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Review

Epigenetic inheritance and reproductive mode in plants and animals

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Epigenetic inheritance is another piece of the puzzle of nongenetic inheritance, although the prevalence, sources, persistence, and phenotypic consequences of heritable epigenetic marks across taxa remain unclear. We systematically reviewed over 500 studies from the past 5 years to identify trends in the frequency of epigenetic inheritance due to differences in reproductive mode and germline development. Genetic, intrinsic (e.g., disease), and extrinsic (e.g., environmental) factors were identified as sources of epigenetic inheritance, with impacts on phenotype and adaptation depending on environmental predictability. Our review shows that multigenerational persistence of epigenomic patterns is common in both plants and animals, but also highlights many knowledge gaps that remain to be filled. We provide a framework to guide future studies towards understanding the generational persistence and eco-evolutionary significance of epigenomic patterns.

Highlights

Epigenetic mechanisms can alter gene expression and allow species to respond rapidly to their environments by modifying their phenotypes.

Reproductive mode (i.e., sexual versus asexual, oviparity versus viviparity in animals) and germline development commonly predict the persistence of epigenetic marks.

The consequences of persistent epigenomic variation vary depending on the sources (intrinsic, genetic, extrinsic).

Environmental predictability is a key factor for determining the consequences of epigenetic inheritance on phenotype and fitness.

We provide a roadmap for future studies to further our understanding of the extent and evolutionary importance of epigenetic inheritance by quantifying: (i) persistence across generations, (ii) contributions to phenotype and fitness, and (iii) cross-taxa comparisons.

The eco-evolutionary significance of epigenomic variation

The inheritance of acquired traits has long fascinated biologists and led to intense debate. In 1956, Conrad Waddington demonstrated that the inheritance of environmentally induced traits was possible [1], while also coining the term '**epigenetics**' (see Glossary). Since then, the meaning of the term epigenetics has changed in different fields; we define it as 'genome-associated mechanisms of non-DNA sequence-based inheritance' [2,3]. The molecular mechanisms mediating the inheritance of acquired traits have been described in several landmark studies [4–6] and the field has rapidly advanced during the last decade (for an historical context, see [7]). In this review, we focus on the three most widely studied epigenetic mechanisms [3]: DNA methylation, histone modifications, and noncoding RNA (ncRNA) expression (Box 1). The roles of these processes in the establishment, maintenance, and regulation of gene expression can significantly affect the eco-evolutionary dynamics of species (recently reviewed in [8–10]).

Epigenomic variation is nearly ubiquitous in plants and animals and can change at a considerably faster rate than genomic variation [11,12] (i.e., within a single generation [13–17]). Epigenetic inheritance, a source of nongenetic inheritance, occurs when epigenetic modifications (Box 1) are passed on through reproduction to the next generation. The persistence of **epigenomic** variation across generations has been heavily debated, partly because underlying mechanisms were not understood [18] and early research in mammals suggested complete epigenome erasure between generations [19,20]. Unlike the genome, the epigenome is tissue-specific and patterns between soma and germline likely differ. Consequently, the germline is the predominant source of epigenetic inheritance in many species, although some species develop gametes from somatic tissue, while others establish distinct germline tissue early in development. Therefore, the mode of epigenetic inheritance is expected to differ depending on reproductive mode and life history.

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The reproductive strategy (sexual vs. asexual), as well as the timing and nature of events leading to germline formation, are expected to influence epigenetic inheritance. For epigenetic inheritance to occur in gametic reproduction, environmentally or intrinsically induced epigenetic changes must be incorporated into the germline [21]. While it was once accepted that the **Weismann barrier** prevented somatic cells from altering the germline after cell differentiation, this idea has been disproven through research on epigenetic inheritance [21,22]. Soma-to-germline communication may be possible through extracellular RNA [23,24]; however, it is unclear to what extent the germline absorbs somatic epigenetic changes after segregation. Therefore, the timing of germline segregation may influence epigenetic inheritance due to the potential for whole-epigenome inheritance upon germline formation, which is unlikely to occur after segregation. In animals where the germline segregates and differentiates early in development, the timing of gametogenesis and mode of reproduction (**oviparity** vs. **viviparity**) are expected to impact epigenetic inheritance. In viviparous mammals, two rounds of extensive erasure of epigenetic patterns occur (during gametogenesis and embryogenesis), resulting in the resetting of most epigenetic marks, although a small number remain intact [19,20]. In other animals, erasure of epigenetic patterns during gametogenesis and embryogenesis is either absent or understudied [25], thus germline-to-soma transmission is expected to be more prevalent. Late segregation of the germline, common in plants but also found in metazoans such as snails, sea urchins, sponges, and cnidarians [26], results in a long period during which environmentally induced epigenetic changes can be incorporated [16]. DNA methylation and histone modifications are maintained during sexual reproduction in plants, although some reprogramming occurs [27,28]. Thus, late germline segregation should increase the potential for epigenetic inheritance. While germline-to-soma transmission is common, there is variation in the frequency of epigenetic inheritance among species.

Here, we systematically reviewed over 500 studies from the past 5 years on the **multigenerational inheritance** of epigenetic marks in plants and animals (see Supplementary File 1 for search criteria and Table S1 for a full list of studies, in the supplemental information online). Our goals were to: (i) assess the frequency of epigenetic inheritance depending on reproductive mode and germline development; (ii) assess the sources, persistence, and consequences of epigenetic inheritance; and (iii) provide a roadmap with guidelines for future studies to answer outstanding questions and challenges.

Epigenetic inheritance through sexual reproduction

Early germline differentiation reduces potential for epigenetic inheritance

Viviparity

Epigenetic inheritance has been extensively studied in viviparous species (77.5% of 570 reviewed studies; Figures 1 and 2A,B; Table 1; reviewed in [18,20,29]). Viviparity is mostly restricted to mammals, with numerous studies in humans (*Homo sapiens*, $n = 230$), mice (*Mus musculus*, $n = 98$), and rats (*Rattus norvegicus*, $n = 87$), although other domesticated and model mammals (e.g., guinea pigs, *Cavia* spp.) were also represented ($n = 25$). For viviparous species, epigenetic inheritance is limited to gametogenesis for paternal effects, while maternal epigenetic inheritance was thought to occur from gametogenesis to **gonadal sex determination** of the offspring [29]. However, several studies identified maternal epigenetic inheritance due to exposures shortly before parturition (i.e., after offspring gonadal development [30–33]).

