Epigenetic Variations in Heredity and Evolution

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Eva Jablonka
Tel Aviv University
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Epigenetic Variations in Heredity and Evolution

E Jablonka[1]

The biological and medical importance of epigenetics is now taken for granted, but the significance of one aspect of it—epigenetic inheritance—is less widely recognized. New data suggest that not only is it ubiquitous, but both the generation and the transmission of epigenetic variations may be affected by developmental conditions. Population studies, formal models, and research on genomic and ecological stresses all suggest that epigenetic inheritance is important in both micro- and macroevolutionary change.

EPIGENETICS IN HEREDITY

Epigenetic inheritance is a hot topic in modern biology, but because epigenetics is a relatively young and growing discipline (albeit one with much older roots), there is no general consensus about which terms are appropriate for the various phenomena involved. For example, some people use "epigenetics" and "epigenetic inheritance" interchangeably. The way my colleagues and I understand some of the terms,[1–3] and the way I use them in this article, is as follows.

Epigenetics is the study, in both prokaryotes and eukaryotes, of the developmental processes that lead to changes in gene activities and organismal states that persist in the absence of the original inducing developmental input.

Epigenetic mechanisms are the systems that lead to persistent developmental effects and underlie developmental plasticity and canalization. At the cellular level, they are involved in establishing and maintaining the changes occurring during cell determination and differentiation in both nondividing (e.g., brain) cells, and dividing (e.g., stem) cells. At a higher level of biological organization, epigenetic mechanisms underlie self-sustaining interactions between groups of cells or between an organism and its environment; these interactions are mediated through physiological (e.g., hormonal) and behavioral means.

Epigenetic inheritance, a component of epigenetics, is the transmission to subsequent generations of cells or organisms of phenotypic variations that do not stem from variations in DNA base sequence. Cellular transmission can occur during asexual, mitotic, cell division and also sometimes during the sexual processes of meiosis and gametogenesis. We refer to the latter as gametic epigenetic inheritance. Mitotic and gametic epigenetic inheritance are mediated by mechanisms such as DNA methylation, modification and restructuring of histone and nonhistone DNA-binding proteins, RNA regulatory systems, three-dimensional structural templating, and self-sustaining cellular metabolic loops. However, transgenerational inheritance can also occur through developmental and behavioral feedback loops that bypass the gametic route. We refer to this type of nongametic, transgenerational, epigenetic inheritance as soma-to-soma transmission. "Soma-to-soma transmission" is an umbrella term covering the many ways in which phenotypes are inherited because variable aspects of the niche in which development takes place are reconstructed in successive generations. These include the transmission of substances that affect development through their inclusion in feces, which are then ingested by the young; transmission of substances through the placenta and milk of mammals; and transmission through the soma-dependent deposition of specific chemicals in the eggs of oviparous animals and plants. The effects of the constraints imposed by maternal morphology, which can lead to self-perpetuating physical features such as size; the effects of socially learned behaviors, which do not require the transfer of materials yet can lead to traditions that may persist for many generations; and the effects of ecological niche construction and inheritance, which lead to developmental interactions among organisms that form coherent, temporally persistent communities. In humans, soma-to-soma transmission occurs through language and other modes of symbol-based representation and information transfer that lead to the construction of human cultures, to cultural transformation, and to cumulative cultural evolution.

Recognizing these multiple channels of information transmission leads to a pluralistic view of heredity.[1,4] Here, for the sake of brevity, I focus mainly on the ubiquitous epigenetic cellular variations that are transmitted through mitosis and meiosis. **Table 1** gives a taste of the range and scope of this type of epigenetic inheritance. It presents some of the results of studies published in the past 3 years that show germline epigenetic inheritance in five model organisms. Given that the DNAs of hundreds of species have now been sequenced, and the epigenomes of a wide variety of "nonmodel" organisms are being explored under a variety of conditions, the table reflects a

[1]Cohn Institute for the History and Philosophy of Science and Ideas, Tel Aviv University, Tel Aviv, Israel. Correspondence: E Jablonka (jablonka@post.tau.ac.il)

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Table 1 Representative studies of epigenetic inheritance in five model organisms

