cases, the main inductive and selective environmental factors are the same, such as with the thermally induced changes in body size that influence the thermo-regulation of *Drosophila melanogaster* adults (Ghosh et al., 2013; **Figure 1A**). In others, the inductive cue is predictive of future environmental conditions but not the main selective agent. This is often the case with polyphenisms, which are environmentally induced alternative discrete phenotypes (see Nijhout, 2003a; Simpson et al., 2011) that are common in relation to alternating seasons (see Kivelä et al., 2013). In the polyphenism of *Bicyclus anynana* butterflies, for example, the temperature experienced during development determines adult pigmentation and life histories (**Figure 1A**) and anticipates seasonal changes in background foliage coverage, favoring season-specific anti-predatory and reproductive strategies (Brakefield et al., 2009; Monteiro, 2015; Beldade and Peralta, 2017). In such seasonal polyphenisms, inductive and selective environments reflect temporal heterogeneity (Brakefield et al., 2007). External factors can also reflect spatial heterogeneity, such as that associated with different levels of predation between ponds inhabited by *Rana temporaria* tadpoles (Van Buskirk, 2017), with the alternative environmentally induced phenotypes being produced on different locations. In other cases of plasticity, the alternative morphs co-occur. For instance, with the nutritional-dependent caste determination in social insects, the heterogeneity in adult “environment,” rather than in any external factor, exists in terms of task allocation inside the colony (Jeanson and Weidenmüller, 2014; Gordon, 2016).

Typically, one same inductive cue will simultaneously affect different traits (e.g. predator presence affects head morphology and body size in *Poecilia reticulata* guppies; Torres-Dowdall et al., 2012), which are often part of the same “**plasticity syndrome**”. In these cases, **different traits can be integrated into functional suites that respond to environmental influences in a concerted manner and that are typically also selected in concert** (e.g. Mateus et al., 2014; Oostra et al., 2014; van Bergen and Beldade, 2019). Such extent of **integration** (or, conversely, **independence**) among plastic traits, some of which might be adaptive, whereas others might be maladaptive, has important implications for phenotypic variation and diversification **as it influences responses to selection**. A classical example of correlated plastic responses is the effect that temperature has on different phenotypes, including development time (e.g. diapause), body size, and other life-history traits in many arthropods. Although diapause is thought to be an adaptive plastic response, this may not be true for correlated traits whose developmental rates are affected by the availability of energy resources (Gotthard and Nylin, 1995). It is also common that one same trait can be simultaneously affected by different environmental cues (e.g. production of the winged morph in aphids affected by tactile stimulation, nutrition, and other factors; Braendle et al., 2006). Exploring how organisms **integrate information** from different external cues is a topic of much current interest, as studies of plasticity start to tackle what is the typical complexity of natural environments, where organisms are exposed to multiple and highly dynamic environmental factors (e.g. Saastamoinen et al., 2013; Fischer et al., 2017; Saxon et al., 2018).



Reaction Norms

Reaction norms (Figures 1B–D), where variation in phenotype is displayed as a function of variation in environment, are a common and very useful way to graphically represent developmental plasticity (Schlichting and Pigliucci, 1998; DeWitt and Scheiner, 2004; Sultan, 2017). These representations reflect the extent and the effects of environmental cues on phenotype expression (Figure 1B). Horizontal (flat) lines represent traits that are invariant, or robust (Félix and Barkoulas, 2015), to environmental conditions. For example, vulval cell fate patterning in *Caenorhabditis elegans* has been shown to be unresponsive to changes in temperature, salinity, or nutrients, which affect other aspects of worm development (Félix, 2012). Diagonal lines, in contrast, reflect a gradual relationship between environment and phenotype, such as temperature-induced differences in insect body size (Nijhout,

2003b; Mirth and Shingleton, 2012); the steeper the line is, the more plastic is the trait. In other cases, such as the polyphenisms described earlier, responses to environmental variation can be discontinuous, with discrete phenotypes below and above some environmental thresholds (e.g. Pfennig, 1992; Kamakura, 2011; Casasa and Moczek, 2018). Well-described examples of non-linear reaction norms resulting in polyphenisms include honey bees, where only larvae that are fed high quantities of royal jelly develop into queens (Kamakura, 2011), and the diet-dependent size of horns in dung beetle males, which is disproportionately large for large males (Moczek, 1998). Some of such discontinuous reaction norms may result from cases where organisms can only produce two alternative phenotypes or from cases where organisms have never been exposed to intermediate environmental conditions, which would otherwise reveal gradual reaction norms.

The degree and type of plastic responses can vary between species, as is the case with the density-dependent swarming responses in locusts and grasshoppers (Song et al., 2017) or with the thermal effects on pigmentation in different mycalesine butterflies (van Bergen et al., 2017). Plastic responses can also differ between populations of the same species (Figures 1B, C). For instance, the effects of oxygen on brain and gill size differ between populations of cichlid fish from different geographical locations (and oxygen regimes; Crispo and Chapman, 2010). Reaction norms typically describe how one environmental factor affects one specific trait for one particular genetic background, and they usually differ between traits, environmental cues, and genotypes. For instance, dung beetle horn size increases more with food quantity than does body size (Moczek, 2002; Casasa and Moczek, 2018). Different melanin-based traits respond in independent (sometimes even opposing) manners to temperature and photoperiod in butterflies (Stoehr and Wojan, 2016). The different responses that genotypes can have to environmental inputs correspond to non-parallel reaction norms and significant genotype-by-environment (GxE) interactions (Saltz et al., 2018; Figures 1C, D). The genes responsible for those inter-genotype differences in reaction norms can presumably fuel the evolution of plasticity and will be further discussed in *Genes for Variation in Plasticity*.

