Evolutionary Quantitative Genetics of Genomic Imprinting

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ABSTRACT Genomic imprinting shapes the genotype–phenotype relationship by creating an asymmetry between the influences of paternally and maternally inherited gene copies. Consequently, imprinting can impact heritable and nonheritable variation, resemblance of relatives, and evolutionary dynamics. Although previous analyses have identified some of the quantitative genetic consequences of imprinting, we lack a framework that cleanly separates the influence of imprinting from other components of variation, particularly dominance. Here we apply a simple orthogonal genetic model to evaluate the roles of genetic (additive and dominance) and epigenetic (imprinting) effects. Imprinting increases the resemblance of relatives who share the expressed allele, and therefore increases variance among families of full or half-siblings. However, only part of this increased variance is heritable and contributes to selection responses. When selection is within, or among, families sharing only a single parent (half-siblings), which is common in selective breeding programs, imprinting can alter overall responses. Selection is more efficient when it acts among families sharing the expressed parent, or within families sharing the parent with lower expression. Imprinting also affects responses to sex-specific selection. When selection is on the sex whose gene copy has lower expression, the response is diminished or delayed the next generation, although the long-term response is unaffected. Our findings have significant implications for understanding patterns of variation, interpretation of short-term selection responses, and the efficacy of selective breeding programs, demonstrating the importance of considering the independent influence of genomic imprinting in quantitative genetics.

KEYWORDS breeding values; epigenetic variation; parent-of-origin effects; resemblance of relatives; selection response

GENOMIC imprinting is an epigenetic phenomenon wherein the expression of the two copies of a gene depends on their parent of origin. The phenomenon of imprinting was first described in insects and may occur in a variety of taxa, but it is best characterized in mammals and angiosperms (Ferguson-Smith 2011). In its simplest and most widely recognized form, imprinting involves the silencing of either the maternally or paternally inherited gene copy at a locus [hereafter matrigenic and patrigenic, following Patten *et al.* (2014)]. However, more complex patterns

of expression can occur, such as partial silencing of the allele from one parent (Wolf *et al.* 2008a,b; Lawson *et al.* 2013; Wang *et al.* 2013) and changes in imprinting status (including a switch in the direction of imprinting) in different tissues or life-history stages (Garfield *et al.* 2011; Prickett and Oakey 2012; Baran *et al.* 2015). Imprinted genes often play important roles in key biological processes such as growth and development, social dominance behavior, and resource provisioning by mothers and demand in offspring (Reik and Walter 2001; Tycko and Morison 2002; Curley 2011). They are also implicated in human diseases including Prader-Willi and Angelman syndromes (Meijers-Heijboer *et al.* 1992; Nicholls *et al.* 1998). Because these types of traits are often critical determinants of fitness, understanding how variation at imprinted loci contributes to trait variation is important for understanding evolutionary processes (e.g., Lorenc *et al.* 2014; Brekke *et al.* 2016).

The impacts of imprinting on patterns of trait variation are a consequence of its effect on the genotype–phenotype

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doi: <https://doi.org/10.1534/genetics.118.301373>

Manuscript received July 18, 2018; accepted for publication October 23, 2018; published Early Online November 2, 2018.

Supplemental material available at Figshare: <https://doi.org/10.25386/genetics.7228958>.

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relationship, which determines patterns of resemblance among relatives (Spencer 2002), and trait evolution under natural or artificial selection (Santure and Spencer 2011). The consequences of imprinting are most obvious in heterozygotes because reciprocal heterozygotes differ in the parent of origin of their alleles, and hence they will express different alleles if a locus is imprinted. Therefore, despite being genetically identical, the reciprocal heterozygotes can show an epigenetic difference in their phenotypes. While the consequences of these effects have been explored previously, models of genetic effects with imprinting have often been constructed in a way that coningles dominance with imprinting (because both are defined with regard to heterozygotes) (Spencer 2002; Santure and Spencer 2011). The conflation of these effects has obscured the impact that genomic imprinting has on quantitative genetic variation, and, particularly, its consequences for evolutionary change. It is unclear from previous models what proportion of the variance contributed by imprinting is heritable, and thus contributes to selection responses. We address this problem using a simple orthogonal quantitative genetic model that captures the fundamental influences of imprinting on evolutionary quantitative genetic patterns and processes. By cleanly separating the influence of imprinting from other patterns of effect at a locus, this model provides for a clear and intuitive understanding of how allelic variation at imprinted loci contributes to variation and evolution.

Imprinted genes may have particularly important implications for selection responses in animal breeding programs. A growing number of imprinted genes have been associated with commercially important traits of livestock (O'Doherty *et al.* 2015), including the callipyge phenotype in sheep (Georges *et al.* 2003), muscle growth and back fat thickness in pigs (de Koning *et al.* 2000; Van Laere *et al.* 2003), and meat quality and milk production in beef and dairy cattle, respectively (Goodall and Schmutz 2007; Bagnicka *et al.* 2010). We therefore use our model to explore the effect of imprinting on the response to selection, by considering an array of selection regimes commonly employed in an animal breeding context, in order to identify the most efficient selection strategies. Examples of imprinting effects on phenotypic variation in wild populations are less prevalent, but Slate *et al.* (2002) detected evidence for maternal expression of a QTL associated with birth weight in red deer (*Cervus elaphus*). The results of our model can also provide insights into how imprinting might affect selection responses (e.g., adaptation to novel environments) in natural populations. Finally, while considering the structure and results of our model it is important to keep in mind that we are not modeling the evolutionary origins of imprinting at a locus (i.e., the phenomena that favor the evolution of imprinting), but rather, the consequences of pre-existing imprinting. Therefore, our framework is agnostic with respect to the processes that originally led to imprinted expression and, moreover, such considerations are beyond the scope of our analysis.

The Model

We consider a single locus with two alleles, A_1 and A_2 , which occur in the population with frequencies of p and q ($= 1-p$) respectively. Unless otherwise specified, we assume a large, randomly mating population, such that the frequencies of the four ordered genotypic classes (A_1A_1 , A_1A_2 , A_2A_1 , A_2A_2) conform to Hardy-Weinberg (H-W) proportions (Table 1). Genotypes are written with the matrigenic allele first, followed by the patrigenic allele. The phenotypic values (mean phenotypes) associated with the four ordered genotypes are designated z_{ij} , with subscripts indicating the identity of the matrigenic (subscript i) and patrigenic (subscript j) alleles (e.g., z_{12} is the phenotypic value associated with the A_1A_2 genotype).

