

The Evolutionary Gene and the Extended Evolutionary Synthesis¹

Qiaoying Lu and Pierrick Bourrat

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.

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1 Introduction

By the 1940s, the marriage between the Darwinian theory of evolution (Darwin [1859]) and Mendelian genetics (Mendel [1866]; Correns [1900]; de

¹ Qiaoying Lu and Pierrick Bourrat contributed equally to this article and author order was decided randomly. Bourrat is corresponding author.

Vries [1900]; Tschermak [1900]) 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 article. 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 article, 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

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 there is an urgent need to rethink what they term the ‘standard evolutionary theory’ (SET) and call for a new extended evolutionary synthesis (EES),³ whereas others argue that 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 Darwin’s theory of natural selection, but rather the MS account that excludes non-random variation or soft inheritance (Jablonka and Lamb [2002]; Jablonka [2013]; Laland *et al.* [2014], [2015]).

² For more on the concept of heritability, see (Downes [2009]; Bourrat [2015]; Lynch and Bourrat [2017]; Bourrat and Lu [forthcoming]).

³ See also (Pigliucci and Muller [2010]; Noble *et al.* [2014]).

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 article, the focus will be on epigenetic inheritance in particular, although our discussion will also have implications for the non-random variation.

The term ‘epigenetics’ was first introduced by Waddington ([1942]) to refer to the study of the interactions between genes and their products during development. More recently, epigenetics has been defined as the study of heritable changes in gene expression that 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 An epiallele, when understood broadly, refers to a transmissible difference maker that underlies epigenetic inheritance in the broad sense. In this article, 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 challenging 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

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]).

Table 1. Definitions of key concepts

Notions	Definitions
Epigenetic inheritance (narrow sense)	'[...] the 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)	'[...] the 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 and 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 9.
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 the 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.

evidence for a substantial role for epigenetic inheritance in the history of evolution might still be regarded as weak, as the opponents of EES argue, we believe it is strong enough to motivate a theoretical discussion of its consequences. We must assess the extent to which current evolutionary theory, with its commitment to the DNA-based genetic inheritance, needs to be revised to take into account 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 about the concept of the gene can be traced back to the 1970s. Dawkins ([1976], pp. 35–6) defines a gene as any portion of the genome that potentially lasts long enough to behave as a unit for natural selection. Stent ([1977]), 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’. Dawkins’s primary interest is in the role genes play in evolution, presuming only 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 onto 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 ‘gene’, resulting in their talking past one another.

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 definition (Fogle [2000]). Faced with these problems, researchers have attempted to develop coherent concepts of the 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 (Falk [1986]; Griffiths and Stotz [2006]).

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 becomes clear 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 in terms of accommodating the phenomena of epigenetic inheritance.

The article will be organized around two questions. First, how should the concept of the gene be understood in the evolutionary sense? Second, if the concept of the evolutionary gene is understood consistently, does epigenetic inheritance represent a conceptual alternative to ‘genetic’ (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 (DNA-based) genes 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 stems from the inheritance of environmentally induced phenotypes via epigenetic modifications, which is claimed to provide evidence for non-random non-genetic variations, something that is ruled out by the MS. However, in 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 does not hold.

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

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 ([1976], p. 136), 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'. (For other authors who use the term in this sense, see Brandon [1990], p. 190; Godfrey-Smith [2009], p. 5.) Evolutionary biologists sometimes use 'gene' as a synonym for 'Mendelian allele'; see, for example, (Endler [1986], p. 5; Falconer and Mackay [1996]; Mousseau and Fox [1998]; Rice [2004], p. 85). 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's account, these verbal formulations either explicitly or implicitly assume that a gene is physically made of DNA. This additional condition, as we will argue, is unnecessary for a sound concept of the evolutionary gene.

