## The Evolutionary Gene and the Extended Evolutionary Synthesis

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**Abstract**

Advocates of an ‘extended evolutionary synthesis’ have claimed that standard evolutionary theory fails to accommodate epigenetic inheritance. The opponents of the extended synthesis argue that the evidence for epigenetic inheritance causing adaptive evolution in nature is insufficient. We suggest that the ambiguity surrounding the conception of the gene represents a background semantic issue in the debate. Starting from Haig’s gene-selectionist framework and Griffiths and Neumann-Held’s notion of the evolutionary gene, we define senses of ‘gene’, ‘environment’ and ‘phenotype’ in a way that makes them consistent with gene-centric evolutionary theory. We argue that the evolutionary gene, when being materialized, need not be restricted to nucleic acids but can encompass other heritable units such as epialleles. If the evolutionary gene is understood more broadly, and the notions of environment and phenotype are defined accordingly, current evolutionary theory does not require a major conceptual change in order to incorporate the mechanisms of epigenetic inheritance.

1. Introduction

2. The Gene-centric Evolutionary Theory and the ‘Evolutionary Gene’

 2.1 The evolutionary gene

 2.2 Genes, phenotypes and environments

3. Epigenetic Inheritance and the Gene-centred Framework

 3.1 Treating the gene as the sole heritable material?

 3.2 Epigenetics and phenotypic plasticity

4. Conclusion

## 1 Introduction

By the 1940s, the marriage between Darwinian theory of evolution (Darwin 1859) and Mendelian genetics (Correns [1900]; Tschermak [1900]; de Vries [1900]; Mendel [1865]) was integrated into a general consensus known as the Modern Synthesis (MS). This synthesis provided theoretical foundations for a quantitative understanding of evolution. It has been regarded as a paradigm for evolutionary theory over the last sixty years. The original MS has been extended in at least three regards. First, since the 1950s, classical population genetics has been generalized to quantitative genetics for continuous traits (Falconer and Mackay [1996], p. 100). Although the former focuses on allele frequencies and genotypes, whereas the latter by its nature begins from the phenotype, the mathematical models of the two can be formally connected (Wade [2006]). Therefore, we will regard both disciplines as formal evolutionary theory in this paper. Second, formal evolutionary theory is now better suited to account for the evolution of microorganisms and plants, which used to be the glaring omission of classical population genetics (Ayala *et al*. [2000]). Third, progress made in various biological sub-fields has extended evolutionary theory in many respects. The discovery of DNA structure in 1953 (Watson and Crick [1953]), for instance, prompted the development of molecular genetics and stimulated the discussion of gene selectionism. Also, the integration of development and evolution resulted in the new research field of evolutionary developmental biology (Goodman and Coughlin [2000]). In spite of these three extensions, current evolutionary theory is still remarkably reliant on the tenets of the MS. One of these tenets, which will be the focus of this paper, is that phenotypic evolution can be explained by changes in gene frequencies in a given environment. This ‘gene-centric view’, relies on genes being the sole heritable material, which, together with the environment, determine the phenotype.[[2]](#footnote-3)

A recent article in *Nature* has questioned whether evolutionary theory needs a rethink (Laland *et al*. [2014]). Some researchers in the areas of epigenetics, developmental biology and ecology claim that ‘yes, it is urgent’ to rethink what they term the ‘standard evolutionary theory’ (SET) and call for a new Extended Evolutionary Synthesis (EES)[[3]](#footnote-4), whereas others argue that ‘no, all is well’ with our current understanding of evolutionary theory (Wray *et al*. [2014]). SET, which EES proponents believe retains the core of the MS, has the following three tenets: ‘new variation arises through random genetic mutation; inheritance occurs through DNA; and natural selection is the sole cause of adaptation, the process by which organisms become well-suited to their environment’ (Laland *et al*. [2014], p. 162). It should be noted that EES advocates do not challenge Darwinism (Darwin’s natural selection theory), but the verbal account of the MS that excludes non-random variation or soft inheritance (Jablonka and Lamb [2002]; Jablonka [2013]; Laland *et al*. [2014]; Laland *et al*. [2015]). To them, SET tells a too simple story with four missing pieces: developmental bias and developmental plasticity, both of which can lead to the production of non-random variation; epigenetic inheritance, the transmission of materials other than DNA; and niche construction, a process by which organisms interact with their environment to influence adaptive evolution. Some EES proponents take all four pieces into consideration and have proposed an alternative framework from an ‘ecological-developmental perspective’ alongside the MS (Laland *et al*. [2015]). In this paper, the focus will specifically be on epigenetic inheritance although our discussion will also have implications for the non-random variation.

The term ‘epigenetics’ was first introduced by Waddington to refer to the study of the interactions between genes and their products during development ([1942]). More recently, epigenetics has been defined as the study of heritable changes in gene expression which are not caused by changes in the DNA sequence (Haig [2004]). ‘Epigenetic inheritance’ refers to the transmission of epigenetic modifications (for example, DNA methylations) via cell division mitotically or meiotically across generations (Griffiths and Stotz [2013], p. 112). The heritable epigenetic modifications that affect gene expression, as used by Jablonka and Raz ([2009]), are called ‘epialleles’. In a broader sense, epigenetic inheritance also includes the inheritance of phenotypic features through causal pathways other than the inheritance of nuclear DNA (for example, the phenomena of maternal effect and niche construction).[[4]](#footnote-5) An epiallele, when understood broadly, refers to a transmissible difference maker that underlies epigenetic inheritance in the broad sense. In this paper, we use epigenetic inheritance and epialleles in the broad sense, and term the set of epialleles that leads to the same phenotypic difference (at a given grain of description) an ‘epigene’. More precise definitions of these terms are reported in Table 1.

EES proponents claim that the existence of epigenetic inheritance posits a significant challenge to the standard gene-centric view of inheritance and evolution. But their opponents question the role that epialleles actually play in adaptive evolution. This reply, as we see it, underestimates the growing number of empirical studies which demonstrate that a wide range of epialleles do affect the production and inheritance of traits which in turn may affect the process of evolution (Jablonka and Lamb [1995], [2014]; Jablonka and Raz [2009]). Researchers from population biology, evolutionary biology and molecular biology also provide evidence that challenges the central role that DNA plays in heredity and evolution; see for example (Mousseau and Fox [1998]; Badyaev and Uller [2009]; Bonduriansky [2012]). Although the existing evidence for a substantial role that epigenetic inheritance plays in the history of evolution might still be regarded as weak as the opponents of EES argue, we believe it is strong enough for putting forward a theoretical discussion. Given the fact that epigenes sometimes do influence the evolutionary trajectory, it is urgent to assess how current evolutionary theory, which regards the gene as the sole heritable material, would have to be changed in order to accommodate epigenetic inheritance.