The additive and dominance effects of the locus follow the definitions from the classic quantitative genetic model, where the additive genotypic value, a , is equal to half the difference between the phenotypic values of the homozygotes (i.e., $a = \frac{1}{2}[z_{11} - z_{22}]$), and the dominance genotypic value, d , is the difference between the unweighted mean phenotypic value of the heterozygote and the unweighted mean phenotypic value of the two homozygote genotypes (i.e., $d = [z_{12} + z_{21}]/2 - [z_{11} + z_{22}]/2$) (Falconer and Mackay 1996; Lynch and Walsh 1998). With imprinting, the phenotypic values of the reciprocal heterozygotes can differ. Following de Koning *et al.* (2002) and Shete and Amos (2002), we define the imprinting genotypic value, i , as half the difference between the phenotypic values of the two (reciprocal) heterozygotes (i.e., $i = \frac{1}{2}[z_{21} - z_{12}]$) (Figure 1). This formulation corresponds to a bias in expression toward the patrigenic allele when a and i have the same sign, and toward the matrigenic allele when their signs differ. The additive, dominance, and imprinting effects together define the expected genotypic values of the four ordered genotypes, measured as deviations from the reference point (R), which is the unweighted average of the phenotypic values of the homozygotes (Figure 1 and Table 1).

In each section that follows, we consider the implications of the special cases where $d = 0$ and $i = \pm a$, giving the canonical patterns of uniparental (i.e., matrigenic or patrigenic) expression. However, we emphasize that this model allows for any arbitrary pattern of variation among the ordered genotypes, thereby allowing it to be used to evaluate the full spectrum of potential expression patterns that can arise due to imprinting (described in Wolf *et al.* 2008a; Lawson *et al.* 2013).

It has previously been shown that, with imprinting, the mean genotypic (and phenotypic, assuming no environmental effect on phenotype) value for the population ($\bar{w}$) is equivalent to that under standard Mendelian expression (de Koning *et al.* 2002; Spencer 2002; Hu *et al.* 2015):

$$\begin{aligned}\bar{w} &= R + p^2a + pq(d + i) + qp(d - i) + q^2(-a), \\ &= R + 2dpq + a(p - q)\end{aligned}\quad (1)$$

Imprinting does not contribute to the mean phenotype of the population because the frequencies of the two heterozygotes are assumed to be equal, and, therefore, the imprinting

Table 1 The frequency, phenotype (fitness), and quantitative genetic properties of the four genotypes at an imprinted locus

Genotype	A_1A_1	A_1A_2	A_2A_1	A_2A_2
Frequencies	p^2	pq	qp	q^2
Phenotype (fitness)	$R + a$	$R + d - i$	$R + d + i$	$R - a$
Dominance deviation	$-2q^2d$	$2dpq$	$2dpq$	$-2p^2d$
Imprinting deviation				
Mean	0	0	0	0
Mothers	$-2qi$	$(p - q)i$	$(p - q)i$	$2pi$
Fathers	$2qi$	$(q - p)i$	$(q - p)i$	$-2pi$
Breeding values				
Mean (= additive deviation)	$2q\alpha_{(all)}$	$(q - p)\alpha_{(all)}$	$(q - p)\alpha_{(all)}$	$-2p\alpha_{(all)}$
Mothers	$2q\alpha_{(dams)}$	$(q - p)\alpha_{(dams)}$	$(q - p)\alpha_{(dams)}$	$-2p\alpha_{(dams)}$
Fathers	$2q\alpha_{(sires)}$	$(q - p)\alpha_{(sires)}$	$(q - p)\alpha_{(sires)}$	$-2p\alpha_{(sires)}$

Genotypes are written with the maternally inherited allele first. The breeding values are the sums of the average effects of the alleles, expressed in terms of the average effect of an allele substitution (α) (given in Equation 2), and differ for sires and dams. The additive and dominance deviations for each genotype match those from the standard model and do not differ between fathers and mothers. The imprinting deviations differ between fathers and mothers for each genotype, but are all equal to 0 when averaged across the two types of parents. Note that the sum of the imprinting and additive deviations gives the breeding value for each genotype of each type of parent.

effect cancels out (since one heterozygote has a genotypic value of $R + d + i$ and the other has a genotypic value of $R + d - i$; Table 1).

Components of phenotypic variation

In the classic quantitative genetic model, alleles coming from mothers and fathers are equivalent, and hence parent-of-origin of alleles is ignored when calculating components of variation. However, imprinting creates an epigenetic difference between the effects of the maternally and paternally inherited alleles (de Koning *et al.* 2002; Spencer 2002; Hu *et al.* 2015), which can contribute a component of trait variation. To understand how this parent-of-origin dependent effect contributes heritable and nonheritable components of variation and resemblance of relatives, we start by deriving the effects of alleles coming from mothers and fathers. For this, we calculate the average effect of an allele substitution, which is defined as the expected difference between the average phenotypes associated with the two alleles, and, hence, characterizes the effect of “exchanging” one allele for the alternate allele. To account for parent-of-origin dependent effects associated with imprinting, we separately calculate the average effect of an allele substitution (α) (corresponding to a change from the A_1 to the A_2 allele) for alleles inherited from fathers (sires) and mothers (dams):

$$\alpha_{(sires)} = a + i + d(q - p) \quad (2a)$$

$$\alpha_{(dams)} = a - i + d(q - p) \quad (2b)$$

The overall average effect of an allele substitution across all individuals in a population ($\alpha_{(all)}$) is the average of the parent-specific values. This averaging results in the cancelling out of the imprinting genotypic value, yielding the standard form for the average effect of an allele substitution: $\alpha_{(all)} = a + d(q - p)$.

The average effects of allele substitutions can be used to define the average excess of each allele, which represents the mean phenotype associated with that allele, expressed as a

deviation from the population mean. Under random mating (which we assume here), the average excess of an allele is equal to its average effect (Lynch and Walsh 1998). Because of this equivalence, most discussions of allelic effects refer to the average effect rather than the average excess, and, thus, for consistency, we use the former term here. The average effects of each allele through each parent are: $\alpha_{1(sires)} = q\alpha_{(sires)}$; $\alpha_{2(sires)} = -p\alpha_{(sires)}$; $\alpha_{1(dams)} = q\alpha_{(dams)}$; $\alpha_{2(dams)} = -p\alpha_{(dams)}$. Note that the average effect of an allele substitution at a locus with two alleles is equivalent to the difference in the average effects of the alternative alleles [e.g., $\alpha_{(sires)} = \alpha_{1(sires)} - \alpha_{2(sires)}$]. The sum of the average effects of the alleles possessed by a genotype define its breeding value. Overall breeding values of each genotype (across both fathers and mothers), as well as the separate breeding values for fathers and mothers, are given in Table 1.

