Environmentally alterable additive genetic effects

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ABSTRACT

Question: How can we measure the effects of exogenous environment in the parental generation on heritable changes in subsequent generations?

Mathematical method: Parent–offspring regression models can be used to estimate additive genetic effects that are caused by environmentally alterable signals.

Key assumption: To be relevant, environmentally alterable additive effects (e.g. environmentally induced epigenetic changes in cytosine methylation or chromatin formation) must be non-negligible compared with direct additive genetic effects.

Predictions: Large environmentally alterable additive genetic variance confounds prediction of evolutionary trajectories, but (1) provides a mechanism by which environmental variance directly increases additive genetic variance, (2) implies that environmental variance can cause evolutionary novelty, (3) provides one of possibly many mechanisms underlying phenotypic plasticity, and (4) may provide an explanation for why plants are more phenotypically plastic than animals.

Conclusion: Environmentally alterable additive genetic effects place molecular epigenetic effects and soft inheritance within a modern neo-Darwinian quantitative genetic framework.

Keywords: cytosine methylation, epigenetic, hard inheritance, heritability, phenotypic plasticity, reaction norm, soft inheritance.

INTRODUCTION

How does ecology impinge on evolution? The simplest and most common answer is via selection, including notions of ecological speciation (Schluter, 1998). But quantitative genetics has also been extended to include other ecological influences, such as genotype-by-environment interactions, phenotypic plasticity and maternal effects (Falconer and Mackay, 1996). In each of these instances, it is the environment of the offspring that affects the mapping from its genotype to phenotype (Lewontin, 1992). Here, I extend these notions to the exogenous environment of the parents heritably affecting the genotypes (including epigenotypes) of their descendants.

Environmental perturbations can heritably alter organisms and are most likely to do so by heritably altering epigenetic signals (McClintock, 1984). It is also important to note that by 'environment' I mean that aspect of the environment that is measured (e.g. Bulmer, 1980) and not

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simply the residual from a regression or analysis of variance (e.g. Fisher, 1930). I use the term 'epigenetic' to refer to molecules that reside on top of DNA nucleotides ('epi-' is Greek for 'on top of'), and not in the sense of developmental signals. There are, however, very large areas of overlap between these two definitions of epigenetic; for example, the model herein is very close to Waddington's (1957) notion of environmentally induced gene mutations and McClintock's (1984) heritable effects of genome shocks. In fact, from a quantitative genetic perspective, there is no distinction between genotype and epigenotype because the term 'genotype' refers to a phenotypic realization, regardless of whether it was caused by nucleotides or epigenetic signals (Gorelick, 2004a).

There are several examples of environmentally alterable epigenetic signals that are heritable across generations through meiosis and syngamy (Holliday, 1987; Silva and White, 1988; Klar, 1998). Parental behaviour and stress responsivity in rats can be due to stress levels heritably altering cytosine methylation signatures (Champagne and Meaney, 2001; Meaney, 2001; Weaver et al., 2002). Coat colour in mice can be heritably altered by feeding the parents varying levels of methyl donors, such as folic acid, which increase cytosine methylation in the genome (Wolff et al., 1998; Rakyan and Whitelaw, 2003). In fact, various components of diet may also alter methylation by shifting availabilities of methyltransferases and by inducing demethylation (Ross, 2003). Heritable changes in cytosine methylation have been implicated in shade avoidance in plants (Tatra et al., 2000). Canalization of genetic sex determination from an ancestral state of temperature-dependent sex determination in several lineages of amphibians, reptiles and plants may be due to inheritance of altered epigenetic signals (Dorazi et al., 1995; Gorelick and Osborne, 2002; Gorelick, 2003; Prahald et al., 2003). Environmentally alterable heritable changes have also been induced in lineages that largely lack cytosine methylation, and instead utilize chromatin formation (including histone acetylation) for regulation, such as Drosophila, the nematode Caenorhabditis elegans and the fission yeast Schizosaccharomyces pombe (Jollos, 1934; Ekwall et al., 1997; Wolffe and Matzke, 1999; Gowher et al., 2000; Lyko et al., 2000).