Organism	Trait (intracellular and/or macroscopic phenotype)	Type of epigenetic mechanism	Inducing conditions	Transmissibility	Ref.
Arabidopsis thaliana (thale cress)	DNA methylation patterns	DNA methylation; 114,287 single methylation polymorphisms and 2,485 differentially methylated regions	Spontaneous	Lower bound of epimutation rate: 4.46×10^{-4} per CpG (cytosine–guanine doublets) per generation	7
	DNA methylation; resistance to pathogens, size, flowering time, etc.	DNA methylation at thousands of sites	Genomic stress (transient introduction of mutation in the methylation pathway)	Already 14 generations (Colot, personal communication)	10,32
	Buffering against genomic incompatibilities in hybrids	Small RNA expression	Hybridization	Stable	33
	Reproductive and morphological traits, including extent of plasticity; DNA methylation patterns	DNA methylation at many sites	External stress (e.g., 5-azaC, herbivory)	Variable stability	34,35
Caenorhabditis elegans (nematode)	Resistance to invading viruses	Small RNAs	Viral infection	More than five generations	12
	Longevity	Chromatin histone modifications; small RNAs?	Transient depletion of specific chromatin modifiers	Two generations	36
	Olfactory imprinting	Unknown; possibly small RNAs	Exposure to odors for four consecutive generations	More than 40 generations	16
Drosophila melanogaster (fruit fly)	Changes in central nervous system transcriptome	Chromatin; gene expression patterns	Exposing adult males to drug pentylenetetrazole	Two generations	37
	Heterochromatin formation; variegated eye color	Chromatin marking associated with transcriptional regulation	Embryonic exposure to heat shock, or continuous osmotic stress for multiple generations	Up to five generations, depending on number of generations of treatment	38
	Drug resistance; various morphological phenotypes; development rate	Chromatin: associated with changes in expression of Polycomb gene proteins	Exposing larvae with drug-resistance genes controlled by various tissue-specific promoters to the drug G418 for one generation	1–24 generations (depending on the promoter)	14
Mus musculus (mouse)	Tail pigmentation; enlarged heart muscle; size	Small RNAs	Injection of small silencing RNAs into eggs	Two generations	39
	Stress-related behavior in adults	DNA methylation	Separation from mother for 3h for 14 days postnatally	Two generations	40
	Silencing of A^{vy} locus; pseudo-agouti phenotype	DNA methylation; many loci affected	Supplementing the diet of isogenic mice with methyl donors for six generations	Progressive but reversible response to selection for six generations	17
Saccharomyces cerevisiae (baker's yeast)	Diverse, frequently beneficial phenotypes	25 Prions (coded by different loci); evidence for additional prions in one-third of wild strains	Spontaneous; frequency increased by stress	Rate of transition between prion and non-prion conformations ~10^{-5}	13 (And references therein)
	Expression of suppressed HIS3 gene	New regulatory circuits	Novel regulatory challenge	Hundreds of generations	15

The list is not exhaustive, and only studies published since 2009 are included.

small part of a far larger database. A 2009 survey of epigenetic inheritance covering all organisms documented 102 studies of epigenetic inheritance involving 42 species,[3] and many more studies have since been published. Together, these studies suggest that heritable epigenetic variations that are transmitted through the germline are numerous and extensive, that the fidelity of their inheritance depends on multiple factors, that several classes of molecular mechanisms are involved in their transmission, and that some epigenetic variations have adaptive significance.

It is worth noting that, although soma-to-soma transmission can be distinguished from gametic inheritance, cellular epigenetic mechanisms such as DNA methylation and RNA-mediated processes may often be part of the processes underlying developmental, somatic reconstruction. One of the few studies that have identified the molecular–epigenetic correlates of soma-to-soma transmission is the well-known series of experiments conducted by Michael Meaney and his colleagues.[5] They showed that variations in a mother rat's style of caring for her young not only influence the mature offspring's responses to stress

(well-licked offspring are more stress-resistant that ill-licked ones) but also affect the maternal care style of the daughters, which reconstruct the behavior of their caregiving (genetic or foster) mother. Moreover, they demonstrated that well-licked offspring have increased expression of a particular gene in the hippocampus, and this is correlated with changes in DNA methylation and DNA-associated proteins in the gene's control region. Once established, the state of this gene persists throughout life, and the pattern is reconstructed in the offspring in the next generation through maternal behavior. It is plausible that other maternal and paternal transgenerational effects, many of which involve soma-to-soma transmission, will be found to have similar molecular–epigenetic correlates. Persistent changes in behavior that are mediated by social learning (not necessarily from parents), and lead to animal traditions and far-reaching changes in the niches animals occupy, are also likely to have distinct molecular–epigenetic correlates.