The environment is another factor that influences the phenotype, and is also defined in different ways by different authors. Williams ([1966], p. 58) distinguishes three levels of external environment: the genetic, the somatic, and the ecological. These refer to environments composed of the population gene pool, the interaction of genes and other factors within the cell during gene expression, and the ecological world, respectively. For Dawkins ([1976], p. 37), the environment refers to the whole of Williams's three levels of external environment. 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, as well as other (DNA-based) genes in what they call the 'total allelic environment'. Similarly, Haig ([2012], p. 461), while defending gene selectionism, defines the environment as 'all parts of the world that are shared by the alternatives being compared'. For Falconer and Mackay ([1996], p. 108), the environment is 'all the non-genetic circumstances that influence the phenotypic value'. 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, (Mousseau and Fox [1998], p. v; Rice [2004], p. 243). 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' (Lamm 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 (DNA-based) molecular gene. Based on this, in Section 2.2, we then define the phenotype and the environment.

2.1 The evolutionary gene

The challenge stemming from epigenetic inheritance is mainly one for 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 Thus, the best way to determine the concept of the gene to which the MS is committed is to examine the role that this gene plays in the formalism. In quantitative genetics, a continuous trait (for example, height) is seen as caused both by many genes and by the environment.⁶ (Note that in classical population genetics, the environment is not supposed to play a role in character variation). The variation of these genes is quantified as the variance due to heritable difference makers, each of which is supposed to make an equal and additive contribution to the phenotype studied. These genes are defined solely by their effects on the phenotype and thus represent hypothetical or theoretical entities that can have different physical realizations.

When the structure of DNA was established in 1953, biologists claimed to have found 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 gene: it obeyed Mendelian laws and 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. Biologists have since referred to genes as DNA sequences, and this has resulted in the common assumption that genes must be made up of DNA. But this step was taken too hastily. If there exists 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 ([1935], p. 315), the father of classical genetics, noted in 1935 that ‘there is not

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 article, we rely on the fact that formal evolutionary models have been and are still regarded as the core of evolutionary theory.

⁶ We use Woodward’s ([2003]) manipulation account of causation throughout the article. See also (Waters [2007]) for an account of causation in formal evolutionary theory based on Woodward’s account.

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'. Fifty years later, 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 is 'the repository of inherited and potentially immortal information' or another term for 'gene' in an evolutionary context.⁷ 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 [2010], p. 422; Laland [2004]). Haig ([2012], p. 469) 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 corresponds 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. 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'. As our focus here is the concept of the gene, rather than gene selectionism, we will not discuss the agential metaphor here. Haig ([2012], p. 478) tends to conceive of the gene as a DNA sequence (rather than other heritable difference makers) because DNA has the ability to self-replicate without compromising autocatalysis, while simultaneously preserving the potential for open-ended adaptive change. 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 ([2004], p. 378), the most DNA-centric of figures, concedes that 'replicators do not have to be made of DNA in order for the logic of Darwinism to work'. 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

⁷ The term 'germ plasm' was introduced by Weismann ([1893]) to denote the determinants that are responsible for the continuity of the germ cell lineage in animals.

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 thus 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 extend this concept of 'gene' to any kind of inheritable nucleic acid difference makers that produce a difference in the phenotype.

Once this step is taken, it becomes natural to include other epialleles (for example, the patterns of DNA methylation) in the concept of 'evolutionary gene'. The increasing evidence of epigenetic marks functioning as heritable difference makers undermines any requirement that the gene meet specific material conditions. 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 unit that causes a difference in the phenotype.⁸ This definition corresponds to the manner in which the formal evolutionary theory treats genes as one of the determinants of trait variance, and also treats genes as the source of inheritance. According to this definition, any physical structure that causes a heritable variation is 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 reflects the legacy of Mendelian genetics 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

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 programme, 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. Contra Gould and Lewontin, by proposing that an evolutionary gene is atomistic, we follow Grafen's pragmatism, namely, that the gambit makes genuine phenotypic explanations possible.