Heuristically, it makes sense that epigenetic signals should be heritable, albeit less so than DNA nucleotides. The combination of DNA nucleotides and the epigenetic signals that reside on top of them are analogous to an electrical wire, with the DNA nucleotides forming the copper conducting portion, the epigenetic signals forming a heterogeneous (variegated) layer of insulation, and the entire genome forming a bundled cable of wires/ chromosomes. The insulation can act by altering the electrical and magnetic signals flowing through the wire (gene regulation), especially if the insulation is thin in places or if there is shorting and crosstalk between individual wires in the bundled cable. Furthermore, it is much easier to damage the insulation (epigenetic signatures), say with a knife or heat, than it is to damage the underlying copper conducting wire (DNA nucleotides). This makes sense from the biological end of this analogy because (1) although much environmental damage to epigenetic signals is corrected during meiosis and syngamy, some of these epigenetic changes are transmitted to successive generations, whereas (2) DNA nucleotide mutations are seldom corrected during meiosis and syngamy, except for the relatively rare occurrences of gene conversion and crossing-over recombination. Another way that this analogy works is that as a bundled cable ages, the insulation around the wires changes (mostly degrades) in a fairly predicable way, which is analogous to telomere degradation with age due to loss of epigenetic signals (Howard, 1996; Tollefsbol and Andrews, 2001). By contrast, the copper conducting portion of the wire appears relatively unaffected, which is analogous to a relative lack of DNA nucleotide mutations (compared with epimutations) with age.

Environmentally alterable effects other than epigenetic signals also exist. For example, in most animals and plants, the condition of maternal parents affects the nutritional provisioning that they provide their embryos, thereby affecting their offspring's phenotype (Robson, 1955; Willham, 1963; Falconer, 1965; Kirkpatrick and Lande, 1989). However, maternal environmental effects only affect the subsequent (i.e. offspring) generation (e.g. Wright, 1926). By contrast, environmentally alterable epigenetic effects get transmitted to many successive generations via metastable (i.e. moderately heritable) changes to the epigenetic signatures.

Another way that environmentally alterable epigenetic effects differ from classical models of maternal effects is that I consider exogenous parental environmental condition to be the environment that the parent was *subjected to*, instead of the environment that the parent *subject their offspring to*. Falconer and Mackay (1996) give as an example of the latter effect maternally modulated nest temperature in mice affecting their offsprings' tail length. In the model presented herein, the focus instead is on exogenous (i.e. ambient, external environmental) temperature that the parent is exposed to, which may heritably alter their genotype (including epigenotype).

One of the remarkable aspects of the early population and quantitative genetic work of Fisher (1930), Wright (1931) and Lush (1937) is that they developed quantitative genetics before biologists realized that DNA is contained in chromosomes (Caspersson and Schultz, 1940 citing Brachet, 1940). Because their quantitative genetic models relied on phenotype (genotype values are merely phenotypes), it did not matter whether these phenotypes were caused by proteins, nucleotides, or their interactions with the environment. Thus, the simple quantitative genetic model that I present below can be used to model any form of environmentally alterable heritable effect, regardless of underlying molecular mechanism.

This paper is a simple extension of existing neo-Darwinian methods and is neither meant as a replacement of theory that has held up very well for three-quarters of a century, nor as a replacement for maternal effects theory that has held up for the past four decades.

QUANTITATIVE GENETIC MODEL

I use a simple linear regression model in which the dependent variable is phenotype of the offspring, $z(t + 1)$, and the independent variables are additive genetic effects of offspring, $a(t + 1)$, stochastic environment of the offspring, $e(t + 1)$, and measured or macro-environment of the offspring, $c(t + 1)$. I assume that $z(t + 1)$, $a(t + 1)$ and $e(t + 1)$ are vectors of the same length, possibly of length one, for each individual. When discussing regression, statisticians will then concatenate these vectors – one for each individual – into a matrix, usually designated by a capital letter, such as $Z(t + 1)$ or $A(t + 1)$. Because I will not delve into the underlying statistical machinery, I will stick with the vector representations for each individual. Because $c(t + 1)$ contains all the environmental factors that are measured, it is a vector of potentially different length from $z(t + 1)$, $a(t + 1)$ and $e(t + 1)$. For example, $c(t + 1)$ will be a vector of length two if we measure the average ambient air temperature and humidity that the eggs are subjected to. I follow Bulmer's (1980) convention of distinguishing the stochastic environment, e, from the measured environment or condition, c. Total environmental effects are therefore the sum of stochastic and measured environmental effects. Following Kirkpatrick and Lande (1989), t represents the parental generation and $t + 1$ the offspring generation. To keep this paper conceptually simple, I have not explicitly included any epistatic effects or non-zero covariances between genotypes and environment, but have included genotype × environment (G × E) interaction terms. Because the additive