On the basis of the work I have summarized in this section, it is safe to maintain that, as far as our idea of heredity is concerned, the view that inherited differences must involve differences in DNA base sequence is now recognized to be wrong. Uncovering the molecular basis of cellular epigenetic inheritance, as well as the more general theoretical rethinking of heredity, has led to an extension of the notion of heredity. The once common argument that epigenetic inheritance is rare, and therefore of little hereditary significance, belongs to a rapidly fading paradigm. The ubiquity of epigenetic inheritance is no longer in question, and its importance—for example, in transgenerational epidemiological research in humans—is widely acknowledged.

There is far less consensus about the idea that epigenetic inheritance plays a significant role in evolution. Although the study of epigenetics within an evolutionary framework is now part of the popular, developmentally informed approach to evolution known as "evo-devo," and the roles of complex gene networks, of plasticity and canalization, and of generic constraints and affordance are gaining general recognition, the study of the direct effects of epigenetic inheritance on evolutionary change is only just beginning to take off. In what follows, I focus on the way in which new data and formal models that explore the direct effects of epigenetic inheritance are influencing ideas about evolution. First, I look at microevolution, the small changes that occur within populations; I then consider macroevolution, the type of large-scale change that is associated with the origin of new morphologies and physiologies, and the formation of new species.

MICROEVOLUTION: ECOLOGICAL STUDIES AND POPULATION MODELS

To estimate the ecological and microevolutionary significance of epigenetic variations, we need to know how often they occur and how persistent they are in natural and experimental populations. We can then use this information to construct theoretical models that explore the long-term effects of stable and transient variations. However, as Richards has stressed,[6] it is first crucial to show that epigenetic variation can be partially or fully decoupled from genetic variation so that epigenetic inheritance cannot be fully reduced to genetic inheritance. **Table 2** extends Richards's scheme for classifying variation by explicitly incorporating the degree to which both the acquisition (induction) and transmission of epigenetic variations such as alternative patterns of methylation marks (epialleles) depend on genetic variation. Only when the transmission of an epigenetic variation is not obligatorily dependent on the DNA sequence can epigenetic inheritance be considered a parallel, autonomous, channel of hereditary transmission.

Although as compared with the extensive information we have on genetic diversity in populations the data on independent epigenetic variation in populations are still scarce, the results from studies of experimental inbred lines and natural populations suggest that epigenetic variation is extensive.[7–9] In fact,

Table 2 Relations between genetic and epigenetic variations (e.g., marks such as methylation patterns) at a particular locus

	Acquisition (induction) of epigenetic variant		
Inheritance of epigenetic variant	**Obligatory**	**Facilitated**	**Independent of DNA sequence variation**
Obligatory	The variant and its inheritance are fully determined by the specific DNA sequence	The DNA sequence affects the likelihood of acquiring particular variants; their inheritance is dependent on the DNA sequence	The DNA sequence does not determine which variant is acquired, but its inheritance is dependent on the DNA sequence
Facilitated	The variant is determined by the DNA sequence; some variants are more likely to be inherited than others	The DNA sequence affects both the likelihood of acquiring particular variants and the likelihood of their inheritance	The DNA sequence does not determine which variant is acquired but does affect the likelihood of it being inherited
Independent of DNA variation	The variant is determined by the DNA sequence, but the likelihood of it being inherited is not	The DNA sequence affects the likelihood of acquiring particular variants but not the likelihood of their being inherited	The DNA sequence determines neither which variant is acquired nor the likelihood of it being inherited

Obligatory acquisition: the specific DNA sequence determines which of several theoretically possible marks can be acquired; *obligatory inheritance*: the DNA sequence determines whether or not the mark is inherited. Changes in the environment do not change the mark, the likelihood of its inheritance, or the fidelity with which it is inherited. *Facilitated acquisition*: the likelihood of acquiring a particular mark is affected by the DNA sequence, but is not fully determined by it; *facilitated inheritance*: the DNA sequence affects, but does not fully determine, the mark's transmission to the next generation. Environmental conditions affect the likelihood of acquiring particular marks, the likelihood that they are inherited, and the fidelity with which they are inherited. *Independent acquisition and transmission*: total independence of DNA variation is, of course, impossible;"independent" acquisition means that for a given genotype, the same DNA sequence can acquire many different marks; "independent" inheritance means that all these different marks can be inherited. The marks acquired and fidelity of transmission are dependent on environmental conditions in ancestral generations.