External environmental cues affect adult phenotype by altering developmental rates and/or trajectories. For this to happen, organisms must be able to somehow sense external conditions and provide information about those conditions to the developing tissues where changes in developmental cascades will result in changes in phenotype (Figure 2A). The cellular and molecular players involved in the sequence of steps that connect variation in external conditions to variation in developmental outcomes have been characterized in a number of cases, such as dauer formation in *C. elegans* nematodes (see Fielenbach and Antebi, 2008; Allen et al., 2015; Figure 2B). The perception of external conditions can involve specific neurons (e.g. temperature-sensitive neurons in *D. melanogaster*; Peng et al., 2007) and/or specific molecules (e.g. ascaroside pheromones that indicate high density in *C. elegans*; Ludewig and Schroeder, 2013). The information about the external conditions is then conveyed to the tissues developing internally, a process that typically involves one or various hormones whose synthesis, degradation, and/or activation depend on environmental conditions (Mirth et al., 2009; Mirth et al., 2014; Vellichirammal et al., 2017). These hormones will then affect gene expression and/or function in the target plastic tissues (e.g. Koyama et al., 2013; Monteiro et al., 2015). In some cases, direct effects of environmental factors on gene expression have been reported, for instance, with temperature presumably directly regulating the transcription of clock genes in zebrafish (Lahiri et al., 2005). Because developmental plasticity refers to the production of different phenotypes from the same genotype, it necessarily involves epigenetic mechanisms, i.e. that are beyond the nucleotide sequence in genomic DNA. Mechanisms such as methylation of DNA or acetylation of histones, for example, are capable of mediating changes in gene expression without changes in gene sequence and have been implicated in plastic development (e.g. caste determination in honeybees and ants; Kucharski et al.,

2008; Lyko et al., 2010; Bonasio et al., 2012; Simola et al., 2013b, Simola et al., 2016). The cascade of events from environmental inputs to alternative phenotypes will involve “effector genes” (cf. Figure 2) whose expression and/or function depend on environmental conditions and underlie developmental changes. These effector genes will be further discussed in *Environmentally Responsive Genes*.

Plasticity and Evolution

Theoretical and *in silico* studies have identified a series of conditions that can influence the evolution of plasticity (e.g. Tufto, 2000; Lande, 2009). These include the predictability of environmental fluctuations and the reliability of inductive environmental cues in predicting the future selective environment (Leimar et al., 2006; Reed et al., 2010), both of which should favor plasticity. The availability and effective assessment of such cues will determine the evolution of plasticity in relation to other possible responses to environmental variation, such as bet-hedging (Simons, 2011; Herman et al., 2014; Tufto, 2015). The evolution of plasticity can also be influenced by other factors, such as potential costs associated with maintaining the sensory and regulatory mechanisms needed for plastic responses (DeWitt, 1998; Tufto, 2000; Callahan et al., 2008; Snell-Rood, 2012; Lande, 2014; Murren et al., 2015). Trade-offs between plasticity and different fitness-related traits have been documented that can presumably constrain the evolution of plasticity. For example, in freshwater snails, the levels of predator-induced plasticity in shell shape have been shown to be negatively correlated with growth rate (DeWitt, 1998) and predator-induced phenotypes have been shown to have lower survival in the presence of a different predator (Hoverman and Relyea, 2009). When the ecological conditions favor plasticity, and because plasticity is itself a heritable trait (Via and Lande, 1985; Scheiner and Lyman, 1989; Scheiner and Lyman, 1991; Thompson, 1991; Carter et al., 2017), plasticity can and does evolve (Box 1). Several studies have documented transitions between plastic and robust development in both natural populations (e.g. Cahan et al., 2004; Aubret and Shine, 2009) and laboratory populations (e.g. Suzuki and Nijhout, 2006; Bento et al., 2010). The loci carrying allelic variation responsible for variation in plasticity that can fuel its evolution will be discussed in *Genes for Variation in Plasticity*.

It is believed that, in most cases, the ancestral condition in trait development is some level of environmental sensitivity, with selection then favoring the ability to buffer environmental effects (Newman and Müller, 2000; Nijhout, 2003a; Nijhout et al., 2017). Selection can act on the regulation of environmentally sensitive phenotypes and adjust the properties and/or magnitude of the plastic responses by a process called genetic accommodation (West-Eberhard, 2003; West-Eberhard, 2005; Crispo, 2007). Well-documented examples include the evolution of thermal plasticity in larval pigmentation in experimental populations of *Manduca sexta* (Suzuki and Nijhout, 2006) and the evolution of developmental rate in response to aridification in spadefoot toads (Gomez-Mestre and Buchholz, 2006; Kulkarni et al., 2017). When genetic accommodation leads to the (genetic) fixation of what was previously an environmentally induced phenotype,

we talk about genetic assimilation (Schlichting and Wund, 2014; Ehrenreich and Pfennig, 2016; Schneider and Meyer, 2017). The occurrence and underlying genetic mechanism of genetic assimilation have what is arguably its classical example in the fixation of a *bithorax* phenotype originally induced by the exposure of *D. melanogaster* to ether (Waddington, 1953; Gibson and Hogness, 1996). More recent studies of genetic assimilation have illustrated how transitions from environmental to genetic control of adaptive traits may happen at a (relatively) fast pace (e.g. loss of plasticity in head size in *Notechis scutatus* snakes within a few thousand years; Aubret and Shine, 2009) and how it can lead to complex interdependence between environmentally and genetically induced phenotypes (e.g. with caste determination in *Pogonomyrmex* harvester ants; Cahan et al., 2004).

