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An Integrative Framework for Understanding the Mechanisms and Multigenerational Consequences of Transgenerational Plasticity

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Abstract

Transgenerational plasticity (TGP) occurs when the environment experienced by a parent influences the development of their offspring. In this article, we develop a framework for understanding the mechanisms and multi-generational consequences of TGP. First, we conceptualize the mechanisms of TGP in the context of communication between parents (senders) and offspring (receivers) by dissecting the steps between an environmental cue received by a parent and its resulting effects on the phenotype of one or more future generations. Breaking down the problem in this way highlights the diversity of mechanisms likely to be involved in the process. Second, we review the literature on multigenerational effects and find that the documented patterns across generations are diverse. We categorize different multigenerational patterns and explore the proximate and ultimate mechanisms that can generate them. Throughout, we highlight opportunities for future work in this dynamic and integrative area of study.

Keywords

epigenetics; nongenetic inheritance; phenotypic plasticity; biological embedding; maternal effects; parental effects; behavioral development

1. INTRODUCTION

Whether the experiences of one generation can influence future generations is a question with profound implications for virtually all areas of biology, from transmission genetics to human health to evolutionary theory. However, this is a controversial topic because it revives the debate about Lamarckian mechanisms of inheritance. The primary scientific grounds for objecting to the idea that the experiences of one generation can influence the next generation

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fall into one of two main categories: (*a*) There are few known mechanisms by which the parental environment can influence multiple subsequent generations (Heard & Martienssen 2014), and (*b*) even if such mechanisms exist, transgenerational environmental effects are of limited importance for long-term evolutionary processes because they are likely to be transient and washed away within a generation (cf. West-Eberhard 2003).

In this article, we explore some of the complexities of these two general objections. We conceptualize the mechanisms of transgenerational plasticity (TGP) in the context of communication between parents (senders) and offspring (receivers). In particular, we dissect the steps between an environmental cue received by a parent and its resulting effects on the phenotype of their offspring and potentially their grandoffspring. Breaking down the problem in this way highlights the diversity of mechanisms likely to be involved in the process, the importance of timing, and the potential for multimodal messaging. Then, we categorize the ways in which an environmental cue experienced in one generation might influence the phenotype of multiple succeeding generations and explore the proximate and ultimate mechanisms underlying the diversity of empirically documented patterns. Throughout, we highlight opportunities for future work.

TGP (also known as parental environmental effects) is a type of phenotypic plasticity that occurs across generations. TGP occurs when the environment experienced by a parent influences the phenotypic development of their offspring. TGP is distinct from within-generation plasticity (WGP), which occurs when the environment experienced by an individual influences their own phenotypic development.

In some cases, offspring respond to parental signals (Laidre & Johnstone 2013) that have evolved for the purpose of conveying information to offspring and elicit a response in offspring that provides a fitness benefit to both parents and offspring. In other cases, offspring respond to parental cues that are informative but have not necessarily evolved for the purpose of conveying information—i.e., they are not signals. For example, food restriction early in life might lead to a small maternal size, and small mothers can produce only small offspring, because of a lack of space in the body cavity. In other words, food restriction for parents leads to a change in a trait (body size) in the offspring, and offspring might use the small size of their mother’s body cavity as an indication that they were living in a low-food environment. In this case, the maternal phenotype is a cue (in that it conveys some information about the future environment) but is not a signal. In still other cases, TGP might occur in response to novel environmental stressors that interfere with development or reproduction (e.g., pollutants, anthropogenic noise) but are neither cues nor signals, and TGP could result in responses that are neither adaptive nor evolved. For the purposes of this review, we focus primarily on parental cues and signals but acknowledge that they may not be involved in all instances of TGP.

TGP is taxonomically widespread—it has been documented in plants, vertebrate and invertebrate animals, bacteria, and fungi (Jablonka & Raz 2009)—and can occur in response to a wide range of biotic and abiotic environmental cues (e.g., temperature, day length, herbivory, toxins, light quality, food availability, and immune challenges). Environmental cues can be experienced by parents either before offspring are born (transmitted via

prefertilization, in ovo, or in utero effects) or after offspring are born (transmitted via parental behavior), and TGP can occur in response to environmental cues that are either short-lived (e.g., a brief encounter with a predator) or long-lasting (e.g., a particularly dry breeding season). For example, TGP occurs when drought-stressed plants produce seedlings with altered root systems (Sultan et al. 2009) or when parents experience a cue before or after fertilization that causes them to change their parental behavior, thereby influencing offspring development (Meaney 2001).

According to this broad definition, TGP might but does not necessarily entail effects of a parent's environment on their grandoffspring. Therefore, TGP is broader than transgenerational epigenetic inheritance (TEI) (Youngson & Whitelaw 2008), which occurs when transgenerational effects are found beyond the F1 or F2 generation (Heard & Martienssen 2014). TEI can be difficult to show conclusively (especially in live-bearing organisms) because the environment experienced by a female live-bearing organism while pregnant is also potentially experienced by the F1 and F2 generation while they are in utero (Heard & Martienssen 2014). In these cases, it is difficult to clearly separate out the effects of TGP on F1 and F2 offspring from developmental plasticity that occurs due to exposure in utero. Therefore, in live-bearing organisms, TEI can be confirmed only when the effects of maternal exposure persist through three generations (two generations for paternal effects) (Heard & Martienssen 2014). Unlike TGP, TEI requires that environmental effects be incorporated into the germline, and TEI has proven to be difficult to demonstrate because (*a*) until recently there were very few known mechanisms that could allow epigenetic marks to escape being erased at fertilization (Bošković & Rando 2018) and (*b*) there are a number of confounding mechanisms such as parental care, DNA sequence mutations, and microbiota that could generate a pattern that resembles TEI but is not bona fide TEI (Heard & Martienssen 2014).

Exploring the proximate and ultimate reasons why the effects of the environment experienced by a parent may or may not persist for multiple generations is one of the goals of this review. In this article, we take the view that TGP has important ecological and evolutionary consequences even if its effects are only apparent in the F1. For instance, TGP might buffer or prepare offspring for living in a new environment, and that might be sufficient to allow a population to become established and persist in the new environment. More generally, the rich and growing literature on the evolution of phenotypic plasticity (Levis & Pfennig 2016, Schlichting & Pigliucci 1998, West-Eberhard 2003) provides a solid framework for appreciating the evolutionary implications of TGP, which have been well articulated in previous reviews (Badyaev & Uller 2009, Bonduriansky & Day 2009, Galloway 2005, Mousseau & Fox 1998, Rossiter 1996, Uller 2008). For example, parental effects can affect the speed of directional evolution (Kirkpatrick & Lande 1989), plasticity can overcome the constraints of adaptive genetic change by decoupling the genotype from phenotype (Bonduriansky & Day 2009, 2018), and TGP can promote population persistence in changing environments (Jablonka et al. 1995, Pal 1998, West-Eberhard 2003). Because TGP can be adaptive for both parents and offspring, the evolution of TGP can be favored under certain environmental conditions (Dall et al. 2015, Hoyle & Ezard 2012, Jablonka et al. 1995, Kirkpatrick & Lande 1989, Kuijper et al. 2014, Leimar & McNamara 2015, Proulx & Teotonio 2017).

