REVIEW

Epigenomic plasticity within populations: its evolutionary significance and potential

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Epigenetics has progressed rapidly from an obscure quirk of heredity into a data-heavy 'omic' science. Our understanding of the molecular mechanisms of epigenomic regulation, and the extent of its importance in nature, are far from complete, but in spite of such drawbacks, population-level studies are extremely valuable: epigenomic regulation is involved in several processes central to evolutionary biology including phenotypic plasticity, evolvability and the mediation of intragenomic conflicts. The first studies of epigenomic variation within populations suggest high levels of phenoty-pically relevant variation, with the patterns of epigenetic regulation varying between individuals and genome regions as well as with environment. Epigenetic mechanisms appear to function primarily as genome defences, but result in the maintenance of plasticity together with a degree of buffering of developmental programmes; periodic breakdown of epigenetic buffering could potentially cause variation in rates of phenotypic evolution.

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Introduction: the potential and pitfalls of population epigenomics

Genomics is to genetics as demography is to biography: it is focused not on individual components, but rather on their statistical properties in the aggregate and their interactions and interconnections in context. Population genetics and epigenetics are now, similarly, going -omic, and they are not alone: the *secretome*, *fermentome*, *junkome*, *diseasome*, and even *human speechome* have all been suggested as objects of study. Indeed, collecting and classifying jargon terms appended by the *-ome* suffix is now a tongue-in-cheek scientific field in itself: *omeomics*, coined by science writer Richard Grant in 2005.

The rapid expansion of the omeome certainly has some amusement value, but it would be wildly inaccurate to dismiss the -omics revolution as simply a jargon spree (Evans, 2000). Unprecedented gluts of data from sequencing and microarray technologies have necessitated new techniques for statistical and computational analysis, and new areas of biological science are developing as previously disparate research fields broaden and merge. One such new field is at the confluence of population genetics, genomics and epigenetics.

The consensus definition of an epigenetic trait obtained at a 2008 Cold Spring Harbor meeting was 'a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence' (Berger *et al.*, 2009). Epigenetics, by extension, is the study of these traits, their heritability and variation. This definition, which we will use throughout this paper, excludes *cis*-regulatory DNA sequence elements such as transcription factor binding sites.

The extension of epigenetics to epigenomics involves a broadening of focus from specific loci to large or complete sets of epigenetic traits affecting the phenotype of an individual. Similarly, one can broaden focus from a single individual to the cloud of related genomes, and their associated epigenomes, which make up a population or species. Population genomics, by detailing and quantifying diversity within species, not only catalogues variation in economically, medically or agriculturally important genes, but also hints at possible evolutionary trajectories. Population epigenomics (Richards, 2008; Vieira *et al.*, 2009) has similar potential, but unfortunately, also some of the same problems, and those exacerbated.

First, as more and longer genomes become complemented by epigenomes and population epigenomes, we may very shortly find we have more data than sense. When genetic information was hard to obtain, individual sequences or sequence alignments were subject to intense analysis and reanalysis to squeeze understanding out of a few precious data. Today, only a small minority of DNA sequences uploaded to databases will ever be looked at by human eyes, much less examined in detail; instead, they will be summarised in vast statistical analyses. We will soon have a similarly plentiful supply of epigenomic data, but with nothing like the toolkit of analytical techniques, the theoretical background or the molecular understanding, which we have built up over the last three decades for genetics and genomics. To appreciate the gap between the two fields, consider that epigenetics papers in broad-focus journals still begin by *defining* epigenetics.