Whereas, in the previous section, we discussed how plasticity is a trait under selection and can evolve, here we will focus on how plasticity might impact adaptive evolution (Box 1). Evolved plasticity is thought to be able to help populations face challenges posed by changing environments (e.g. de Jong, 2005; Xue and Leibler, 2018; Fox et al., 2019), allow them to cope with environmental heterogeneity (e.g. West-Eberhard, 2003; Lande, 2009; Levis et al., 2018), and aid the colonization of novel environments (e.g. Lande, 2015; Snell-Rood et al., 2018). More than plasticity potentially enabling persistence under novel conditions and thereby “buying time” for adaptation to occur (Corl et al., 2018; Pennisi, 2018), it has been suggested that plasticity may actually promote adaptive evolution and diversification (e.g. see Wund, 2012; Smith and Ritchie, 2013; Gilbert et al., 2015). This idea has been proposed with a number of variations, sometimes subtle, that emphasize different mechanisms and/or outcomes. Modeling work has sustained that plasticity might be able to foster an increase in the levels of genetic variation in a population (e.g. Draghi and Whitlock, 2012), thereby impacting adaptive evolution. A particular type of genetic variation often associated with plasticity is called cryptic genetic variation, i.e. genetic variation that is normally not expressed but can be uncovered by environmental or genetic perturbation (e.g. Gibson and Dworkin, 2004; McGuigan et al., 2011; Paaby and Rockman, 2014; Schneider and Meyer, 2017). Plasticity has been argued to favor both the accumulation of cryptic genetic variation (e.g. in genes not expressed under certain environmental conditions) and its release (e.g. upon environmental conditions outside the range typically experienced by the population). Such genetic variation can then fuel evolutionary change (Gibson and Dworkin, 2004; Ledón-Rettig et al., 2010; Paaby and Rockman, 2014; Schneider and Meyer, 2017). Furthermore, the evolutionary potential of plasticity has been illustrated by the contribution of plasticity to reproductive isolation, which includes cases where plastic traits affect mating (e.g. pigmentation patterns in butterflies; Westerman et al., 2014) or timing of organismal life-events (e.g. phenological shifts in grasshoppers; Buckley et al., 2015).

The range of phenotypic variation generated by plasticity has been proposed to be able to initiate and accelerate the pace of adaptive evolution and to promote morphological as well as phylogenetic diversification (West-Eberhard, 2003; West-Eberhard, 2005; Pfennig et al., 2010; Wund, 2012). This relies on

the suggestion that plasticity could be an immediate source of initial inter-individual differences in phenotypes (and in fitness) that could then become genetically fixed by genetic assimilation (West-Eberhard, 2003; Wund et al., 2008; Susoy et al., 2015; Levis and Pfennig, 2016; Gibert, 2017; Levis and Pfennig, 2019), leading to increased phenotypic diversification among populations. This same idea is at the basis of what have been called the “plasticity-first” model (Levis and Pfennig, 2016; Levis and Pfennig, 2018) and the “flexible stem” hypothesis, with the latter specifically suggesting that a “plastic ancestor” more readily originates phylogenetic divergence and adaptive radiations (West-Eberhard, 2003; Standen et al., 2014; Schneider and Meyer, 2017). This distinction between the two models is not always made; the terms have sometimes been used inter-changeably but are also often discussed separately (Wund et al., 2008; Muschick et al., 2011; Levis and Pfennig, 2016; Gibert, 2017). For instance, the invasion of new niches by amphibian species is proposed to represent a natural example of the “plasticity first” model, with nutrition-induced plasticity fostering the origin of carnivore morphs in some species (Levis et al., 2018). In contrast, evolutionary diversifications in threespine stickleback fish (with head and mouth shape variation across ecotypes; Wund et al., 2008) and tetrapods (with the origin of “terrestrialization” traits; Standen et al., 2014) have been discussed as examples supporting the “flexible stem” hypothesis. The study of plasticity and its (potential) impact on adaptive evolution has generated substantial interest but also much discussion (e.g. Pigliucci, 2007; Laland et al., 2014; Forsman, 2015; Nicoglou, 2015; Turcotte and Levine, 2016; Charlesworth et al., 2017; Futuyama, 2017). This includes controversy about definitions for plasticity as well as some level of lack of clarity about distinction and integration of different models proposed to account for the role of plasticity in adaptation and diversification.

GENOMICS OF PLASTICITY

Development can either respond to or resist environmental perturbation and the balance between such plasticity and/or robustness is crucial for organismal fitness. We know about different molecular mechanisms involved in buffering effects of environmental variation (i.e. conferring robustness to development; see Nijhout et al., 2017), including redundancy in gene enhancers (Frankel et al., 2010) and error-correcting systems (e.g. heat shock proteins; Queitsch et al., 2002; Sangster et al., 2004). Plasticity, on the other hand, has been proposed to be eased by modularity in molecular networks (Snell-Rood et al., 2010) and/or by expansion of certain gene families/classes some textbook models of plasticity, such as water fleas, aphids, and ants and other social insects (e.g. International Aphid Genomics Consortium, 2010; Colbourne et al., 2011; Wurm et al., 2011; Simola et al., 2013a).

Developmental plasticity refers to the effect of environmental conditions on developmental outcomes; as such, it pertains to the environmental component of the total phenotypic variation that exists for a trait (Figure 2C). Yet, there is obviously a genetic basis for plasticity and studies that have attempted to tackle it

from different angles (e.g. Tétard-Jones et al., 2011; Projecto-Garcia et al., 2017; Wellband and Heath, 2017; **Figure 3**). In this section, we focus on recent studies **using gene-candidate and genome-wide approaches** to unravel the genomics of plasticity. We will distinguish between two categories of genes: genes whose expression and/or function change across environments to affect developmental outcome (i.e. the effectors genes in **Figure 2**) and

genes harboring allelic variants responsible for inter-genotype differences in reaction norms (as illustrated in **Figure 1C**). Although this distinction separates genes whose expression/function is environmentally dependent at the organismal level and loci whose effects determine differences in plasticity at the population level, the actual genes in the two categories can overlap to a certain extent (**Figure 3**).