Despite evidence that TGP can be adaptive, controversy exists about how to assess its adaptive significance (Engqvist & Reinhold 2016, Uller et al. 2013), and it can be difficult to assess its fitness consequences without measuring an entire suite of traits at multiple points in development. For example, TGP might generate adaptive offspring traits for overcoming specific environmental stressors (e.g., environmental toxins) but at the same time reduce overall survival (Marshall 2008). Further, TGP might have potentially adaptive benefits at one life stage (e.g., improved larval survival) that might generate fitness costs later in life (e.g., reduced reproductive potential). Alternatively, TGP can be maladaptive when, for example, parents encounter novel environmental stressors or toxins, face ecological traps [in which a parental cue that was previously adaptive is no longer adaptive due to changes in the environment (Schlaepfer et al. 2002)], or transmit effects of pathology, stress, or senescence.

2. THE STEPS OF TRANSGENERATIONAL PLASTICITY

TGP can be viewed as a multistep communication process in which an environmental cue experienced in one generation (sender) influences the phenotype of a later generation (receiver) (Figure 1). For a parent's experience to affect future generations, a parent must first detect an environmental cue (step 1). After receiving the cue, the parent then processes the information that is provided by the cue (step 2). Step 2 likely involves so-called integrator mechanisms (Martin et al. 2011) for processing information (e.g., a change in physiology, hormones, or gene expression). The information-processing step could involve diverse processes ranging from a change in state (e.g., body condition), restoration of homeostasis, phenotypic plasticity, dispersal away from the source of the cue, and integration of the cue with information from other sources (e.g., genes, parents, personal experience, horizontally acquired information) (Dall et al. 2015, Stamps & Krishnan 2014). Adaptive TGP is more likely when the initial environmental cue is highly reliable and when the parent has correctly interpreted the cue (Moran 1992).

After processing the cue, the parent then uses information that was provided by the environmental cue to either alter the environment experienced by the offspring [e.g., habitat choice, oviposition site, niche construction (Donohue 2005, Laland et al. 2016)] or produce a different cue or signal that the parent transmits to their offspring (step 3). A wide variety of cues can be transmitted between parents and offspring, such as hormones in eggs or seeds, microRNAs (miRNAs) in gametes, chromatin structure in germ stem cells or mature sperm, parental behavior, egg protein content, gut endosymbionts, and seed coat in maternal tissue or accessory gland products (reviewed in Jablonka & Raz 2009). In some cases, offspring appear to cue in on a physiological process in their parent that is involved in coping with the environment (step 2), thereby merging steps 2 and 3. For example, in vertebrates, circulating levels of cortisol increase in mothers in response to a stressor and maternally derived cortisol accumulates in egg lipids, which could go on to influence offspring development (McCormick 1998).

For a cue transmitted by parents to influence offspring development, offspring must detect the cue (step 4). This step could occur while offspring are in utero (e.g., via binding sites for small RNAs in the embryo or placenta, hormone receptors) or post birth (e.g., nutrition, parental care). Offspring then process the information in their parent's cue (step

5), integrating it with other sources of information (genes, personal experience, etc.) (Dall et al. 2015) in potentially nonadditive ways, and possibly use this information to influence phenotypic development. For example, a cue received from the parent could trigger changes in methylation or histone modifications that could influence gene expression in the developing offspring, causing long-lasting effects on offspring morphological, physiological, life history, and behavioral traits as well as fitness (Jablonka & Raz 2009). However, offspring do not always respond to parental cues and are not always just passive recipients (see the sidebar titled Transgenerational Plasticity and Parent–Offspring Relations). Indeed, offspring have evolved mechanisms for coping with potentially misleading parental cues. For example, some vertebrate embryos have evolved mechanisms for metabolizing (Paitz et al. 2011) or buffering themselves (Paitz et al. 2016) from maternal steroids (see also Groothuis & Schwabl 2007). Interestingly, the extent to which offspring attend to cues of their parent can depend on the sex of the parent (see the sidebar titled When Transgenerational Plasticity Depends on the Sex of the Parent) or their own sex (see the sidebar titled When Transgenerational Plasticity Depends on the Sex of the Offspring).

Offspring may or may not then transmit a cue to the next generation (step 6), via the same or different mechanisms as in step 3. For example, Gapp et al. (2014) found that male mice that experienced early life stress produced sperm miRNAs that influenced the development of the stress response system of their offspring; however, sperm miRNAs do not appear to be the mechanism underlying the transmission of the altered phenotype across subsequent generations. One of the most controversial questions in the study of TEI has to do with whether and how epigenetic modifications to the germline of the F1—such as cytosine methylation and histone modifications—can be maintained across generations. Interestingly, environmental effects persist across multiple generations in both plants and animals (see Section 3) even though mammals have widespread resetting of epigenetic marks, whereas plants have very limited reprogramming (Heard & Martienssen 2014), indicating that the molecular mechanisms of epigenetic inheritance are diverse but still poorly understood. Exciting recent work on genomic imprinting in mammals is starting to reveal the sophisticated mechanisms that enable methylation imprints to resist postfertilization reprogramming (Messerschmidt 2012), and studies in *Caenorhabditis elegans* are showing how small RNAs can enter the germline and mediate heritable transcriptional silencing in subsequent generations (Ashe et al. 2012; reviewed in Bošković & Rando 2018).

2.1. The Importance of Timing

Breaking down the steps of TGP in this way highlights the importance of timing. From the parent's perspective, the age at which a parent experiences the environmental cue could have important implications for how parents detect, process, and transmit a cue to their offspring (steps 1–3) and the extent to which offspring attend to a parental cue (steps 4 and 5) (McNamara et al. 2016). From an informational perspective, TGP is especially likely to occur when parents experience an environmental cue soon before their offspring are born, and if the cue is informative about the environment their offspring are likely to encounter soon after birth (McNamara et al. 2016). For example, if parents receive a cue just prior to breeding that a predator that specializes on early life stages

is abundant, it seems reasonable to suppose that the parents should pass information about this predator to their offspring. In contrast, cues that parents experience when they were juveniles might not be relevant to transmit transgenerationally. However, parental experiences as juveniles could be important if a good match exists between parental juvenile and offspring juvenile environments (Burton & Metcalfe 2014, Taborsky 2006). For example, amphibians that undergo metamorphosis might transmit information to offspring about the aquatic environment they experienced as a juvenile. Similarly, parental experiences early in life might have a stronger effect on state (e.g., body condition), habitat selection, or the way the parents construct their environment, which then has a greater influence on offspring phenotypes. Finally, it is also worth considering that parents may have time points (sensitive windows, ages, seasonal or life history stages) when they are more likely to be exposed to given environmental cues (step 1), when they are better at receiving and processing cues (steps 1 and 2), or when cues have a particularly strong influence on the parents' neurogenomic or physiological state (step 2) (Zannas & Chrousos 2017). For example, in humans, exposure to environmental stressors during mid-childhood has stronger consequences for future generations compared with exposure during other stages of development (reviewed in Pembrey et al. 2014).