We argue that a profound conceptual change to current evolutionary theory is unnecessary because the apparent conflict is to a large extent terminological. Semantic confusion with the concept of the gene can be traced back to the 1970s. In *The Selfish Gene,* Dawkins ([1976], pp. 35–36) defines a gene as any portion of the genome that potentially lasts long enough to behave as a unit for natural selection. Stent, a molecular biologist, criticized Dawkins for holding a notion of gene that ‘denatures the meaningful and well-established central concept of genetics into a fuzzy and heuristically useless notion’ (Stent [1977]). Dawkin’s primary interest is the role genes play in evolution with a loose association between genes and DNA. For Stent, the association between genes and DNA is much stronger: genes are functional DNA molecules. Thus, Stent criticizes Dawkins for holding an old concept of the gene that does not take into account all our hard-won knowledge from molecular biology. Here, Stent and Dawkins appeal to two distinct notions of the gene causing them to talk past each other.

A similar semantic confusion underlies the epigenetic inheritance debate. To clear up this confusion we propose to distinguish the notion of gene in the evolutionary sense from the notion defined in molecular biology. A molecular gene is typically understood as a stretch of DNA that contains an open reading frame with a promoter sequence, and functions in transcription and–or translation processes to create a genetic product (Griffiths and Stotz [2013], p. 73). The existence of the non-coding region and alternative post-transcriptional processing raises problems for this stereotyped definition (Fogle [2000]). Facing these problems, researchers attempt to develop coherent concepts of molecular gene. For example, Waters ([1994], p. 178) defines it as ‘a linear sequence in a product at some stage of genetic expression’, which also includes replicated RNA segments. Griffiths and Stotz ([2006]) regard DNA sequences that are identified by their functions as ‘nominal molecular genes’, and the collections of DNA elements that template for gene products as ‘postgenomic molecular genes’. One common feature of the molecular gene recognized by most molecular biologists, such as Stent, is that it is fundamentally about DNA sequences.

 It has long been recognized that the concept of the gene used in evolutionary biology, which is usually referred to as the ‘Mendelian gene’, is not always identical to molecular genes (Griffiths and Stotz [2006]; Falk [1986]). This mismatch leads philosophers, such as Moss ([2004]) to distinguish two notions of the gene: gene-P, for ‘phenotype’, ‘prediction’ and ‘preformation’; and gene-D, for ‘development’. Gene-Ps are defined by their phenotypic effects and are very similar to Mendelian genes whereas Gene-Ds are defined by their capacity as templates for gene products in the molecular sense. Once this distinction is made, it can be seen more easily that the debate between Stent and Dawkins is semantic with Dawkins referring to the notion of the gene in the evolutionary sense and Stent in the molecular sense. As we will show, a similar phenomenon is at play in the debate over epigenetic inheritance, and a clarification of these two notions of the gene can relieve much of the burden for current evolutionary theory to accommodate the phenomena of epigenetic inheritance.

The paper will be organised around two questions. First, how should the concept of the gene be understood in the evolutionary sense? Second, if the evolutionary gene is understood consistently, does epigenetic inheritance represent a conceptual alternative to genetic (gene as being DNA based) inheritance in the evolutionary sense? In Section 2, we provide an analysis of the concepts of ‘gene’, ‘phenotype’ and ‘environment’ as they are understood in gene-centric evolutionary theory. We claim that the notion of the gene used in formal evolutionary models is defined by its effects and does not have to be exclusively made up of DNA. We argue that the notions of ‘environment’ and ‘phenotype’, if being defined in accordance with the evolutionary gene, should be gene-centred, not organism-centred. In Section 3, we address two challenges to the MS stemming from epigenetic inheritance. The first challenge is the view that the existence of epialleles weakens the idea of treating genes (as being made of DNA) as the sole source of inheritance. We argue that once one realizes that the evolutionary gene can also encompass epialleles, this claim does not threaten current evolutionary theory. The second challenge is that the phenomena of inheritance of environmentally induced phenotype via epigenetic modifications provide evidence for non-random non-genetic variations, which are excluded in the MS. By demonstrating the roles that epialleles play in different circumstances, we show that when the concepts of gene and environment are understood properly, this objection to current evolutionary theory is not upheld.

## 2 The Gene-centric Evolutionary Theory and the ‘Evolutionary Gene’

The term ‘gene’ appears inevitably in almost every reference in biology. For example, Williams ([1966], p. 25) claims that a gene can be ‘any hereditary information for which there is a favorable or unfavorable selection bias equal to several or many times its rate of endogenous change’. Dawkins, following Williams, fully materializes the informational sense of the gene and defines it ‘as a piece of chromosome which is sufficiently short for it to last, potentially, long enough for it to function as a significant unit of natural selection’ ([1976], p. 136). Some authors use the term in the same sense; see for example (Brandon [1990], p. 190; Godfrey-Smith [2009], p. 5). Evolutionary biologists sometimes use the ‘gene’ as a synonym for ‘Mendelian allele’; see for example (Rice [2004], p. 85; Endler [1986], p. 5; Mousseau and Fox [1998]; Falconer and Mackay [1996]). In other circumstances, they explicitly refer to genes as pieces of DNA. For example, Bonduriansky ([2012], p. 330) defines non-genetic inheritance as ‘inheritance mediated by the transmission to offspring of elements of the parental phenotype or environment, […] but excluding DNA sequences’, which implies that DNA sequences are regarded as genes. With perhaps the exception of Williams’ account, the above verbal formulations either explicitly or implicitly assume that a gene is conditioned to be physically made up of DNA. This additional condition, as we will argue, is unnecessary for the concept of evolutionary gene.

