A role for epigenetic inheritance in modern evolutionary theory? A comment in response to Dickins and Rahman

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In taking issue with the idea of soft inheritance and an ‘extended evolutionary synthesis’, Dickins & Rahman [1] have questioned the ability of epigenetic systems to act as direct mediators of inheritance. At the heart of Dickins & Rahman’s argument is the idea that epigenetic states are themselves genetically encoded, so that inheritance of an epigenetic state reflects the inheritance of a genetic state. Their views are justified in regard to some forms of ‘soft’ inheritance, which they define as ‘the inheritance of variations that are the result of non-genetic effects’ (p. 2913 of [1]). But this should not extend to epigenetic inheritance itself: as we will discuss, there is abundant evidence that alternative epigenetic states can arise and be maintained on the same genotype. Pure epigenetic inheritance stems from the germline transmission of an epigenetic state [2]; this definition excludes the inheritance of epigenetic states that are determined by genetic states. Pure epigenetic inheritance is fully capable of serving as an ultimate mechanism of evolution in the sense in which Dickins & Rahman have used that term: if an epigenetic variant is sufficiently stable over multiple generations, then its associated phenotype may be subject to natural selection. No paradigm shift is required: the modern synthesis is based on chromosomal inheritance, and epigenetic inheritance, although not purely mediated by DNA sequence, is still mediated by chromosomes. In support of this view, we provide definitions of epigenetic variation and epigenetic inheritance, and cite evidence for pure epigenetic inheritance in a wide variety of species.

Epigenetics is the study of phenomena in which highly complex molecular accretions to the genome determine stable states of gene expression [3]. An epigenetic state is a functional state (active or inactive) of a transcriptional regulatory element such as a promoter or enhancer. Such alternative states are part of normal processes of gene regulation, as in cell differentiation, but they can also occur as aberrations, which may be termed epigenetic variants or ‘epimutations’. Variant epigenetic states can be influenced or determined by genome sequence [2], but this is not always the case: multiple examples are known in which variant epigenetic states occur without any genetic variation to account for them (see below). These are considered ‘pure’ epigenetic variants [2].

Epigenetic inheritance is the intergenerational transmission of a purely epigenetic variant. This form of inheritance requires that a variant epigenetic state arise in the germline (or in cells that give rise to germ cells as in plants), and be maintained in the germline for one or more generations. Because epigenetic inheritance is based on complex accretions to DNA [4], and these are less stable and replicable than DNA sequence, the transmissibility of an epigenetic variant may be wildly different from the predictable pattern of Mendelian inheritance, which is based on the faithful replication and orderly transmission of DNA. The molecular complexity of epigenetic states explains why examples of epigenetic inheritance exhibit such a variety of inheritance patterns: the precise molecular composition of an epigenetic variant is quite unlikely to be the same at two different loci. Nevertheless, in some cases, an epigenetic state may be so stable in the germline that its transmission occurs in lockstep with
the DNA on which it sits, in which case it may appear to be inherited as a Mendelian allele [4,5].

The phenomenon of epigenetic inheritance as defined here is well documented in multiple plant and animal species, beginning with Brink’s [6] and Coe’s [5] descriptions of paramutation in maize in the 1950s (see also [7–8]); in recent years, many more cases have been described. Plants have been the most abundant source of examples, perhaps because epigenetic variants arising in somatic cells can be inherited (reviewed by Hauser et al. [4] and Yakutani [9]). Although animals segregate a germline within which any heritable information must be established and maintained, epigenetic inheritance has been found in multiple animal species: some examples are the behaviour of the Fab-7 element [10] and heterochromatin alterations [11,12] in *Drosophila*, heritable transgene silencing [13,14] as well as the *A<sup>y</sup>* [15] and *axin(Fu)* [16] alleles in mice, *MLH1* in humans [17,18], and several others [19,20]. A pertinent but often overlooked example is the appearance and inheritance of neocentromeres. Investigation of neocentromeres has established that centromeres are purely epigenetic structures that can arise as chance events on a variety of sequences lacking common features, and can be transmitted. Centromere repositioning, which involves the formation of a neocentromere and often the inactivation of an older centromere, is linked to speciation [21].

There is no question that epigenetic states can be determined by *cis-* or *trans-*acting genetic factors; our point is that in some cases, perhaps many cases, they are not. The examples cited by Dickins & Rahman [1] are not epigenetic inheritance as defined above; we would describe them as serial parental programming of a trait, which need not involve any change in the germline, either genetic or epigenetic. The example of monozygotic/dizygotic twins cited by Dickins & Rahman, while it suggests that much epigenetic variation is genetically driven, does not address purely epigenetic variation or epigenetic inheritance.

In order to be certain that a purely epigenetic variant or state is inheritable, one must eliminate genetic variation as a cause, and also demonstrate that transmission does not result from the programming of one generation by some physiological or behavioural trait in the parental generation. In practice, this can be extremely difficult: for a successful example, consider our demonstration of epigenetic inheritance at the *A<sup>y</sup>*/allele in mice [15], which required isogenic mice and a breeding strategy that ruled out an effect of maternal metabolism on the phenotypes of offspring. In natural populations, which are genetically heterogeneous and not subject to controlled breeding, such a demonstration is not currently feasible [22].

In conclusion, there is clear and abundant evidence for multigenerational inheritance of epigenetic states that are independent of genotype. This makes it possible for purely epigenetic states to participate in evolution if the traits they specify are subject to natural selection [22–25]. Nevertheless, when studying a locus that has been subject to natural selection, it might be difficult to distinguish epigenetic and Mendelian mechanisms, because an epigenetic state will be inherited, and selected, along with the particular DNA sequence on which it arose; this problem is very much like finding the causative mutation among all the variants present in a haplotype that has been associated with a phenotype. Although the answer to the question posed in the title is a definite yes, the scope of epigenetic inheritance is not yet clear, and tracking epigenetic states over evolutionary timescales will be challenging.

References