A second note of caution should be sounded regarding model systems. When cheap, rapid sequencing became available, the very concept of the model system began to

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seem outmoded. Reports of its demise have been greatly exaggerated, or are, at the very least, premature: although genome sequences are becoming available for increasingly obscure organisms, the bulk of epigenomics research centres on the molecular biology workhorse *Arabidopsis*, supported by other established model systems such as *Drosophila*, mice, maize and humans. In population genomics, too, the classic model systems reign: currently, the largest population data sets are for yeasts (Tsai *et al.*, 2008; Liti *et al.*, 2009), and hundreds of *Drosophila* individuals are in the process of being sequenced (Ledford, 2008). Yet it appears that many traditional model systems are atypical as regards the epigenetic control of their genomes. The very convenience for which laboratory organisms have been adopted makes them unusual in that most have rapid and precocious development, and small genomes with a low complement of repetitive and selfish elements. This suggests that they could be less prone to transcriptional noise (Bird, 1995), and may be likely to need less epigenetic silencing or genome defence. Model organisms have also typically undergone intense artificial selection and population bottlenecks in the process of domestication; these cause inbreeding which may affect epigenetic regulation (Walbot, 2009). Finally, those organisms that have become established as models have clear-cut systems of heredity that lend themselves to straightforward genetic analysis, and can readily be transformed with foreign DNA, which might tend to exclude species with epigenetic genome defence systems (*Neurospora crassa* being a notable exception (Selker, 1990)).

This may mean that we have unintentionally focused on model systems with an atypically low capability for complex epigenetic control. *Drosophila melanogaster* shows debatable evidence even of DNA methylation, containing only one recognisable DNA methyltransferase (Marhold *et al.*, 2004) compared with several in its relatives *Drosophila pseudoobscura* and *Anopheles gambiae*. Similarly, the budding yeast *Saccharomyces cerevisiae* has lost its capacity to regulate genes through RNA interference while its relatives *Saccharomyces castelli* and *Candida albicans* retain this system (Drinnenberg *et al.*, 2009). Not even the laboratory mouse is above suspicion, as many commonly used strains are the result of hybridisation between several subspecies (Wade *et al.*, 2002), and hybrids too may have atypical epigenomes (Hegarty *et al.*, 2008).

Maize, of course, is studied because of its economic importance rather than genetic tractability, so may provide our best hope of a 'normal' epigenome, although the extremely low population sizes that prevailed during its recent domestication bode less well for its showing typical population genomics (Wang *et al.*, 1999). Indeed, epimutations were first described in maize, in 1956 (Brink, 1956 for a historical perspective, see Chandler and Alleman, 2008). It is perhaps no coincidence that maize was the study system of Barbara McClintock, who mistrusted the molecular genetics of her day and saw her discovery of transposable elements as a glaring counter-example to others' reductionist thinking (Comfort, 1995). To her, epigenetic and positional effects were of such paramount importance that she even avoided the use of the word 'gene,' and aligned herself with Goldschmidt (McClintock, 1951), who argued the gene was analogous

to a finger on a violin string, in that its position was more important than its composition (Goldschmidt, 1951).

If genomics technologies adapt readily to new species, the distinction between model and non-model system may indeed fade in the near future. This would be advantageous not just because more data allow for better analyses, but because non-model systems are likely to be more representative of biological normality.

Finally, there is a temptation to be sensationalist regarding new and intriguing findings. Naïve or contrarian interpretations of epigenetic discoveries can raise the spectre of Lamarck, as they allow for the limited inheritance of acquired characteristics, or even that of Lysenko, who believed that environmental manipulations could induce radical and heritable phenotypic change. It is therefore important to stress, first, that many epigenetic responses are determined and controlled by DNA genes, and second and more fundamentally, it makes no difference to the basic mathematics of evolution by natural selection whether or not the heritable changes involved consist solely of alterations in DNA sequence. A full understanding of epigenomics may make important and unexpected contributions to evolutionary and developmental biology, but this will extend, not overthrow, the Darwinian synthesis.

History: plasticity, populations and evolution

A realistic grasp of the extent and the mechanisms of epigenomic control will be of immense value to population geneticists and evolutionary biologists because it is largely through epigenomic means that organisms achieve phenotypic plasticity: the capacity for a single genotype to result in different phenotypes tailored to the environment. This is observed most clearly in plants, which, for obvious reasons, are more strongly obligated than most animals to make the best of potentially unfavourable local conditions. Debates regarding the ecological importance and evolutionary consequences of plasticity within populations have a long and occasionally acrimonious history (reviewed by Pigliucci *et al.*, 2006), but two necessary prerequisites to adequately assess its importance and effect are only now becoming available: first, an understanding of the molecular basis of that plasticity, and second, sufficient relevant data regarding the epigenetic states of large numbers of genes per individual, replicated within populations. Population epigenomics provides a chance to resurrect these debates and resolve them—or perhaps rethink them.