The environment is another factor that influences the phenotype, and is also defined differently between authors. Williams ([1966], p. 58) distinguishes three levels of external environment, including the genetic, the somatic, and the ecological environment, which refer to the environment composed by the population gene pool, by the interaction of the genes and factors in the cell during gene expression, and by the ecological world, respectively. For Dawkins, the environment refers to the whole of Williams’ three levels of external environment ([1976], p. 37). Sterelny and Kitcher ([1988], p. 354) argue that a consistent account of environment for gene selectionism should incorporate other corresponding alleles at the same locus together with other genes (DNA based conception) in what they call the ‘total allelic environment’. Similarly, Haig, while defending gene selectionism, defines the environment as ‘all parts of the world that are shared by the alternatives being compared’ ([2012], p. 461). For Falconer and Mackay, the environment is ‘all the non-genetic circumstances that influence the phenotypic value’ ([1996], p. 108). In other accounts it is not always clear whether the environment refers to the environment of a given allele, a complex of genes or an organism; see for example (Rice [2004], p. 243; Mousseau and Fox [1998], p. v). Molecular biologists usually separate the environment from the physical boundaries of the organism. For instance, common phrases are ‘between an organism and its environment’ (Jablonka [2012], p. 1) and ‘an organism to survive in an environment’ (Lamb and Jablonka [2008], p. 308).

Surveying the above literature raises the question of whether the various views of the gene and the environment are compatible with each other, and whether they hinder mutual understanding between scholars from different fields. In what follows, we first distinguish the conception of the evolutionary gene from that of the molecular gene (DNA based conception), and then, in light of this, two conceptions of the phenotype and the environment in Section 2.2.

## 2.1 The evolutionary gene

The challenge stemming from epigenetic inheritance is mainly targeted on the gene-centric view of the MS. The verbal account of the MS is generalized from formal evolutionary theory, in which researchers use mathematical tools to describe how the gene frequencies, under the influence of various factors including natural selection, change over time.[[5]](#footnote-6) Therefore, the best way to determine what views about the gene the MS is committed to is to examine the role that the gene plays in the formalism. In quantitative genetics, a continuous trait (for example height) is seen as caused[[6]](#footnote-7) both by many genes and by the environment. (Note that in classical population genetics the environment is supposed to play no role in character variation). The variation of these genes is quantified as the variance due to heritable difference makers, each of which makes an equal and additive contribution to the phenotype studied (Falconer and Mackay [1996]). These genes are defined solely by their effects on the phenotype and thus represent hypothetical or theoretical entities which are not physically restricted.

Be that as it may, when the structure of DNA was established in 1953, biologists seemed to trumpet at finding the exact physical basis for the theoretical difference makers of formal evolutionary models. With the capacity to faithfully replicate itself, DNA seemed to be a perfect candidate to fit the role of the hypothetical genes, for it obeyed Mendelian laws but also explained biological phenomena such as mutation and protein production (Schaffner [1969]). In other words, while the terms ‘gene’ and ‘genotype’ have been proposed by Johannsen ([2014], pp. 990–1) to refer to the Mendelian ‘unit-factors’ in the gametes and to distinguish them from the phenotype, biologists could finally locate the genes precisely in DNA molecules. Since then, as we presented earlier, biologists commonly refer to genes as DNA sequences in their verbal accounts and this has resulted in many biologists thinking that genes must be made up of DNA. But this step was taken too hastily. If there is physical material, other than DNA pieces, that can affect the phenotype and be transmitted across generations, then there would be nothing to prevent this material from being included in the concept of gene in the evolutionary sense.

Two quotes from biologists before and after the unravelling of DNA structure reflect the theoretical role the gene plays in evolutionary biology. Morgan, the father of classical genetics, noted in 1935 that ‘[t]here is not consensus of opinion amongst geneticists as to what genes are—whether they are real or purely fictitious—because at the level at which genetic experiments lie, it does not make the slightest difference whether the gene is a hypothetical unit, or whether the gene is a material particle’ ([1935], p. 315). Fifty years later, in a *Nature* correspondence, Grafen ([1988], p. 526) claimed that ‘not quite all chromosomal DNA is germ plasm, and not quite all germ plasm is DNA’. For Grafen ([1988], p. 525), the germ plasm[[7]](#footnote-8) is ‘the repository of inherited and potentially immortal information’ or another term for ‘gene’ in an evolutionary context. This shows that even after discovering DNA, the heritable unit is not always considered as being made of DNA. This indirectly suggests that the gene still plays a theoretical role in evolutionary biology.

To define the evolutionary gene, we begin with Haig’s recent defence of gene selectionism. Gene selectionism represents a strong version of the gene-centric view of formal evolutionary theory (Hull [2000], p. 422; Laland [2004]). Haig ([2012]) develops the notion of the ‘strategic gene’ in accordance with the common characterization of evolution as ‘changes in gene frequency and phenotypic effects of these changes’. For him, a gene refers to a determinant of difference in the phenotype that correspond to a set of gene tokens, mainly DNA pieces. The crucial point we retain from Haig’s account is that a gene in an evolutionary context is a difference maker. For defending gene selectionism, Haig ([2012], p. 470) regards a gene as ‘a strategist in an evolutionary game played with other strategic genes’, hence his use of the term ‘strategic’. Since our focus is purely on the concepts of the gene rather than gene selectionism, we will not discuss the agential metaphor here. Haig also regards the gene mainly on the basis of DNA sequence (rather than other heritable difference makers) for the reason that DNA has the ability to self-replicate without compromising autocatalysis while simultaneously preserve the potential for open-ended adaptive change ([2012], p. 478). It is certainly crucial for us to acknowledge the remarkable features of DNA replicators. However, this should not prevent us from searching for other materialized heritable difference makers (for example epialleles) and their effects in evolution. Even Dawkins, the most DNA-centric figure, concedes that ‘replicators do not have to be made of DNA in order for the logic of Darwinism to work’ ([2004], p. 378). Thus we claim that other transmissible factors that give rise to the same effects as DNA based alleles should also be explicitly considered as instances of evolutionary genes.