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 'evolutionary gene', as 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 'all "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 is 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 phenotypes 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 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.⁹ An 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 beaver genes, making the dam (which is external to the physical boundaries of a beaver) part of the phenotype of these genes, rather than part of the environment (that is, the gene-centred environment, which we will define below). A toy example of an extended phenotype is habitat choice. Consider an organism 'choosing' to live 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. According to the extended phenotype account, the rainy and sunny habitats are not environmental variations; rather, they are part of the organism's phenotype. Environmental variations are only those things left when we have excluded anything that might explain why the organism lives in one habitat or another.¹⁰ These and similar examples will be problematic cases if by 'environment' one understands any variable beyond the physical boundaries of the organisms 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.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 ([1988], p. 354), who claim that 'the specification of the total environment' of an allele 'should be understood relative to the total allelic environment'. 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 that are not causally influenced by evolutionary genes—that is, that are 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], [2014]). They are concerned with

⁹ For a version of this argument in the context of heritability, see (Lynch and Bourrat [2017]).

¹⁰ For a similar distinction when discussing niche construction, see (Pocheville [2010], Chapter 2).

¹¹ The causal influences of the gene and the environment may not be statistically independent of one another. The contribution of gene-environment interactions and any correlations should also be taken into account for trait variance in the population. For details, see (Falconer and Mackay [1996], pp. 131–3).

external factors that affect an organism's development and render the external environment crucial to individual development. But this understanding of 'environment' represents a notion that is quite different from that of the evolutionary gene-centred account: the latter can also include parts of the organism. Making this distinction, as we will argue, might be a first step in encouraging gene-centric evolutionary biologists to think more about the role of developmental factors in evolution.

To summarize so far, we proposed that the conception of gene in formal evolutionary models, from which was derived the gene-centric view, differs from the notion in molecular biology. The conceptions of environment and phenotype from a gene-centric evolutionary perspective also differ 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 the different approaches. Thus, these two ways of partitioning the world should not be mixed.

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 exists 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], [2015]). Our position is two-fold. On the one hand, we argue for an extended understanding of the gene in evolutionary theory, rather than the restricted DNA-based account as adopted by most authors. This extension, as we have shown in Section 2.1, corresponds well to formal evolutionary theory and thus also to the gene-centric tenet of the MS. On the other hand, as we will argue in

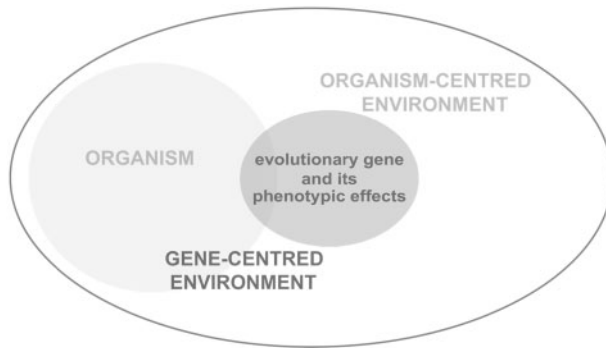


Figure 1. Gene-centred framework for the concepts of ‘gene’, ‘environment’, and ‘phenotype’ (dark grey) contrasted with the organism-centred framework (light grey). The organism-centred framework partitions the biological world into the organism and its environment. The gene-centred framework consists of the ‘evolutionary gene and its phenotypic effects’ and the ‘gene-centred environment’. The evolutionary gene is within the organism, and encompasses all the inheritable materials that make a difference to the target phenotype, compared to alternative phenotypes. According to certain grains of description, the gene-centred phenotype can be understood as 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.

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 differ in their ability 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 the sorts of entities that 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 fur colours, which are the result of different 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 its 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], p. 138).