In general, the extent to which parents are informed about the environment their offspring are likely to experience depends on the probability of a match between the environmental cue and the environment, the temporal stability of the environment, and the rate of juvenile migration from parental habitats (Leimar & McNamara 2015). It is also worth noting that the reliability of the environmental cue received by the parents about the current and future environment will strongly influence whether TGP is adaptive (Moran 1992).

From the offspring's perspective, timing is important because the way that offspring receive and integrate parental cues (steps 4 and 5) depends on the developmental stage at which they receive the cue. For example, a parental cue (e.g., miRNAs, hormones in eggs) will only influence offspring phenotypes if offspring have developed the systems needed to detect the cue (e.g., binding sites, hormone receptors) and if they can initiate an appropriate developmental response to the information provided by the cue; otherwise, the message will be lost. In addition, the age of the offspring at the time they detect the cue might influence the degree to which they respond to it. For example, we might expect cues received early in embryonic development to have a stronger effect on offspring development compared with cues received later in development because of the epiphenotype problem —i.e., once a system starts to develop in one direction, it becomes harder to move in another direction (Frankenhuis & Panchanathan 2011). Consequently, timing might impose evolutionary constraints on the types of parental cues that can be transmitted by different mechanisms, depending on the age at which the parent receives the environmental cue and the age at which offspring receive the parental cue. In general, we know little about windows of sensitivity to parental cues or how the evolution of parental signaling systems, offspring receiver systems, and sensitive periods is influenced by timing constraints.

2.2. Transgenerational Plasticity as Multimodal Signaling

Multiple cues are likely to play an important (but relatively understudied) role in TGP because offspring might receive multiple cues from their parents via different modalities (multimodal signaling; see Hebets & Papaj 2005). For example, parents might provide cues to their offspring via both prefertilization (e.g., sperm) and postfertilization (e.g., parental care) parental cues. Alternatively, or additionally, parents might influence the development of their offspring via parental state, parental phenotype, parental cues, or the environment they provide for their developing offspring. At the same time, it is likely that offspring receive cues from both their mother and their father, either simultaneously (e.g., via eggs and sperm at fertilization) or sequentially (e.g., via sperm and maternal care).

The possibility of multimodal signaling raises fascinating questions about the ways in which multiple parental cues might combine together to influence TGP. First, multiple parental cues might increase the specificity of information parents can transmit to their offspring by improving signal detection and discrimination thresholds, overcoming constraints on the amount of information that can be transferred via a single modality, or overcoming noise in one modality (Hebets & Papaj 2005). If parents can transmit information via more than one cue, this might be a mechanism for ensuring communication in a noisy environment. Second, different parental cues might convey different information or information about conditions that offspring are likely to encounter at different stages of development (multiple message hypothesis; see Johnstone 1996). Third, different parental cues might act as a backup (backup signaling hypothesis; see Johnstone 1996) in the event that one modality is not available. Fourth, multiple modalities might provide flexibility so that parents can use different modalities depending on their immediate environment (Johnstone 1996). In a system with extrapair paternity, for instance, fathers might rely on communication via sperm when they have no opportunity to communicate with their offspring via paternal behavior. Finally, multiple cues raise the possibility that offspring might only respond to cues when they receive information through more than one modality (threshold hypothesis; see Bradbury & Vehrencamp 2011), or from more than one source—for example, from the mother and father or when parental cues are corroborated by personal experience. We know little about how multiple parental cues combine together to influence offspring phenotypes (i.e., whether they are interactive, additive, redundant, etc.).

It is also worth considering that most studies of TGP to date have focused on a single parental cue/environment (e.g., sunlight, pollutants, food restriction, predation risk, severe weather), but it is likely that parents simultaneously receive and process multiple environmental cues (steps 1–3), all of which are likely to influence how parents influence their offspring in potentially nonadditive ways.

2.3. Implications of This Framework

This framework has several implications for how we study and conceptualize TGP. A large part of the skepticism about epigenetic inheritance has to do with our lack of understanding of how signals can be incorporated into the germline and transmitted across multiple generations. However, the framework proposed here draws attention to the idea that transmission (step 3) and incorporation/processing (step 5) are just two steps of a

multistep process. A full understanding of TGP entails consideration of how parents respond to environmental cues (steps 1–2), how offspring differ as a function of their parents' experience (step 5), and different mechanisms of transmission and reception of parental cues (steps 3–4).

Recent work on sperm RNAs is coming close to connecting the dots between environmental cues, parental cues, and offspring phenotypes (Gapp et al. 2014, 2018; Rodgers et al. 2015). For example, paternal stress prior to mating caused male mice to produce offspring with altered stress response systems, and miRNAs were differentially expressed in the sperm of stressed versus control fathers (Rodgers et al. 2015). When the differentially expressed miRNAs were injected into embryos fertilized by unstressed fathers, the authors recapitulated the effects of paternal stress on offspring (Rodgers et al. 2015). To further link parents and offspring, it would be fascinating for future studies to identify differentially expressed genes in offspring embryos (steps 4 or 5) and ask whether there are binding sites for the differentially expressed miRNAs upstream of differentially expressed genes in embryos. If so, those binding sites are good candidate mechanisms that allow offspring to process parental cues (step 4), which could be tested by blocking those binding sites. Another promising future direction is to study the ways in which natural selection has shaped how parental cues are processed, transmitted, and received by simultaneously examining the mechanisms underlying step 2 (e.g., cortisol), step 3 (e.g., sperm miRNAs), and step 4 (e.g., DNA sequence variation in miRNA binding sites) across related populations or species that exhibit variation in TGP.

From an evolutionary perspective, the variety of mechanisms operating at different steps of this process provides multiple opportunities for natural selection to shape TGP, because the processes involved in one step are not necessarily the same processes involved in other steps. For example, the mechanisms involved in the information processing step (e.g., hormonal response) could be different from the mechanisms involved in the transmission step (e.g., miRNAs) (Pang et al. 2017). Provided genetic variation, all components of this communication system could potentially respond to selection, opening the possibility of multiple solutions to the problem of whether and how TGP will evolve. For example, if TGP is not favored in a particular environment (e.g., parental environments do not predict offspring environments), natural selection could act on genetic variation for detecting an environmental cue (step 1), producing a cue (step 3), or receiving a parental cue (step 4) to prevent TGP; therefore, different populations might lose TGP via different mechanisms. Alternatively, if TGP is strongly favored, selection could act on genetic variation at all of the steps to potentially increase the probability and strength of TGP.