This latter point can be illustrated by some studies showing that RNA is able to ferry information for multiple generations (Costa [2008]; Rechavi *et al.* [2011]). For example, when experimenting on a strain of heterozygote mice with a mutant allele of the Kit gene that produces a white tail tip, researchers found that most of their offspring that inherited two wild-type alleles still had a white tail tip (Rassoulzadegan *et al.* [2006]). This pattern is transmitted for about five generations. Further research demonstrated that the inheritance pattern is caused by the RNA molecules manufactured by the mutant Kit gene in the male parent being delivered via the sperm to the offspring. (Rassoulzadegan *et al.* [2006]) This means that RNA, like DNA, might also be trans-generationally transmitted and influence trait production, which echoes both Morgan’s and Grafen’s claims quoted earlier. The existence of RNA alleles (an instance of epialleles) that play the same role as DNA alleles gives us a good reason to extend Haig’s notion of gene to include both DNA and RNA pieces, that is, to inheritable nucleic acid difference makers of any kind in producing a difference in the phenotype.

Once this step is taken, it becomes natural to include other epialleles (for example, the patterns of DNA methylation) under the notion of evolutionary gene. The increasing evidence of epigenetic marks functioning as heritable difference makers seriously challenges the need for any specific material conditions on the gene concept. Hence we suggest a stripped-down notion of the gene that includes only the minimal requirements for it to play the role in formal evolutionary models. Griffiths and Neumann-Held’s ([1999]) conception of the evolutionary gene fits well with our aim. They define the evolutionary gene as a heritable atomistic[[8]](#footnote-9) unit that causes a difference in the phenotype. This definition corresponds to the formal evolutionary theory treating genes as one of the determinants of trait variance, and treating genes as the source of inheritance. According to this definition, any physical structure that causes a heritable variation should be seen as what we call a ‘materialized evolutionary gene’.

The evolutionary gene is not exactly the same as the Mendelian gene. The fact that the terms ‘Mendelian alleles’ and ‘Mendelian genes’ are often used in the literature is a legacy of the influence that Mendelian genetics had on classical population genetics (Depew and Weber [1995]). Mendelian genes are defined ‘through their effects on phenotypes rather than by appeal to their intrinsic physical structures’ (Sterelny and Griffiths [1999], p. 114), and they are used in genetics as ‘a hypothetical material entity’ that has effects on the phenotype (Griffiths and Stotz [2013], chapter 2). Given that the term ‘Mendelian gene’ has come to refer to a general notion of the gene as a heritable difference maker in current usage, it captures much of the meaning of the gene in the evolutionary sense. However, the term ‘Mendelian’ may give the impression that Mendelian genes should obey Mendel’s original two laws, which apply only to diploid sexual organisms in the absence of segregation distortion. To avoid this possible confusion, we prefer the more neutral term ‘evolutionary gene’ used by Griffiths and Neumann-Held ([1999]).

## 2.2 Genes, phenotypes and environments

As we showed at the beginning of Section 2, theorists also use the notion of ‘environment’ in different ways. In what follows, we define the notions of ‘phenotype’ and ‘environment’ in accordance with the concept of evolutionary gene we just provided.

The phenotypes have originally been characterized as ‘[a]ll “types” of organisms, distinguishable by direct inspection or only by finer methods of measuring or description’ (Johannsen [2014], p. 991). The phenotype is now typically understood as a ‘class to which that organism belongs as determined by the description of the physical and behavioral characteristics of the organism’ (Lewontin [2011]). In this organism-centred sense, the phenotype is considered descriptively regardless of its causes.

Haig ([2012], p. 461), building his notion of phenotype from the notion of gene, defines a phenotype as ‘a gene’s effects relative to some alternative’, which is not organism-centred, but is coupled to the notion of gene. Two things should be noted. First, as we have mentioned several times, the evolutionary gene is defined by its heritable effects on the phenotype. Hence, to define the phenotype as ‘a gene’s effects’ corresponds well to the concept of evolutionary gene. Second, the requirement of the existence of some alternative seems to mean that if there is no alternative, then there is no phenotype. This is not as problematic as it may first seem to be for three reasons. First, in Johannsen’s original definition, phenotypes refer to distinguishable ‘types’ of organisms, which implicitly assumes a comparison being made. Second, evolution, as it is classically understood, only occurs when the target population satisfies the condition of variation (Lewontin [1970]). Even in the limit cases where there is no variation in the population at a particular time, because for instance one variant invaded the population, heritable variations are regularly produced. Finally, under the manipulationist account, causation can only be established when at least two alternatives are compared. Thus, we regard the existence of alternative phenotype(s) in an evolutionary context as a reasonable assumption.

Inspired by Haig’s definition, we define the phenotype of an evolutionary gene as everything that the gene makes a difference to when compared to another gene. *Prima facie* this definition seems to weaken the physical distinction between genotype and phenotype, especially in the case of prions. We will address this issue later in Section 3.2. Our definition implies two things. First, a phenotype may refer to any part of an organism that is not the gene itself. Second there is no restriction on whether parts of the phenotype can extend beyond the physical boundaries of the organism. A classical example proposed by Dawkins ([1982], p. 200) is a beaver’s dam. The fact that beavers build dams is supposed to be an effect of the beaver’s genes, makes the dam (which is external to the physical boundaries of a beaver) part of the phenotype of these genes (the hypothetical genes’ effects compared to alternatives) rather than part of the environment (gene-centred environment as we will define below). A toy example of extended phenotype is habitat choice. Consider an organism choosing of living under the sun or under the rain depending on (evolutionary) genetic factors. Suppose also that both habitats ‘rainy’ and ‘sunny’ have an influence on an organism’s height. In this case, the rainy and sunny habitats are not environmental variations, as they are part of the organism’s phenotype. Only when there is nothing related to the organism that could explain why it chooses to live under the rain or under the sun, then the rainy and sunny habitats can be counted as environmental variations.[[9]](#footnote-10) These and similar examples will be problematic cases if by ‘environment’ one understands any variable beyond the physical boundaries of the organisms of the population studied.

The environment, to be defined consistently with the evolutionary gene and the gene-centred notion of phenotype, should be understood as the set of variables that are not causally influenced by evolutionary genes but that might causally influence a target trait.[[10]](#footnote-11) Physically speaking, the gene-centred environment of a given evolutionary allele can include other allele(s) at the same locus, other parts and mechanisms of the organism and the extra-organismic world. This position is very similar to that of Sterelny and Kitcher who claim that ‘the specification of the total environment’ of an allele ‘should be understood relative to the total allelic environment’ ([1988], p. 354). The difference is that they regard an allele as consisting solely of DNA pieces. Following our framework, one can see that on the one hand it is possible for part of the phenotype to be extended beyond the organism. On the other hand, it is also possible for some molecules or mechanisms inside the organism not causally influenced by evolutionary genes, that is, insensitive to genetic variations, to count as part of the gene-centred environment.