Using the average effects and breeding values, we can calculate the heritable (additive genetic) variance, V_A . Without imprinting at an autosomal locus, V_A can be calculated as twice the variance in the average effects of the alleles or as the variance in the breeding values of the genotypes (Falconer and Mackay 1996), and is the same through both fathers and mothers. The standard value of V_A is calculated across the entire population (across both fathers and mothers), and is defined as $V_A = 2pq\alpha_{(all)}^2 = 2pq(a + d(q - p))^2$. However, because imprinting leads to a difference in the average effects of alleles and the breeding values (for a given allele or genotype respectively) of fathers and mothers, the additive genetic variance (V_A) will depend on which parent is used to calculate it (or whether both parents are used). We refer to the values of “ V_A ” calculated separately for fathers and mothers as the parent-specific breeding variances [$V_{B(sires)}$ and $V_{B(dams)}$], which represent the variance in the parent-specific breeding values (or twice the variance in the parent-specific average effects):

$$V_{B(sires)} = 2pq\alpha_{(sires)}^2 = 2pq(a + i + d(q - p))^2 \quad (3a)$$

$$V_{B(dams)} = 2pq\alpha_{(dams)}^2 = 2pq(a - i + d(q - p))^2 \quad (3b)$$

Figure 1 Models for the genotypic values of the four possible genotypes at a locus with two alleles. (A) the standard model without imprinting (see Falconer and Mackay 1996), (B) genotypic values for an imprinted locus following the model of Spencer (2002), and (C) genotypic values used in the orthogonal model presented here. In all cases, the reference point (R) indicates the midpoint (unweighted mean) of the homozygote phenotypes. The mean genotypic value of the heterozygotes in our model is d , as in Falconer and Mackay (1996), but with imprinting the genotypic values of the two heterozygotes A_1A_2 and A_2A_1 deviate from d by $-i$ and i respectively. Genotypes are presented with the maternal allele followed by the paternal allele.

We can clearly see that, although imprinting does not contribute to the overall additive genetic variance, it creates a difference in the breeding variances measured through each type of parent [$V_{B(\text{sires})} \neq V_{B(\text{dams})} | i \neq 0$]. When gene expression (in terms of the effect on a trait) is biased toward the patrigenic gene copy (where a and i are of the same sign), the breeding variance through fathers [$V_{B(\text{sires})}$] is larger than that through mothers [$V_{B(\text{dams})}$], and vice versa when there is matrigenic expression. Therefore, V_A for a population will be overestimated if it is calculated from the variance in breeding values of the parent contributing the gene copy with higher expression, and it is assumed that breeding values of both sexes are equal, as they are under the standard model. In the canonical case, where there is complete silencing of the gene copy from one parent ($d = 0, i = \pm a$), V_B is zero through the parent whose copy is silenced and increased fourfold (relative to the expectation without imprinting) for the parent whose copy is expressed.

To partition the additive and imprinting contributions to the breeding values through fathers and mothers, we define the average imprinting effects of the alleles and imprinting deviations for each of the genotypes (Table 1). The average imprinting effect of an allele is half the difference in the average effect of an allele coming from fathers vs. mothers (and hence represents the parent-of-origin dependent effect of the allele). In fathers, the average imprinting effect of the

A_1 allele is qi , and of the A_2 allele is $-pi$ (calculated as the average effect in fathers minus the average in mothers). In mothers, the average imprinting effects of the A_1 and A_2 alleles are $-qi$ and pi , respectively (calculated as the average effect in mothers minus the average in fathers). These average imprinting effects can then be used to obtain the epigenetic (imprinting) deviations for each genotype in each parent, by summing the average imprinting effects of the two alleles. The imprinting deviations can also be defined as half the difference in the breeding values of a genotype in fathers and mothers. Subtracting the imprinting deviations from the parent-specific breeding values yields the overall mean breeding values (the additive deviation; Table 1). Hence, the breeding values of fathers and mothers can be divided into an additive deviation, which does not differ between the parents (and has the same value as a locus without imprinting, which is equivalent to the mean breeding value of a genotype) and an imprinting deviation. Consequently, the variance of the additive deviations necessarily recovers the standard expression for the additive genetic variance $V_A = 2pq(a + d(q-p))^2$. Although the imprinting deviations differ between fathers and mothers, the imprinting variance through both parents is the same and is equal to the imprinting variance, denoted as V_O (where O stands for “origin”) (see also Álvarez-Castro 2014), where $V_O = 2pqi^2$.

Importantly, the sum of the additive and imprinting variances does not give the breeding variance through fathers or mothers. This is because there is also a covariance between the additive and imprinting deviations in each type of parent. This covariance between additive and imprinting deviations of a locus occurs because imprinting causes alleles to have similar effects in heterozygotes and homozygotes. For example, if a locus is paternally expressed, the heterozygotes and homozygotes that inherited the same allele from their fathers will have the same phenotype, and, hence, the allele will have the same additive and imprinting deviations. Although it has previously been shown using a different (nonorthogonal) parameterization, that imprinting creates a covariance between the additive and the nonadditive (dominance + imprinting) deviations through each parent (Spencer 2002), it was not possible to separate dominance and imprinting. Therefore, the cause and consequence of this covariance was unclear. This covariance between the additive and imprinting deviations is equal but of opposite sign through fathers and mothers:

$$\begin{aligned} \text{cov}_{A, O(\text{sires})} &= 2pqi(a + d(q-p)) \\ &= 2pqi\alpha_{(\text{all})} \end{aligned} \quad (4a)$$

$$\begin{aligned} \text{cov}_{A, O(\text{dams})} &= -2pqi(a + d(q-p)) \\ &= -2pqi\alpha_{(\text{all})} \end{aligned} \quad (4b)$$

Because the covariances in each type of parent are of equal magnitude but opposite sign we define a term $\text{cov}_{A, O(\text{all})}$ as the absolute value of the covariances through each parent (i.e., $\text{cov}_{A, O(\text{all})} = 2pqi\alpha_{(\text{all})}$). Substituting this value into

Equation 3, we can rewrite the expressions for the breeding variances for fathers and mothers as:

$$V_{B(\text{sires})} = V_A + V_O + 2\text{cov}_{A,O(\text{all})} \quad (5a)$$

$$V_{B(\text{dams})} = V_A + V_O - 2\text{cov}_{A,O(\text{all})} \quad (5b)$$

Note that, because the covariance between the additive and imprinting deviations is positive in the parent whose gene copy is more highly expressed (*i.e.*, fathers when $i > 0$ and mothers when $i < 0$) and negative in the other parent, it increases V_B through the more highly expressed parent and decreases it by an equal amount through the other parent.

Note that taking the average of the breeding variances (Equation 5) for the two types of parents [$V_{B(\text{mean})}$] does not yield the standard value for V_A expected for a locus without imprinting, as it also includes the variance due to imprinting:

$$\begin{aligned} V_{B(\text{mean})} &= \frac{1}{2} V_{B(\text{sires})} + \frac{1}{2} V_{B(\text{dams})} \\ &= 2pq(a + d(q - p))^2 + 2pqi^2 \\ &= V_A + V_O \end{aligned} \quad (6)$$

Hence, the average of the breeding variances measured through the two types of parents differs from the true additive genetic variance by a factor of the imprinting variance, V_O . To recover the standard value of the additive genetic variance, it is necessary to calculate the variance of the mean breeding values or mean average effects (*i.e.*, averaged across fathers and mothers; see Table 1).

