The Correlation Between Relatives on the Supposition of Genomic Imprinting

Hamish G. Spencer

Department of Zoology, University of Otago, Dunedin, New Zealand

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ABSTRACT

Standard genetic analyses assume that reciprocal heterozygotes are, on average, phenotypically identical. If a locus is subject to genomic imprinting, however, this assumption does not hold. We incorporate imprinting into the standard quantitative-genetic model for two alleles at a single locus, deriving expressions for the additive and dominance components of genetic variance, as well as measures of resemblance among relatives. We show that, in contrast to the case with Mendelian expression, the additive and dominance deviations are correlated. In principle, this correlation allows imprinting to be detected solely on the basis of different measures of familial resemblances, but in practice, the standard error of the estimate is likely to be too large for a test to have much statistical power. The effects of genomic imprinting will need to be incorporated into quantitative-genetic models of many traits, for example, those concerned with mammalian birthweight.

The expression of a gene at a genomically imprinted locus depends on the parent from which it was inherited. For example, in most fetal tissues of all eutherian and marsupial species examined to date, the maternal copy of the insulin-like growth factor II (Igf-2) gene is inactive, only the paternal copy being transcribed (DeChiara et al. 1991; Giannoukakis et al. 1993; Pedone et al. 1994; Vrana et al. 1998; McLaren and Montgomery 1999; Nezer et al. 1999; O’Neill et al. 2000). For most (if not all) imprinted loci, however, both copies of the gene are expressed in some tissues at some stage of development. In the embryogenesis of rats and mice, for instance, standard biallelic or Mendelian expression of Igf-2 occurs in the choroid plexus and leptomeninges (DeChiara et al. 1991; Pedone et al. 1994). Moreover, imprinting may not entail the complete inactivation of a gene. In a study of human IGF2 from peripheral blood leukocytes, for example, some 10% of a sample of phenotypically normal individuals (i.e., not cancer patients) showed biallelic expression, although in all cases the level of maternally derived gene product was lower than that of paternal (Sakatani et al. 2001). Hence, from the individual’s point of view, imprinting is not manifested as simple haploid (i.e., monoaicolic) expression; rather, an imprinted gene shows diploid expression, with maternal and paternal copies having different levels of expression.

Under standard Mendelian expression, the number of phenotypic classes at a locus with \( k \) alleles is \( k(k + 1)/2 \). Complete inactivation of one allele would reduce the number of phenotypic classes to \( k \). The more general view of imprinting outlined above, however, means that reciprocal heterozygotes need not have the same average phenotype. Consequently, the number of phenotypic classes is \( k^2 \), greater than under Mendelian expression. This increase has a number of implications for standard population-genetic processes and phenomena. For instance, because it discriminates among different phenotypic classes, natural selection acts differently (Pearce and Spencer 1992; Anderson and Spencer 1999; Spencer 2000). In this article we examine the difference imprinting makes to the standard two-allele single-locus model of quantitative genetics. In particular, we are concerned with how genetic variance may be partitioned and the consequences of this partitioning for resemblances among relatives.

This article thus adds to the literature on the effect of sex differences on quantitative characters, previous work considering models of sex-linked inheritance (Bohidar 1964; James 1973; Grossman and Eisen 1989), sex-dependent expression (Grossman and Eisen 1989), and haplodiploidy (Liu and Smith 2000). The only previous work on the quantitative genetics of imprinting of which we are aware is that of Hill and Keightley (1988). Although their model considered multiple loci, they limited their analysis to the special case of complete inactivation.

MODEL

We consider a locus subject to imprinting, which has two alleles, \( A_1 \) and \( A_2 \). By denoting a genotype \( A_iA_j \), we mean that the \( A_i \) allele is maternally derived and the \( A_j \) allele is paternally derived. Imprinting means that reciprocal heterozygotes may differ in their average phenotypes. In the case of complete inactivation of the
maternally derived gene, for instance, the average $A_1A_2$ phenotype is the same as that of the $A_2A_1$ homozygotes, whereas the average $A_2A_1$ phenotype is the same as that of $A_1A_1$ homozygotes. Since most cases of imprinting show some degree of biallelic expression in some tissues at some stage of development, however, we do not assume that heterozygotes are phenotypically equivalent to one or another homozygote.