Phenotypic plasticity has been recognised since the beginnings of quantitative genetics, when variation was first partitioned into genetic and environmental components. Even before Mendelian genetics was understood, natural historians grasped that plastic development, capable of responding to environmental signals, could be a powerful adaptation: JM Baldwin (1896) noted that *'The creatures which can stand the 'storm and stress' of the physical influences of the environment, and of the changes which occur in the environment, by undergoing modifications of their congenital functions or of the structures which they get congenitally—these creatures will live; while those which cannot, will not'*.

Over the following 50 years, the triumph of the chromosome theory, and the huge advances in genetics that followed, fostered a less mystical attitude to

organismal development: although the processes involved were not understood in any detail, they were at least acknowledged as investigable, and tentatively named. When Waddington coined 'epigenetics', his definition encompassed most of what we would now call developmental biology, but he stressed that any phenotype was a product of interaction between the inherent genetics of the organism and the influence of the environment—that is, plasticity was built into this definition. Our definition of epigenetics has since changed, but is still closely related to plasticity, as epigenetics is heavily involved in creating a multi-purpose genome, allowing for the same genetic information to yield multiple cell types, highly dissimilar life cycle stages, and the existence of alternative developmental pathways for a single organism based on its own and its ancestors' environment.

The evolutionary origins of epigenomic mechanisms have also been the subject of intriguing debate and speculation, although their original and current functions may be drastically different. DNA methylation, for example, could have arisen as a means to distinguish between the original and newly synthesised strand in mismatch repair—a function it still fulfils today (Modrich, 1989). Remethylation of hemimethylated DNA before the next replication cycle would result in more or less precise heritability of methylation patterns. However, it seems more likely that epigenetic modification evolved to fulfil a function it still holds, as a genome defence against invaders such as viruses or transposable elements (reviewed by Johnson, 2007); bacterial restriction-digestion systems are a well-known example of methylation as genome defence in prokaryotes.

Measuring epigenetic variation in populations

Of the three major methods of epigenetic regulation—methylation, histone modification and RNA interference—the best whole-genome information currently available pertains to methylation patterns. Even here, our understanding is patchy. Unlike genotyping, which can be performed using almost any tissue sample, epigenotyping should ideally match individuals for tissue type and life-history stage, as tissue types differ drastically in their methylation profiles (Lister *et al.*, 2009) and this variation within the individual organism could be confounded with between-individual variation. There is then a risk that any findings may be relevant only to that specific cellular context, and these difficulties are further compounded by the complex interactions between environment, epigenotype, and also in some cases maternal effects (Kadota *et al.*, 2007). The ENCODE (ENCODE Project Consortium, 2004) and modENCODE (Celniker *et al.*, 2009) projects, which aim to characterise all functional elements in the human genome, and in the fly and worm genomes, respectively, include chromatin structure marks as well as DNA sequence-based functional elements and aim to compile cell- and tissue-specific reference data. These will be of great value in quantifying intra-individual variation, but to disentangle this from inter-individual variation may require new analytical methods, perhaps similar to the systems biology approaches currently being used to elucidate the structure of gene and protein networks (Albert, 2007).

Techniques incorporating genetic and epigenetic analyses are now revealing, for a few species, the extent of existing epigenetic variation, and the types of genes and genome regions in which we might expect phenotypically relevant epigenetic variation. A recent review by Richards (Richards, 2008) establishes that there is significant and function-affecting genetic variability in the genes responsible for epigenetic control. Data are largely confined to mammals and flowering plants, and we will consider these two groups separately, in spite of the similarity of the techniques used. Evolutionary divergence between these groups, whose last common ancestor is estimated to have lived 1.6 billion years ago (Meyerowitz, 2002), far exceeds that within, as humans and mice diverged around 100 million years ago (Bininda-Emonds *et al.*, 2007), and maize and *Arabidopsis* around 250 million years ago (Brandl *et al.*, 1992). Until the tree of life is better covered, we cannot know which features of plant and mammalian epigenetic systems are independently derived: indeed, such similarities as are observed should perhaps surprise us.