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 (DNA-based) genes 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) towards her pups causes the development of different traits in the pups (Youngson and Whitelaw [2008]). A stressed mother not lick and groom her pups with the same frequency, causing a decreased level of serotonin (a neurotransmitter associated with nerve impulses) to be produced in the pup's brain. This decreased serotonin increases the DNA-methylation pattern on the glucocorticoid receptor gene, leading to high levels of stress-reactivity behaviour in the offspring. The result is that stressed mothers produce stressed daughters, who go on to become stressed mothers themselves. In this example, the behaviour of the mother is reproduced in later generations by means that are not DNA-based, but instead via the reconstruction during development of a complex network of interactions that include DNA-methylation patterns. These and similar examples strongly indicate that nuclear DNA cannot be the sole heritable material influencing the production of phenotypic variations. This has led some authors to argue for a pluralistic view of heredity (Bonduriansky [2012]; Jablonka and Lamb [2014]) or an inclusive inheritance (Laland *et al.* [2015]).

Contrary to what is stated in 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—as in the case of the agouti gene in mice—then this epiallele can certainly be considered to be a materialized evolutionary gene.¹² The ciliary pattern that is inherited, and the

¹² 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 us 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]).

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 mother's transmissible internal difference makers,¹³ there is no good reason to deny that these difference makers are evolutionary genes. To summarize, 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 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, with the same effects in the offspring. This new variation is thus maintained by epigenetic inheritance. In such cases, if this alternative, new phenotype has a different adaptive value in the population, then evolution by natural selection can occur without a change in DNA sequences. If such cases are possible, then this has two immediate consequences that challenge the SET. First, besides (DNA-based) genetic mutations, there are non-genetic mutations (in this restricted sense of 'genetic'). 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. The heritable epigenetic modification (the epiallele) is an instance of our notion of materialized evolutionary gene, and hence an epimutation can be counted as a genetic mutation (where 'genetic' here is understood in the evolutionary gene sense).

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 ([2012]) reasoning, if the methylation pattern changes back and forth, in response to the changes in the environmental

¹³ 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 the methylation pattern is present in the parent(s), then it should be found in the offspring, and (2) had the pattern not been present in the parent(s), then it should not have been found in the offspring.

inducer, then this switching ability should be regarded as a reaction norm and part of a phenotype of some other evolutionary genes. Thus, the same DNA-methylation pattern might be considered to be an evolutionary gene if it is heritable, or part of a phenotype in a changing environment when the pattern changes accordingly. This may seem arbitrary, but it is not a problem for the gene-centred framework we propose: ‘genes’ and ‘environments’ are concepts that do not need 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, depending on one’s point of view. The case of prions illustrates 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-grained description, the genotype of a given prion could potentially be identified as the information contained in the shape of the protein, while its phenotype would be identified as all the effects of this information, including on the rate of conversion of other proteins into this particular shape.¹⁴

Let us move now to the second consequence, namely, that environmentally induced variation might be non-random or directed.¹⁵ A special case of this phenomenon occurs when a heritable, environmentally induced phenotype is favoured by the selective environment, and is thus adaptive. For example, a recent study has demonstrated that mice acquire the fear of a sweet smell when researchers gave the mice a mild footshock every time the smell was present (Dias and Ressler [2014]). The fear is associated with a decreased level of methylation on a particular DNA sequence (the *Olftr151* gene), and the epigenetic pattern is transmitted stably, causing the descendants to also fear that

¹⁴ Considering the concept of ‘evolutionary genes’ 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 might be considered to count 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 from this that our concept of the gene (or its cultural analogue) is inapplicable to cultural evolution once the term ‘information’ has been defined.

¹⁵ Merlin ([2010], p. 13) 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’. Here, ‘in an advantageous manner’ roughly means adaptive. In 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, which we will introduce shortly.

odour. In this example, the epimutation is non-random or directed, and this 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 further examples of non-random epimutation and 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): ‘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’.¹⁶ To see this point, imagine a large population of two asexual types reproducing in discrete generations. Suppose that there are no evolutionary forces other than mutation and natural selection. Now consider the following scenarios: In the first case, the mutations are random or undirected, thus the mutations do not, on average, make any difference in the frequencies of the types. So changes in gene frequencies from one generation to the next will be explained solely 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 gene frequencies will be explained by non-random or directed mutation, as well as 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 this trajectory.