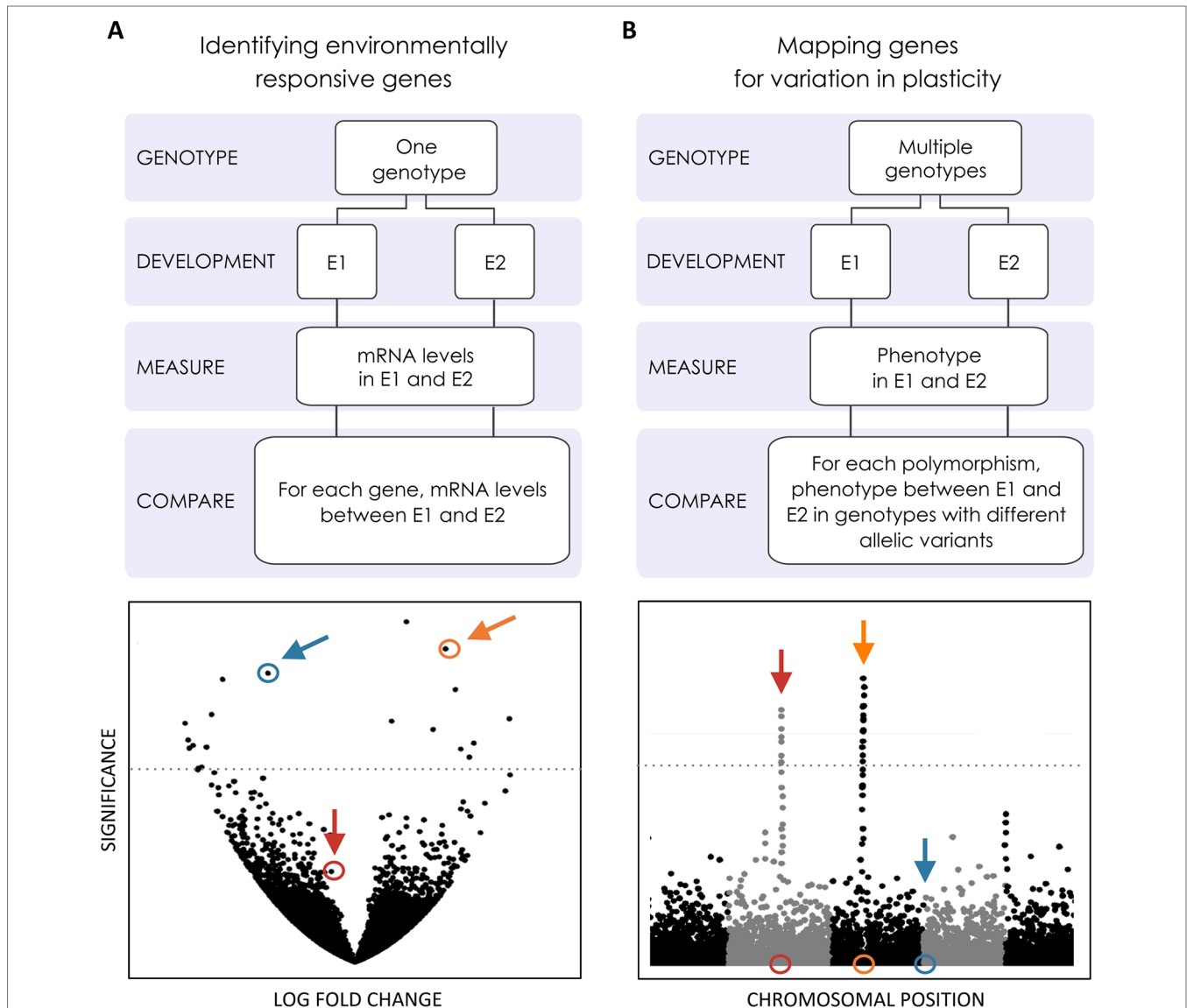


FIGURE 3 | Genome-wide searches for the genetic basis of plasticity. Efforts to explore the genomics of plasticity include transcriptomics and mapping studies [e.g. genome-wide association studies (GWAS)] to identify **genes whose expression changes across environments and loci contributing to variation in plasticity**, respectively. These genes might or might not be the same, as illustrated by the colored loci in **(A)** and **(B)**. **(A)** Volcano plot where the significance in gene expression differences (Y-axis) is displayed as a function of fold change expression across environments (X-axis). Two genes showing significant expression differences (above significance threshold represented by the horizontal line) are highlighted in blue and orange. One where expression is not statistically significantly difference is highlighted in red. **(B)** Manhattan plot where statistical significance in the association with inter-genotype differences in reaction norms (Y-axis) is displayed for each polymorphic site along the chromosomes (X-axis). The location of two polymorphisms showing statistically significant association with plasticity variation is highlighted in red and orange, respectively. One below the statistical significance threshold is highlighted in blue. Genes whose expression is plastic across environments may (gene in orange) or may not (gene in blue) harbor allelic variants contributing to variation in plasticity. Conversely, genes associated with variation in plasticity may (gene in orange) or may not (gene in red) differ in expression between environments.