The total phenotypic variance (V_P) contributed by a locus, defined as the variance of the genotypic values, is the sum of the additive and imprinting variance defined above, plus the dominance variance V_D :

$$\begin{aligned} V_P &= 2pq(a + d(q - p))^2 + (2pqd)^2 + 2pqi^2 \\ &= V_A + V_D + V_O, \end{aligned} \quad (7)$$

which emphasizes that, in a randomly mating population (conforming to H-W frequencies), the imprinting effect i contributes solely to the imprinting variance, and not to the overall additive and dominance variances. Using Equation 6, we can also express the total phenotypic variance (V_P) as:

$$V_P = \frac{1}{2} V_{B(\text{sires})} + \frac{1}{2} V_{B(\text{dams})} + V_D \quad (8)$$

demonstrating that the total phenotypic variance reflects the variation in breeding values of males and females, plus a separate dominance variance. The fact that the dominance variance is still separate from the breeding variance (which contains both the additive and imprinting variances) was not clear from some previous models of the quantitative genetics of imprinting, where the imprinting variance was not cleanly separated from the dominance component of variance (Spencer 2002).

Resemblance of relatives

In practice, components of quantitative genetic variation (*e.g.*, V_A and V_D) are typically estimated by measuring the phenotypic resemblance of different types of relatives (Falconer and Mackay 1996). It is important to understand how these are changed by imprinting, because components of variance may be over or underestimated if imprinting is ignored (Hu *et al.* 2015). The phenotypic resemblances of relatives (parent-offspring, and full and half-siblings) for a locus with imprinting are summarized in Table 2.

Under the standard model without imprinting, the mid-parent-offspring covariance (the covariance between the mean of the two parental phenotypes and the mean phenotype of their offspring), which provides a measure of the resemblance of parents and their offspring, is simply $\frac{1}{2}V_A$ (Falconer and Mackay 1996). Because it measures the average resemblance of both parents with their offspring, this is unaffected by imprinting (Figure 2 and Table 2). However, imprinting affects the parent-offspring resemblance when just one parent is considered because it creates an asymmetry in the expression of the gene copies from each parent in the offspring. Without imprinting, mother-offspring and father-offspring resemblance (measured as a covariance) are both equal to $\frac{1}{2}V_A$ (Falconer and Mackay 1996). However, with imprinting the parent-offspring resemblance is increased for the parent from which alleles are more highly expressed, by an amount equal to half the covariance of the additive and imprinting deviations ($\text{cov}_{A,O}$). There is a corresponding decrease in the resemblance of offspring with the parent whose gene copy has reduced expression (Figure 2 and Table 2). It can be seen from Figure 2 and Table 2 that, in the canonical case where the gene copy from one parent is completely silenced ($i = \pm a$, $d = 0$), the contribution of the locus to the phenotypic covariance of parents and offspring is zero for the parent whose copy is silenced, while for the parent whose copy is expressed it has a value equal to the value of V_A . This pattern occurs because the covariance between additive and imprinting deviations has a value that is equal to that of the additive genetic variance when the locus shows complete imprinting (*i.e.*, substituting a for $\pm i$ in Equation 4 would result in either $\{\text{cov}_{A,O(\text{sires})} = V_A, \text{cov}_{A,O(\text{dams})} = -V_A\} | a = i$, or $\{\text{cov}_{A,O(\text{dams})} = V_A, \text{cov}_{A,O(\text{sires})} = -V_A\} | a = -i$).

Imprinting changes the resemblance of half-siblings (*i.e.*, siblings sharing one parent) relative to that expected for an unimprinted locus, with the impact depending on whether siblings are related through their mother or father. Without imprinting, the expected covariance of half-siblings is $\frac{1}{4}V_B$ (Falconer and Mackay 1996). However, with imprinting it is necessary to use the value of the breeding variance, V_B , for the shared parent (given by Equation 3 and Equation 5), rather than V_A . For half-siblings sharing the parent whose alleles they express, resemblance due to this locus is equal to $\frac{1}{4}V_B$ through that parent. With complete imprinting, this value will be equal to the value of V_A (which is achieved by substituting the value of a for i , see Figure 2 and Table 2),

Table 2 Phenotypic resemblance among relatives, given by their covariation in a randomly mating population

Relationship	Covariance	Components of variance
Mid-parent-offspring	$pq\alpha_{(all)}^2$	$1/2V_A$
Mother-offspring	$pq\alpha_{(all)}\alpha_{(dams)}$	$1/2V_A - 1/2\text{COV}_{A,O(all)} = 1/2V_{h(dams)}$
Father-offspring	$pq\alpha_{(all)}\alpha_{(sires)}$	$1/2V_A + 1/2\text{COV}_{A,O(all)} = 1/2V_{h(sires)}$
Maternal half-siblings	$1/2pq\alpha_{(dams)}^2$	$1/4V_A + 1/4V_O - 1/2\text{COV}_{A,O(all)} = 1/4V_{B(dams)} = 1/4[V_{h(dams)} + V_{\tau(dams)}]$
Paternal half-siblings	$1/2pq\alpha_{(sires)}^2$	$1/4V_A + 1/4V_O + 1/2\text{COV}_{A,O(all)} = 1/4V_{B(sires)} = 1/4[V_{h(sires)} + V_{\tau(sires)}]$
Full-siblings	$1/2pq\alpha_{(dams)}^2 + 1/2pq\alpha_{(sires)}^2 + (pqd)^2$	$1/2V_A + 1/2V_O + 1/4V_D$

Also shown are the covariances expressed in terms of the components of variance (additive, dominance and imprinting (co)variances).

and the locus will make no contribution to the covariance of half-siblings that share the parent whose gene copy is silenced.

The resemblance of full-siblings is also affected by imprinting (Figure 2 and Table 2). Under the standard model, the expected phenotypic covariance of full-siblings is $1/2V_A + 1/4V_D$ (Falconer and Mackay 1996). At a locus with imprinting, the resemblance is increased by a value equal to half of the imprinting variance (V_O) (Table 2). With complete imprinting (where $d = 0$ and $i = \pm a$), the total covariance of full-siblings has a value that is equal to the value of V_A (since $d = 0$ and $V_A = V_I$ under this scenario, and, hence, substituting a for i would convert V_O to V_A , making the covariance of full-siblings V_A) (Table 2).

Comparison of the resemblances of different types of relatives (see Table 2) reveals that the breeding variance V_B through each type of parent consists of both heritable and nonheritable components. The heritable component, which we will denote V_h , contributes to the phenotypic resemblance both within (i.e., between siblings) and between (i.e., between parents and offspring) generations. The remaining variance is a transitory (epigenetic) component (denoted V_τ) that contributes to phenotypic resemblance within a generation (e.g., between half-siblings), but not between generations. This variation is transitory because imprints are reset each generation, and, hence, half of the time an offspring will inherit the allele from a given parent that the parent itself inherited from their opposite-sex parent, leading to a decoupling of the effect of that allele in the parent and offspring (e.g., if the parent is a father but passes on the allele it inherited from its mother to its offspring). For a fully imprinted locus, the resetting of the imprint means that the effect of the locus in the offspring will be completely uncorrelated with the effect it had in that particular parent (since it would be silenced in one of the two, depending on the direction of imprinting at the locus). The heritable variance (V_h) through each parent is:

$$V_{h(sires)} = V_A + \text{COV}_{A,O(all)} \quad (9a)$$

$$V_{h(dams)} = V_A - \text{COV}_{A,O(all)} \quad (9b)$$

Note that the parent-offspring resemblance for fathers or mothers is equal to one half of the relevant heritable variance [i.e., $V_{h(sires)}$ or $V_{h(dams)}$] (Table 2).