The methylome of *Arabidopsis thaliana* (Zhang *et al.*, 2006) was the first to be published in 2006, and population variation is also best understood in this species. Interestingly, patterns of DNA methylation vary between genome regions such that particular genome regions are rich in polymorphic sites whereas others, such as those rich in transposable elements, are almost always methylated (Riddle and Richards, 2002).

Arabidopsis studies have also made use of epigenetic inbred lines (Richards, 2009), which maximise epigenetic and minimise genetic variation. These show phenotypic variation for several important traits (Johannes *et al.*, 2009), which is heritable over at least eight generations in a uniform environment, and maintain epi-allelic plasticity (Reinders *et al.*, 2009). Ecotypes of *Arabidopsis* collected from drastically differing environments have also been compared in several epigenomic studies. As well as DNA methylation differences (Vaughn *et al.*, 2007), ecotypes differ in their short interfering RNA complements (Zhai *et al.*, 2008).

An alternative and equally promising approach, used in both *Arabidopsis* and maize, has been to use mutants in genes involved in methylation to identify target genes whose expression varies between mutant and wild type. These can then be presumed to be under particularly strong epigenetic control and subjected to further epigenetic and genetic analysis. As expected under this scenario, the expression of genes identified in this way varied drastically between inbred lines of maize (Makarevitch *et al.*, 2007) and epigenetically repressed *Arabidopsis* transposable elements differed in their activities in methylation mutants (Rangwala and Richards, 2007). Evolutionary studies of these sets of genes would also be valuable.

In mammals, variation in epigenetic states such as methylation, and in level of epigenetic control, also appears to differ in complex ways both between genome regions and between individuals. Genes in areas of low gene density in the human genome show greater environmental sensitivity, and this appears to be because of epigenetic factors such as chromatin structure, which is suggested to be more changeable in gene-sparse regions containing few housekeeping genes (Choi and Kim, 2007). Extending the human epigenome project to a

population-wide study showed intriguing differences between CpG-rich and CpG-poor regions of the genome: CpG-rich regions have low but consistent methylation *levels* in most individuals, but the methylated *sites* are variable. In CpG-poor regions, by contrast, there is more variance in the average proportion of methylated sites, but the precise sites that are methylated are more consistent across individuals (Bock *et al.*, 2008).

As in plants, one tactic used in the search for epigenetic variation is to compare individuals who are as near as possible genetically identical, so that heritable differences are likely because of epigenetic variation. In this vein, monozygotic twin rats can be made by separating a single blastocyst, and have been found to be more similar to one another, for multiple traits, than are genetically identical twin sisters from extremely inbred lines showing no heterozygosity, whose origin is dizygotic (Gartner, 1990). The fact that epigenetic variation is observed even between these individuals, who are closely related by ancestry as well as genetically identical, and share maternal effects as well as environment, suggests we might expect high levels of phenotypically relevant epigenomic variation in mammalian populations.

The second tactic is to use genetically divergent lines, as with ecotypes of *Arabidopsis*. In this study, epigenetic differences are greater, but more difficult to disentangle from genetic effects. Using mice from divergent selection experiments, Hager *et al.* (2009) found that epigenetic imprinting effects were small and precise, but common; 30% of loci with an additive effect on bodyweight showed imprinting.

Human epigenomic studies are hampered by the technical difficulties and ethical problems of sampling diverse human populations systematically in different tissues and life stages. However, both tactics have been used. Identical twins show some epigenetic divergence, which increases with age and differing lifestyles (Fraga *et al.*, 2005), and an analysis of cell lines sampled from diverse individuals showed that chromatin state clusters by family (Kadota *et al.*, 2007). Cancer genetics has also developed an epigenetic wing, as it seems germline epimutations or epigenetic variants may confer increased susceptibility to some cancers (Zingg and Jones, 1997).