Environmentally Responsive Genes

Context-dependent gene expression is at the heart of development, transforming a single cell into spatially organized different cell types that make up multicellular organisms (Gilbert, 2000). In the case of developmental plasticity, the environmental regulation of development requires gene expression and/or function to depend also on external context. Here, we will focus on effector genes whose expression changes in plastic tissues to alter developmental fate (Figure 2). Efforts to identify such genes have documented differences in expression between environments for whole developing organisms or specific developing organs and either targeting specific candidate genes/pathways or doing transcriptome-wide scans (Figure 3A).

Candidate gene approaches to probe the genetic basis of environmentally regulated development have ranged from studies of gene expression levels (e.g. using quantitative polymerase chain reaction; e.g. Dalton et al., 2015) to studies of spatial expression patterns on specific organs (e.g. using *in situ* hybridization methods; Gibert et al., 2016). They have also included both *in vivo* (e.g. kairomone-driven regulation of patterning genes during production of the anti-predator defense morph in *Daphnia* water fleas; Miyakawa et al., 2010) and *in vitro* (e.g. temperature-dependent expression of sex-determining genes in turtle gonad cultures; Shoemaker-Daly et al., 2010) approaches as well as single-species (e.g. allatotropin expression under starvation in *M. sexta*; Lee and Horodyski, 2006) and multi-species (e.g. wing-patterning genes in polyphenic ants; Abouheif and Wray, 2002) analyses. Detailed studies of specific and well-known developmental pathways in emblematic plasticity models, such as pigmentation in *Drosophila* (e.g. De Castro et al., 2018), body and organ size in different insects (e.g. Lee and Horodyski, 2006; Mendes and Mirth, 2016), and wing development in ants (e.g. Abouheif and Wray, 2002), have been very insightful. The systematic investigation of melanogenesis enzymes underlying pigmentation development in *D. melanogaster* revealed how the environmental regulation of gene expression can happen *via* modulation of enhancer activity (Gibert et al., 2016; Gibert et al., 2017b; De Castro et al., 2018) or *via* effects on chromatin regulation (Gibert et al., 2007). The investigation of the hormonal mechanisms that underlie the nutritional regulation of body and organ size in different insects, on the other hand, demonstrated tissue and stage specificity of the effects of nutrition on the expression and sensitivity of several players from the insulin and target of rapamycin pathways (Mirth and Shingleton, 2014; Koyama et al., 2016; Mendes and Mirth, 2016). Finally, the analysis of the expression of wing development genes in workers versus queens in different ant species revealed dissociation (and modularity) of wing-patterning genes, which presumably influenced the evolutionary lability of this polyphenism (Abouheif and Wray, 2002; Béhague et al., 2018).

Genome-wide scans of different types have allowed for a more unbiased search of (putative) effector genes, including for traits for which the underlying developmental genetic basis is not well understood. Transcriptomic differences due to differences in developmental environments have been characterized for various species and in relation to various environmental cues,

for instance, nutrition in beetles (Kijimoto et al., 2014) and ant castes (Evans and Wheeler, 2000), temperature in fish (Wellband and Heath, 2017), and multiple environmental cues in flies (Zhou et al., 2012). External environmental factors can affect the expression of a large number of genes, with 15% of the *D. melanogaster* genome being differentially expressed (Zhou et al., 2012) and 10% of the expressed genes being differentially spliced (Jakšić and Schlötterer, 2016) between temperatures. Aside from providing valuable quantitative insights into the distribution of environmental effects on gene expression levels (e.g. Zhou et al., 2012) and allowing researchers to draw transcriptomic reaction norms (Aubin-Horth and Renn, 2009; Gao et al., 2015; Oomen and Hutchings, 2017), transcriptomic scans have been very valuable at identifying candidate effector genes or pathways (see Figure 3) for further detailed analysis, which can be more or less obvious from the onset. Examples include specific gene classes/families differently expressed between castes in social insects (Evans and Wheeler, 2000), the down-regulation of growth and metabolism genes influencing the duration of larval stage in *Strongylocentrotus droebachiensis* sea urchins under food scarcity (Carrier et al., 2015), the differential expression of endocrine and pigmentation-related genes that underlie the seasonal pigmentation morphs in *Junonia coenia* butterflies (Daniels et al., 2014), and the caste-specific expression of chemoreception genes in termites (Mitaka et al., 2016). Whereas most studies have used transcriptomic approaches (e.g. Levine et al., 2011; Zhou et al., 2012; Chen et al., 2015) to investigate environmental effects on the levels and regulation of mRNAs and different types of non-coding RNAs (e.g. Garrett and Rosenthal, 2012; Jakšić and Schlötterer, 2016; Healy and Schulte, 2019), others have focused on environmentally induced changes in levels of protein (using proteomic approaches; e.g. Silvestre et al., 2012) and metabolites (using metabolomic approaches; see Bundy et al., 2009). Although such whole-genome scans can provide valuable insights onto the magnitude and nature of environmental effects on gene expression, it is crucial to remember that the identified differences in gene-product quantity do not necessarily translate into differences in organismal phenotypes (see Evans, 2015).

Genes for Variation in Plasticity

The environmental sensitivity of development is a property of a genotype (e.g. Gockel et al., 2002; Nussey et al., 2005; Lardies, 2008; Saltz et al., 2018). For any specific trait and cue, genotypes can differ in various properties of the corresponding reaction norms (Figure 1D). This includes variation in intercept (e.g. thermal reaction norms for life-history traits in *Ischnura elegans* damselflies; Bouton et al., 2011), shape (e.g. thermal reaction norms for pigmentation in *Drosophila mediopunctata* flies; Rocha et al., 2009), and slope (e.g. thermal reaction norms for growth rate in *Orchesella cincta* springtails; Driessen et al., 2007). Genotypes can also differ in the environmental cue that triggers change or in the environmental threshold for the induction of phenotypic change (e.g. for hormesis in *C. elegans*; Sikink et al., 2014). The genes responsible for variation in reaction norms provide the raw material for selection to drive the evolution of

plasticity (see DeWitt and Scheiner, 2004). There is evidence for both the polygenic nature of artificially selected changes in shape and height of reaction norms (e.g. Wijngaarden and Brakefield, 2000) and the single allelic variants that cause loss (e.g. Bento et al., 2010; Ragsdale et al., 2013; Ragsdale and Ivers, 2016) or gain (e.g. Suzuki and Nijhout, 2006) of environmental sensitivity.