The transitory component of the breeding variance (V_τ) through each parent is:

$$V_{\tau(sires)} = V_O + \text{COV}_{A,O(all)} \quad (10a)$$

$$V_{\tau(dams)} = V_O - \text{COV}_{A,O(all)} \quad (10b)$$

Note that, for a given type of parent, the heritable (V_h) and transitory (nonheritable) (V_τ) components, respectively, sum to give the breeding variance (V_B) for that type of parent, as defined in Equation 3 and Equation 5.

Response to selection

We explore the evolutionary consequences of imprinting by evaluating the response to selection applied at different levels: within vs. among families of full or half-siblings, or on males vs. females. These cases reflect the different selection regimes that may be used in a controlled breeding program for genetic improvement of commercially important species, and are also relevant to selection that may occur in some natural populations.

We assume that selection operates on adults prior to reproduction, such that the allele frequencies in the parental population after selection are equal to those in the offspring before selection. We consider selection to be sufficiently weak that deviations from H-W genotypic frequencies in the parental population (and hence the offspring generation) are negligible i.e., that the population is in “quasi-H-W” (QHW) equilibrium. (Nagylaki 1976). It has been shown that deviations from H-W proportions are negligible when selection is weak (e.g., see Wolf and Wade 2016).

To explore the response to selection under different scenarios, we assume a linear relationship, β_x , between the trait described by the model and fitness, where the subscript x indicates the form of selection (e.g., selection on all individuals, or only on one sex). This means that the equation for the trait mean (Equation 1) can be used to evaluate the change in mean fitness, $\bar{w}$. If we assume that the trait described by the model is fitness, the equation for the trait mean (Equation 1) gives mean fitness $\bar{w}$. The total change in frequency of the A_1 allele (Δp) is given by its absolute fitness relative fitness (expressed in terms of the average effect of an allele substitution divided by $\bar{w}$; Table 3). We can see from this expression that imprinting does not contribute to the total selection response within a population since it cancels out in terms of

Figure 2 The effect of imprinting on the phenotypic covariance among different types of relatives. Each figure shows the covariance in relation to the frequency of the A_1 allele (p) for different values of the imprinting genotypic value (i). For each type of covariance, the left-hand panel (in blue, labeled A.1, etc.) shows the pattern for a maternally expressed locus while the one on the right (in red, labeled A.2, etc.) shows the pattern for a paternally expressed locus. Covariances were calculated using the expressions shown in Table 2 under the assumption that $a = 1$ and $d = 0$. In all figures the solid line shows the covariance without imprinting ($i = 0$), the dotted line shows the covariance with partial imprinting ($i = 0.5$), and the dashed line shows the covariance with complete imprinting ($i = 1$). The panels show the following covariances: (A) Midparent-offspring, (B) Mother-offspring, (C) Father-offspring, (D) Maternal half-siblings, (E) Paternal half-siblings, and (F) Full-siblings.

expected phenotypes and mean fitness. That is, if selection is based on the phenotypes of all individuals (*i.e.*, mass selection), the response will be the same as that predicted by the standard model without imprinting. The equilibrium frequencies of the A_1 allele ($\hat{p}$) represent peaks on the mean fitness surface, and can be obtained by setting the partial derivative of mean fitness with respect to p equal to zero. Aside from the trivial equilibria where one allele is fixed ($p = 0$ or 1), there is an equilibrium at $p = (a + d)/2d$, confirming that imprinting does not affect the shape of the mean fitness surface (Table 3).

Imprinting can, however, change the selection response if selection is applied at the family level (*i.e.*, within or among families), or if there is sex-specific selection (selection is only on males or females), both of which are common in plant and

animal breeding [see Walsh and Lynch (2018), Chapter 21]. We explore each of these cases below.

Among- and within-family selection: Family-level selection involves selection of either entire families (“among-family” selection), or of individuals from within each family (“within-family” selection), and these are used as the breeding individuals in the next generation (Wade 2000). Selection among families is equivalent to assigning each individual their family’s mean fitness. Following Wade (2000) and Gardner (2008), we use the covariance of mean fitness and the frequency of the A_1 allele in each family, as described by the Price Equation (Price 1970), to derive the change in the frequency of the A_1 allele due to selection among families. The remainder of the total selection response shown above

Table 3 Response to within and among family selection in a randomly mating population under weak selection

Level of selection	Change in frequency of A_1 allele (Δp)	Equilibrium values of p ($\Delta p = 0$)	Change in population mean phenotype ($\Delta \bar{z}$)
Among families			
Full-siblings	$pq\alpha_{(all)}/2\bar{w}$	$(a + d)/2d$	$V_A/2\bar{w}$
Maternal half-siblings	$pq\alpha_{(dams)}/4\bar{w}$	$(a + d - i)/2d$	$(V_A - \text{COV}_{A,O(alt)})/4\bar{w} = V_{h(dams)}/4\bar{w}$
Paternal half-siblings	$pq\alpha_{(sires)}/4\bar{w}$	$(a + d + i)/2d$	$(V_A + \text{COV}_{A,O(alt)})/4\bar{w} = V_{h(sires)}/4\bar{w}$
Within families			
Full-siblings	$pq\alpha_{(all)}/2\bar{w}$	$(a + d)/2d$	$V_A/2\bar{w}$
Maternal half-siblings	$pq\alpha_{(all)}/2\bar{w} + pq\alpha_{(sires)}/4\bar{w}$	$(a + d)/2d + i/6d$	$V_A/2\bar{w} + (V_A + \text{COV}_{A,O(alt)})/4\bar{w} = V_A/2\bar{w} + V_{h(sires)}/4\bar{w}$
Paternal half-siblings	$pq\alpha_{(all)}/2\bar{w} + pq\alpha_{(dams)}/4\bar{w}$	$(a + d)/2d - i/6d$	$V_A/2\bar{w} + (V_A - \text{COV}_{A,O(alt)})/4\bar{w} = V_A/2\bar{w} + V_{h(dams)}/4\bar{w}$
Total (=Among + Within)	$pq\alpha_{(all)}/2\bar{w}$	$(a + d)/2d$	$V_A/2\bar{w}$

Responses to selection are shown for selection applied within and among full-sibling, maternal half-sibling and paternal half-sibling families. In each case, the response is given in terms of the change in the frequency of the A_1 allele (Δp) and in terms of the change in mean phenotype ($\Delta \bar{z}$) observed in offspring after one generation of selection. The values for the phenotypic response to selection will be in relation to the strength of selection applied (i.e., in each case the value shown will be multiplied by the strength of selection, β_x). Also shown are equilibrium values of p , where $\Delta p = 0$ (ignoring the trivial equilibria where $p = 0$ or 1).

comes from selection within families, which is equivalent to setting variation in fitness among families to zero.