genetic effects of offspring, $a(t + 1)$, are not directly observable, invoke the almost universally accepted assumption that the mid-parent phenotype, $z(t)$, can be used as its proxy in computing the direct additive genetic effects from parent–offspring regression (Lush, 1940; Lynch and Walsh, 1998, pp. 48–49). Begin with the following standard parent–offspring regression model, where lower-case bold symbols are vectors, upper-case bold symbols are matrices, and lower-case non-bold symbols are scalars:

$$
\begin{aligned}
z_{ij}(t + 1) = Gz_i(t) \quad & \text{(direct additive genetic effects)} \\
+ Cc_j(t + 1) \quad & \text{(measured environmental effects)} \\
+ e_i(t + 1) \quad & \text{(stochastic environmental effects)} \quad (1) \\
+ Iz_i(t) \cdot c_j(t + 1) \quad & \text{(G} \times \text{E}_{\text{offspring}} \text{ interaction effects)} \\
+ b(t + 1) \quad & \text{(regression bias)}
\end{aligned}
$$

where i designates families and j designates conditions, and where b is a vector of the same length as z, a and e. G is the matrix of additive genetic effects, while C measures the measured (macro-) environmental influences. If no environmental variables are measured, simply delete C and c from equation (1). I is the G × E interaction matrix.

Examining variances in the scalar case of equation (1) and assuming that covariances between genotypes and environment are zero, yields the well-known quantitative genetic variance decomposition, $V_P = V_A + (V_C + V_E) + V_{G \times E}$, where V_P is the phenotypic variance–covariance matrix, V_C and V_E are the environmental variance–covariance matrices (non-stochastic and stochastic parts, respectively), and $V_{G \times E}$ is the interaction covariance matrix between the offspring's genotype and its measured environment. The nature versus nurture dichotomy arises naturally from this variance decomposition, especially when $V_{G \times E}$ is zero: V_A is nature and $(V_C + V_E)$ is nurture.

If the measured parental exogenous environment affects offspring phenotype, then it should be added to the parent–offspring regression. With this new time-lagged independent variable of measured exogenous parental environment, $c_j(t)$, we must add two new terms to equation (1), yielding:

$$
\begin{aligned}
z_{ij}(t + 1) = Gz_i(t) \quad & \text{(direct additive genetic effects)} \\
+ Hc_j(t) \quad & \text{(environmentally alterable additive genetic effects)} \\
+ Cc_j(t + 1) \quad & \text{(measured environmental effects)} \\
+ e_i(t + 1) \quad & \text{(stochastic environmental effects)} \quad (2) \\
+ Iz_i(t) \cdot c_j(t + 1) \quad & \text{(G} \times \text{E}_{\text{offspring}} \text{ interaction effects)} \\
+ Jz_i(t) \cdot c_j(t) \quad & \text{(G} \times \text{E}_{\text{parent}} \text{ interaction effects)} \\
+ b(t + 1) \quad & \text{(regression bias)}
\end{aligned}
$$

Call the variance of H, V_{EA}, the environmentally alterable additive genetic variance because it depends on the measured parental environment. V_{EA} is additive because it contains no non-linearities (i.e. no dominance or epistasis). In fact, because this is a parent–offspring regression, within-locus dominance does not contribute to the variance of offspring phenotype. Plus we assumed no epistasis. Consider a single scalar phenotype and a single genetic locus. The term $Hc_j(t)$ represents an independent effect upon the offspring's genotype and phenotype, in addition to classical additive genetic effects, which are

themselves usually thought to be immutable in the face of exogenous environmental effects. Of course, there could be no environmentally alterable additive genetic effect, if we empirically determine that $H = 0$. Environmentally alterable additive genetic effects appear to be new in quantitative genetics. G and V_A represent hard inheritance, while H and V_{EA} represent soft inheritance (Mayr, 1982).