it is often much greater than genetic variation in these populations, and the generation and transmission of a substantial part of it are almost certainly not dependent on the specific DNA sequence at the loci involved, although some sequences may be more likely to acquire and/or transmit the sequence than others. When there is so much heritable epigenetic variation, it is almost inevitable that there will be variants that are adaptive. Indeed, it has already been shown that some of the epiallelic variations in *Arabidopsis* epiRILs (epigenetic inbred lines that are genetically nearly identical but have dissimilar methylomes) are associated with potentially adaptive phenotypes.[10] Similarly, in two parental and four recombinant inbred lines of the monkey flower *Mimulus guttatus*, heritable variations in gene expression, probably associated with DNA methylation differences, were found to underlie the inheritance of the damage-induced adaptive increase in density of trichomes (the thin hairs that defend leaves against insect grazing).[11]

However, epigenetic mechanisms do more than generate frequent, spontaneous, and sometimes adaptive epialleles. They can also underlie adaptive epigenetic strategies. For example, the nematode *Caenorhabditis elegans* has an epigenetic, RNA interference–based mechanism that provides long-term immunity against viruses. Once a virus infects the worm, small, independently heritable RNAs that are complementary to sections of the viral genome are generated, causing destruction of the virus; these RNAs are transmitted for many generations independently of the viral template.[12] A very different kind of adaptive strategy has been found in yeast, where the use of new methodologies has led to the discovery of prions in hundreds of wild strains. Because the rate of switching between prion and nonprion states is influenced by environmental conditions, and many of the prion proteins affect gene expression, the presence of prions can lead to large and diverse phenotypic changes, some of which can be beneficial. Consequently, it is believed that prion formation is an evolved strategy facilitating adaptive responses to new challenges.[13] Further evidence that yeast, and also *Drosophila*, have remarkable adaptive epigenetic strategies comes from studies in which these organisms were exposed to novel environmental challenges after being genetically engineered in a way that meant that their regulatory networks had to be reorganized to overcome the challenges. In both cases, exploratory intracellular and intraorganismal processes involving epigenetic mechanisms led to heritable regulatory adaptations.[14,15] It therefore seems that, in addition to spontaneous and environmentally induced epigenetic variations, epigenetic mechanisms underlie systemic adaptive strategies.

How do these new spontaneous, induced, and systemic heritable epigenetic variations affect the evolutionary dynamics of populations? How can the contribution of epigenetic inheritance to population changes be modeled? Models must take into account factors that affect both genetic and epigenetic variations (selection, drift, migration, and population structure), as well as those that are specific to the epigenetic systems. The most significant epigenetics-specific factors are as follows. (i) Inducibility: if variations are induced, the history of lineages with respect to the ancestral inducing environment may significantly affect the dynamics of evolutionary change. Incorporating epigenetic inducibility into models means including the fitness cost of induction, the percentage of the population affected, and the potentially cumulative effects of repeated induction.[16,17] (ii) Paramutability: the acquired epigenetic state of one locus is sometimes transferred to homologous loci, thus biasing the transmission of the variant.[18] It is the epigenetic equivalent of gene conversion. (iii) Transmissibility: the existing data suggest that this can be locus-specific and highly variable[3] (**Table 1**). Hereditary stability may depend on the genetic context, the intensity and persistence of the inducing conditions, the pattern of transmission, and, probably, many other features of the developing organism and its environment.[2,3]

Models incorporating some of these epigenetics-specific factors have been constructed since the 1990s, but only recently has modeling the effects of epigenetic inheritance on microevolution really gained momentum. The most general model, which is based on an extended version of the Price equation, has shown surprising and dramatic changes in the evolutionary dynamics of populations once epigenetic variations are incorporated.[19] Other theoreticians have adapted classic population genetic models to include epigenetic variations, and they too have found significant changes in evolutionary dynamics.[20] For example, with selection, adaptation can be very rapid because epigenetic variations can be induced in many individuals at the same time. In addition to adapting population genetics models, theoreticians have also extended the classic quantitative genetic equations, thereby enabling rough estimates of the contribution of heritable epigenetic variation to phenotypic variance to be made.[21] Models exploring the conditions promoting the genetic evolution of epigenetic strategies have also been constructed.[22–24]