Under the standard model without imprinting, the response to selection applied within or among full-sibling families is equal (i.e., half of the total possible response in each case). For maternal or paternal half-sibling families, one-quarter of the total response is obtained from selection applied among families and three-quarters from selection within families.

With imprinting, we find that the response to selection among or within full-sibling families remains unchanged (Figure 3 and Table 3), despite the increased resemblance of full-siblings (and therefore of variance among full-sibling families) with imprinting (Table 2). However, imprinting does change the response to selection among and within maternal and paternal half-sibling families. The response to selection among half-sibling families increases when it is applied among families of half-siblings sharing the parent whose gene copy is more highly expressed, with a corresponding decrease in the response to selection among half-sibling families sharing the parent whose gene copy is less expressed (Figure 3 and Table 3). This can be seen in terms of the change in allele frequency (Δp), which depends on the average effect of an allele substitution for the type of parent through which the individuals are related, and in terms of the phenotypic response ($\Delta \bar{z}$), which likewise depends on the heritable variance for the type of parent through which the individuals are related.

When selection is applied within half-sibling families, the response is altered (i.e., changed from that expected for a nonimprinted locus) by an amount determined by the average effect of an allele substitution (for the change in allele frequency, Δp) or heritable variance (for the phenotypic response, $\Delta \bar{z}$) for the type of parent through which individuals are unrelated. For example, if selection is within maternal half-sibling families, then it is the heritable variance through fathers ($V_{h(sires)}$) that matters. This is logical since the variation within families of maternal half-siblings will necessarily reflect the variation across the fathers of the offspring within those families (in addition to the variation in alleles coming from mothers). Therefore, we expect to see a greater

response to selection when it is applied within families sharing the parent with lower expression compared to among those families sharing the parent with higher expression (Figure 3 and Table 3). For example, in the case of selection within maternal half-sibling families, if a locus is maternally expressed, the alleles coming from fathers will be silenced and hence will not contribute to within-family variation (i.e., $V_{h(sires)} = 0$), whereas, for a paternally expressed locus, we expect increased variation across the offspring from different fathers and hence more variation within maternal half-sibling families.

Putting the response to selection within and among families together we see that, with complete silencing of the gene copy from one parent and no dominance ($i = \pm a$, $d = 0$), there is no response to selection among half-sibling families sharing the parent whose copy is silenced, and all of the response comes from selection within half-sibling families (Figure 3 and Table 3). For half-sibling families sharing the parent whose gene copy is expressed, half of the total possible response comes from selection among families, and the remaining half from selection within families, the same as we see for full-siblings (Figure 3 and Table 3). This response to selection among half-sibling families is double the response expected under the standard model without imprinting. However, we have shown in the previous section that the resemblance of half-siblings sharing the parent whose gene copy is expressed is four times that expected without imprinting (Table 2), meaning that only half of this variance contributes to a response to selection among families. Likewise, full-sibling resemblance is doubled when there is complete imprinting (Figure 2 and Table 2), but there is no increase in the response to selection among full-sibling families. This is because although the imprinting variance (V_O) increases the variance among half and full-sibling families (Table 2), imprinting contributes to the selection response only through its covariance with the additive deviation (cov_{AO}). This can be seen clearly from the phenotypic response to selection (change in mean phenotype $\Delta \bar{z}$), shown in Table 3.

We can also see that imprinting changes the shape of the mean fitness surface when selection is applied among or

Figure 3 Change in the frequency of the A_1 allele (Δp) in response to selection within and among different types of families (with the strength of selection being the same in all cases). The change in allele frequency is shown as a function of the preselection frequency of the A_1 allele (p). The allele frequency change in response to selection was calculated using the expressions shown in Table 3, under the assumption that $a = 1$ and $d = 0$. For each form of selection, the left-hand panel (in blue, labeled A.1, etc.) shows the pattern for a maternally expressed locus while the one on the right (in red, labeled A.2, etc.) shows the pattern for a paternally expressed locus. In all figures, the solid line shows the pattern without imprinting ($i = 0$), the dotted line shows the pattern with partial imprinting ($i = 0.5$), and the dashed line shows the pattern with complete imprinting ($i = 1$). The left-hand column of figures shows the responses to among-family selection while the right-hand column shows the response to within-family selection for that same type of family. Changes in allele frequencies are shown for selection within and among families of full-siblings (A and B), maternal half-siblings (C and D), and paternal half-siblings (E and F).

within half-sibling families, but not full-sibling families. With selection among or within half-sibling families, the equilibrium value of p is shifted away from the value that maximizes mean fitness in the population. For a given selection regime, the magnitude of this shift depends on the degree of imprinting (i), while the direction is determined by the expression pattern (i.e., matrigenic vs. patrigenic) (Table 3). As in the standard model, there is only an intermediate equilibrium value of p (i.e., other than at $p = 0$ or 1) if there is dominance at the locus ($d \neq 0$).

Sex-specific selection: Males and females have the same genotype-phenotype relationship, therefore selection on either

sex will result in the same change in the frequency of the A_1 allele (Δp), and this will be half the response seen with selection on both sexes (Table 4). However, with imprinting the relationship between the genotype of a parent and the mean phenotype of their offspring varies depending whether the parent is male or female, as illustrated by their different breeding values (Table 1). Therefore, the phenotypic response (change in mean phenotype $\Delta \bar{z}_{(t)}$) in the offspring generation (t) following selection on either males or females in the previous generation ($t-1$) is affected by imprinting. From the responses to selection (given in Figure 4 and Table 4), we can see that the phenotypic response in this single generation (from $t-1$ to t) is increased if selection is on the sex whose

Table 4 Response to selection applied only to males or females, or to all individuals, in terms of the change in the frequency of the A_1 allele in the offspring (Δp_t), and the change in the population mean phenotype in the offspring ($\Delta \bar{z}_t$) and grand-offspring ($\Delta \bar{z}_{t+1}$) of the generation in which selection is imposed (which is generation $t-1$)

Target of selection (generation $t-1$)	Change in frequency of A_1 allele (Δp_t)	Response in offspring ($\Delta \bar{z}_t$)	Response in grand-offspring ($\Delta \bar{z}_{t+1}$)	Total response ($\Delta \bar{z}$)
Females	$pq\alpha_{(all)}/2\bar{w}$	$(V_A - \text{COV}_{A,O (all)})/2\bar{w} = V_{h(\text{dams})}/2\bar{w}$	$\text{COV}_{A,O (all)}/2\bar{w}$	$V_A/2\bar{w}$
Males	$pq\alpha_{(all)}/2\bar{w}$	$(V_A + \text{COV}_{A,O (all)})/2\bar{w} = V_{h(\text{sires})}/2\bar{w}$	$-\text{COV}_{A,O (all)}/2\bar{w}$	$V_A/2\bar{w}$
All	$pq\alpha_{(all)}/\bar{w}$	$V_A/\bar{w}$	0	$V_A/\bar{w}$