Organisms ‘have, for centuries, served as the paradigmatic individuals inhabiting the natural world’ (Bouchard and Huneman [2013], p. 1). For molecular biologists and those whose primary concern is development, the notion of environment usually refers to the part of the world external to the organism (Jablonka and Lamb [1995]; Jablonka and Lamb [2014]). They are concerned with external factors affect an organism’s development resulting in an adult trait, which renders the external environment a crucial role in individual development. But this understanding of the environment represents a notion that is quite different from the evolutionary gene-centred notion of the environment for the latter also includes parts of the organism in comparison of two or more traits in a population. Making this distinction, as we will argue, might be a first step to encourage gene-centric evolutionary biologists to think more about developmental factors playing in evolution.

To summarise so far, we proposed that the conception of gene in the formal evolutionary models, from which derived the gene-centric view, is different from the notion in molecular biology. The conceptions of environment and phenotype from a gene-centric evolutionary perspective are also different from the organism-centred notions used by developmentally minded biologists. The definitions for each concept can be seen in Table 1. Figure 1 is an illustration of the two frameworks: the evolutionary framework centred on the gene, and the developmental framework centred on organisms. From a formal evolutionary point of view, the gene can encompass not only DNA pieces, but also epialleles that give rise to the same effects. The gene-centred phenotype, that is the effect(s) an evolutionary gene is responsible for, can partially correspond to the organism-centred environment; and the gene-centred environment can correspond to some part of an organism. Since an imperfect overlap exists between corresponding concepts—‘gene’ with ‘organism’, and ‘gene-centred environment’ with ‘organism-centred environment’—this can potentially lead to confusions between different disciplines. Therefore, these two ways of partitioning the world should not be mixed.

[Insert figure 1 about here]

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## 3 Epigenetic Inheritance and the Gene-centred Framework

With the conceptions of gene, environment and phenotype for gene-centric evolutionary theory in place, we now assess the question of whether evolutionary theory requires a major conceptual change to accommodate epigenetic inheritance. There seems to be a spectrum from conservative to more radical views on this issue. Some think that epigenetic inheritance may have the potential to play an important role in evolutionary processes, but that it is not a contradiction of the classic view on genetic inheritance, only an augmentation (Haig [2007]; Pigliucci [2009]). Others claim that the incorporation of new data and ideas about hereditary variation requires a version of Darwinism that is very different from the gene-centric view (Jablonka and Lamb [2007]; Laland *et al.* [2014]; Laland *et al.* [2015]). Our position is twofold. On the one hand, we argue for an extended understanding of the gene in evolutionary theory, rather than a restricted DNA-based account as adopted by most authors. This extension, as we have shown in Section 2.1, corresponds well to the formal evolutionary theory and thus also to the gene-centric tenet of the MS. On the other hand, as we will argue in the following section, given our framework, evolutionary theory can accommodate mechanisms of epigenetic inheritance without a profound conceptual change. Our position is very close to Helanterä and Uller’s ([2010]) suggestion that different inheritance systems may share conceptually similar features but may have different abilities to couple inheritance and selection. Two major challenges to the MS brought up by epigenetic inheritance will be considered.

## 3.1 Treating the gene as the sole heritable material?

The first challenge concerns what sorts of entities can be inherited and affect evolution. Jablonka and Raz ([2009]) claim that defining evolutionary processes as changes in the gene frequencies of populations is ‘too narrow because it does not incorporate all sources of heritable variations’. By other ‘sources of heritable variations’, they mean variations that are caused by heritable epigenetic modifications. A classical example of epigenetic inheritance comes from a study on the agouti gene in mice (Morgan *et al.* [1999]). In this study mice with the same genotype display a range of colours of their fur, which are due to a difference in DNA methylation levels on the promoter of the dominant agouti gene. The patterns of DNA methylation can be inherited through generations and cause heritable variations. Epigenetic factors such as self-sustaining loops, chromatin modifications and three-dimensional structures in the cell can also be transmitted over multiple generations (Jablonka and Lamb [1995]). For example, the ciliary protozoan *Paramecium* uses the organization of the cilia in the parental cells’ membrane as a template to form their own cilia without changing the DNA sequences (Beisson and Sonneborn, [1965]). Studies on various species suggest that epigenetic inheritance is likely to be ‘ubiquitous’ (Jablonka and Raz [2009]).

Another classical example of non-DNA based variation comes from parental effects. A parental effect is a phenotypic correlation between the individual and its parent(s) that is neither caused by the parental genes (DNA based conception) nor by the direct environment of the individual (organism-centred environment) (Wade [1998], p. 5). For example, in rats the quality of a mother’s care behaviour (licking and grooming) to its pups causes different traits in its offspring (Youngson and Whitelaw [2008]). A stressed mother will lower its licking and grooming causing a decreased level of serotonin (a neurotransmitter associated with nerve impulses) in the pup’s brain. This decreased serotonin increases the DNA methylation pattern on the glucocorticoid receptor gene, leading to high stress-reactivity behaviour in the offspring. The result is that stressed mothers produce stressed daughters who then become stressed mothers. In this example, the behaviour of the mother is reproduced during later generations by means that are not DNA based, but via the reconstruction of a complex network during development with certain methylation patterns being involved. These and similar examples strongly indicate that nuclear DNA cannot be the sole heritable material influencing the production of phenotypic variations. This leads some authors to argue for a pluralistic view of heredity (Jablonka and Lamb [2014]; Bonduriansky [2012]) or an inclusive inheritance (Laland *et al.* [2015]).

Contrary to what is stated in verbal SET, namely that ‘inheritance occurs through DNA’ (Laland *et al.* [2014]), we have argued that evolutionary theory does not have to commit to DNA as the sole material support for the genes. If a methylation pattern is faithfully inherited causing a different fur colour, as in the agouti gene in mice, then this epiallele can certainly be considered as a materialized evolutionary gene[[11]](#footnote-12). The ciliary pattern that is inherited and templates for the organization of the cilia in the next generation can also be regarded as an evolutionary gene. As for the stressed mother rat example, if the stressed behaviour recurs in successive generations and can be traced back to the mothers’ transmissible internal difference makers[[12]](#footnote-13), there is no reason not to consider those difference makers as evolutionary genes. To summarise, an evolutionary gene can also refer to epialleles such as RNA molecules, DNA methylation patterns and other internal factors of the organism. We thus claim that there is no fundamental quarrel between a pluralistic view of heredity and the gene-centric evolutionary theory. This is a conclusion that we believe both the EES proponents and their opponents should consider.