Finally, it is that unlikely that any of the steps in this process are error free, so each additional step that is required between the initial detection of an environmental cue and the production of an offspring phenotype in response to a parental cue is likely to add noise and uncertainty to the estimates of the state of the environment that were provided by the initial environmental cue. Therefore, there might be more opportunities for information to get degraded in TGP compared with WGP, which might partially explain why the magnitude of TGP is often less than WGP (Auge et al. 2017, but see Donelan & Trussell 2018, Stein et al. 2018). Further, unlike WGP, in which offspring can directly detect cues in the environment,

TGP requires that offspring trust the reliability of signals from their parents, which may not be adaptive when parent–offspring conflict is high (see the sidebar titled Transgenerational Plasticity and Parent–Offspring Relations).

3. MULTIGENERATIONAL EFFECTS

A growing number of studies in model and nonmodel organisms have started to track changes in an induced phenotype across generations following exposure to an environmental cue in the F0 generation and are finding diverse patterns across the F1, F2, and subsequent generations. We reviewed the literature and found evidence for six different multigenerational patterns (Figure 2): bounce back, weaken, persist, accumulate, delay, and reverse. Table 1 lists a few illustrative examples of each pattern. Below, we discuss the mechanisms that might generate each pattern, empirical examples of the pattern, and the selective conditions that might favor different patterns, and we conclude by considering the complexities involved in differentiating among the patterns. In the scenarios described below, we assume that the F0 generation was exposed to an environmental cue and that individuals in the F1 and F2 generations were reared and measured under control environments, unless noted otherwise.

3.1. Bounce Back

The “bounce back” pattern occurs when the phenotype of the F1 generation is influenced by a cue experienced in the F0 generation but the effects of F0 exposure are not evident in the F2 (i.e., the phenotype bounces back). An example of this pattern comes from studies of *Arabidopsis* in which parental plants exposed to hyperosmotic stress produced offspring with higher survival in high-salt conditions; this adaptive response was maintained across multiple generations in the continued presence of hyperosmotic stress but was lost in the F2 generation when the F1 was raised under control conditions (Wibowo et al. 2016). The bounce back pattern might result when there is not a mechanism by which a cue can be incorporated into the germline (i.e., no way to pass between steps 6 and 7 in Figure 1). This may occur when epigenetic marks (e.g., methylation) are completely reset between generations. In some systems, epigenetic marks are stably inherited across multiple unexposed generations when the initial triggering cue is present for many consecutive generations but not if the initial cue is experienced only for one generation (Remy 2010).

3.2. Weaken

The “weaken” pattern occurs when the phenotype of the F1 and F2 generations is influenced by a cue experienced in the F0 generation but the effects weaken between the F1 and F2 generations (i.e., grandparental effects are weaker than parental effects; e.g., see Prizak et al. 2014, Shama & Wegner 2014). Although this idea initially seems straightforward, there are at least three ways in which effects might weaken across generations. First, the average effect of a cue experienced in the F0 generation on a particular trait in the F1 might be greater than the average effect on that trait in the F2 generation (i.e., an effect on means). Second, the weakening effect might manifest as increased variance, such that the proportion of individuals that are influenced by conditions experienced in the F0 decreases with each subsequent generation (Ashe et al. 2012). Presently, it is difficult to distinguish between

these different types of weakening in the literature. Finally, another way in which effects might weaken is when a cue experienced in the F0 generation influences an entire suite of traits in the F1 but fewer traits are influenced in the F2 generation (McCarthy et al. 2018, Pentinat et al. 2010). We know little about the relative frequency of these different outcomes in natural populations, and it is unknown whether the molecular mechanisms underlying different types of weakening are similar or different.

3.3. Persist

The "persist" pattern occurs when a cue experienced in the F0 generation equally influences the phenotype of the F1 and F2 generations. This pattern was documented in mice: Mice that were trained to associate an odor with foot shock produced F1 and F2 offspring that behaved differently in response to that odor, even though they themselves had never been trained (Dias & Ressler 2014). The "persist" pattern might occur when the mechanism that generated a phenotype in the exposed generation causes individuals in the F1 generation to retain an epigenetic mark that can generate the same phenotype in a future generation. Persistence might reflect evolutionary momentum, which occurs when an induced phenotype persists across generations after the cue that induced the phenotype is no longer present (Bonduriansky & Day 2009). Additionally, the persistence pattern might reflect cases when transgenerational and developmental plasticity are combined (e.g., in utero effects in mammals, habitat selection by parents), when offspring mimic the parental behavior of their parents, when individuals inherit their parents' environment, or when individuals inherit the environmental modifications caused by the niche construction activities of their parents (Danchin et al. 2011). For examples of cases when the effects persisted into the F2 generation but not to the F3, see Cropley et al. (2016) and Kishimoto et al. (2017).

3.4. Accumulate

The "accumulate" pattern occurs when the phenotype of the F2 or F3 generation exceeds the value of the phenotype induced in the F1 generation—i.e., the induced phenotype accumulates. For example, when F0 females were exposed to pollutants during gestation, the incidence of disease and obesity was higher in the resulting F3 generation compared with the F1 generation, even though the F1, F2, and F3 generations were not directly exposed (Manikkam et al. 2013, Skinner et al. 2018). The "accumulate" pattern might be particularly likely to occur when pregnant live-bearing females are exposed, because both the developing F1 offspring and their F2 germ cells are indirectly exposed to an environmental cue along with the F0 generation (i.e., multiple generations are simultaneously exposed). However, accumulation effects have also been observed in nonmammals, for example, when both parents and grandparents were exposed to the same cue (fish, Le Roy et al. 2017; springtails, Hafer et al. 2011; plants, Herman et al. 2012) or when both parents and offspring were exposed to the same cue (TGP and WGP are additive; damselfish, Donelson et al. 2011). In general, then, the "accumulation" pattern might be especially likely to occur when the environmental cue is present for more than one generation or when it comes from more than one source, perhaps because it becomes more reliable. This might have maladaptive consequences in the context of harmful stressors (Manikkam et al. 2013, Skinner et al. 2018) but could potentially increase the ability of organisms to cope with novel environmental conditions (Le Roy et al. 2017).