Epigenomics and evolution

In spite of the difficulties and caveats outlined above, to achieve a true understanding of evolutionary epigenomics, it will be vital to consider population level and evolutionary processes. Just like new genomic variation, epigenomic variation must succeed and invade at the population level before it can either contribute to between-species divergence or constitute a significant means of gene regulation. For this reason, although there is no reason novel epimutations should be adaptive, an epigenomic trait that occurs in a whole population in response to a previously encountered environmental condition can generally be expected to have an adaptive value, in the same sense as that in which physiological responses are generally assumed to benefit the organism.

Intergenic and gene promoter epigenetic marks can be re-set and re-localised after meiosis, and these processes are involved in directing post-zygotic development: for example, the epigenetically regulated Flowering Locus C determines flowering time in winter-annual *Arabidopsis* from high latitudes (Choi *et al.*, 2009) in addition to its involvement in chromatin silencing elsewhere in the genome (Baurle *et al.*, 2007). Epigenetic control, paradoxically, can also function as a noise-generating system, which can contribute to developmental programs by allowing heterogeneity in genetically identical cells (Hemberger *et al.*, 2009) and breaking symmetries when needed (Gordon *et al.*, 2009).

Adaptive epigenetic mechanisms can have detrimental side effects. Repeat-counting mechanisms that may have evolved to monitor copy number of genomic parasites (Chandler and Alleman, 2008) also trigger the epigenetic regulation of copy number variation in endogenous genes (Riddle and Richards, 2002). Epigenetics, therefore, also influences evolution by restricting the range of possible gene duplications—the most dramatic example being repeat-induced point mutation, which has effectively halted gene duplication in *Neurospora crassa* (Galagan *et al.*, 2003).

Developmental and regulatory plasticity itself offers obvious advantages at an individual level, as Baldwin saw (1896, quoted above). However, the advantages and drawbacks of plasticity at the level of the population, or of the evolutionary lineage, have been more hotly contested and are more poorly understood.

Complicating matters, genotype and epigenotype can be tightly or loosely correlated, and epigenotype at one locus can often be determined by genotype at another. The generation and transmission dynamics of epigenetic variants may also differ greatly from those of conventional DNA genes, which show low constant mutation rates and Mendelian inheritance. Fortunately, population geneticists already deal with some such quirky behaviour in the context of mobile elements and intragenomic conflicts (Burt and Trivers, 2006).

In this study, we will cover three areas in which epigenomics will hold particular interest for population and evolutionary geneticists: the effects of epigenomic variability on evolvability; the intriguing possibility of punctuational 'genome shock' caused either by hybridisation or breakdown of epigenomic control; and the possibilities for evolutionary conflict either within the epigenome, or between the genome and epigenome.

Plasticity and evolvability

One of the most intriguing aspects of epigenetic discoveries is the potential effect of plastic epigenetic control systems on the evolvability of phenotypic traits, and therefore of species and diversity. The extent and type of epigenetic variation determines how a trait will evolve (Wolf *et al.*, 2009). Generally, plasticity has been understood to facilitate phenotypic evolution, first by the simple means of allowing populations to survive long enough to adapt (the Baldwin effect (Crispo, 2007)), and second by canalisation, in which facultative plastic responses become obligate stages of development. Canalisation does not necessarily require any epigenetics in the modern sense, and could realistically be achieved solely through changes at the DNA sequence level, such as, for example, an alteration to a promoter sequence causing the constitutive expression of a previously developmentally regulated protein. We would suggest, however, that epigenetic regulation is likely to become

involved in this kind of adaptation because it allows for an intermediate level of control, providing stable repression through replication cycles and, potentially, the gradual assumption of a plastic response into the co-ordinated higher-order DNA replication structure (reviewed in Corpet and Almouzni, 2009).

The extra layer of regulatory control provided by epigenomic regulation also adds more axes to the adaptive landscape, which can smooth craggy adaptive landscapes and facilitate the evolution of complex phenotypes (Arnold et al., 2001).

However, plasticity may have counteracting negative effects on evolvability (Price et al., 2003); for instance, it can reduce the correlation between an individual's genotype and its fitness, weakening the effect of natural selection. Whitlock (1996) draws a parallel between adaptive plasticity and the concept of niche breadth in ecology: plasticity allows for a broader niche, so response to selection is slower and genetic load higher.