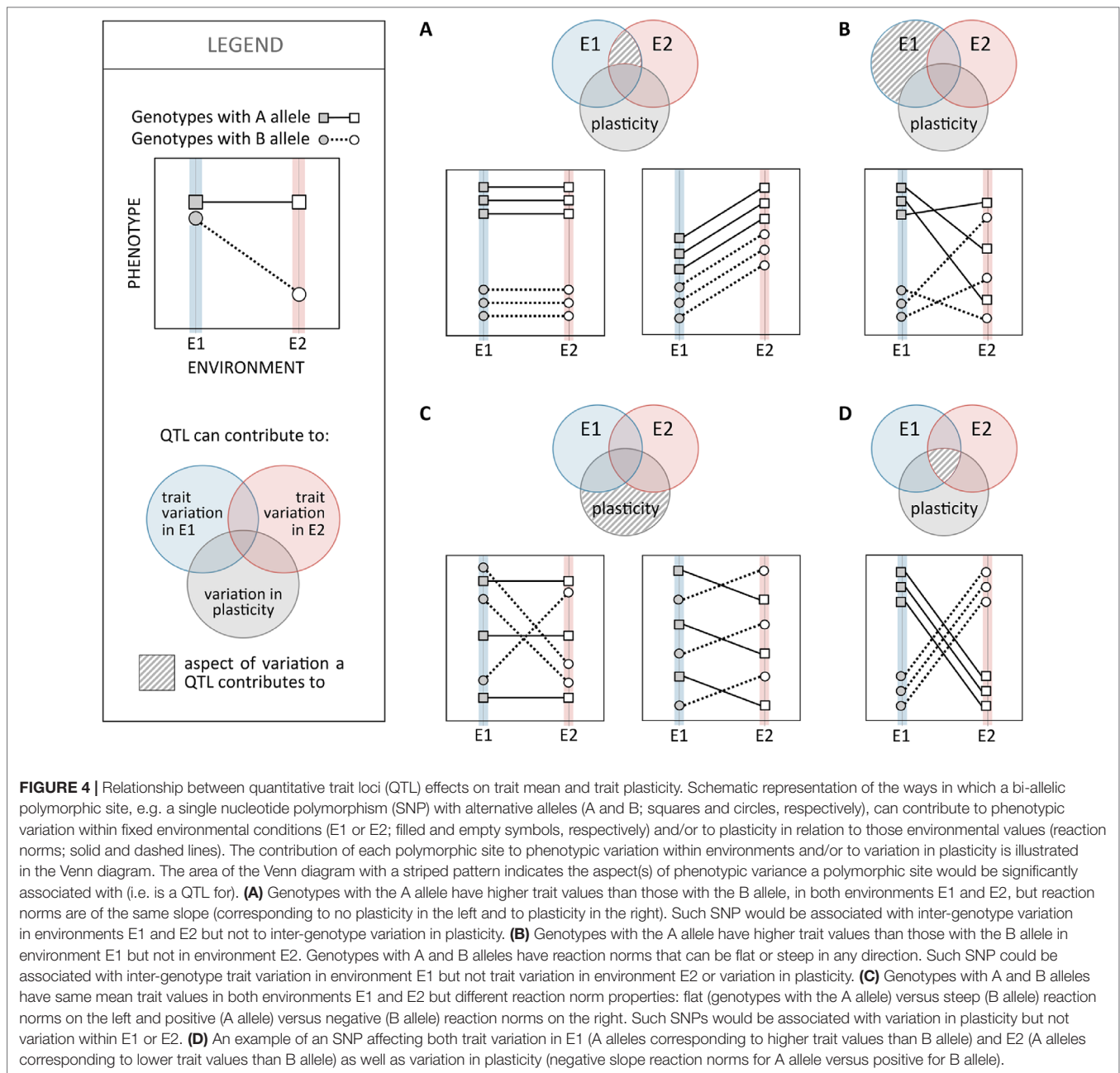
To identify loci contributing to inter-genotype variation in plasticity, researchers have compared reaction norms between allelic variants of specific candidate genes or used genome-wide mapping scans of different types. Studies of thermal plasticity in *D. melanogaster* development, for example, illustrate both approaches: differences in reaction norms for abdominal pigmentation for mutant versus wild-type alleles of different melanogenesis genes (Gibert et al., 2007; Gibert et al., 2017b) and mapping of loci with allelic variation associated with variation in the slope of reaction norms for body size (Lafuente et al., 2018). Although, in the past couple of decades, we have seen great progress in unraveling the genetic basis of phenotypic variation and adaptation, covering many different traits and species (e.g. Barrett and Hoekstra, 2011; Martin and Orgogozo, 2013; Savolainen et al., 2013; Pardo-Diaz et al., 2015), relatively little is known about the genetic basis of variation in plasticity (see Pigliucci, 2005). In fact, most quantitative trait loci (QTL) mapping studies have tracked phenotypic variation under one single environmental condition, precluding the assessment of environment-specific or gene-by-environment effects. Studies that did include phenotyping under different environments (e.g. survival after heat stress in zebrafish; Hosseini et al., 2018), as is necessary to characterize the genetic basis of variation in plasticity, revealed a prevalence for environment-specific QTL (Dilda and Mackay, 2002; Green et al., 2014), which are QTL that are expressed differently in different environments. Studies mapping variation in *D. melanogaster* at different temperatures showed large proportions of QTLs exhibiting QTL-by-environment interactions, for example, 70% (in Gurganus et al., 1998) and 33% to 50% (in Dilda and Mackay, 2002) for bristle number and 83% for reproductive performance (Fry et al., 1998). Environment-specific QTL also includes cases with alleles having antagonistic effects in different environments (e.g. up to 59% of QTLs for variation in life span at different temperatures and nutritional regimes in *D. melanogaster*; Vieira et al., 2000). Although QTL-by-environment interactions certainly reflect inter-genotype differences in reaction norms, they are not necessarily QTLs contributing to inter-genotype variation in plasticity (Figure 4). To unravel such loci, mapping has used the slope of reaction norms as the target quantitative trait. Examples include the identification of QTLs associated with the slope of reaction norms for thermal regulation of life-history traits in *C. elegans* (Gutteling et al., 2007) and of body size (Lafuente et al., 2018) and cold tolerance (Ørsted et al., 2018) in *D. melanogaster*. These studies identified QTLs corresponding to different types of genomic regions (e.g. regulatory and coding) and different putative biological functions (e.g. regulation of development, components of the nervous system, and environmental stress responsive genes), including regulatory genes (Ørsted et al., 2018), which are thought to play key roles on the genetic control of plasticity (Schlichting and Pigliucci, 1993).