3.5. Delay

The “delay” pattern occurs when the phenotype of the F2 generation is influenced by a cue experienced in the F0 generation, but the phenotype of the F1 generation is not influenced (i.e., the effect is delayed). For example, one study found that, in humans, grandparents’ food availability strongly influenced their grandchildren’s mortality risk, but parents’ food availability had a very weak effect on their children’s mortality risk (Vågerö et al. 2018). In contrast to the “accumulate” pattern, in which F1 effects are weaker or fewer than effects in subsequent generations, in the “delayed” pattern, minimal effects are observed in the F1 generation.

Delayed effects might occur if mothers are exposed to an environmental cue after their offspring have passed a sensitive period in development. For example, if mothers were exposed to an environmental cue late in gestation, phenotypic effects may not be evident in the F1 generation, even though the environmental cue influenced the F1 germline and could be transmitted to future generations (Fang et al. 2016). Another potential mechanism by which effects might skip a generation is different methylation patterns in the developing embryo between germ cells and somatic cells, such that altered methylation in F1 germ cells gives rise to a modified phenotype in the F2 generation even though altered methylation in F1 somatic cells did not give rise to a modified phenotype in the F1 generation (Rodgers & Bale 2015).

3.6. Reverse

Finally, some evidence shows that effects in the F1 generation can reverse across generations, such that the phenotypes of the F1 and F2 generations vary in opposite directions in response to a cue experienced in the F0 generation (i.e., it is reversed). For example, Sentis et al. (2018) observed that predation risk caused aphid mothers to produce a high frequency of winged F1 morphs, but one generation after the cue was removed, the frequency of winged morphs dropped below levels in the control group for two to three generations before returning to the baseline frequency. This pattern might be caused by negative maternal effects, which occur when the phenotypes of offspring and mothers are negatively correlated. For example, Falconer & Mackay (1996) found that large mice gave birth to larger litters, which caused competition for maternal resources and ultimately resulted in offspring smaller than those born to small mothers.

3.7. Ultimate Explanations for Different Multigenerational Patterns

From an evolutionary point of view, these diverse multigenerational patterns raise questions about when and why the experiences of one generation override cues from previous generations. It is tempting to assume—like Lamarck—that it is always advantageous for adaptive gains acquired in one generation to be passed on to future generations. However, acquired traits may be mal-adaptive if they do not match the current environment (Herman et al. 2014). Why, for example, should F1 individuals maintain a phenotype that was induced by a predator in the F0 generation if F1 and F2 individuals never encounter that predator? Evolutionary theory predicts that the multigenerational effects of TGP will evolve according to the rate of environmental change (e.g., within versus across generations, seasonality, etc.), correlations between the parental and offspring environments, and genetic variation (Dall

et al. 2015, Leimar & McNamara 2015). The following discussion assumes that TGP has evolved to optimize phenotypes in a given environment; however, as we noted in previous sections, TGP can also reflect responses that are neither adaptive nor evolved (e.g., exposure to toxins).

The “bounce back” pattern might be adaptive when the environment is temporally variable: Although it might be adaptive for offspring to attend to cues from the previous generation, the phenotype may not persist into the F2 generation either if those cues are not predictive of conditions in two or three future generations or if the altered phenotype is too costly to maintain when the cue is not reinforced. It is also worth considering that the “bounce back” pattern might result when it is adaptive for within-generational environmental effects to override TGP. For example, early life exercise can counter the symptoms associated with having an obese father in mice (Falcão-Tebas et al. 2019).

The evolutionary consequences of “weakening” can be slightly different from the “bounce back” pattern and depend on the type of weakening: Selective inheritance might reflect bethedging in the face of environmental uncertainty (Crean & Marshall 2009, Simons 2011), whereas a general average weakening effect might result when it is maladaptive to attend to previous cues, as those cues become less and less relevant over time, especially when organisms live in changing environments (error management theory; see Sheriff et al. 2018).

“Persistence” across multiple generations might be adaptive when environmental conditions are consistent over generations, such that future generations experience conditions similar to previous ones. Effects may persist or weaken (as opposed to bouncing back) for several reasons, including weak selection against the induced phenotype, a high cost of failing to maintain the induced phenotype (e.g., high cost of having a safe phenotype if the environment is actually dangerous; see Sheriff et al. 2018), and carryover effects of parental condition, parental care, or parental niche construction (Laland et al. 2016, Nephew et al. 2017). Intriguingly, studies showing sex-specific lineage effects of TGP—whereby phenotypic changes are transmitted to only one sex or via the maternal or paternal lineage —suggest that some mechanisms allow only a subset of individuals in future generations to inherit particular phenotypes (see the sidebar titled When Transgenerational Plasticity Depends on the Sex of the Grandparent).

The “delay” and “accumulate” patterns are likely to be favored by different ultimate, selective mechanisms. For example, delayed effects might be adaptive in cyclical or seasonal environments, in which the F2 or F3 individuals are more likely to encounter an environment more similar to that of the F0 generation than the F1 generation (Leimar & McNamara 2015), whereas accumulation effects might be more adaptive in changing environments that continue to change in the same direction (e.g., global warming). If reversal across generations is caused by negative maternal effects, it might be more likely to evolve in highly stable environments, as negative maternal effects can lower phenotypic variance around the optimal phenotype and maximize mean fitness (Hoyle & Ezard 2012, Kuijper & Hoyle 2015). Similarly, negative maternal effects can be favored when environmental change is rapid, such that the environments experienced by the parent and offspring are only weakly or negatively correlated (Kuijper & Hoyle 2015).

3.8. Implications of Different Multigenerational Patterns

Altogether, this synthesis highlights the diversity of proximate and ultimate mechanisms that can favor the same or different multigenerational patterns. The inheritance of epigenetic marks is taxonomically variable (Heard & Martienssen 2014, Potok et al. 2013, Tabuchi et al. 2018), but similar patterns have been documented in different taxonomic groups; therefore, the same outcomes can emerge via different molecular mechanisms (Table 1). Generally, understanding more about the mechanisms of TGP is important for predicting when and the degree to which environmental effects become biologically embedded—transient changes in state versus long-lasting epigenetic changes to the germline, for example—and therefore for how long environmental effects persist across generations. Current theoretical work largely does not consider how different mechanisms of TGP affect the persistence of a cue, and this question is an important area for future work.

It is also worth noting that, although we identified studies that provide good examples of each of the six different patterns, the realities are often much more complex. For example, within a single study, different traits can show different multigenerational patterns: In response to maternal exposure to the pesticide methoxychlor, the incidence of ovary disease exhibited a pattern more consistent with “accumulate,” whereas the incidence of male obesity exhibited a pattern more consistent with “delay” (Manikkam et al. 2014). The dose (Rehan et al. 2012) and timing (Fang et al. 2016) of parental exposure to a cue can also generate different multigenerational patterns. Finally, within a single species, there is genetic variation for different multigenerational patterns: In *Daphnia*, for example, clones exhibit different transgenerational responses to cues of predation risk (Walsh et al. 2016), and in *Plantago lanceolata*, families differ in the effect of maternal and offspring temperature on seed (Alexander & Wulff 1985) and adult (Case et al. 1996) characters.