**Genetic components of variance:** Following standard genetic models (see, e.g., Falconer and Mackay 1996; Roff 1997; Lynch and Walsh 1998), let us assume that on some suitable scale (see Figure 1) the mean phenotype (called the genotypic value) of $A_1A_1$ homozygotes is $a$ and that of $A_2A_2$ homozygotes $-a$. With Mendelian expression all heterozygotes have the same genotypic score, usually denoted as $d$. Under imprinting, however, the two classes of heterozygotes have different genotypic values, say, $d_1$ for $A_1A_2$ and $d_2$ for $A_2A_1$. When the maternal allele is completely silenced we have $d_1 = -a$ and $d_2 = a$ and vice versa for total paternal silencing. It also seems reasonable that $-a \leq d_1, d_2 \leq a$, since partial inactivation of a gene is unlikely to produce a more extreme phenotype than that of the homozygote for the unimprinted copy. Nevertheless, we do not make this assumption in most of what follows.

The mean genotypic value over the whole population is given by

$$
\mu = p^2 \cdot a + pq \cdot d_1 + qp \cdot d_2 + q^2 \cdot -a
= a(p - q) + (d_1 + d_2)pq.
$$

(1)

When $d_1 = d_2$ we recover the standard Mendelian value of $a(p - q) + 2dpq$ (Falconer and Mackay 1996).

The genotypic deviation of a particular genotype, the difference between its genotypic value and the population mean, can then be calculated. For instance, the genotypic deviation of the $A_1A_2$ genotype is given by

$$
d_1 - \mu = a(q - p) + d_1(1 - pq) - d_2pq.
$$

(2)

Values for the three other genotypes are found similarly and are shown in Table 1.

We can now calculate the breeding values for each of the four genotypic classes. A breeding value is defined to be twice the difference between the mean genotypic value of that class’s offspring and the population mean (Falconer and Mackay 1996). Under imprinting, these deviations are different for males and females because the genotypic classes arising from reciprocal crosses may be different. For example, the breeding value for $A_1A_1$ males involves the product of the probability that its $A_1$ sperm fertilize an $A_1$ egg, $q$, with the geno-

TABLE 1

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequencies</th>
<th>Genotypic value deviation</th>
<th>Population mean deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_2A_2$</td>
<td>$p^2$</td>
<td>$a$</td>
<td>$a - a(p - q) - 2dpq$</td>
</tr>
<tr>
<td>$A_1A_2$</td>
<td>$pq$</td>
<td>$a(q - p) + d_1(1 - pq) - d_2pq$</td>
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Figure 2.—Genotypic values (solid diamonds, left axis) and breeding values (female, open circles; male, open squares) of the four possible genotypes for $p = 0.75$ (and hence $q = 0.25$), $d_1 = -0.25a$, $d_2 = 0.75a$. These values give $\mu = 19a/32$, $\alpha_1 = 3a/8$, and $\alpha_2 = 11a/8$. Note that the breeding values are relative to the population mean and so 0 on the right-hand axis corresponds to the value for $\mu$ on the left.

typic value of the resultant $A_2A_1$, $d_2$. The breeding value for $A_1A_1$ females, however, involves the product of the probability that its $A_1$ eggs are fertilized by $A_2$ sperm, $q$, with the genotypic value of the resultant $A_1A_2$, $d_1$. Hence the mean genotypic value of offspring of $A_1A_1$ males is $p \cdot a + q \cdot d_1$ and so the breeding value is given by

$$2(p \alpha + q d_2 - \mu) = 2q \alpha_m,$$

in which $\alpha_m = a + d_2q - d_2p$. Similarly, the breeding value for $A_1A_2$ females is given by

$$2(p \alpha + q d_1 - \mu) = 2q \alpha_i,$$

in which $\alpha_i = a + d_1q - d_1p$. When $d_1 = d_2 = d$ we have $\alpha_m = \alpha_i = \alpha$, say, and we recover the standard Mendelian breeding value for $A_1A_1$ homozygotes of $2p\alpha$ (Falconer and Mackay 1996). Breeding values for the other genotypic classes are derived similarly and shown in Table 1 and Figure 2. Note that, for a given sex, the breeding values of reciprocal heterozygotes are the same, even though their genotypic values and deviations are not. For a population in Hardy-Weinberg equilibrium, the mean male and female breeding values are easily shown to be zero, as is the case for Mendelian expression.