Taken together, the experimental data and models suggest that the old view of adaptive evolution taking place mainly through the slow and gradual accumulation of randomly generated genetic variations needs updating. Recognizing that epigenetic variations can be inherited changes the picture of adaptive evolution, especially in situations in which changes in environmental conditions lead to the widespread induction of new variants in many individuals. Epigenetic differences within a population can also initiate effects that go beyond the population level, when two subpopulations become geographically isolated, accumulated epigenetic differences may lead to reproductive isolation though epigenetic incompatibilities, especially in chromatin marks located on the sex chromosomes, which result in misimprinting and the death or impaired development of hybrids.[25,26] Hence, speciation, one of the macroevolutionary changes we discuss in the next section, can result from accumulated epigenetic changes in populations.

MACROEVOLUTION: EPIGENETIC MECHANISMS AND SYSTEMIC EPIGENOMIC VARIATIONS

Changes in environmental conditions and other forms of stress sometimes lead to changes that go beyond the typically local and gradual changes that occur during microevolution; they can lead to the macroevolutionary changes that are seen as morphological innovations and sometimes very rapid speciation. Climatic and

other abiotic stresses, the genomic stress of hybridization, and stresses due to infection can activate epigenetic mechanisms that cause systemic changes in transcription, chromatin structure, and genomic organization.[2,3,27] DNA methylation, small RNA profiles, and transposition are all known to manifest extensive changes as a result of such shocks.

There is strong evidence that epigenetic control mechanisms play a key role in speciation through polyploidization and hybridization, which are of particular importance in plant evolution. Many recent studies show that in natural and experimentally constructed plant polyploids and hybrids, there are widespread alterations in DNA methylation patterns, in small interfering RNAs and microRNAs, and in gene expression profiles.[28,29] In wheat, it has been found that some of these changes are targeted to particular chromosomal regions, and that immediately following allopolyploidization (interspecific hybridization followed by genome duplication), there is a "revolutionary" phase lasting for a few generations, characterized by a burst of selectable variation, followed by stabilization.[28] The processes involved may be seen as an attractor-tracking system, during which, over a period of several generations, the genomes of allopolyploid individuals seem to be "searching" for a new, stable, physiological state. Often the result is plants that are physiologically and morphologically very different from the original parents. Other stress conditions also seem to be conducive to macroevolutionary changes, and epigenetic variations and mechanisms seem to be part of the molecular processes that produce them.

Extensive, stress-induced, epigenetic variations may underlie another aspect of macroevolution: morphological innovation. An important model for morphological evolution in animals is domestication, which imposes enormous stresses on the species involved. It is accompanied by remarkable changes in physiology and morphology that appear over very short evolutionary time spans. For example, 50 years of selection for tameness in silver foxes led not only to the rapid evolution of docile animals but also to changes in their pigmentation, modifications in their skeletal morphology and hormonal profiles, altered vocalization, and the more frequent presence of B chromosomes.[30] The mechanisms underlying these rapid changes probably involved heritable epigenetic mechanisms, as some variations showed non-Mendelian patterns of inheritance. Although the molecular–epigenetic basis of the variation has not yet been investigated in silver foxes, there is evidence from work with chickens that domestication can involve massive, genome-wide changes in DNA methylation.[31]

Stress-induced mechanisms that lead to wide-ranging epigenetic, and sometimes genetic, modifications have therefore probably been significant in the origin of many morphological and physiological features, as well as in adaptive evolutions within populations. By definition, in stressful conditions the existing range of variations is inadequate and fitness is reduced. Therefore, stress-induced epigenetic changes occur just when they are needed, and the phenotypic modifications associated with them are potentially adaptive. However, we still do not fully understand the epigenomic stress response, and at present there are more questions than answers. Can we find methods to identify epigenetic repatterning processes in recent speciation events? What are the differences, if any, in the response to genomic and environmental stresses? Do the epigenomic mechanisms of adaptation found in the laboratory operate in natural conditions? How should we construct formal models of macroevolution that are informed by epigenetic mechanisms? These are just some of the important evolutionary questions awaiting new experiments and new conceptualizations.