This synthesis also illustrates that we have only a vague understanding of the selective conditions that favor different transgenerational patterns (Herman et al. 2014). At present, we have neither a good conceptual framework nor the experimental tools to systematically study the influence of the rate of environmental change on the fitness benefits of different transgenerational outcomes. Similarly, we know little about how grandparental and parental effects combine with developmental plasticity to produce different transgenerational patterns, despite the fact that these different forms of plasticity are likely to occur simultaneously.

Finally, the possibility that different multigenerational patterns reflect different mechanistic and evolutionary causes draws attention to the need to distinguish among them empirically. However, high statistical power is needed to distinguish among them—for example, it is empirically challenging to distinguish between “delay” and “accumulate” and between “bounce back” and “weaken.” Future studies in tractable systems with rapid generation times such as *C. elegans*, *Arabidopsis*, and *Daphnia* are likely to make important headway on these outstanding issues.

4. CONCLUSIONS

Here, we have developed a framework for dissecting the ways in which ancestral experiences can be transmitted across generations by conceptualizing parents as senders of and offspring as receivers of cues. We propose an integrative framework for understanding the multigenerational consequences of TGP from both proximate and ultimate perspectives. Moving forward, further empirical and theoretical work on the integration of genetic variation, WGP, and TGP will help advance our understanding of intra- and interspecific variation in TGP and how induced phenotypes persist or amplify across generations. Furthermore, although mounting work has revealed the ways in which TGP induces phenotypic changes in future generations, we know less about the reversibility of these phenotypic changes: How might environmental enrichment or changing conditions induce control or ancestral phenotypes? The extent to which TGP can be reversed will determine which multigenerational pattern will arise and whether TGP is adaptive or maladaptive. Overall, a better understanding of nongenetic inheritance, in all its forms, will lead to a better understanding of how individuals cope with natural and human-induced environmental change.

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TRANSGENERATIONAL PLASTICITY AND PARENT–OFFSPRING RELATIONS

Parent–offspring conflict can arise because offspring value their own survival more than that of current or future siblings, whereas parents value all offspring equally (Trivers 1974). Parent–offspring conflict may limit the evolution of TGP, as it may not be optimal for offspring to rely on parental cues in situations in which parents would benefit from manipulating the developmental trajectories of their offspring toward their own fitness optimum and away from that of their offspring (Kuijper & Johnstone 2018). Consequently, parent–offspring conflict might favor the evolution of mechanisms for coping with receiver uncertainty (Johnstone & Grafen 1993), enforcing the honesty of maternal signals (Kuijper & Johnstone 2018), ignoring parental signals, or exploiting parents. However, offspring must weigh the benefits of avoiding maternal manipulation with the cost of ignoring potentially important maternal cues about environmental conditions (Tobler & Smith 2010). Collectively, more empirical work is needed to understand how parent–offspring conflict might lead to the breakdown of informative signaling from parents to offspring (Godfray & Johnstone 2000, Kuijper & Johnstone 2018, Uller 2008, but see Uller & Pen 2011) and whether TGP is more likely to evolve when parent–offspring conflict is weak (Kuijper & Johnstone 2018).

WHEN TRANSGENERATIONAL PLASTICITY DEPENDS ON THE SEX OF THE PARENT

Until recently, it was assumed that maternal effects are more pervasive and more important than paternal effects (Crean & Bonduriansky 2014). However, growing evidence for paternal effects is drawing attention to the similarities and differences between maternally and paternally mediated TGP; for example, there are stronger maternal effects in some systems (Yehuda et al. 2008) and stronger paternal effects in others (Beemelmanns & Roth 2016, Zuccolo et al. 2016). It seems reasonable to suppose that the parent who is a more reliable source of information about the future environment should be more likely to influence their offspring, such as might occur when there is sex-specific dispersal or when uniparental care is provided, giving the parent that provides care a greater influence. Given that paternal and maternal effects are probably transmitted via different mechanisms (e.g., sperm, eggs) or at different points in development (e.g., prefertilization paternal cues versus maternal cues in utero), maternal and paternal experiences may influence different traits in offspring or have opposing influences on the same traits (Crean & Bonduriansky 2014). Our understanding of maternal versus paternal effects and their combined influence is in its infancy but is potentially of great significance, as it could help clarify evolutionary phenomena such as genomic imprinting, which is thought to arise from sexual conflict over resource allocation to offspring.

WHEN TRANSGENERATIONAL PLASTICITY DEPENDS ON THE SEX OF THE OFFSPRING

Sex-specific parental effects—when the environment experienced by a parent has different consequences for their sons versus daughters—can take many forms (for reviews, see Bale 2011, Glover & Hill 2012). For example, parental cues can have opposing effects on the same trait in male versus female offspring, influence different traits in male versus female offspring, or have a stronger influence on male versus female offspring (reviewed in Bale 2011, Glover & Hill 2012). As nearly all work on sex-specific effects has been in mammals with respect to parental stress, more work is needed to understand the ecological and evolutionary implications of sex-specific effects in other organisms and for other environmental cues. This is a fascinating area for future work, as nongenetic inheritance functioning in a sex-specific manner can potentially mitigate the severity of intersexual inheritance (e.g., when selection favors different phenotypes for sons and daughters; see Day & Bonduriansky 2011).

WHEN TRANSGENERATIONAL PLASTICITY DEPENDS ON THE SEX OF THE GRANDPARENT

Sex lineage effects—when environmental cues from past generations are transmitted past the F1 generation via either the paternal or maternal lineage—are being increasingly documented. Lineage effects can be sex specific (e.g., through the male lineage only) (Pembrey et al. 2006) or can be more complicated, such as epigenetic inheritance to female descendants (F2 and F3 individuals) via the paternal lineage, a pattern which has been documented in several studies (e.g., Dunn & Bale 2011, Saavedra-Rodríguez & Feig 2013). Sex-specific lineage effects are fascinating because they illustrate how epigenetic transmission can be decoupled from the induced phenotype; individuals may be silent carriers of epigenetic information, with males transmitting the phenotype to their female offspring without actually displaying the phenotype themselves, for example. Furthermore, paternal lineage effects can occur even when the mother initially experienced the stressor (passed down to F2/F3 individuals via F1 males) (Dunn & Bale 2011, Saavedra-Rodríguez & Feig 2013), indicating that the sex of the parent that transmits the information across generations may be distinct from the sex of the parent that initially experienced the cue. This suggests that phenotypes that are adaptive in one sex but not the other may be able to selectively persist across generations.