More than identifying specific genes and describing their function, studies of the genetic basis of plasticity have shed light onto old debates about the existence and nature of plasticity genes (Via, 1993; DeWitt and Scheiner, 2004; Nicoglou, 2015). The proposed models had distinguished between scenarios where plasticity is a side effect of selection on the (plastic) trait versus where plasticity is itself a direct target of selection (Via and Lande, 1985; Scheiner and Lyman, 1991; Schlichting and Pigliucci, 1993;). Whereas positive genetic correlations between trait values and trait plasticity and environmentally dependent allelic effects are presumably consistent with the former (e.g. Fry et al., 1998), examples where selection on plasticity is independent of selection on trait mean (e.g. thermal plasticity in the timing of egg-laying in *Ficedula albicollis* collared flycatchers; Brommer et al., 2005, and in thorax size in *D. melanogaster*; Scheiner and Lyman, 1991) and/or where selection on trait mean does not constrain plastic responses (e.g. for cold tolerance in *B. anynana* butterflies; Franke et al., 2012) are consistent with the latter. In fact, several recent mapping studies have reported little overlap between genes contributing to variation in trait means with those contributing to variation in trait plasticity (e.g. Lafuente et al., 2018; Ørsted et al., 2018). This suggests a distinct genetic basis for trait plasticity versus the genetic basis for phenotypic variation in the trait itself (at any given environment) and points to the potential for independent evolution of the two.

Integration and Challenges

Several studies in animals have combined the high-throughput gene expression analysis under different environments with forward genetic approaches to identify the genetic basis underlying environmentally dependent gene expression differences (Runcie et al., 2012). These studies, which involve assessing gene expression under different environmental conditions in different genotypes [for the so-called eQTL analysis or genome-wide association studies (GWAS) of gene expression; e.g. Li et al., 2006], allowed to link gene expression differences to genomic markers or allelic variants (see Grishkevich and Yanai, 2013). By associating variation in genotype to variation in environmentally regulated gene expression, researchers have not only characterized GxE interactions in gene expression and their underlying genetic basis but also identified genomic features distinguishing genes with GxE interactions from other types of genes. Work in *C. elegans*, for example, revealed that genes that exhibited GxE interactions tend to show distinct promoter architecture (e.g. long promoter with a high concentration of regulatory motifs) as well as mid-range expression level (Grishkevich et al., 2012), both of which are characteristic of tightly regulated genes (Promislow, 2005).

We have explicitly focused on genomic work studying genes involved in the regulation of plastic responses, i.e. those that respond to environmental inputs and affect trait expression, and genes potentially involved in the evolution of plastic responses, i.e. those that harbor allelic variants contributing to differences in reaction norms. There is, of course, some overlap in the genes involved in trait development, trait plasticity, and plasticity variation (e.g. orange gene in Figure 3). A compelling



example comes from studies of abdominal pigmentation in *Drosophila*. The gene *tan*, encoding one of the melanogenesis enzymes (True, 2003), has been implicated in inter-individual variation in pigmentation within a given temperature (e.g. allelic variants of *tan* underlie differences in pigmentation; Dembeck et al., 2015), regulation of pigmentation plasticity (e.g. flies with reduced expression of *tan* have lighter pigmentation; Kalay et al., 2016), and variation in pigmentation plasticity (e.g. different *tan* alleles correspond to different reaction norms; Gibert et al., 2016). However, there does not need to be a complete overlap between the genes involved in plasticity regulation and those that contribute to plasticity variation/evolution (Figure 3). Indeed, a gene that is differentially expressed between developmental

environments might not harbor allelic variants contributing to variation in reaction norms (e.g. blue in Figure 3). Similarly, a gene contributing to variation in reaction norms does not need to differ in expression across environments (e.g. red in Figure 3).