CONCLUSIONS

A pluralistic view of heredity that includes the transfer of information across generations by nongenetic means has implications for clinical therapeutics, as many human disorders are turning out to have epigenetic correlates that are the consequences of environmental pollutants, nutritional imbalances, and psychological stresses. As emphasized in this article, an epigenetically informed pluralistic approach to heredity and evolution also has broad theoretical implications: it leads to an evolutionary theory that goes beyond the gene-based modern synthesis that has dominated evolutionary thinking for the past 60 years. The current extended synthesis includes both the Darwinian emphasis on selection and the Lamarckian focus on plasticity and the generation of variation, thereby leading to an enriched, extended, developmentally informed view of evolution.

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CONFLICT OF INTEREST

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1. Jablonka, E. & Lamb, M.J. *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral and Symbolic Variation in the History of Life*. (MIT Press, Cambridge, MA, 2005).
2. Jablonka, E. & Lamb, M.J. *Transgenerational epigenetic inheritance. In Evolution the Extended Synthesis* (eds. Pigluicci, M. & Müller, G.B.).137–174. (MIT Press, Cambridge, MA, 2010).
3. Jablonka, E. & Raz, G. Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution. *Q. Rev. Biol.* **84**, 131–176 (2009).
4. Bonduriansky, R. Rethinking heredity, again. *Trends Ecol. Evol. (Amst.)* **27**, 330–336 (2012).
5. Weaver, I.C. *et al*. Epigenetic programming by maternal behavior. *Nat. Neurosci.* **7**, 847–854 (2004).
6. Richards, E.J. Inherited epigenetic variation–revisiting soft inheritance. *Nat. Rev. Genet.* **7**, 395–401 (2006).
7. Schmitz, R.J. *et al*. Transgenerational epigenetic instability is a source of novel methylation variants. *Science* **334**, 369–373 (2011).
8. Lira-Medeiros, C.F., Parisod, C., Fernandes, R.A., Mata, C.S., Cardoso, M.A. & Ferreira, P.C. Epigenetic variation in mangrove plants occurring in contrasting natural environment. *PLoS ONE* **5**, e10326 (2010).
9. Eichten, S.R. *et al*. Heritable epigenetic variation among maize inbreds. *PLoS Genet.* **7**, e1002372 (2011).
10. Johannes, F. *et al*. Assessing the impact of transgenerational epigenetic variation on complex traits. *PLoS Genet.* **5**, e1000530 (2009).
11. Scoville, A.G., Barnett, L.L., Bodbyl-Roels, S., Kelly, J.K. & Hileman, L.C. Differential regulation of a MYB transcription factor is correlated with transgenerational epigenetic inheritance of trichome density in *Mimulus guttatus*. *New Phytol.* **191**, 251–263 (2011).
12. Rechavi, O., Minevich, G. & Hobert, O. Transgenerational inheritance of an acquired small RNA-based antiviral response in *C. elegans*. *Cell* **147**, 1248–1256 (2011).