## 3.2 Epigenetics and phenotypic plasticity

The second challenge concerning epigenetic inheritance relates to phenotypic plasticity. Phenotypic plasticity is understood as the capacity of a single genotype to give rise to different phenotypes according to different environmental conditions (organism-centred environment). The change of a given environmental inducer (organism-centred environment) might cause a change in the trait through some epigenetic modifications. Suppose that the new epigenetic modifications can be passed on to the next generation and have the same new effects in the offspring. This new variation is thus maintained by epigenetic inheritance. In such cases, if the alternative new phenotype has a different adaptive value in the population, then evolution can happen without a change of DNA sequences. If such cases are possible, then this has two immediate consequences that challenge the SET. First, besides genetic (DNA based conception) mutations, there is non-genetic (DNA based conception) mutations. Second, since the variation is environmentally induced, it is non-randomly generated.

Considering the first consequence, the response is immediate: the concept of mutation can be extended to non-DNA mutation. In the above case, the heritable epigenetic modification (the epiallele) is an instance of our notion of materialized evolutionary gene, and hence an epimutation can be counted as genetic (genetic with the gene being the evolutionary gene) mutation.

Before going further, it is important to note that not all non-DNA changes can be counted as epimutation. Take the case of a particular DNA methylation pattern as an example. Following Haig’s reasoning ([2012]), if the methylation pattern changes back and forth according to the change of the environmental inducer, then this switching ability should be regarded as a reaction norm and part of a phenotype of some other evolutionary genes. Therefore, the same DNA methylation pattern could be considered either as an evolutionary gene if it is inheritable or as part of a phenotype in a changing environment when it changes accordingly. This may seem arbitrary, but it is not a problem for the gene-centred framework we propose since genes and environment are concepts that do not need to commit to specific physical structures.

As we mentioned in Section 2 when defining the gene-centred phenotype, the physical boundary of genotype and phenotype cannot be clearly defined, either. That said, the genotype–phenotype distinction is also conceptual and thus can accommodate cases in which the same material entities appear to be both genes and phenotypes from different points of view. The case of prions can be used to illustrate this point. First, the determinants of the phenotypic difference and their effects in prions can be distinguished in functional terms even if they are located on one and the same entity (the protein). Second, under a fine grain of description the genotype of the prions could potentially be identified as the certain conformational information[[13]](#footnote-14) of the prion protein and its phenotype as the effect it has on the rate at which a prion converts other proteins into the same conformation as a particular type of prions.

Let us move now to the second consequence, namely that environmentally induced variation might be non-random or directed[[14]](#footnote-15). A special case of this phenomenon is when a heritable environmentally induced phenotype is favoured by the selective environment, and therefore adaptive. For example, a recent study shows that mice acquire the fear of a sweet smell when researchers give a mild footshock to them every time the smell is present (Dias and Ressler [2014]). The fear is associated with a decrease level of methylation on a particular DNA sequence (the Olfr151 gene), and the epigenetic pattern is transmitted stably causing the descendants to also fear that odour. In this example, the epimutation is non-random or directed that leads to an adaptive phenotype. The selection process that results in the fixation of certain epimutations is called epigenetic assimilation (Esteller [2008], p. 248; Jablonka and Raz [2009], p. 161). Jablonka and colleagues also provide examples of non-random epimutation and thus call for a revival of soft inheritance (Jablonka and Lamb [2008]) or Lamarckian inheritance (Jablonka and Lamb [1995]; Gissis and Jablonka [2011]). Others disagree with the Lamarckian claim; see for example (Haig [2007]). Nevertheless, the question we are interested in is whether the existence of non-random epimutations (and adaptively phenotypic response as a special case) represents an insurmountable challenge to current evolutionary theory. We think it does not.

We follow here Godfrey-Smith ([2007], p. 493) as he puts it, ‘Darwinian evolution can occur on variation that is directional, even adaptively ‘directed’. In these cases natural selection may have less explanatory importance than it has when variation is random, but it can still exist.’[[15]](#footnote-16) To see this point, imagine a large size population of two asexual types reproducing in discrete generations. Suppose that there are no evolutionary forces other than mutation and natural selection. Consider the following two cases. In the first case, the mutations are random or undirected. Thus mutations on average do not make any difference in the frequencies of the types. So the change of gene frequencies from one generation to the other will be solely explained by natural selection. In the second case, suppose that the mutations are directed, that is one type when compared to the other has a higher chance to appear. In such a case, the resulting change in the frequencies of types will be explained both by non-random or directed mutation and natural selection. Compare the two cases, we can see that the presence of the effects by non-random or directed mutation on the evolutionary trajectory of a population is to undermine the effects of natural selection on the trajectory.

The MS (and the SET) gives a lot of weight to random genetic (DNA based conception) mutations (Merlin 2010; Futuyma [2006], p. 12), and we expect most MS advocates would not accept non-random mutation as a common mechanism to generate inheritable variations. Hence, it is reasonable for Jablonka and others to claim that epigenetic results challenge the MS (Jablonka and Lamb [2014]; Laland *et al.* [2015]). However, formal models in current evolutionary theory that lay claim to the MS are more flexible as they allow to incorporate other forces of evolution (Arnold [2014]), including non-random mutation. That said, the fact that formal models can incorporate non-random mutation, in itself, does not permit to assess the amount of conceptual change required in evolutionary theory.

There is a more profound consequence on evolutionary theory stemming from the challenge of epigenetic inheritance related to phenotypic plasticity. Phenotypic plasticity, a phenomenon that uniquely arises from development, combined with epigenetic inheritance, may lead to the inheritance of variation generated during developmental processes. Such a mechanism reinforces the idea proposed by ecologists and evolutionary developmental biologists that natural selection is sometimes ‘guided along specific routes opened up by the processes of development’ (Laland *et al.* [2014]). It thus makes Mayr’s distinction between developmental (proximate) causes and evolutionary (ultimate) not be as clear-cut as it was once thought to be (Danchin and Pocheville [2014]; Uller [2008]; Scholl and Pigliucci [2014]). Moreover, epigenetic inheritance may pave the way for genetic (gene as being DNA based) accommodation. The notion of genetic accommodation has been elaborated by West-Eberhard[[16]](#footnote-17) (Jablonka and Lamb [2014], pp. 408–9). When a novel or recurrent environmental change constantly induces an adaptive phenotypic response caused by phenotypic plasticity, genetic changes that facilitate the production of that phenotype may be selected. In this process, epigenetic inheritance becomes a mediator between phenotypic plasticity and genetic accommodation (or DNA accommodation)[[17]](#footnote-18), and thus a mediator between development and evolution.