In the previous sections, we highlighted different genomic studies to identify the genes involved in the regulation and evolution of plasticity, including transcriptomics or genetic mapping approaches. Although extremely powerful at identifying candidate genes, these genome-wide scans are also very prone to false positives and not very informative about the actual role of those genes. As such, it is crucial to independently run functional analysis (Gibert et al., 2017a) to validate candidate genes, something not always easily accessible. Tools for the

manipulation of gene function (e.g. transgenic knock-downs or knock-outs to reduce and abolish gene expression) as well as the manipulation of specific sites (e.g. *via* allelic replacements) were typically only easily accessible in established models. However, fast advances in analytical tools, for both genomic and functional studies, are now enabling us to move from model organisms to less established models (e.g. Marinković et al., 2012; Santure and Garant, 2018; see Russell et al., 2017). The progress in methods is also aiding researchers to move from laboratory strains to natural populations, often including more realistic scenarios in terms of the diversity in genetic backgrounds and demographic parameters and of the complexity of external environments. All these factors are bound to affect phenotype expression and/or evolution (Braendle and Félix, 2008; Chevin, 2013; Piggott et al., 2015; Bretman et al., 2016; Matsui and Ehrenreich, 2016; Fischer et al., 2017). How organisms perceive and integrate information from complex environments, with multiple factors that can vary more or less independently, including within the time it takes to complete development (Warkentin, 2011; Fischer et al., 2017; Rodrigues et al., 2017), is a fascinating topic in need of deeper characterization.

Studies investigating the genes underlying plastic responses are rapidly increasing. Previous research using a variety of systems illustrated that environmentally induced changes in gene expression are pervasive and can include a variety of molecular and functional genes classes (e.g. Zhou et al., 2012; Kijimoto et al., 2014), as reviewed here. Future work exploring changes in gene expression beyond a single species (or a single population), and beyond a single environmental cue, could potentially help to identify general patterns about the effector genes underlying developmental plasticity, whether they belong to particular functional classes or are shared between cues. Moreover, as much more is known about the molecular mechanisms and the genetics of environmentally induced phenotypes in plants (see Sultan, 2000; Sultan, 2017), these are exciting times to start integrating studies on plasticity from animals and plants, which could provide insights on the potential commonalities in the mechanisms controlling whether phenotypes would respond to (or buffer) environmental variation.

CONCLUDING REMARKS

Developmental plasticity can result in a better match between adult phenotype and adult environment, thus helping organisms cope with environmental heterogeneity. An adaptive value for plasticity is compellingly illustrated by examples of seasonal polyphenisms, when the same genetic background produces phenotypes adjusted to the different conditions of alternating seasons as a response to environmental factors that anticipate those conditions (see Kivelä et al., 2013). Recent work has provided evidence that some phenotypes traditionally associated with environmental differences, such as those that vary seasonally, are in fact due to genetic differentiation under strong temporally variable selection (e.g. Bergland et al., 2014; Foucault et al., 2018).

Examples such as these open up the possibility that other fast phenotypic changes assigned to plasticity could be due to rapid adaptation, an area that will certainly get increased future attention.

Plasticity can provide the means of rapidly adjusting to external change; for that reason, its study is getting increased attention in relation to the ability of organisms to deal with climate change (see Merilä and Hendry, 2014; Sgrò et al., 2016; Kelly, 2019). Plasticity may mitigate the negative effects that climate change can have on population persistence (Charmantier et al., 2008; Teplitsky et al., 2008; Kingsolver and Buckley, 2017; Burggren, 2018) by producing phenotypes better adjusted to the new climatic conditions (e.g. Przybylo et al., 2000; Réale et al., 2003; Gienapp et al., 2013) or by enabling plastic species (or populations) to track environmental changes and cope with a wider range of environments than non-plastic ones (e.g. Charmantier et al., 2008). Changes in breeding timing in mammals (e.g. *Tamiasciurus hudsonicus* red squirrels; Réale et al., 2003) and birds (e.g. *Parus major* great tits; Charmantier et al., 2008) represent examples in which plasticity has presumably contributed to phenotypic trends associated with contemporary climate change. However, plasticity may also make populations more vulnerable to climate change (e.g. Mills et al., 2013; Zimova et al., 2016), for instance, if the previously established association between inductive and selective environments is disrupted (Visser et al., 2010; Oostra et al., 2018) or in cases of species with temperature-dependent sex determination, when climate change can alter the hatchling sex ratio and survivorship and therefore impact population demographics and/or persistence (Fuentes et al., 2011; Jensen et al., 2018). Examples such as these will be valuable for assessing the role of plasticity in coping with climate or other types of global change.

Much has been written about the contribution of plasticity to evolution in recent years (e.g. Forsman, 2015; Gilbert et al., 2015; Turcotte and Levine, 2016; Schneider and Meyer, 2017; Levis and Pfennig, 2018). Controversially (e.g. Laland et al., 2014; Charlesworth et al., 2017; Futuyma, 2017), some authors defend a need for an “extended evolutionary synthesis” (Jablonka et al., 2014; Laland et al., 2015) to explicitly incorporate plasticity, as well as other aspects of organismal development, inheritance and fitness, into evolutionary models (Jablonka et al., 2014; Pigliucci, 2007; Pigliucci, 2009; Gisis and Jablonka, 2011; Laland et al., 2014, Laland et al., 2015). There is undoubtedly a recent increase in interest on the adaptive value of plasticity, its role in adaptation, and its genetic basis. We have summarized recent insights onto two aspects of the genetic basis of plasticity in animals: genes whose expression (and function) depends on environmental conditions and lead to changes in development and genes that harbor allelic variants associated with differences in plasticity between genotypes and provide the raw material for natural selection to drive the evolution of plasticity. Given the availability of sophisticated tools, it is now becoming accessible to explore the regulation and evolution of plasticity in natural populations that deal with complex environments. This is a fascinating area of research for which we can surely expect more insights in years to come.

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EL and PB conceived and wrote the manuscript.

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