Transgenerational inheritance is complicated by viviparity since intrauterine development implies the simultaneous presence of three generations via the female germline: the gestating mother (F_0), the embryo (F_1), and the germline of the embryo (F_2) [34]. Thus, while epigenetic inheritance in viviparous species is only considered 'truly' transgenerational when transmitted to the unexposed

Glossary

Agamogenesis: type of asexual reproduction where only female gametes are produced (i.e., no male gamete is involved).
Apomixis: asexual reproduction in plants where fertilization is absent (i.e., the female gamete develops without fertilization).
Copy number variation (CNV): variation in the number of copies of a nucleotide sequence between individuals.
CpG: a cytosine adjacent to a guanine residue in the DNA sequence. The main site of DNA methylation in animal genomes.
Diversified bet-hedging: phenotypic variability of individuals with the same genotype increases, resulting in higher variance of fitness, which can buffer survival of the genotype in unpredictable environments.
Epigenator signals: transient environmental cues and downstream intracellular signaling pathways that trigger epigenetic changes.
Epigenetic buffering: epigenomic changes contributing to phenotypic resilience of a population facing fluctuating environments.
Epigenetics: genome-associated mechanisms of heritable changes not dependent on changes to DNA sequence.
Epigenetic trap: an intrinsically or extrinsically induced epigenetic change that is maladaptive and does not contribute to diversified bet-hedging strategies.
Epigenomics: epigenetic changes across the whole genome.
Epigenomic variation: interindividual variation in the molecular epigenetic marks.
Facilitated epigenetic variation: epigenetic variation that is induced by environmental stimuli in the context of a specific genotype.
Genetic assimilation: a phenotype shifts from being environmentally induced to genetically encoded when the environment/trigger is stable.
Gonadal sex determination: development of the bipotential gonad into testis or ovary.
H3K9me2: dimethylation of histone H3 lysine 9, a repressive histone modification that condenses the DNA.
H3K9me3: trimethylation of histone H3 lysine 9, a repressive histone modification that condenses the DNA.
Intergenerational inheritance: persistence of effects from parent to offspring.

F_3 generation, increased capacity for maternal epigenetic inheritance in the F_1 and even directly to the F_2 generations exists due to *in utero* development. The abundance of mammalian studies has clarified the optimal timing of parental exposure for epigenetic inheritance to occur, allowing the informed design of studies that maximize the potential for inheritance. This, coupled with the increased potential for epigenetic inheritance due to intrauterine development, explains why examples of viviparous epigenetic inheritance are abundant in the literature. Noteworthy examples include transgenerational studies on maternal exposure to environmental chemicals on complete germline epigenetic inheritance (DNA methylation, ncRNA, and histone modifications) in F_1 through to F_3 sperm in rats [35–37].

Oviparity

Studies in oviparous organisms detected epigenetic inheritance despite their under-representation in the literature (9.82% of 570 reviewed studies), although at a lower frequency (86.1%) than viviparous organisms (91.4%) (Figures 1 and 2C; Table 1). Oviparous, sexually reproducing animals were represented in our review by birds (n = 9 studies), fishes (n = 25), insects (n = 9), crustaceans (n = 2), echinoderms (n = 1), molluscs (n = 3), and one nematode (n = 7). For oviparous reproduction, germline epigenetic changes must be incorporated before the release of gametes, thus there is a strict cut-off for transmission. This was thought to be limited to the short period of gamete maturation in animals, although a recent study in zebrafish (*Danio rerio*) exposed to the pesticide chlorpyrifos-oxon 4 hours to 5 days postfertilization identified differences in DNA methylation that persisted to F_2 [38].

We identified considerable **parental effects** on the offspring epigenome, although few studies discriminated between maternal and paternal effects in oviparous animals. Paternal epigenetic inheritance was less studied in animals (n = 4), but research in Atlantic salmon (*Salmo salar*) [39], European sea bass (*Dicentrarchus labrax*) [40], and Pacific oyster (*Crassostrea gigas*) [41] identified paternal effects on DNA methylation. Maternal epigenetic inheritance was more frequently studied (n = 6), with maternal inheritance of ncRNA expression reported in chicken (*Gallus gallus domesticus*) [42] and annual killifish (*Austrofundulus limnaeus*) [43], as well as maternally-inherited DNA methylation in chicken [44,45] and Chinook salmon (*Oncorhynchus tshawytscha*) [46]. Thus, due to the lack of intrauterine development (i.e., increased maternal influence over offspring epigenetics in viviparous organisms), there is a greater capacity for paternal epigenetic inheritance in oviparous organisms, although maternal effects are more common and frequently studied due to higher maternal investment into gametes.

Late germline differentiation increases the critical window for inheritance

Species with late germline segregation, including plants (n = 46) and one echinoderm, showed high capacity for epigenetic inheritance (Figure 2C). These organisms have an extended time window for epigenetic inheritance due to the creation of germline cells from somatic tissue, hypothetically leading to increased potential for epigenetic inheritance. Consistent with this, there were few studies in plants where epigenetic marks were not transmitted to F_1 and F_2 generations (Figure 1). Parental dominance effects in plants influenced DNA methylation [47,48] and ncRNA expression [48], depending on whether a genotype was used as mother or father. Maternal environment affected DNA methylation in the offspring of purple sea urchin (*Strongylocentrotus purpuratus*) [49].

Self-pollination

Many plants are capable of both self- and cross-pollination [34] and several studies considered the effects of self-pollination on the offspring epigenome (n = 9; Table 1). Studies that involved self-pollination showed long-term persistence of epigenetic inheritance. Cross-pollination between species or lines to induce hybridization followed by self-pollination to produce genetically

Multigenerational inheritance: persistence of effects across generations regardless of exposure to the initial trigger.
Obligatory epigenetic variation: epigenetic variation that is completely dependent on the underlying genetic variation.
Oviparity: a sexual reproductive mode where oocyte and sperm combine to produce offspring, either internally or externally, but egg development occurs outside the body.
Parental effects: effects of parental genotype or environment on offspring phenotype or function that are not due to genetic inheritance.
Parthenogenesis: an asexual reproductive mode where an unfertilized oocyte develops into a viable offspring.
Pure epigenetic variation: epigenetic variation that arises due to developmental stochasticity.
Transgenerational inheritance: persistence of effects up to the first generation completely unexposed, even as germline cells, to the initial trigger.
Vegetative reproduction: an asexual reproductive mode where offspring develops directly from a segment of parental tissue, without the use of gametes.
Viviparity: a sexual reproductive mode where oocyte and sperm combine to produce an embryo that develops inside the parent.
Weismann barrier: concept that the germline is separate from and cannot be influenced by somatic cells.

uniform descendants (n = 12) resulted in inheritance of ncRNA expression until F_{12} in rice (*Oryza sativa*) [50] and of DNA methylation until F_6 in brown mustard (*Brassica juncea*) [51]. Thus, self-pollination can lead to increased similarity in the epigenetic marks carried by parent and offspring compared with cross-pollination between different individuals, with potential long-term effects on the offspring epigenome.

Epigenetic inheritance in asexual organisms

Epigenetic inheritance in agamogenesis

Epigenetic inheritance could be particularly beneficial to asexual organisms, allowing them to cope with environmental stress in the absence of generational genetic variation, resulting in epigenetic mechanisms expanding the range of phenotypes encoded by their genome (Box 2) [52–54]. Despite the potential importance of epigenetic inheritance for asexual organisms, we found only three studies in **parthenogenetic** animals and two in **apomictic** plants. Similar to sexually reproducing organisms, gamete-producing asexual organisms would need to incorporate changes before gamete maturation, although they have the potential for increased control over the offspring epigenome due to uniparental inheritance of epigenetic marks. Asexual organisms that can switch between sexual reproduction and parthenogenesis, such as Cape honey bee (*Apis mellifera capensis*), transmit different methylation patterns, depending on the reproductive strategy used [55].