The MS and the SET give a lot of weight to random (DNA-based) genetic mutations (Futuyma [2006], p. 12; Merlin [2010]), and we expect most MS advocates would not accept non-random mutation as a common mechanism generating heritable variations. Thus 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; they can incorporate into evolution other factors (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.

¹⁶ See also (Bourrat [2014], Chapter 2).

There is a more profound consequence for evolutionary theory that stems 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) and evolutionary (ultimate) causes less clear-cut than it was once thought to be (Uller [2008]; Danchin and Pocheville [2014]; Scholl and Pigliucci [2014]). Moreover, epigenetic inheritance may pave the way for (DNA-based) genetic accommodation. The notion of genetic accommodation has been elaborated by West-Eberhard ([2003]).¹⁷ When a novel or recurrent environmental change constantly induces an adaptive phenotypic response via 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),¹⁸ and thus a mediator between development and evolution.

Our view on this profound consequence is two-fold. 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. 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 heritable difference makers, not only DNA pieces, and the environment is defined relative to this gene. Then, the developmental factors neglected in the previous case will no longer be so; instead, they will be considered to be either genes or part of the environment. Clarifying the distinction between organism-centred and gene-centred environments may open up 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, as proposed by EES advocates. The emphasis on development has already been made by gene-centric evolutionary developmental biologists, who have suggested that modifications in

¹⁷ According to West-Eberhard, genetic accommodation refers to (DNA-based) genetic 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]).

¹⁸ Specific models have been built to represent the process of genetic accommodation through epigenetic inheritance. For details, see (Pocheville and Danchin [forthcoming]).

developmental processes 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, bringing new perspectives that a gene-centric view cannot. But it does not necessarily follow from this that the alternative approach represents a revolution in current gene-centric evolutionary theory. As Sterelny ([2000], p. S371) notes, ‘no 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 be to accommodate epigenetic inheritance. Epigenetic inheritance 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 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 besides DNA alleles, such as parts of the (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 (DNA-based) genetic factors represents a different use of the terms ‘gene’ and ‘environment’ from the gene-centred framework we provide. Characterized by their effects on the phenotype, the DNA alleles and epialleles in these studies are both instances of our notion of materialized evolutionary genes. The difference of note between them concerns the different mechanisms by which these effects are transmitted (which will often involved different rates of (epi)mutation). This distinction represents an alternative way to characterize the evolutionary process, and it is fully compatible with the concept of evolutionary gene we have proposed.

Even if the term ‘gene’ comes to be used to refer to the molecular gene exclusively, and theorists employ another term (such as ‘replicator’) when referring to our concept of evolutionary gene, the conceptual analysis we provide will still be valuable insofar as it highlights two things: First,

researchers should define the concepts they use and carefully interpret works from different fields; this is crucial for productive interdisciplinary discussion.¹⁹ Second, the discovery of DNA as the material basis for genetic information, understood in the evolutionary sense, does not mean that it is the only basis for it. Hence, we are confident that current evolutionary theory is resilient and adaptive enough to incorporate new hereditary materials without requiring profound conceptual changes.

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Qiaoying Lu
Department of Philosophy
Sun Yat-sen University
China
 uqiaoy@mail2.sysu.edu.cn

Pierrick Bourrat
Department of Philosophy
Macquarie University
Sydney Australia
 and
Department of Philosophy, HPS Unit,
and the Charles Perkins Centre
The University of Sydney
Sydney, Australia
 p.bourrat@gmail.com

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¹⁹ For a recent application of our work within the context of the missing heritability problem, see (Bourrat and Lu [forthcoming]).

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