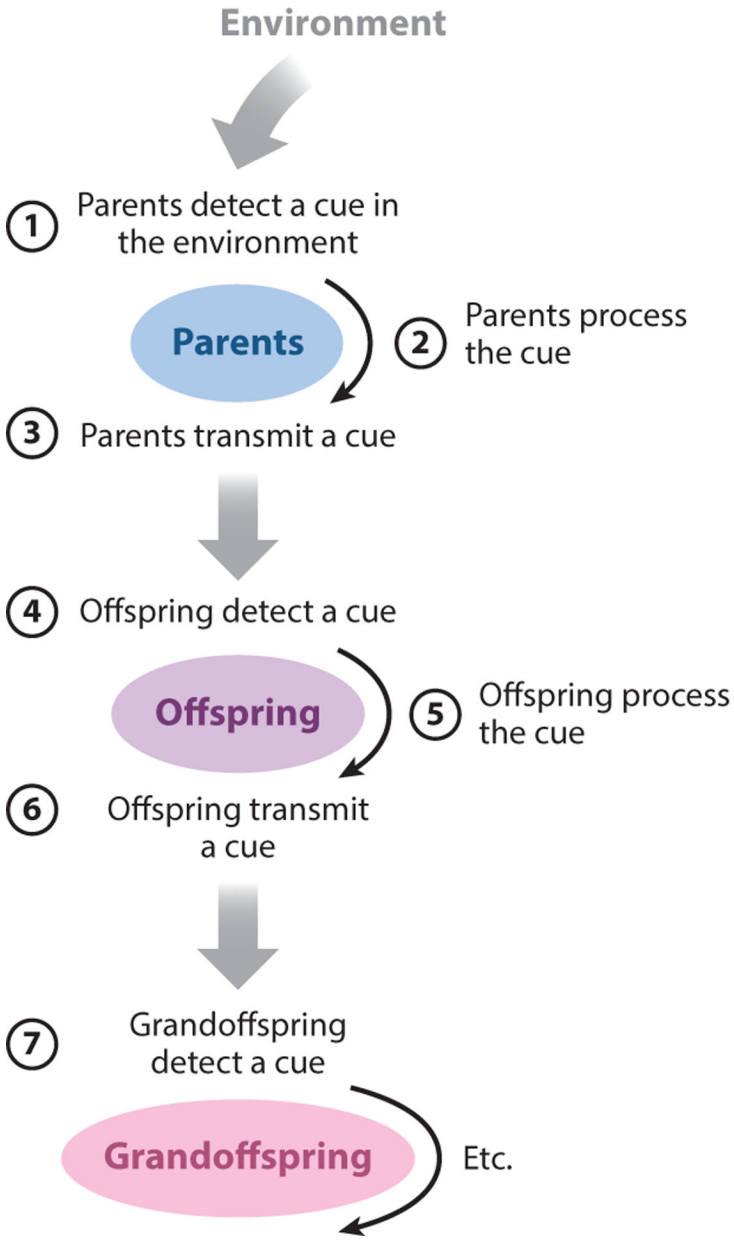

Figure 1.

Conceptual framework for understanding the steps of transgenerational plasticity. Parents ① detect an environmental cue, to produce ② process the information provided by it, and ③ then use this information and transmit a cue to offspring. Then, their offspring ④ detect and ⑤ process the information in this cue and ⑥ use this information to affect their phenotype. ⑦ Offspring may or may not produce and transmit a cue to grandoffspring, etc.

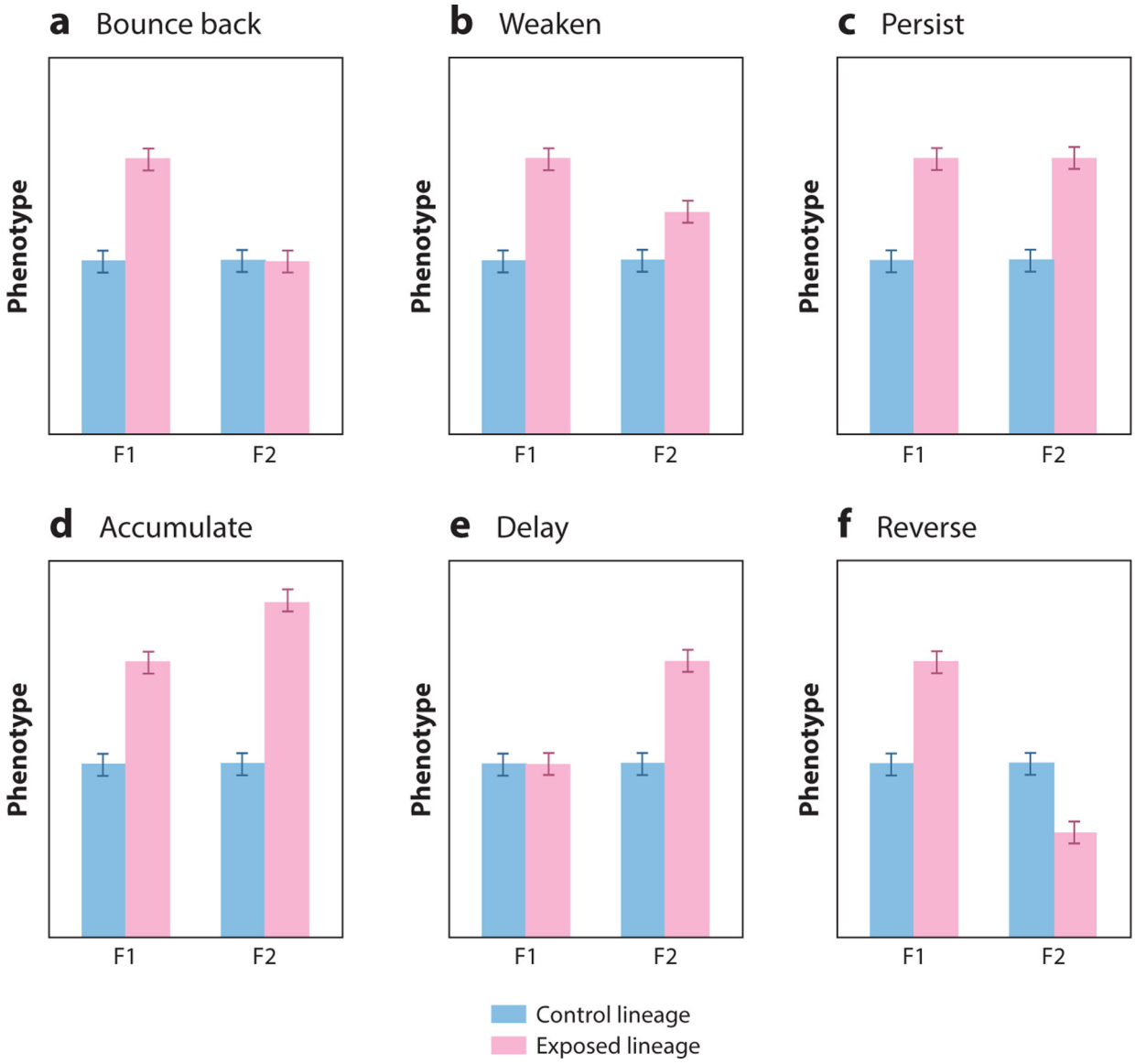

Figure 2.