Despite the dearth of studies in organisms reproducing through **agamogenesis**, epigenetic inheritance can have important implications for offspring survival. A study in the parthenogenetic brown citrus aphid (*Aphis citricidus*) found that maternal crowding decreased offspring aci-miR-9b miRNA expression, resulting in winged offspring that could escape crowded habitats [56]. In apomictic dandelions (*Taraxacum* spp.), altered DNA methylation and ncRNA expression induced by drought were inherited for two to three generations in unexposed offspring [57,58], highlighting the potential for long-term epigenetic inheritance in organisms reproducing asexually without fertilization. Asexual organisms can make use of both plasticity and epigenetically

Box 1. Epigenetic mechanisms

Useful concepts introduced recently, such as 'nongenetic interpretive machinery' [116] and 'inherited gene regulation' [77], encompass various nongenetic molecular mechanisms, but there are three widely accepted epigenetic mechanisms [3].

DNA methylation commonly refers to the addition of a methyl group ($–CH_3$) to the 5′ carbon of cytosine nucleotides, although there are other forms such as 5-hydroxymethylation, the oxidized derivative of cytosine methylation [126]. DNA methylation primarily occurs in a **CpG** context in animals, although CpHpG and CpHpH contexts (where H is an A, T, or C) are common in plants [127]. DNA methylation generally results in the suppression of transcription in a nonlinear, time- and context-dependent manner, but can also be associated with active transcription [128,129].

Histone modifications (including acetylation, phosphorylation, and methylation) occur on specific amino acids of histone proteins, influencing chromatin structure and the transcriptional activity of proximal genes [130,131]. Histone acetylation and phosphorylation reduce chromatin compaction due to their slight negative charge reducing the strength of electrostatic effects between histones and DNA, thus allowing transcriptional machinery to access and transcribe the DNA [130]. Histone methylation can result in either transcriptional activation or repression, depending on where it occurs. For example, **H3K9me3** results in transcriptional activation, while H3K9me2 is associated with transcriptional repression [130]. In animal sperm, histones are usually replaced by protamines, however, part of the histones with their associated modifications may be retained (histone retention) [132].

Noncoding RNAs (ncRNA), including small RNAs and long ncRNAs, do not code for proteins, but instead post-transcriptionally regulate gene expression [133,134], often by binding and silencing complementary RNA molecules [134].

Epigenetic variation is induced by **epigenator signals** from environmental cues [135]. This triggers intracellular pathways that translate signals into chromatin changes via the epigenetic initiators (e.g., ncRNA or DNA-binding molecules) [135,136]. These changes can be converted to permanent states via epigenetic maintainers (e.g., DNA methylation and histone modifications) [135,136]. DNA methylation and histone modifications are altered (either deposited or removed) through enzymatic mechanisms that also function to preserve DNA methylation and histone modifications through cell division and beyond [134]. Richards [78] proposed that epigenetic variation can arise due to genetic effects (obligatory), stochastic environmental or developmental effects regardless of genotype (pure), or a stochastic effect that can occur due to an individual's genotype (facilitated; Figure I). Obligatory and pure represent the two extremes of dependency between epigenetic and genetic variation.

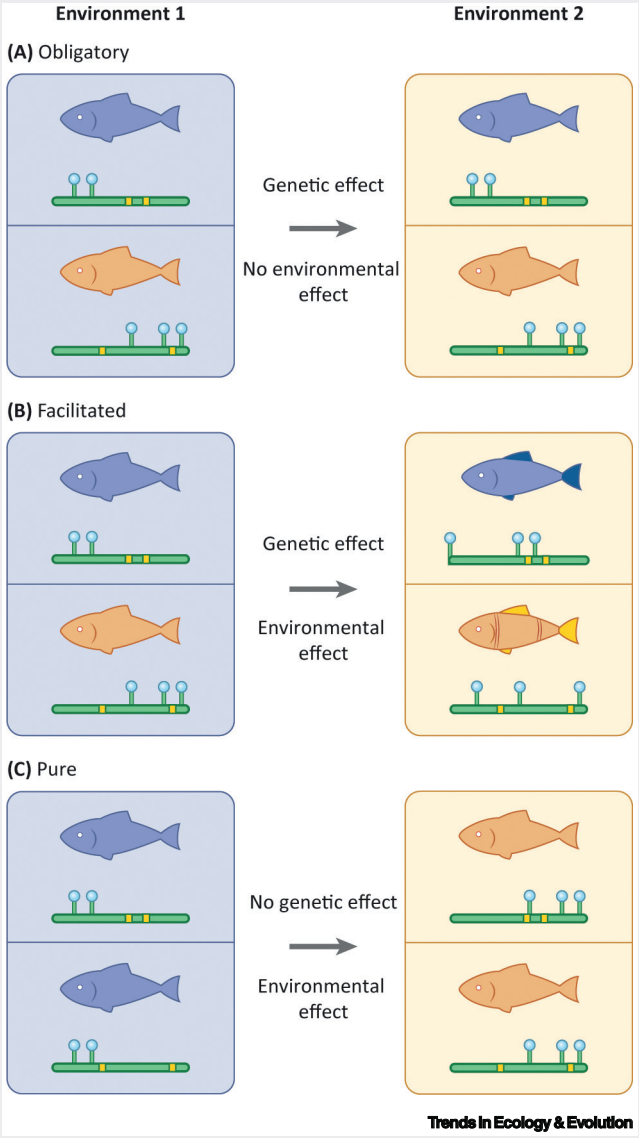

Figure I. Obligatory, facilitated, and **pure epigenomic variants** can arise depending on the relative importance of genetic variation in determining epigenetic marks, with implications for phenotype. Lollipops represent epigenetic modifications on top of the DNA sequence, while yellow bars represent genetic variants. Two different environments are shown by red and green backgrounds. Novel phenotypes are indicated by altered fish color. (A) Obligatory epigenetic variants are entirely due to genotype, thus, result in the same phenotype regardless of the difference between environments. (B) Different genotypes allow the induction of unique facilitated epigenotypes associated with different phenotypes in contrasting environments (i.e., different genotypes develop different epigenotypes in response to the same environmental shift). (C) Pure epigenetic variants are not associated with the genotype and thus result in plastic phenotypic changes that are common in different environments.

inherited **diversified bet-hedging** in response to the same stressor (Box 2). Interestingly in dandelions, ncRNA expression showed intergenerational plasticity [57], while variation in DNA methylation among offspring increased [58], suggesting that closely related organisms can make use of both strategies in response to the same stressor.

Epigenetic inheritance in vegetative reproduction

Organisms utilizing **vegetative reproduction** should have the greatest propensity for epigenetic inheritance. There is no distinct germline in vegetative organisms; offspring arise as a fragment of the parent, with any somatic epigenetic changes passed on to offspring. Studies involving vegetative reproduction were rare in plants ($n = 6$) and animals ($n = 2$). These studies showed high fidelity of epigenetic inheritance. Relative to sexually produced offspring, vegetative offspring had either