In all cases, the response is in comparison to the previous generation (*i.e.*, offspring vs. their parents). We assume that selection is applied to adults prior to reproduction, such that the allele frequencies after selection are equal to those in their offspring. There is no further change in allele frequency from offspring to grand-offspring because we assume that no further selection is applied beyond this first generation. Therefore, the phenotypic response seen in the grand-offspring is a result of selection applied to their grandparents. The values for the phenotypic response to selection will be in relation to the strength of selection applied (*i.e.*, in each case the value shown will be multiplied by the strength of selection, β_s).

gene copy is more highly expressed in their offspring and reduced if selection is on the other sex. With uniparental expression ($d = 0$, $i = \pm a$), there is no phenotypic response in generation (t) when selection acts on the sex whose allele is not expressed (Figure 4, Table 4, and Supplemental Material, Table S1). This lack of response occurs because, although selection in generation $t-1$ would have resulted in a change in allele frequencies in the allele pool coming from the parent whose sex is under selection, that change would be invisible at the phenotypic level in their offspring (*i.e.*, in generation t) because those alleles are silenced. However, a response would be seen in the generation following (*i.e.*, the grand-offspring in generation $t+1$ when selection is applied in generation $t-1$), even if no further selection is applied to the population. This delayed response occurs because the change in allele frequency that occurred as a result of selection on one sex in generation $t-1$ is present in both sexes in generation t and will therefore be manifested in generation $t+1$ (Figure 4, Table 4, and Table S1).

For example, consider the case of a locus with matrigenic expression, and selection exclusively on males in generation $t-1$ that favors the A_1 allele. Selection will increase the frequency of the A_1 allele in males, but not females, in generation $t-1$. Therefore, the offspring genotypes will have the preselection frequency of A_1 in the pool coming from their mothers and the postselection frequency in the pool coming from their fathers. Since the patrigenic copy is silent, the offspring will have the same average phenotype as their parents had before selection. However, because the imprints are reset each generation, the generation $t+1$ offspring will manifest the change in phenotype associated with the underlying change in allele frequency. Likewise, when selection acts on the sex whose gene copy is expressed in their offspring, part of the selection response is lost in their grand-offspring. Consider the example above, but with the pattern of selection reversed such that selection on females favors the A_1 allele at a locus with matrigenic expression. Selection would increase the frequency of A_1 alleles in females but not males in generation $t-1$, and, since only the matrigenic copy is expressed, that full change in frequency would be manifested as a change in phenotype in generation t (despite only half of the allele pool being under selection). However, resetting of imprinting going from generation t to $t+1$ offspring mixes

the selected and unselected pools of alleles, and, therefore, some of the response seen in generation t will be lost in generation $t+1$. Thus, the total response to selection is ultimately equal for both sexes, when summed across the two generations (Figure 4 and Table 4). Therefore, imprinting changes the short-term, but not the long-term, response to selection on one sex.

Data availability

The authors state that all data necessary for confirming the conclusions presented in the article are represented fully within the article. Table S1 shows the predicted phenotypic response to selection on males, females or both for different patterns of expression at an imprinted locus. Supplemental material available at Figshare: <https://doi.org/10.25386/genetics.7228958>.

Discussion

By using an orthogonal model of genetic effects, we have provided a general extension of the classic quantitative genetic model that incorporates genomic imprinting. Our model cleanly separates imprinting from the standard (additive and dominance) genetic effects, providing for a clear understanding of how imprinting contributes to both nonheritable and heritable variation and, hence, evolutionary processes. While a similar formulation of genetic effects has been used by others to partition variation (de Koning *et al.* 2002; Shete and Amos 2002; Mantey *et al.* 2005; Álvarez-Castro 2014; Hu *et al.* 2015), these studies have not examined the consequences of imprinting for evolution. A previous study has evaluated how imprinting impacts the responses to selection (Santure and Spencer 2011), but because it is built on a nonorthogonal model of genetic effects it did not allow the effects of imprinting and dominance to be disentangled. Our approach captures all of the previous findings, while providing for a much deeper understanding by explicitly demonstrating how imprinting (separate from other components of variation) affects partitioning of variation through each sex, resemblance of relatives, and responses to selection. Crucially, we find that it is the covariance of imprinting and additive deviations that explains why the variances in breeding values of males and females differ with imprinting (see also Spencer

Figure 4 The effect of imprinting on the phenotypic response to sex-specific selection. Selection occurs in generation $t-1$ on either females or males and the response (change in the mean phenotype across generations, $\Delta \bar{z}$) is measured in the offspring ($\Delta \bar{z}_t$) and grandoffspring ($\Delta \bar{z}_{t+1}$) of those individuals (i.e., change in the mean phenotype from generation $t-1$ to t and from t to $t+1$ respectively). For each set of panels, the one on the left (in blue, labeled A.1, etc.) shows the pattern for a maternally expressed locus while the one on the right (in red, labeled A.2, etc.) shows the pattern for a paternally expressed locus. In all figures the solid line shows the pattern without imprinting ($i = 0$), the dotted line shows the pattern with partial imprinting ($|i| = 0.5$), and the dashed line shows the pattern with complete imprinting ($|i| = 1$). The top row shows the response to selection on females observed in their offspring (A.1 and A.2) and grandoffspring (B.1 and B.2) for the cases of a maternally (A.1 and B.1) and paternally (A.2 and B.2) expressed locus. The bottom row shows the response to selection on males observed in their offspring (C.1 and C.2) and grandoffspring (D.1 and D.2) for the cases of a maternally (C.1 and D.1) and paternally (C.2 and D.2) expressed locus.

2002; Santure and Spencer 2011), and the extent to which selection responses differ from those predicted under a standard additive model. Additive deviations (which reflect the parent-of-origin independent influence of a locus) and imprinting deviations (which reflect the parent-of-origin dependent effect) covary in the presence of imprinting because a given allele will produce the same phenotype (or a similar phenotype if there is incomplete imprinting) in both heterozygous and homozygous offspring.