Potential multigenerational outcomes of a cue experienced in the F0 generation. We assume that the F0 generation is exposed to an environmental cue. (*a*) The phenotype of the F1 generation is influenced by the cue experienced in the F0 generation, but the effects do not persist into the F2—i.e., the phenotype bounces back. (*b*) The phenotype of the F1 and F2 generations is influenced by the cue experienced in the F0 generation, but the mean effects weaken between the F1 and F2 generations (for further complexities, see text). (*c*) The phenotypes of the F1 and F2 generation are similarly influenced by the cue experienced in the F0 generation—i.e., the induced phenotype persists. (*d*) The phenotype of the F3 generation exceeds the mean of the phenotype induced in the F2 generation, which exceeds the phenotype of the F1 generation—i.e., the induced phenotype accumulates. (*e*) The phenotype of the F2 generation is influenced by the cue experienced in the F0 generation, but the phenotype of the F1 generation is not—i.e., it is delayed. (*f*) The phenotypes of

the F1 and F2 change in opposite directions in response to a cue experienced in the F0 generation—i.e., they are reversed. Here, we have depicted scenarios in which the mean phenotype increases in response to parental cues, but the direction is arbitrary.

Table 1

Multigenerational patterns in the literature: bounce back, weaken, persist, accumulate, delay, and reverse[a]

Study	Species	Parent	Cue	Generations[b]	Trait(s) in descendants
Bounce back					
Wibowo et al. 2016	*Arabidopsis thaliana*	Self-pollinated	Hyperosmotic stress	2	Adaptive stress responses
Remy 2010	*Caenorhabditis elegans*	Hermaphroditic	Olfactory	40	Olfactory imprinting
Zhou et al. 2018	*Mus musculus* (mouse)	Paternal	High-fat diet	2	Cognitive function, methylation
Weaken					
Pentinat et al. 2010	*Mus musculus* (mouse)	Paternal	Neonatal overnutrition	2	Metabolic syndromes
Dunn & Bale 2011	*Mus musculus* (mouse)	Maternal	High-fat diet	3	Body size, insulin sensitivity
Short et al. 2016	*Mus musculus* (mouse)	Paternal	Corticosterone	2	Anxiety and depressive phenotypes
McCarthy et al. 2018	*Mus musculus* (mouse)	Paternal	Nicotine	2	Reversal learning, activity, memory, attention
Liang et al. 2007	*Cricetulus triton* (hamster)	Maternal	Food restriction	2	Early development
Vassoler et al. 2017	*Rattus norvegicus* (brown rat)	Maternal	Opioid	2	Morphine self-administration, gene expression
Groot et al. 2016	*Arabidopsis thaliana*	Self-pollinated	Salt stress	3	Performance
Kamstra et al. 2018	*Danio rerio* (zebrafish)	Maternal and paternal	Ionizing radiation	3	Methylation
Wang et al. 2019	*Caenorhabditis elegans*	Hermaphroditic	Diesel particulate matter	5	Germ cell apoptosis, brood size
Persist					
Burdge et al. 2007	*Mus musculus* (mouse)	Maternal	Proteinrestricted diet	2	Peroxisomal proliferator-activated receptor and glucocorticoid receptor promoter methylation
He et al. 2016	*Mus musculus* (mouse)	Maternal and paternal	Restraint or social instability	2	Anxiety, cortisol, glucocorticoid receptor expression, brain-derived neurotrophic factor
Anway et al. 2005	*Mus musculus* (mouse)	Maternal	Endocrine disruptors	4	Male fertility
Dias & Ressler 2014	*Mus musculus* (mouse)	Paternal	Odor fear conditioning	2	Odor sensitivity
Cropley et al. 2016	*Mus musculus* (mouse)	Paternal	Obesity	3	Metabolic reprogramming
Rasmann et al. 2012	*Arabidopsis thaliana*	Self-pollinated	Herbivory	3	Caterpillar growth
Kishimoto et al. 2017	*Caenorhabditis elegans*	Hermaphroditic	Hormesis	4	Oxidative stress resistance, proteotoxicity
Klosin et al. 2017	*Caenorhabditis elegans*	Hermaphroditic	Temperature	15	Transgene expression

Study	Species	Parent	Cue	Generations[b]	Trait(s) in descendants
Kou et al. 2011	*Oryza sativa* (rice)	Self-pollinated	Nitrogen deficiency	3	Methylation
Accumulate					
Nilsson et al. 2012 [c]	*Mus musculus* (mouse)	Maternal	Environmental toxicants	3	Ovarian disease
Skinner et al. 2013 [c]	*Mus musculus* (mouse)	Maternal	Environmental toxicant	3	Disease, obesity
Skinner et al. 2018	*Mus musculus* (mouse)	Maternal	Environmental toxicant	3	Sperm methylation, noncoding RNA, histone retention
Manikkam et al. 2013	*Mus musculus* (mouse)	Maternal	Endocrine disruptors	3	Disease, obesity
Manikkam et al. 2014 *c*	*Mus musculus* (mouse)	Maternal	Methoxychlor (pesticide)	3	Disease, obesity
Gapp et al. 2014	*Mus musculus* (mouse)	Paternal	Early life stress	2	Glucose metabolism, hypermetabolism
Delay					
Crocker & Hunter 2018	*Acheta domesticus* (cricket)	Maternal	Nutrition quality	2	Egg ecdysteroid hormones, egg production
Panacek et al. 2011	*Drosophila melanogaster*	Maternal and paternal	Silver nanoparticles	8	Fecundity
Kim et al. 2013	*Caenorhabditis elegans*	Hermaphroditic	Gold nanoparticles	4	Survival and reproduction
Reverse					
Sentis et al. 2018	*Acyrthosiphon pisum* (pea aphid)	Clonal	Predation risk	5	Frequency of winged morphs
Alfonso et al. 2019	*Danio rerio* (zebrafish)	Maternal and paternal	Organic pollutants	4	Behavioral defects, methylation
Magiafoglou & Hoffmann 2003	*Drosophila serrata*	Maternal and paternal	Cold shock	2	Viability, development time, productivity

[a] Criteria for inclusion in Table 1 were that the study (*a*) manipulated the environment experienced in the F0 generation; (*b*) maintained the subsequent generations under control conditions that were the same as the control condition in the F0 generation; and (*c*) tracked phenotypes for at least two generations following the F0 generation.

[b] The number of generations investigated after the F0 generation.

[c] Reported data for the F1 and F3 generations but not the F2 generation.