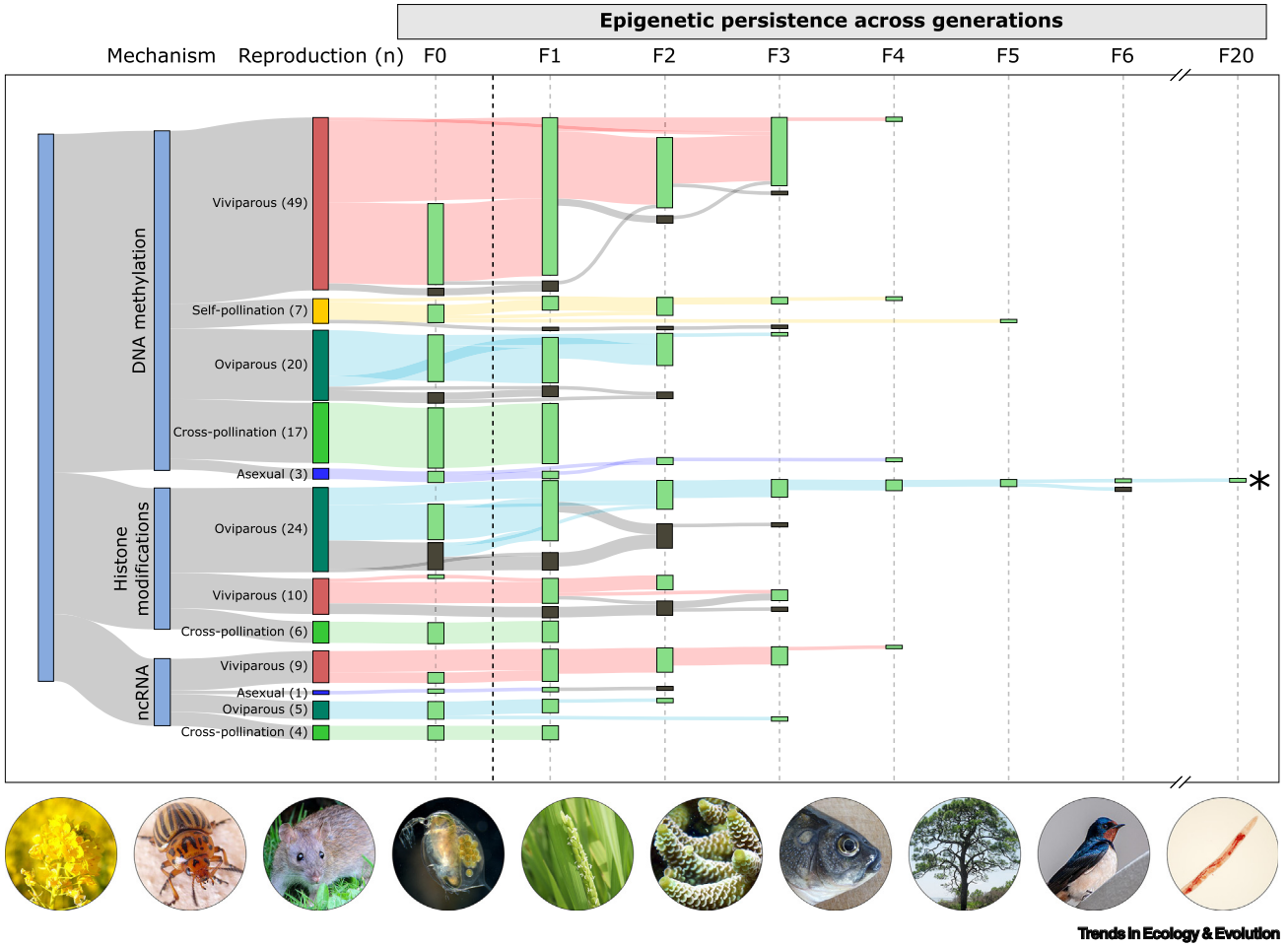

Figure 1. Frequency and persistence of epigenetic inheritance across generations based on the analysis of different epigenetic mechanisms (DNA methylation, noncoding RNA expression, and histone modifications) and reproductive modes performed on multigenerational studies across a diversity of plant and animal taxa. Analyses involved 155 tests of epigenetic inheritance based on 127 unique multigenerational studies, while studies using multiple reproductive modes within a lineage were excluded. See Table 1 for taxon-specific information. Flow width is proportional to the number of studies at each node. The number of individual tests of epigenetic inheritance for each reproductive mode is given in brackets next to the reproductive mode and subsequent flows are color-coded by reproductive mode. Green bars indicate confirmed epigenetic inheritance while gray bars indicate lack of epigenetic inheritance. The black dotted line indicates inheritance from F_0 (germline or soma) tissue to descendants. One study on histone modifications in *Caenorhabditis elegans*, marked with an asterisk at the center right of the figure, found evidence for epigenetic inheritance through F_1–F_{20} generations (F_7–F_{19} omitted for brevity). Round photos underneath the graph display some of the study species that were included in this review.

equal (potato, *Solanum tuberosum*) [59,60] or increased (apple, *Malus domestica*) [61] fidelity of epigenetic inheritance, resulting in increased parental control and heritability of epigenetic marks among generations. Studies on vegetative organisms, including reef-building corals (*Acropora millepora*) and green algae (*Chlamydomonas reinhardtii*), support plasticity rather than diversified bet-hedging and suggest that epigenetic inheritance can improve offspring fitness [62,63]. However, we cannot rule out diversified bet-hedging due to the small number of relevant studies.

Sources, persistence, and consequences of epigenetic inheritance

Intrinsic and extrinsic sources

Epigenetic variation is influenced by intrinsic and extrinsic effects. Intrinsic effects, such as health and physiological status of parents, can have considerable effects on the offspring epigenome.