The regression coefficient J and its variance $V_{G \times E_{parent}}$ are measures of the interaction between offspring environment and exogenous *parental* condition. The scalar case of the variance decomposition (with zero covariances) arising from equation (2) is $V_P = (V_A + V_{EA}) + (V_C + V_E) + (V_{G \times E_{offspring}} + V_{G \times E_{parent}})$, where $(V_A + V_{EA})$ is the additive component of variance, $(V_C + V_E)$ is the environmental component of variance, and $(V_{G \times E_{offspring}} + V_{G \times E_{parent}})$ is the genotype-by-environment interaction component of variance. Actually, because H and J have been omitted as independent variables from all previous parent–offspring regression models, those previous models may have sometimes produced seemingly anomalous and non-linear behaviours. A regression model has to allocate these effects to some independent variable that has been included in the model. Omission of one or more variables from a regression model results in a positive bias in estimates of scalar variance – and a positive definite bias in estimates of covariance – of all included variables (Greene, 1997).

DISCUSSION

Naysayers might argue that environmentally alterable effects are simply another form of mutation and should therefore be incorporated into existing quantitative genetic models. Such an approach, however, ignores the correlation between two important independent variables that are already in those very models. Both direct additive genetic effects, $a(t + 1)$, and their proxy in parent–offspring regressions, mid-parent phenotype, $z(t)$, can be dependent upon the exogenous measured environment of the parent, $c_i(t)$. For example, environmental perturbations can alter the genotype – especially if that term includes the epigenotype – of the germ line in metazoan animals or totipotent cell lines in plants and other non-metazoans in systematic ways (e.g. by suppressing maintenance methylation). Ignoring this correlation between exogenous parental environment and offspring additive genetic effects is tantamount to ignoring a possibly important underlying genetic/epigenetic mechanism – the mechanism that we were trying to model in the first place!

Consider equation (1) in which there are no environmentally alterable additive genetic effects. With the standard assumption that G is constant over time, the phenotype of one generation can be used to predict the phenotypes of subsequent generations using the standard formula $\Delta\bar{z} = GP^{-1}\beta$, where P is phenotypic variance, β is the selection coefficient, and this equation can be iterated over successive generations (Lande and Arnold, 1983). By contrast, if environmentally alterable additive genetic variance for a trait (or suite of traits) is large compared with direct additive genetic variance, then this decimates the predictive power of this quantitative genetic model. With environmentally alterable additive genetic variance as modelled by equation (2), $\Delta\bar{z}$ is a function of $c(t)$. Thus, with non-negligible environmentally alterable additive genetic variance, the only way to predict the evolutionary trajectory is to know the time history of measured environmental condition. Environmentally alterable additive genetic effects provide a possible underlying cause for the 'biological uncertainty principle' (Petronis, 2004) by which it is impossible to predict evolutionary trajectories even with complete knowledge of the genome.

The fact that standard quantitative genetic models such as equation (1) have worked so well for many decades indicates that environmentally alterable additive genetic effects are either not that common or not that large. Nonetheless, the fact that standard quantitative genetic models sometimes do not appear valid indicates that we should in some instances consider environmentally alterable additive genetic effects.

Although the presence of environmentally alterable additive genetic variance confounds quantitative genetic prediction, it also provides a simple route by which exogenous spatial or temporal environmental variation injects additive genetic variation into a population. In this way, environmental variance can cause additive genetic variance even in populations for which additive genetic variance was originally zero. Environmentally alterable additive genetic effects can be a source of evolutionary novelty (McClintock, 1984). This could play a role in such phenomena as El Niño southern oscillations and glacial–interglacial cycles.

The exogenous parental environment, $c(t)$, is different from the endogenous offspring environment that is due to indirect genetic effects, such as the offspring environment created by parents or other conspecifics (Moore *et al.*, 1997; Wolf and Brodie, 1998; Wolf, 2003). Equation (2) allows us to estimate how the exogenous parental environment affects evolutionary trajectories. By knowing the time history of parental environmental conditions, we can estimate the response of a population to selection. Additive genetic variance decomposes into an endogenous piece describing classical direct and indirect additive genetic effects (where the indirect piece includes classical maternal and paternal effects) and an exogenous piece describing environmentally alterable additive genetic variance. Environmentally alterable additive genetic variance, V_{EA}, provides a linear measure of what were probably often previously referred to as non-linear reaction norms. I have also introduced a truly non-linear component of phenotypic plasticity, J, which measures the interaction between offspring genetics and parental environment and can contribute to phenotypic plasticity (see below).