Our view on this profound consequence is twofold. On the one hand, we think that the controversy surrounding the relation between evolution and development is partially caused by the ambiguous use of terms. This can be shown as follows. Suppose first that one understands genes solely as DNA pieces and the environment as the ‘organism-centred environment’. Then many developmental factors within the physical boundaries of organisms that might affect evolution will be excluded from the analysis. Suppose now that the evolutionary gene is understood in the way that includes any inheritable difference makers, not only DNA pieces, and the environment is defined relatively to the gene. In such a case, the developmental factors neglected in the previous case, will no longer be so, and they will be either considered as the genes or as part of the environment. Clarifying the distinction between organism-centred and gene-centred environments may open some theoretical space for thinking more about developmental factors.

On the other hand, we fully embrace the idea of calling for an integration of development with evolution proposed by EES advocates. The emphasis on development has already been made by gene-centric evolutionary developmental biologists who suggested that modifications of development can lead to the production of novel features and thus the process of development itself biases evolution (Raff [2000]). Without denying that gene-centric evolutionary theory can at least incorporate some aspects of development, both evolutionary developmental biologists and EES proponents claim that a complete understanding of evolution requires a substantial integration of development and evolution (Laland *et al.* [2015]). We believe that the alternative ecological-developmental perspective put forward by EES proponents might be a promising approach that can bring new perspectives that a gene-centric view cannot. But it does not necessarily follow that the alternative approach represents a revolution of current gene-centric evolutionary theory. As Sterelny ([2000], p. S371) notes ‘[n]o very revolutionary shift is needed to incorporate developmental insights into an evolutionary perspective’. Even if a revolution was required for current evolutionary theory to incorporate development, it would not because of epigenetic inheritance, for it only adds a new twist to the idea that an adequate understanding of evolutionary dynamics requires taking development out of its ‘black box’.

## 4 Conclusion

We have argued that the challenges posed by the existence of epigenetic inheritance to the evolutionary theory is partly caused by the ambiguous use of the words ‘gene’, ‘phenotype’ and ‘environment’. Our analysis from a formal evolutionary perspective reveals that the evolutionary gene can include molecular genes as well as epigenes. Some work in quantitative genetics has singled out transmitted factors other than DNA alleles and the environment (organism-centred environment), referred to as ‘maternal effects’ (Kirkpatrick and Lande [1989]; Mousseau and Fox [1998]), ‘non-genetic components’ (Day and Bonduriansky [2011]) or ‘epigenetic variance’ (Tal *et al.* [2010]). The separation of epigenetic and genetic (DNA based conception) factors represents a different use of terms of ‘gene’ and ‘environment’ from the gene-centred framework we provide. To be noted, DNA alleles and epialleles in these studies, if characterized by their effects on the phenotype, are both instances of our notion of materialized evolutionary genes and the basis for their separation is the difference in mechanisms by which the effects are transmitted (which often involves different rates of (epi)mutation). This separation represents an alternative way to characterize an evolutionary process, and it is fully compatible with the concept of evolutionary gene we have proposed.

Even if eventually the term ‘gene’ is used to refer exclusively to the molecular gene, and theorists use another term (such as ‘replicator’) when referring to our concept of evolutionary gene, the conceptual analysis we provide will still be valuable to at least highlight two things. First, researchers should define the concepts they use and carefully interpret works from different fields, as this is crucial for a productive interdisciplinary discussion. Second, the discovery of DNA as being one support for genetic information understood in the evolutionary sense does not mean that it is the only support of it. Hence, we are confident that current evolutionary theory is resilient and adaptive enough to incorporate new hereditary materials without profound conceptual changes.

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**Figure 1.** Gene-centred framework for the concepts of ‘gene’, ‘environment’ and ‘phenotype’ (dark grey) contrasted with the organism-centred framework (light grey). The organism-centred framework partitions the biological world into the organism and its environment. The gene-centred framework consists of “evolutionary gene and its phenotypic effects” and “gene-centred environment”. The evolutionary gene is within the organism, which encompasses all the inheritable materials that make a difference to target phenotype compared to alternative phenotype(s). According to certain grains of description, the gene-centred phenotype can be molecules or mechanisms within the organism, traits of the organism, or properties that extend beyond the organism. The gene-centred environment includes factors in the rest of the biological world that causally influence the phenotype, and can include parts of the organism and parts of the organism-centred environment.

**Table 1.** Definitions of key concepts.

|  |  |
| --- | --- |
| Notions | Definitions |
| Epigenetic inheritance(narrow sense) | ‘[T]he inheritance of genome expression patterns across generations (e.g. through meiosis) in the absence of a continuing stimulus’ (Griffiths and Stotz [2013], p. 112). Also known as ‘transgenerational epigenetic inheritance’ (Daxinger and Whitelaw [2012]). |
| Epigenetic inheritance(broad sense) | ‘[T]he inheritance of phenotypic features via causal pathways other than the inheritance of nuclear DNA.’ (Griffiths and Stotz [2013], p. 112)  |
| Epigenetic modification | ‘Chemical additions to the DNA and histones that are stably maintained and do not change the primary DNA sequence.’ (Feil and Fraga [2012]) |
| Epiallele & epigene  | An epiallele is one of a number of alternative difference makers such as alternative epigenetic modifications that cause epigenetic inheritance. The set of epialleles that leads to the same phenotypic difference (at a given grain of description) represents an epigene. |
| Evolutionary gene | A heritable atomistic change that causes a difference in the phenotype (Griffiths and Neumann-Held [1999]). The term ‘atomistic’ is used to make what Grafen calls ‘the phenotypic gambit’, namely, to examine traits as if each was controlled by a single distinct allele. See also Footnote 8. |
| Gene-centred phenotype | Everything that an evolutionary gene makes a difference to when compared to another evolutionary gene. |
| Gene-centred environment | A difference maker that is not itself causally influenced by an evolutionary gene, and that might causally influence the phenotype. |
| Molecular gene | A stretch of DNA that contains an open reading frame with a promoter sequence, and functions in transcription and–or translation processes to create a genetic product. (Griffiths and Stotz [2013], p. 73) It is a stereotyped definition of the molecular gene. For more discussions, see Griffiths and Stotz ([2013]) and main text. |
| Organism-centred phenotype | A ‘class to which that organism belongs as determined by the description of the physical and behavioral characteristics of the organism’ (Lewontin [2011]). This notion is equivalent to the notion of ‘trait’ of an organism or the products of development. |
| Organism-centred environment | Anything beyond the physical boundaries of an organism. |