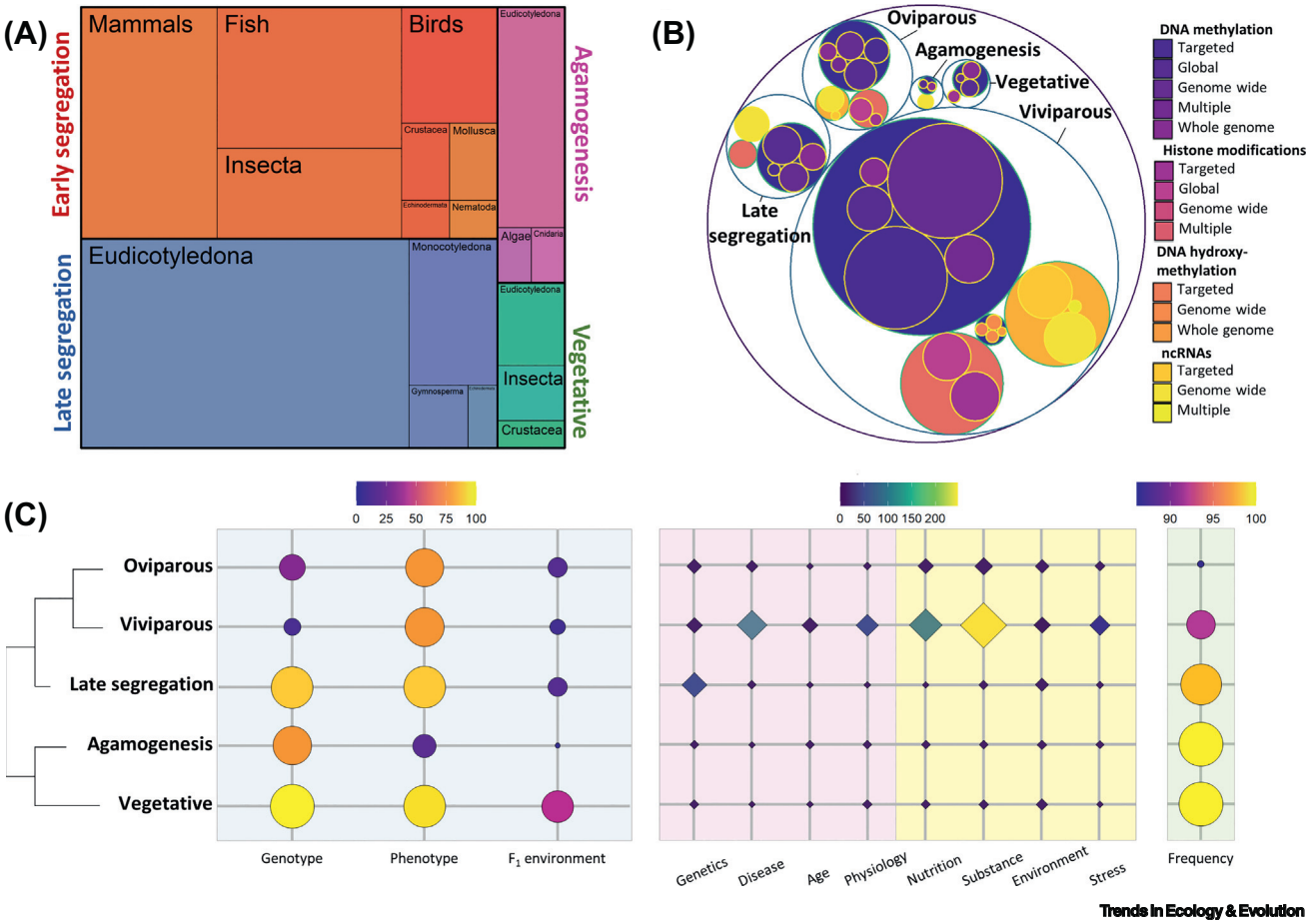

Figure 2. Summary of the reviewed literature by reproductive mode. Sexual reproduction is divided into early and late germline segregation, with early germline segregation further divided into oviparous and viviparous reproduction. Asexual reproduction includes agamogenesis (gamete-producing organisms) and vegetative reproduction. See Table 1 for detailed numbers. (A) Overview of the number of species (not studies) represented in the literature review, colored by reproductive mode. (B) Epigenetic mechanisms and methods used to study them based on reproductive mode represented by open circles. Early segregation mode is divided in oviparous and viviparous. The filled circles within each mode represent epigenetic mechanisms and within each of them, colors represent specific methods used for each epigenetic mechanism, as shown in the legend. Methods are grouped as global (low resolution), targeted, genome wide, whole genome, or multiple approaches used in combination. (C) Frequency of assessment of genetic effects, phenotypic consequences, offspring fitness in matched–mismatched environments, intrinsic and extrinsic drivers of epigenetic inheritance, as well as the frequency of epigenetic inheritance depending on reproductive mode. Early segregation mode is divided in oviparous and viviparous. Bubble sizes are proportional to frequency (0–100%) and rhomboid sizes are proportional to number of studies and colored as shown in the legends. Background colors in the middle panel correspond to intrinsic (pink) or extrinsic (yellow) sources of epigenetic inheritance.

Intrinsic parental effects are often associated with maladaptive phenotypes and lead to **epigenetic traps** [64]. Studies identified epigenetic inheritance due to age (e.g., [65–67]), obesity (e.g., [68,69]), and, in mammals, maternal and gestational diseases (e.g., [70–72]), which typically have negative effects [64].

Despite extrinsic factors such as environmental exposures often being transient, they can have long-lasting effects. Well-known examples of altered DNA methylation patterns in humans persisted for decades after parturition, such as starvation during the Dutch Famine of World War II [73] and maternal smoking [74]. Exposure of Colorado potato beetle (*Leptinotarsa decemlineata*) to insecticides [75], dandelions to salicylic acid [58], and rice to heavy metals [76] resulted in epigenetic changes in F_2 progeny.

Table 1. Summary of literature review per taxa[a]

Reproduction mode	Taxa (species)	Studies	Epigenetic mechanism and method[b]	Effect	Genotype	Phenotype	F_1 environment	Frequency
1. Sexual reproduction (615/672)								
1.1 Early germline segregation (550/606)	Nematoda (1)	7	Histone modifications (G, 1; CG, 1; GW, 2)	Genetics (I, 1), environment (E, 1), nutrition (E, 1), substance exposure (E, 1)	Y (1), N (3)	Y (3), N (2)	N (4)	4/7
			ncRNA (GW, 3)	Genetics (I, 1), disease (I, 1), substance exposure (E, 1)	N (3)	Y (2), N (1)	N (3)	3/3
	Crustacea (2)	2	DNA methylation (G)	Substance exposure (E)	N	Y	Y	1/1
			Histone modifications (G)	Disease (I)	N	Y	N	2/3
	Mollusca (2)	3	DNA methylation (G, 2; MA, 1)	Substance exposure (E, 3)	Y (1), N (2)	Y (3)	N (3)	2/3
	Echinodermata (1)	1	ncRNAs (GW)	Genetics (I)	Y	Y	N	1/1
	Insecta (9)	9	DNA methylation (G, 3; GW, 1; WG, 1)	Genetics (I, 1), disease (I, 1), stress (E, 1), substance exposure (E, 2)	Y (2), N (3)	Y (3), N (2)	N (5)	4/5
			Histone modifications (G, 3; GW, 1)	Genetics (I, 1), disease (I, 1), nutrition (E, 1), substance exposure (E, 1)	Y (2), N (2)	Y (3), N (1)	Y (2), N (2)	5/5
			ncRNA (GW)	Genetics (I)	Y	Y	N	1/1
	Fish (14)	25	DNA methylation (G, 6; CG, 4; GW, 8; WG,2; MA, 2)	Genetics (I, 3), physiological status (I, 1), environment (E, 6), nutrition (E, 3), substance exposure (E, 9)	Y (9), N (13)	Y (17), N (5)	Y (3), N (19)	20/22
			histone modifications (G, 2; CG, 1)	Substance exposure (E, 3)	N (3)	Y (2), N (1)	N (3)	8/9
			ncRNAs (CG, 1; GW, 1)	genetics (I, 1), substance exposure (E, 1)	N (2)	Y (1), N (1)	N (2)	3/3
	Birds (6)	9	DNA methylation (G, 1; CG, 4; GW, 1; WG, 1)	Genetics (I, 1), disease (I, 1), stress (E, 1), environment (E, 1), substance exposure (E, 2)	Y (1), N (6)	Y (4), N (3)	Y (1), N (6)	6/7
			ncRNAs (GW, 2)	nutrition (E, 2), environment (E, 1)	N (2)	Y (2)	N (2)	2/2
	Mammals (17)	441	DNA hydroxymethylation (G, 3; CG, 2; GW, 2; WG, 1)	Physiological status (I, 2), nutrition (E, 2), substance exposure (E, 5)	Y (1), N (7)	Y (7), N (1)	Y (1), N (7)	8/8

Table 1. (continued)