The heritable nature of epigenomic control differentiates it from other plasticity mechanisms. There is evidence from wild plant populations that transgenerational plasticity is adaptive and leads to increased fitness (Galloway and Etterson, 2007) and from microorganism populations that 'environmental anticipation has been selected for during evolution' (Mitchell et al., 2009). Transgenerational inheritance of epigenetic marks increases phenotypic variation in a manner that appears to condition the organism for stabilising selection (Rando and Verstrepen, 2007).

The longevity of epigenetic memory can also vary and evolve. Theoretical work suggests that a long epigenetic memory will increase optimal plasticity, and the optimal length of epigenetic memory depends on existing adaptation (Pal, 1998). Dual inheritance of genetic and epigenetic information is particularly favourable if the population is far from as adaptive peak. Importantly, plasticity combined with memory allows for the maintenance of high levels of genetic variation although a population is close to phenotypic optimum. This last gives solid theoretical support to the previously somewhat nebulous concept of 'evolutionary capacitance': the idea that silent genetic variation can build up over generations, to be expressed or released periodically.

Capacitance and genome shock

Concepts of capacitance
The conditions that are postulated to trigger a release from evolutionary capacitance, and reveal unexpected variability in a population, are not subtle shifts in selective pressures but drastic events with genome-wide consequences. These include prion accumulation, selfish element invasion, hybridisation, inbreeding or physiological stresses brought about by extreme environmental change. 'Omics' approaches are therefore particularly appropriate for investigating capacitance.

Heat shock proteins, and other molecular chaperones, are potential mediators of evolutionary capacitance. By allowing a range of mutant proteins to fold normally, they can mask variation which is revealed in mutants. Disruption of the HSP90 heat-shock protein, which acts as a molecular chaperone for over 100 signalling proteins, increases variability (Rutherford and Lindquist, 1998) and has been shown to leave a functional, heritable epigenetic 'mark' in isogenic Drosophila melanogaster (Sollars et al., 2003). At the whole genome or population level, although, not all of these responses have a consistent epigenetic basis, and recent work (Specchia et al., 2010) suggests an alternative explanation for increased variability, namely that mutation of HSP90 frees transposons from suppression and so increases insertional mutation.

Heat shock proteins have a known role in facilitating the folding of non-mutant proteins; as with the yeast prion previously proclaimed as an evolvability switch (Partridge and Barton, 2000), there is as yet no evidence that heat shock mutations are ever adaptive in the wild, let alone that their role in periodically revealing genetic variation can truly be regarded as a function.

The bistable, periodic nature of capacitance and release irresistibly calls to mind the theories of punctuated equilibrium first developed and espoused by palaeontologists (Gould and Eldredge, 1977), and supported by some recent work in molecular phylogenetics (Pagel et al., 2006). Many researchers have indeed made this connection, suggesting that adaptive spurts are caused by physiological stress disrupting epigenetic variation. Some add extra accelerants to these evolutionary explosions, pointing out that gene conversion or recombination can be accelerated by changes in chromatin conformation (Cummings et al., 2007) or that transposable elements, freed from the restraint of epigenomic genome defences, could quickly expand and restructure the genome (Zeh et al., 2009). Hybridisation may trigger these processes, as hybrids show extensive epigenetic dysfunction (reviewed by Michalak, 2008).

Polyploidy is another potential trigger for epigenetic revolution. The advantages of changes in gene expression (Ni et al., 2009) and restructuring in hybrids (Pennington et al., 2008) and stable allopolyploid plants, Leitch and Leitch (2008) argue, are responsible for much of their diversity and success. If epigenomic cryptic variation is revealed in response to shock or challenge, it should lead to rapid adaptation and increased population evolvability (sensu Hansen (2006)). Rapid evolution of novel allopolyploids has been shown in several species, including fireweeds in which rapid changes result from population-level interactions with diploid parental species (Husband and Sabara, 2004). Buggs et al. (2009) have also shown that in salsify (Tragopon) allopolyploids, the silencing of homeologous chromosomes varies between different populations. Rapid divergence is observed in expression pattern between gene duplicates, particularly under stress (Liu and Adams, 2007). The broad synthesis emerging from large molecular data sets is that these genomic processes are, in large part, epigenetically directed (reviewed by Madlung and Comai, 2004).