In a randomly mating population without imprinting, the response to a single generation of selection (in terms of the change in mean phenotype $\Delta \bar{z}$) is predicted by the breeder's equation $\Delta \bar{z} = h^2 S$ (Lush 1937), where h^2 is the trait heritability ($=V_A/V_P$) and S is the strength of selection (which in a plant or animal breeding context is often measured as the difference between the population mean and the mean of the selected individuals). Using a different (nonorthogonal) parameterization of genetic effects, it has been shown previously that when there is complete imprinting and no dominance, the actual response to a single generation of selection can be as little as half that predicted from the

breeder's equation (Santure and Spencer 2011). Our model replicates this finding and identifies a clear explanation for why it occurs: part of the influence of imprinting on the resemblance of half-siblings is transitory, and, therefore, is not truly heritable because it is lost when the imprints are reset each generation. As a result, the covariance of half-siblings will provide an incorrect estimate of the heritable variance in the presence of imprinting. For example, the contribution of an imprinted locus to the variance among half-sibling families sharing the parent whose gene copy is expressed is equal to the additive genetic variance (since $i = \pm a$), but is only $1/4 V_A$, for an unimprinted locus (i.e., it is four times that expected under the standard model without imprinting; (Falconer and Mackay 1996). However, the phenotypic response to selection among half-sibling families sharing the parent whose alleles are expressed is proportional to only half of the additive variance. This discrepancy exists because imprinting increases the resemblance of half-siblings sharing the expressed gene copy, both directly and through its covariance with additive deviations. However, imprinting only contributes to the selection response (the change in allele

frequency Δp) via its positive covariance with additive deviations. Unlike half-siblings, the parent–offspring resemblance still reflects the true heritable component of variance with imprinting. If only one parent is measured, this covariance is increased for the parent with higher expression and decreased in the other parent, again due to the effect of the additive-imprinting covariance, and there will be a corresponding increase in the response to selection among offspring of this more expressed parent. Therefore, where imprinting is suspected to affect a trait of interest, a more accurate prediction of its response to selection may be obtained if heritability is estimated from the parent–offspring resemblance, rather than the resemblance of half-siblings.

Both family-level and sex-specific selection are common in animal breeding (Lynch and Walsh 1998; Goddard and Hayes 2009), and we show that responses to both can be affected by genomic imprinting. Family-level selection may be adopted because it is more efficient than individual selection if trait heritability is low, or if the environmental variation is large, and may be the only option available when phenotypes cannot be measured prior to breeding (e.g., carcass traits). Sex-specific selection is regularly used in animal breeding, for example in cases where target traits are only present in one sex (e.g., egg production, milk yield), and is also likely to be common in natural populations. For example, the strength of selection on body size differs between males and females in bighorn sheep (Poissant *et al.* 2008). By changing the partitioning of heritable genetic variation, imprinting has a major effect on the efficiency of selection applied within or among families. When selection is among families, the response will be greater if members of those families share the parent whose gene copy is more highly expressed. By contrast, a greater proportion of the heritable variation will be partitioned within half-sibling families sharing the less expressed parent, making within-family selection more efficient. When selection is applied only to one sex, it can cause a delay in the phenotypic response to selection if this is the sex whose gene copy has reduced expression in their offspring. There will be a phenotypic change in the subsequent generation that means the long-term response is unaffected, however the initial failure to respond may lead breeders to abandon or revise their selection regimes if they are unaware of the cause. Identifying genomic imprinting in genes associated with traits of interest, and incorporating imprinting effects into models of quantitative genetic variation, is therefore crucial for accurate prediction of responses to artificial and natural selection.

The evolutionary consequences of imprinting that we have identified may partly explain the large variation among traits and species in the rate at which genetic gains have been made through selective breeding (Hill 2014). There are several well-known examples of imprinted genes associated with traits targeted for selective breeding in domesticated plant and animal species (Ruvinsky 1999; Patten and Haig 2008), including pigmentation in maize endosperm (Kermicle and Alleman 1990), muscular hypertrophy in sheep (Cockett *et al.* 1996), body composition in pigs (de Koning *et al.*

2000), and ovulation and twinning in cattle (Allan *et al.* 2009). It has previously been noted that the efficiency of sex-specific selection varies depending upon the pattern of expression at imprinted genes (Patten and Haig 2008). There is not sufficient information on the contribution of imprinting to most of the traits targeted by animal and plant breeders to make a formal comparison. However, it is worth noting that body weight in chickens (in which there is no evidence for imprinting) exhibits some of the largest and most rapid responses to selective breeding (e.g., Dunnington *et al.* 2013), while the rate of genetic gains in some mammal species, including dairy cattle (Thornton 2010) and racehorses (Hill 1988) has been slower than predicted based on genetic variation in target traits (Thornton 2010; Hill 2014). Our results also raise the intriguing possibility that the selection regime employed by animal breeders could itself affect patterns of imprinting. For example, if selection is applied at the family level and is among paternal half-sibling families (e.g., selection among different bulls on the basis of traits in their offspring), genes with patrigenic expression will produce greater phenotypic variance among families than will those with maternal expression, and will result in a faster response to selection. Therefore, an allele at a modifier locus that results in patrigenic expression of a gene underlying the trait of interest would be favored. Whether artificial selection has indeed favored the evolution of imprinting in domesticated species remains to be tested with data.

The results of our model reveal several signatures that may prove useful for identifying an effect of genomic imprinting on a quantitative trait, although some of these can also result from other processes that are not explicitly modeled here. For example, previous authors have highlighted that differences between mother–offspring and father–offspring phenotypic covariances, and/or maternal and paternal half-sibling covariances may be useful for identifying quantitative traits affected by imprinting (Santure and Spencer 2011). However, similar observations can also be produced by maternal (or paternal) effects (Santure and Spencer 2006; Wolf and Wade 2016). Similarly, the observation that the response to selection in a trait affected by imprinting is often less than that expected from its additive genetic variance, V_A (if V_A is estimated from the covariance of certain types of relatives) may also result from genotype by environment interactions (Falconer 1952), or genetic correlations with other, unmeasured traits (e.g., Blows and Hoffmann 2005; Walsh and Blows 2009). From the model presented here, we can add to this list the novel finding that when selection is applied only on the sex whose gene copy has lower expression, the phenotypic response will be partially or fully delayed by a generation. This finding is not easily explained by other phenomena, and so may provide a useful test for the contribution of imprinting to trait variation, particularly if it is observed in conjunction with one or more of the other signatures of genomic imprinting outlined above.

As with the classic quantitative genetic model, the overall results of our simple model with a single locus and two alleles

should hold for multi-locus systems and where there are multiple alleles at a locus. The presence of multiple loci also offers the possibility of epistatic interactions among loci, and therefore the possibility of epistatic interactions that involve imprinting effects. The same orthogonal model of genetic effects with imprinting used here has been used to construct a model with epistatic interactions (Wolf and Cheverud 2009; see also Álvarez-Castro (2014)). However, analyses of epistasis with imprinting have been restricted to defining genetic effects and, to a limited degree, total variances. A consideration of such an epistatic model is beyond the scope of this paper, but the model structure used here is amenable to the inclusion of epistasis. The overall results of such a model should have analogous properties to those seen in the single locus model, with interactions among loci modifying the parent-of-origin dependent effects of loci (*e.g.*, the presence of an imprinting effect or the direction of imprinting at one locus depends on the alleles present at another locus), which feed into the phenomena we have analyzed for the single-locus case.

Acknowledgments

We thank the editor and two anonymous reviewers for helpful comments on an earlier version that greatly improved this paper. This work was supported by grants (BB/L002604/1 and BB/M01035X/1) from the UK Biotechnology and Biological Sciences Research Council.

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Communicating editor: G. Churchill