Reproduction mode	Taxa (species)	Studies	Epigenetic mechanism and method[b]	Effect	Genotype	Phenotype	F_1 environment	Frequency
			DNA methylation (G, 26; CG, 134; GW, 167; WG, 10; MA, 30)	Age (14), genetics (15), disease (59), physiological status (35), stress (31), environment (16), nutrition (76), substance exposure (157)	Y (37), N (330)	Y (260), N (107)	Y (18), N (349)	341/367
			Histone modifications (G, 29; CG, 31; GW, 26; MA, 1)	Disease (18), physiological status (1), stress (2), environment (3), nutrition (15), substance exposure (53)	Y (1), N (86)	Y (76), N (11)	Y (7), N (80)	71/87
			ncRNAs (CG, 37; GW, 33; MA, 2)	Age (2), genetics (1), disease (16), physiological status (8), stress (3), nutrition (16), substance exposure (31)	Y (4), N (68)	Y (51), N (21)	Y (7), N (65)	68/72
1.2 Late germline segregation (65/66)	Echinodermata (1)	1	DNA methylation (GW)	Environment (E)	Y	Y	Y	1/1
	Gymnosperma (2)	1	DNA methylation (G)	Genetics (I)	N	Y	N	1/1
	Monocotyledona (7)	10	DNA methylation (G, 2; CG, 1; WG, 1)	Genetics (I, 2), environment (E, 1), substance exposure (E, 1)	Y (3), N (1)	Y (4)	Y (1), N (3)	4/4
			Histone modification (GW, 2)	Genetics (I, 2)	Y (2)	Y (2)	N (2)	2/2
			ncRNA (GW, 5)	Genetics (I, 4), environment (E, 1)	Y (5)	Y (3), N (2)	N (5)	5/5
	Eudicotidae (37)	45	DNA methylation (G, 16; CG, 1; GW, 10; WG, 8)	Genetics (I, 27), disease (I, 1), stress (E, 1), environment (E, 4), substance exposure (E, 2)	Y (32), N (3)	Y (33), N (2)	Y (7), N (28)	34/35
			Histone modifications (GW, 8)	Genetics (I, 8)	Y (8)	Y (8)	N (8)	8/8
			ncRNAs (GW, 10)	Genetics (I, 9), environment (E, 1)	Y (9), N (1)	Y (7), N (3)	N (10)	10/10
2. Asexual reproduction (16/16)								
2.1 Gamete-producing (5/5)	Crustacea (1)	1	ncRNAs (GW)	Age (I), nutrition (E)	Y	N	N	1/1
	Insecta (2)	2	DNA methylation (WG)	Physiological status (I)	Y	N	N	1/1
			ncRNAs (GW)	Stress (E)	N	Y	N	1/1

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Table 1. (continued)

Reproduction mode	Taxa (species)	Studies	Epigenetic mechanism and method[b]	Effect	Genotype	Phenotype	F_1 environment	Frequency
	Eudicotidae (3)	2	DNA methylation (G)	Genetics (I), substance exposure (E), environment (E)	Y	N	N	1/1
			ncRNAs (GW)	Substance exposure (E), environment (E)	Y	N	N	1/1
2.2 Vegetative (11/11)	Algae (1)	1	DNA methylation (WG)	Environment (E)	Y	Y	Y	1/1
	Cnidaria (1)	1	DNA methylation (GW)	Environment (E)	Y	Y	Y	1/1
	Eudicotidae (8)	9	DNA methylation (G, 4; WG, 3)	Genetics (I, 2), physiological status (I, 2), environment (E, 3), substance exposure (E, 1)	Y (7)	Y (6), N (1)	Y (1), N (6)	7/7
			Histone modifications (CG, 2)	Substance exposure (E, 2)	Y (2)	Y (2)	Y (2)	2/2

[a]Numbers in parentheses represent instances unless otherwise stated. Studies that assessed inheritance of more than one mechanism have multiple entries. For full list of references, see Table S1 in the supplemental information online.
[b]CG, candidate gene; E, extrinsic; G, global (low resolution); GW, genome wide; I, intrinsic; MA, multiple approaches; N, no; WG, whole genome; Y, yes.

Genetic effects

Epigenetic variation can be linked to genetic variation, which should thus be considered in multigenerational studies. This link is a continuum ranging from complete dependence, where epigenetic variation is strictly genetically encoded and associated with predictable phenotypes, to independence, where epigenetic variation may be unpredictable since it arises due to developmental stochasticity regardless of genotype (Box 1) [16,77,78]. When inheritance is partially or fully genetically encoded, epigenetic inheritance should occur regardless of reproductive mode. We found 126 studies that considered genotype (Figure 2C), generally without investigating interdependence of genetic and epigenetic variation. There is some evidence for genetic variation driving epigenetic inheritance, including a study in *Caenorhabditis elegans* that identified genetically driven increases in **H3K9me2** levels until F_{20} [79]. Extensive research has characterized polyploidization and/or hybridization effects on **intergenerational inheritance** in plants (e.g., [80–84]), including a study in rice hybrids showing parental dominance in ncRNA expression in F_{12} [50]. A few studies have also characterized polyploidization and/or hybridization effects in insects [85,86] and fish [87,88]. However, epigenetic variation arises rapidly compared with genetic variation [89,90]. A landmark study in thale cress (*Arabidopsis thaliana*) showed the rate of epimutations was sufficient to uncouple genetic and epigenetic variation [89]. Thus, the relative influence of genotype on epigenetic marks (**obligatory epigenetic variation** vs. **facilitated epigenetic variation**) and the permanency of these effects across generations are likely system-dependent.

Persistence of epigenetic inheritance

While adaptive phenotypes can be epigenetically induced within a single generation, transgenerational epigenetic inheritance is expected to be important for evolution since it can persist for many generations and thus be subject to selection. However, the processes associated with germline segregation likely affect the persistence of epigenetic inheritance. Exceptional

Box 2. Epigenetic plasticity, diversified heritable bet-hedging, and genetic assimilation

Epigenetic variation can increase the phenotypic range encoded by a single genome [52]. Plastic phenotypic responses via a targeted increase or decrease in DNA methylation, ncRNA expression, or specific histone modifications in offspring can be facilitated by epigenetic inheritance from parental generation(s). However, this leads to a uniform response among siblings, which can be maladaptive if the parent incorrectly predicts the environment of the offspring, creating a mismatch between the two environments. An alternative strategy is diversified bet-hedging, which increases epigenetic and phenotypic variation in offspring and their chances to cope with the environment [16,64,137]. Plasticity and diversified bet-hedging are hypothesized to be of particular importance for asexual organisms [52] or genetically impoverished populations (e.g., invasive species), as mechanisms to increase phenotypic diversity despite the lack of genetic variation among full-sibling progeny [52,108]. However, it is expected that diversified bet-hedging would be more important than plasticity for organisms living in highly stochastic, unpredictable environments [108,137]. Epigenetics provide mechanisms for phenotypes induced by bet-hedging strategies to be heritable, thus leading to heritable bet-hedging [64]. These strategies may lead to epigenetic buffering and allow populations to persist in rapidly changing and unpredictable environments [16,64].

When environmental conditions persist and epigenetic variation is maintained across generations, genetic assimilation may occur wherein a plastic phenotype becomes genetically encoded. Epigenetically facilitated genetic assimilation can occur due to cytosine methylation and other DNA modifications becoming spontaneously deaminated, commonly resulting in a point mutation from C to T [11,138], although mutations to A and G are also possible [138], with frequency of mutation 10–50 times more than unmethylated cytosines [139]. Histone modifications and ncRNA expression also contribute to increased mutagenesis [11]. Genetic assimilation may occur via increased mutagenesis, but also through differential marking of transposable element machinery or through promoting differential silencing and activation of **copy number variations (CNVs)** [108,119,121]. Either of these processes may lead to genetic assimilation of phenotypic variants (Figure I), resulting in transgenerational epigenetic inheritance becoming stably genetically encoded (Figure I) [11]. Thus, epigenetic mechanisms can, over generational time, contribute to the genetic evolution of organisms.