Conflicts and antagonistic coevolution
Epigenetic regulation also strongly influences population-level processes by mediating genetic conflicts, in particular that between the endogenous nuclear genome and selfish mobile elements such as transposons, retroviruses and retrotransposons. Another review in this issue deals with the epigenomics of transposable element

control, so here it will be sufficient to state that the intensity of conflicts varies across genomes, populations and environments, again favouring an -omics approach to the study of these global, omic-level controls, which give the individual an advantage over its genomic parasites, toward whom the battle is otherwise unfairly skewed. Epigenetic regulation of transposable elements can be position dependent or otherwise nonuniformly distributed across the genome—for example, transposons within a heterochromatic domain can be silenced en masse (Grewal and Moazed, 2003)—and in addition can depend on environmental conditions, such as temperature in the case of Drosophila P elements (Vieira *et al.*, 2009). Some transposable elements are also targeted to particular chromatin forms—in the 'ecology of the genome' (Brookfield, 2005) this amounts to habitat specialisation—and cell type and developmental stage also has a role. In animal somatic cells, or plant cells irreversibly committed to vegetative growth, for example, there is no conflict over somatic suppression.

The role of imprinting in intersexual conflict over offspring provisioning is a famous example of epigenetic conflict, and inherited adaptive plasticity results in parent–offspring conflict too. To prevent such conflict, maternal genomes can be actively demethylated in the zygote, effectively 'disarming' sperm (Bird, 2002).

Intrasexual conflicts also involve epigenetics. Diet-derived and condition-dependent sexual signals, which are by definition epigenetic *sensu* Waddington, seem also to be epigenetic in the molecular, non-DNA modification sense.

It is of course important to remember that a single epigene—a locus or other inherited factor whose phenotypic effect is not associated with DNA sequence variation—can evolve more than one function, and can hold those functions sequentially or simultaneously. PEG10 is a transposon-derived placental gene: its orthologue in wallabies is the first imprinting-associated differently methylated region found in marsupials, but there is no orthologue in the platypus (Suzuki *et al.*, 2007); this indicates that the gene originated, probably through transposition, and acquired its imprinted status before the marsupial-placental spilt, but acquired its function in the placenta more recently. In an interesting convergence, imprinting appears to have been similarly co-opted from transposon silencing in plants (Gehring *et al.*, 2009). Transposon-induced epigenetic changes have also been instrumental in causing evolutionary change in plant breeding systems (Martin *et al.*, 2009).

Distinctions
Pedantic although it may seem, it is important to draw a strict distinction between a system that incidentally increases evolvability but is maintained by selection for other reasons, and an 'evolvability mechanism' *sensu stricto*. Evolvability can indeed evolve under fluctuating selection (Draghi and Wagner, 2009), but increased evolvability could also be simply a by-product of plasticity—and the fact that this increased evolvability has had important consequences, or even been vital to the evolution of life's current diversity, is irrelevant to the question of whether the evolvability itself is an adaptation. Two parallels may be illustrative. Mutation is essential for evolution and mutation rates are under

some degree of genetic control, yet mutation is not an adaptation, as all available evidence supported by theoretical work shows that low mutation rates are almost always favoured in sexual populations; actual mutation rates are likely to be a trade-off between accuracy and energetic expenditure without evolvability being a factor (Sniegowski *et al.*, 2000). Sex, on the other hand, truly is best explained as an evolvability mechanism according to our current understanding: the 'Red Queen' theory, plus that of Weismann (Burt, 2000) and those based on Hill–Robertson effects (Barton and Otto, 2005) are variations on this theme.