1. PB and QL contributed equally to this manuscript. They are therefore both first authors. Author order has been decided randomly. [↑](#footnote-ref-2)
2. For more on the concept of heritability see Downes ([2009]) and Bourrat ([2015]). [↑](#footnote-ref-3)
3. See also Pigliucci and Muller ([2010]) and Noble *et al*. ([2014]). [↑](#footnote-ref-4)
4. Epigenetic inheritance in the broad sense is also termed ‘exogenetic inheritance’ by Griffiths and Stotz ([2013], p. 112) and ‘extra-genetic inheritance’ by Laland *et al*. ([2014]). [↑](#footnote-ref-5)
5. The analysis of variance used by quantitative genetics and its explanatory power have long been questioned (Lewontin [2006]). We recognize that this method does have limitations in explaining underlying causal mechanisms and thus is probably better understood as a complementary or more abstract explanatory approach than an approach aiming at the elucidation of mechanisms (Tabery [2014]). In this paper, we rely on the fact that formal evolutionary models have been and are still regarded as the core of evolutionary theory. [↑](#footnote-ref-6)
6. We use Woodward’s manipulation account of causation ([2003]) throughout the paper. See also Waters ([2007]) for an account of causation in formal evolutionary theory based on Woodward’s account. [↑](#footnote-ref-7)
7. The term ‘germ plasm’ was introduced by Weismann to denote the determinants that are responsible for the continuity of the germ cell linage in animals (Weismann [1893]). [↑](#footnote-ref-8)
8. We use the term ‘atomistic’ following Griffiths and Neumann-Held who themselves follow Gould and Lewontin’s ([1979], p. 585) characterization of the adaptationist program, which sees organisms as being ‘atomized into “traits”’. Underlying this view is what Grafen ([1991], p. 6) calls the ‘phenotypic gambit’. Making the phenotypic gambit is to examine traits as if each was controlled by a single distinct allele. By proposing that an evolutionary gene is atomistic we follow Grafen’s (contra Gould and Lewontin) pragmatism that the gambit makes genuine phenotypic explanations possible. [↑](#footnote-ref-9)
9. For a similar distinction when discussing niche construction, see Pocheville ([2010], chapter 2). [↑](#footnote-ref-10)
10. To be noted, the causal influences of the gene and the environment may not be statistically independent with each other. The contribution of gene-environment interactions and (or) correlations should also be taken into account for trait variance in the population. For details see Falconer and Mackay ([1996], pp. 131–3). [↑](#footnote-ref-11)
11. The transmission of epialleles is often less persistent when compared to DNA transmission because the former is more easily subject to change (Jablonka and Raz [2009]). The instability feature might be a reason to question the effect epigenetic inheritance has on evolution compared to DNA transmission. However, in principle this should not lead to reject epialleles as proper materialized evolutionary genes since evolution represents minimally a phenotypic change at the population level after one generation. A recent study on *Arabidopsis Thaliana* shows that epimutation rates might be low enough to sustain new epialleles, but long enough for selection responses (Van der Graaf *et al.* [2015]). [↑](#footnote-ref-12)
12. Two conditions are required for a property to be a ‘transmissible internal difference maker’, or an evolutionary gene. To take the stressed mother rat as an example. A given methylation pattern is considered as an internal difference maker only if, 1) Given that methylation pattern is present in the parent(s), then it should be found in the offspring; 2) had the pattern not been present in the parent(s), then it should not have been found in the offspring. [↑](#footnote-ref-13)
13. Putting the concept of evolutionary gene in terms of information as we do here renders it quite general so that (too) many entities are considered as evolutionary genes. For instance, under our account, the information transmitted through symbols and social learning should potentially be considered as evolutionary genes. As pointed out in the literature on cultural evolution, there are many disanalogies between cultural and biological evolution such as with respect to the modes of transmission of information (see for instance Claidière and André [2012]). For that reason, the package of concepts (including the concept of the gene) used in evolutionary theory might be much less fruitful when considering cultural evolution. But it does not follow that our concept of the gene (or its cultural analog) is inapplicable to cultural evolution once the term ‘information’ has been defined practically. [↑](#footnote-ref-14)
14. Merlin defines non-random mutation for the MS as when it is ‘specifically produced in an (exclusively) advantageous manner in response to a given environmental challenge’ ([2010], p. 13). Here, ‘in an advantageous manner’ roughly means adaptive. In the formal evolutionary models, non-random or directed mutation usually refers to the same variation either relatively more probable or less probable (than other variations in the same environment) when it is relatively more beneficial (than other variations in the same environment) when considered in different environments (Pocheville and Danchin, [forthcoming]). We use the later meaning here to be consistent with Godfrey-Smith’s account we will introduce later on. [↑](#footnote-ref-15)
15. See also Bourrat ([2014], chapter 2). [↑](#footnote-ref-16)
16. According to West-Eberhard, genetic accommodation refers to gene (DNA based conception) frequency change manifested in stabilization of adaptive phenotype, and/or the amelioration of the negative side effects of the phenotype, or stabilization of adaptive phenotypic plasticity. The first process is called ‘genetic assimilation’ by Waddington ([1953]), though his example is about stabilization of non-adaptive phenotypic variation (Pigliucci *et al.* [2006]). See also Jablonka ([2006]). [↑](#footnote-ref-17)
17. Specific models have been built to represent the process of genetic accommodation through epigenetic inheritance. (For details, see Pocheville and Danchin, [forthcoming]). [↑](#footnote-ref-18)