13. Halfmann, R., Jarosz, D.F., Jones, S.K., Chang, A., Lancaster, A.K. & Lindquist, S. Prions are a common mechanism for phenotypic inheritance in wild yeasts. *Nature* **482**, 363–368 (2012).
14. Stern, S., Fridmann-Sirkis, Y., Braun, E. & Soen, Y. Epigenetically heritable alteration of fly development in response to toxic challenge. *Cell Rep.* **1**, 528–542 (2012).
15. Braun, E. & David, L. The role of cellular plasticity in the evolution of regulatory novelty. In *Transformations of Lamarckism: From Subtle Fluids to Molecular Biology* (eds. Gissis, S.B. & Jablonka, E.) 181–191 (MIT Press, Cambridge, MA, 2011).
16. Remy, J.J. Stable inheritance of an acquired behavior in *Caenorhabditis elegans*. *Curr. Biol.* **20**, R877–R878 (2010).
17. Cropley, J.E., Dang, T.H., Martin, D.I. & Suter, C.M. The penetrance of an epigenetic trait in mice is progressively yet reversibly increased by selection and environment. *Proc. Biol. Sci.* **279**, 2347–2353 (2012).
18. Erhard, K.F. Jr & Hollick, J.B. Paramutation: a process for acquiring trans-generational regulatory states. *Curr. Opin. Plant Biol.* **14**, 210–216 (2011).
19. Day, T. & Bonduriansky, R. A unified approach to the evolutionary consequences of genetic and nongenetic inheritance. *Am. Nat.* **178**, E18–E36 (2011).
20. Geoghegan, J.L. & Spencer, H.G. Population-epigenetic models of selection. *Theor. Popul. Biol.* **81**, 232–242 (2012).
21. Tal, O., Kisdi, E. & Jablonka, E. Epigenetic contribution to covariance between relatives. *Genetics* **184**, 1037–1050 (2010).
22. Lachmann, M. & Jablonka, E. The inheritance of phenotypes: an adaptation to fluctuating environments. *J. Theor. Biol.* **181**, 1–9 (1996).
23. Masel, J. & Bergman, A. The evolution of the evolvability properties of the yeast prion [PSI+]. *Evolution* **57**, 1498–1512 (2003).
24. Feinberg, A.P. & Irizarry, R.A. Stochastic epigenetic variation as a driving force of development, evolutionary adaptation, and disease. *Proc. Natl. Acad. Sci. USA* **107** (suppl. 1), 1757–1764 (2010).
25. Jablonka, E. & Lamb, M.J. *Epigenetic Inheritance and Evolution: the Lamarckian Dimension*. (Oxford University Press, Oxford, UK, 1995).
26. Durand, S., Bouché, N., Perez Strand, E., Loudet, O. & Camilleri, C. Rapid establishment of genetic incompatibility through natural epigenetic variation. *Curr. Biol.* **22**, 326–331 (2012).
27. Shapiro, J.A. *Evolution: A View From the 21st Century*. (FT Press Science, Upper Saddle River, NJ, 2012).
28. Feldman, M. & Levy, A. Instantaneous genetic and epigenetic alterations in the wheat genome caused by allopolyploidization. In *Transformations of Lamarckism: From Subtle Fluids to Molecular Biology* (eds. Gissis, S.B. & Jablonka, E.) 261–270 (MIT Press, Cambridge, MA, 2011).
29. Shivaprasad, P.V., Dunn, R.M., Santos, B.A., Bassett, A. & Baulcombe, D.C. Extraordinary transgressive phenotypes of hybrid tomato are influenced by epigenetics and small silencing RNAs. *EMBO J.* **31**, 257–266 (2012).
30. Markel, A.L. & Trut, L.N. Behavior, stress, and evolution in the light of the Novosibirsk selection experiments. In *Transformations of Lamarckism: From Subtle Fluids to Molecular Biology* (eds. Gissis, S.B. & Jablonka, E.) 171–180 (MIT Press, Cambridge, MA, 2011).
31. Nätt, D. *et al*. Heritable genome-wide variation of gene expression and promoter methylation between wild and domesticated chickens. *BMC Genomics* **13**, 59 (2012).
32. Roux, F. *et al*. Genome-wide epigenetic perturbation jump-starts patterns of heritable variation found in nature. *Genetics* **188**, 1015–1017 (2011).
33. Ha, M. *et al*. Small RNAs serve as a genetic buffer against genomic shock in *Arabidopsis* interspecific hybrids and allopolyploids. *Proc. Natl. Acad. Sci. USA* **106**, 17835–17840 (2009).
34. Bossdorf, O., Arcuri, D., Richards, C.L. & Pigliucci, M. E xperimental alteration of DNA methylation affects the phenotypic plasticity of ecologically relevant traits in *Arabidopsis thaliana*. *Evol. Ecol*. **24**, 541–553 (2010).
35. Rasmann, S. *et al*. Herbivory in the previous generation primes plants for enhanced insect resistance. *Plant Physiol.* **158**, 854–863 (2012).
36. Greer, E.L. *et al*. Transgenerational epigenetic inheritance of longevity in *Caenorhabditis elegans*. *Nature* **479**, 365–371 (2011).
37. Sharma, A. & Singh, P. Detection of transgenerational spermatogenic inheritance of adult male acquired CNS gene expression characteristics using a *Drosophila* systems model. *PLoS ONE* **4**, e5763 (2009).
38. Seong, K.H., Li, D., Shimizu, H., Nakamura, R. & Ishii, S. Inheritance of stress-induced, ATF-2-dependent epigenetic change. *Cell* **145**, 1049–1061 (2011).
39. Rassulzadegan, M. An evolutionary role for RNA-mediated epigenetic variation? In *Transformations of Lamarckism: From Subtle Fluids to Molecular Biology* (eds. Gissis, S.B. & Jablonka, E.) 227–235 (MIT Press, Cambridge, MA, 2011).
40. Franklin, T.B. *et al*. Epigenetic transmission of the impact of early stress across generations. *Biol. Psychiatry* **68**, 408–415 (2010).