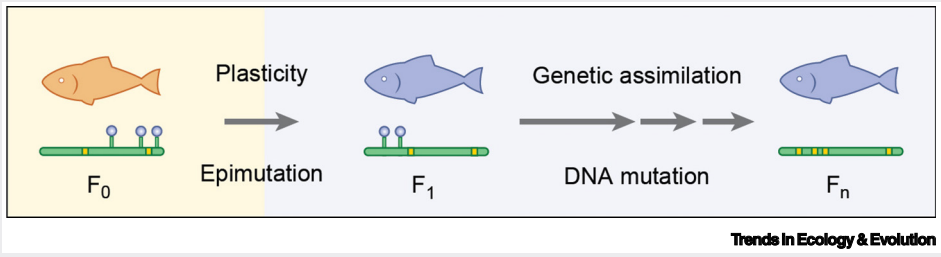

Figure I. Genetic assimilation of plastic epigenetic changes after prolonged environmental conditions. Environmental change induces epigenetic differences, which, after a sufficiently long period of environmental stability, result in point mutations and genetic assimilation. Pure and facilitated epigenetic variants in F_1 may result in genetic variants in F_n. Lollipops represent epigenetic modifications, while yellow bars represent genetic variation. Two different environments are shown by red and blue backgrounds. Novel phenotypes are indicated by altered fish color.

cases of epigenetic inheritance were reported in plants, likely due to late germline segregation and the lack of epigenetic resetting both favoring long-term inheritance. After five generations of selection in *A. thaliana*, novel phenotypes induced in the F_6 were linked to epigenomic patterns stably inherited for two generations, contributing to rapid adaptation (Figure 1) [91]. Expression of ncRNA induced by a polyploidization event persisted for six to 12 generations in hybrids between Asian rice (*O. sativa)* and perennial wild rice (*Oryza longistaminata)* (Figure 1) [50,92]. Other exceptional examples of multigenerational inheritance found persistence of DNA methylation in F_4 [80,93], F_5 [94], and F_6 [51], and ncRNA expression in F_6 [92] and F_{12} [95,96]. These exceptional instances of inheritance often involve a genetic basis underlying epigenetic variation.

While long-term epigenetic inheritance is less likely in organisms with early germline segregation and some extent of germline epigenome reprogramming, the persistence of epigenetic marks in some oviparous organisms rivals that of plants. For instance, studies in *C. elegans*,

a hermaphroditic metazoan with early germline segregation and frequent self-fertilization [97], detected inheritance up to F_4 [98], F_5 [99], and F_{20} [79]. Epigenetic inheritance in viviparous and other oviparous species was often significant to F_3 or F_4 but rarely assessed beyond these generations.

Phenotypic consequences

Persistent epigenetic effects can impact offspring phenotype and fitness, which was assessed in 418 studies (Figure 2C). While some of these studies show that the interplay between epigenetic variation, genetic variation, and gene expression is dynamic [77], epigenetic effects on RNA and downstream molecular phenotypes were only assessed in 128 and 106 studies, respectively. Other studies evaluated effects on morphology (n = 140), function (n = 93), behavior (n = 39), performance (e.g., growth, yield; n = 11), and health (n = 38). Epigenetic inheritance has been associated with behavior [100–102], longevity [79], and growth and survival [41]. In the agricultural context, epigenetic inheritance can influence phenotypes relevant to crop domestication by improving performance traits such as growth [94,103] and pathogen resistance [104].

Environmental predictability

Regardless of reproductive mode, multigenerational inheritance can be adaptive when parents accurately 'predict' the future offspring environment but are likely maladaptive otherwise [64,105–108]. Offspring fitness in matched versus mismatched environments is understudied (n = 45), yet evidence indicates that correct parental prediction of the offspring environment increases offspring fitness. For instance, reciprocally transplanted vegetative reef building corals that modified DNA methylation to resemble local, established corals had higher fitness [62]. In predictable chronic stress experiments, altered DNA methylation was reported for 200 generations of asexual unicellular green alga [63]. Disruption of epigenetic inheritance reduced algal adaptability, highlighting the importance of environmental predictability on the adaptive value of epigenetic inheritance [63]. This suggests that intergenerational inheritance can be maladaptive when environments are incorrectly predicted and offspring are unable to override parental effects. Environmental predictability may be related to a species' lifespan rather than reproductive mode, with short-lived species having higher environmental similarity between generations than long-lived species. However, multigenerational studies in long-lived species pose considerable logistical issues.

A framework for understanding the eco-evolutionary significance of epigenomic variation

Our review shows that multigenerational persistence of epigenomic patterns is common, but also highlights many knowledge gaps that remain to be filled. Most of the current literature focuses on DNA methylation, likely due to the straightforward methods associated with methylation analysis, and the stability of this mark. There are multitudes of studies on model mammals (mouse, rat, human) due to the biomedical field pioneering the study of epigenetic inheritance. This has led to the repeated confirmation that epigenetic inheritance is common in viviparous animals, although highly diverse oviparous taxa (e.g., fishes, insects) are understudied. Here, we propose a roadmap as a potential guide for future research to better understand the persistence and evolutionary significance of epigenomic patterns across generations via three independent but interconnected steps (Figure 3).

In Step 1, we suggest further research on the identification, characterization, and phenotypic consequences of epigenomic variation, which is the focus of most current studies. Quantitative epigenomic studies assessing the relative importance of environmental versus genetic sources