Environmentally alterable heritable epigenetic signals provide a molecular mechanism that may underlie genotype-by-environment interactions. If the environmentally altered epigenetic signal is reset during meiosis or syngamy, then this results in a standard $G \times E_{offspring}$ interaction. If the environmentally altered epigenetic signal is transmitted to offspring, then this results in a $G \times E_{parent}$ interaction. In either instance, $G \times E$ interactions are still non-linearities in an otherwise linear model, but epigenetic theory allows $G \times E$ interactions to be something other than mere statistical artifacts.

Focusing on cytosine methylation for a moment, environmentally alterable additive genetic effects may provide a source for phenotypic plasticity. Cytosine methylation signatures are relatively fluid over evolutionary time, at least when compared with nucleotide signatures, and therefore cytosine methylation provides a potentially large source of environmentally alterable additive genetic variance that has previously largely been disregarded. Scheiner and Goodnight (1984) defined phenotypic plasticity as $V_{PL} = V_G + V_{G \times E}$. If phenotypic plasticity includes both the exogenous environment of the offspring and the parent – that is, $V_{PL} = V_G + V_{G \times E_{offspring}} + V_{G \times E_{parent}}$ (which was probably never their intent) – then environmentally alterable epigenetic effects can contribute to phenotypic plasticity via the term $J z_i(t) \cdot c_j(t)$ in equation (2).

Focusing again on cytosine methylation, environmentally alterable additive genetic effects may provide an explanation for why plants seem to be more phenotypically plastic than animals. Meiotic genomes primarily only have methylation on their cytosine nucleotides that are in CpG dinucleotides (cytosine-phosphate-guanine) or, much more rarely, in

CpNpG trinucleotides, where N can be any nucleotide (Ramsahoye *et al.*, 2000). Animals generally have less than 5% of their CpG dinucleotides methylated, whereas plants have 10–30% of their CpG dinucleotides methylated (Shapiro, 1976; Finnegan and Kovac, 2000). A test of the assertion that cytosine methylation fosters phenotypic plasticity would be to see whether the highest incidences of phenotypic plasticity occur in those taxa with high cytosine methylation levels and that the highest incidences of canalization occur in those taxa with little or no cytosine methylation. We would have to examine a broad array of plant and animal taxa, realizing that not all environmentally alterable epigenetic signals are based on cytosine methylation [e.g. histone acetylation (Prahald *et al.*, 2003)].

There are both theoretical and practical implications of this work. Evolutionary theorists are always looking for mechanisms that increase additive genetic variance. Here that is done by converting environmental variance to additive genetic variance. Environmentally alterable additive genetic effects, especially those associated with heritable changes in epigenetic signatures, are a modern reincarnation of soft inheritance (Mayr, 1982). Unfortunately, studies of soft inheritance were largely abandoned just before Fisher and Wright first published their pioneering works on population and quantitative genetics (Cook, 1999). This may explain why the regression model in equation (2) seems novel. Yet, evolutionary theorists have recently shown a renewed interest in soft inheritance (Jablonka and Lamb, 1995).

Some pragmatic implications of environmentally alterable additive genetic effects are discussed in Petronis (2001) and Gorelick (2004b). For example, if pollutants adversely affect organisms by heritably altering their epigenetic signals, then environmental remediation will not remove the problem. Once pollutants have adversely altered an individual's epigenetic signals, this harm will be transmitted to future generations even if they are not exposed to the pollutants. It is vitally important to estimate this environmentally alterable component, V_{EA}, of additive genetic variance. In fact, a primary goal of this paper is to encourage empirical quantitative geneticists to estimate V_{EA}. Assuming that the interaction variances are zero (i.e. $V_{G \times E}$, $V_{G \times E\text{-parent}}$, and that epistatic variance is zero), if V_{EA} is zero, then we can decompose phenotypic variance into components due to nature (V_A) and nurture ($V_C + V_E$), respectively. If, however, V_{EA} is a substantial portion of V_P, especially compared with V_A, then it will be impossible to disentangle the effects of nature and nurture.

For those environmentally alterable additive genetic effects that are due to epigenetic signals, Waddington (1957, p. ix) showed great foresight in saying that 'Neo-Darwinism involves a breach between organism and nature as complete as the Cartesian dualism of mind and matter; an epigenetic consideration of evolution goes some way towards healing it'.

ACKNOWLEDGEMENTS

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