For the reasons above—the smoothing of adaptive landscapes and the maintenance of genetic variation—we take the view that epigenetic variation very likely does make species more evolvable and contributes to the evolutionary success of some lineages. Taken together, studies to date strongly suggest that epigenomic responses are canalisation factors. They maintain cryptic variation in the epigenome, reducing direct genome effects while enabling phenotypic plasticity. To resolve whether this evolvability is an adaptation, however, we need more theoretical and practical understanding of the molecular basis and the short- and long-term costs of epigenomic plasticity and a quantitative measure of the extent to which this plasticity aids evolution (such as those being calculated for the benefits of recombination (Agrawal *et al.*, 2005)), plus observational evidence such as the long-term maintenance of a gene with no other function than increasing evolvability. Relevant theoretical calculations of this nature have been attempted with regards to the evolutionary capacitance theory of the maintenance of psi prion of yeast which, assuming large population sizes, low mutation rates and a low cost of maintenance, must provide a new adaptive change every million years to survive mutational degeneration (Masel and Bergman, 2003). Similar work on the more complex plasticity of animals and plants would be extremely valuable.

We should also consider the contribution of transposable element population dynamics affecting the evolvability of the lineages they infest: what we think of as evidence of adaptation at or above the level of the individual may be the result of selfish activity at a lower level.

Summary and pressing questions
Patterns of epigenetic regulation vary between individuals, and across populations—including populations of transposable elements (Rangwala *et al.*, 2006)—between genome regions, over time, and with environmental stresses both biotic and abiotic (Molinier *et al.*, 2006), and there are complex interactions between the above factors.

Epigenetic mechanisms seem to function primarily as genome defences, but also adaptively or otherwise result in the maintenance of plasticity together with a degree of buffering of developmental programmes (Parkinson *et al.*, 2007). Although epigenetic silencing could potentially be an all-purpose control mechanism-like transcription factors, it is most heavily used in certain areas of genome function, such as defence, noise reduction, mediation of genetic conflicts and the facilitation of plastic responses to environment, which require rapid but sustainable responses.

In population genetics, a population has a diversity, number of genotypes, variance in fitness, effective population size and other emergent, collective properties. In the same way, whole epigenomes and population data sets have properties an individual epigenotype at a single locus does not. We need new measures of epigenomic influence on these population-level, rather than individual, characteristics, and an extension of statistical data analysis techniques to deal with them. As an example of the advantages of 'omic' analysis, recall that, using gene-level sequence-based methods, proving the effects of natural selection at any one locus or site was extremely difficult: today, the percentage of sites under natural selection can be estimated using whole-genome data (Eyre-Walker, 2006).

Particularly interesting questions for which data will soon be available are, first, are highly epigenetically regulated genes fast- or slow-evolving? Drosophila polycomb response elements are surprisingly fast-evolving (Hauenschild et al., 2008), and silencing proteins also diverge rapidly (Fabre et al., 2005), which could be suggestive of antagonistic coevolution caused by intragenomic or epigenomic conflict.

Second, as data from more species become available, the effect of ecology can be examined. Are plants with high dispersal more plastic, with more variable epigenomes, or more of the genome under some form of epigenomic control? Is this true of generalists, weeds and invasive species?

Third, comparative and evolutionary analyses, particularly those involving intragenomic populations of transposable elements, can shed light on the timescales of epigenetic and genetic adaptation, and determine which is responsible for short- and long-term phenotypic change. This will also clarify the question of the frequency and intensity of 'genome shocks': periods of instability resulting in rapid, drastic restructuring.

Theoretical understanding will be as important as molecular. We might ask: are epigenetic networks wired up to 'help' or 'work with' selection at the genetic level? What are the limits of plasticity (Whitlock, 1996), and are these ecologically imposed or molecular constraints? We also need to combine an understanding of plasticity into other areas of evolutionary biology, as has to some extent been achieved in the area of the evolution of sex and recombination rates (Agrawal et al., 2005). Quantitative and population genetics are largely based on population-level phenomena, such as heritabilities and responses to selection, that depend on the way in which variability is generated; it remains to be observed whether the population-level implications of epigenomic modifications will necessitate a mere tweak, or a wholesale rethink, of the fundamental concepts of evolutionary biology.

Conflict of interest

The authors declare no conflict of interest.

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