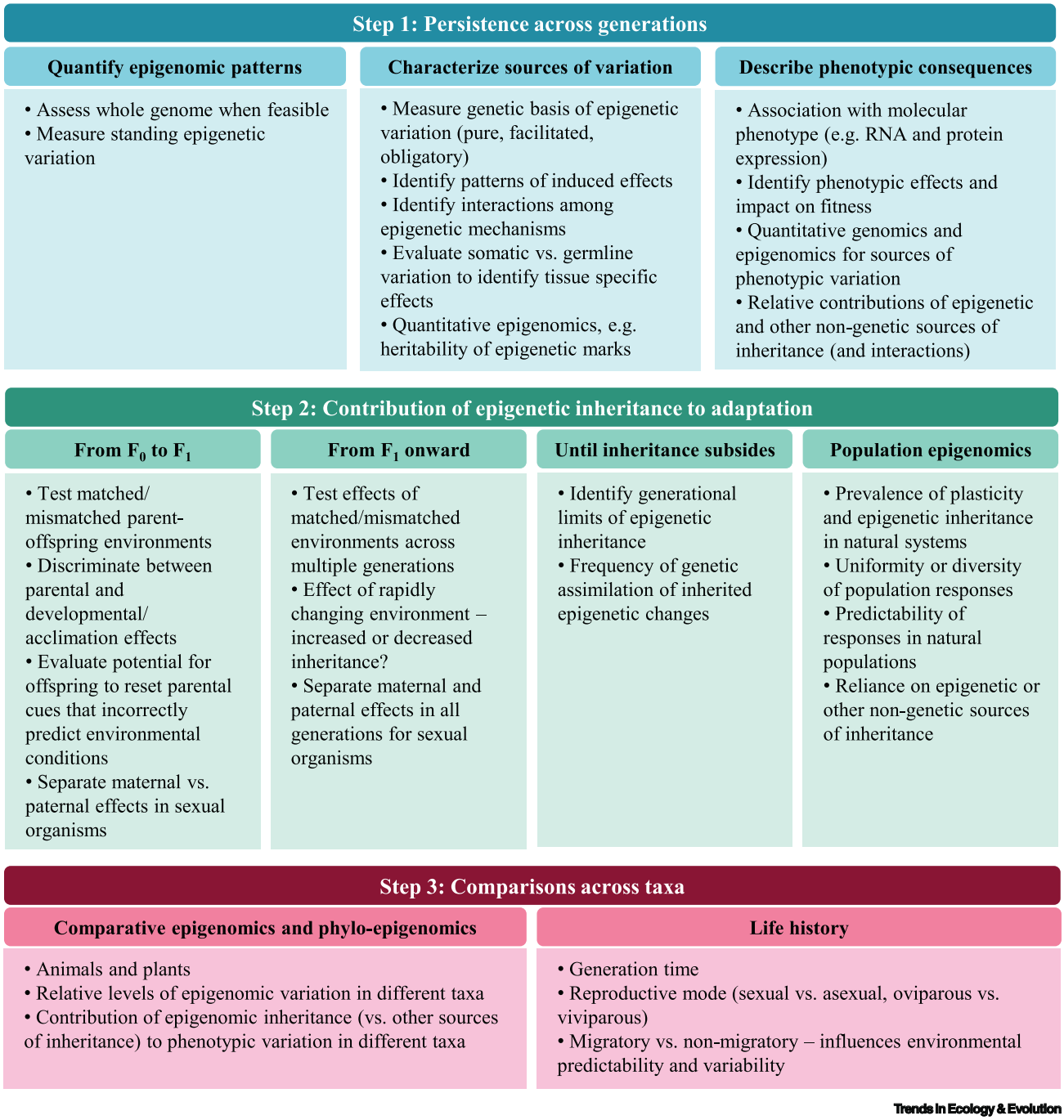

Figure 3. Research roadmap to study the persistence and eco-evolutionary significance of epigenomic patterns over generational time.

of epigenetic variation (e.g., [109–111]), as well as studies linking phenotypic variation to an epigenetic basis, will inform our understanding of the sources and heritability of epigenetic variation. Studies should assess epigenetic inheritance and phenotypic outcomes until inheritance subsides (in some cases, for tens to hundreds of generations) to understand the long-term impacts

of epigenetic inheritance with different reproductive modes and timing of germline segregation, as outlined in Step 1 (Figure 3).

Step 2 focuses on studying the adaptive potential of epigenetic inheritance to clarify its role in the persistence of organisms. Novel phenotypes can be rapidly induced in response to environmental change [16,112] via epigenetic mechanisms and, when inherited, the offspring is primed for an environment predicted based on parental experience [12,113,114]. Thus, even in a single generation, epigenetically induced phenotypes can be adaptive in the face of environmental change through **epigenetic buffering**. However, multigenerational epigenomic patterns are expected to play a more important role for adaptation. Epigenetic inheritance can result in intergenerational inheritance of phenotypes and cellular states, although an organism's epigenetic state can also be subject to selection (for reviews see [115–117]). Theory predicts that epigenetic inheritance will accelerate adaptation if epigenetic changes are stable and have a small effect, while they will slow adaptation if they have the same fitness effects as genetic variation [118]. Organisms with phenotype switching can have an 'epigenetic advantage' in rapidly changing or temporally complex environments, contributing to population adaptability: environmentally induced epigenetic phenotypes can arise simultaneously in many individuals to cope with transient environments and, unlike mutations, can be reversed [10,112]. However, long-term multigenerational studies of natural populations are rare due to the effort and resources required to quantify epigenetic inheritance in such settings. Multigenerational epigenetic changes may also be genetically assimilated to form stable genetic variants (Box 2) [64,108,119]. There is evidence for DNA mutations arising and becoming assimilated in the genome due to DNA methylation [120,121], histone modifications [122,123], and ncRNAs [124]. Thus, epigenetic mechanisms can result in short-term modifications to phenotype and function. They can also create permanent genetic variation when **genetic assimilation** occurs. The importance of epigenetic inheritance in adaptation and the creation of novel genetic mutations can be clarified through proposed research in Step 2 (Figure 3).

Comparisons of patterns and outcomes of epigenomic variation will determine the role of epigenetics in the eco-evolutionary history of species, as outlined in Step 3 (Figure 3). Phylo-epigenetic trees of 176 mammalian species followed evolutionary distances of genetic phylogenetic trees and showed that epigenetic marks relate to life history traits such as age and lifespan [125]. Thus, epigenetic mechanisms likely contribute to evolution and align with genetic measures of evolution, potentially through partial or complete genetic control over the epigenome. However, other sources of nongenetic inheritance should be considered in tandem with epigenetic mechanisms to understand the broad molecular basis of inheritance and adaptation. Representation of species with diverse life history traits (e.g., generation time, migratory behavior) that affect environmental predictability across generations will help to disentangle the relative importance of epigenetic inheritance in response to changing environments. Wide representation of all reproductive modes across taxa is necessary to evaluate the realized significance of epigenetic inheritance in eco-evolutionary potential across the tree of life.

Concluding remarks

Studying the sources and consequences of epigenetic inheritance is critical to understanding nongenetic inheritance, phenotype, and the adaptive potential of populations and species. Our synthesis suggests that reproductive mode and germline development influence the prevalence and persistence of epigenetic inheritance, although many questions remain (see Outstanding questions). It is of utmost importance that the sources, sensitive windows, persistence, fitness consequences, and life history implications of epigenetic inheritance are quantified to better understand their contribution to adaptation and evolution, particularly in the context of rapid environmental change.

Outstanding questions

Do reproductive mode and germline segregation timing affect the genomic extent of epigenome inheritance intergenerationally and transgenerationally? Is there variation in the relative inheritance of different epigenetic marks (histones, ncRNA expression, and DNA methylation)?

What extent of epigenetic changes are communicated between soma and germline once germline segregation is complete?

How do reproductive mode and germline development affect the generation at which epigenetic inheritance subsides? How does this differ among epigenetic mechanisms? Among sexes?

Do the links between epigenetic and genetic variation vary according to reproductive mode? What fraction of epigenetic inheritance is due to parental genotype?

To what extent do reproductive mode and timing of germline segregation influence the contribution of epigenetic variation to nongenetic phenotypic inheritance?

What is the relative importance of epigenetic variation versus other sources of genetic and nongenetic inheritance (e.g., hormones, microbiomes, nutrient provisioning, behavior, habitat choice), and are there interactions among different inheritance mechanisms?

What are the consequences of epigenetic inheritance when parents correctly or incorrectly predict offspring environment? Can offspring modify maladaptive inherited epigenetic marks? Can epigenetic inheritance result in parent–offspring conflict?

Do taxa with different reproductive modes differ with respect to levels of epigenetic variation and inheritance? Does the contribution of epigenetic inheritance to phenotype differ among taxa based on life history?

How does epigenetic inheritance contribute to the persistence of natural populations reproducing sexually and asexually?

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Declaration of interests

No interests are declared.

Supplemental information

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Do populations of a species differ in their capacity for epigenetic inheritance (e.g., due to genetic and environmental differences)?

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