The dominance deviation for a genotypic class is defined as the difference between the genotypic deviation and the breeding value. Since the latter differs for males and females, so too does the dominance deviation. A little algebra gives the values shown in Table 1; again their mean is zero and when $d_1 = d_2$, the sex difference disappears, and we recover the standard Mendelian values. Note also that, as is the case without imprinting, these values are independent of $a$ and are zero when $d_1 = d_2 = 0$.

The overall genetic variance of the population is the variance of the genotypic deviations:

$$\sigma^2 = p^2(2a - (d_1 + d_2)p)^2 + p q(a(q - p) + d_1(1 - pq) - d_2p)^2 + q^2((-p(2a + (d_1 + d_2)q)^2$$

$$= pq(2a\alpha_m + pq(d_1 + d_2)^2 + (d_1 - d_2)^2).$$

When $d_1 = d_2 = d$, this equation reduces to $\sigma^2 = 2pq\alpha^2 + (2pqd)^2$, the standard value.

The additive genetic variances for males and females are given by the respective variances of their breeding values,

$$\sigma^2_m = p^2 \cdot (2p\alpha_m)^2 + pq \cdot ((q - p)\alpha_m)^2 + q p \cdot ((q - p)\alpha_m)^2$$

$$+ q^2 \cdot (-2p\alpha_m)^2 = 2pq\alpha_m^2,$$

and similarly,

$$\sigma^2_m = 2pq\alpha_f^2.$$ 

The dominance genetic variance for each sex is, by definition, the variance of dominance deviations. For males, this variance is given by

$$\sigma^2_m = p^2 \cdot ((q(2d_1p - d_1(1 + q)))^2 + pq \cdot (d_1(1 - p^2) - d_1p^2)^2 + pq \cdot (d_1(1 - q^2) - d_1q^2)^2 + q^2 \cdot ((d_1q - d_1(1 + p))^2$$

$$= pq(pq(d_1 + d_1)^2 + (d_1 - d_1)^2)$$

and for females it is

$$\sigma^2_m = p^2 \cdot ((q(2d_2p - d_2(1 + q)))^2 + pq \cdot (d_2(1 - q^2) - d_2q^2)^2 + pq \cdot (d_2(1 - p^2) - d_2p^2)^2 + q^2 \cdot ((d_2q - d_2(1 + p))^2$$

$$= pq(pq(d_1 + d_1)^2 + (d_1 - d_1)^2)$$

say. Even though the dominance deviations are different for males and females, their variances are the same. Again, as expected, $\sigma^2_d$ is independent of $a$, and when $d_1 = d_2 = d$ reduces to the Mendelian $(2pq\alpha d)^2$, which is zero when $d = 0$. Note, however, that $\sigma^2_d \neq 0$ when the average of the heterozygote genotypic values [i.e., $\frac{1}{2}(d_1 + d_2)]$ is zero (unless $d_1 = d_2 = 0$).

With Mendelian expression the breeding values and dominance deviations are uncorrelated, but this result does not hold under imprinting. The covariance for males is given by

$$\sigma_{\alpha_m} = p^2 \cdot 2p\alpha_m \cdot q(2d_1p - d_1(1 + q)) + pq \cdot (q - p)\alpha_m$$

$$\cdot (d_1(1 - p^2) - d_1q^2) + pq \cdot (q - p)\alpha_m \cdot (d_1(1 - q^2) - d_1p^2)$$

$$+ q^2 \cdot 2p\alpha_m \cdot p(2d_1q - d_1(1 + p)) = p\alpha_m(d_1 - d_1),$$

whereas that for females is similarly shown to be
above components of variance, comparing the expres- additive variance:

We can immediately see that both these covariances are zero in the absence of imprinting. Moreover, since the sum of each genotype’s breeding value and dominance deviation is its genotypic deviation \( G = A + D \), we should have

\[
\sigma_G^2 = \sigma_A^2 + \sigma_D^2 + 2\sigma_{ADm} = \sigma_A^2 + \sigma_D^2 + 2\sigma_{ADM},
\]

which is easily verified.

The male and female correlations between breeding values and dominance deviations are therefore given by, respectively,

\[
\rho_{ADM} = \frac{\sigma_{ADM}}{\sigma_A \sigma_D} = \frac{d_1 - d_2}{\sqrt{2pq(d_1 + d_2)^2 + 2(d_1 - d_2)^2}}
\]

and

\[
\rho_{ADf} = \frac{\sigma_{ADf}}{\sigma_A \sigma_D} = \frac{d_1 - d_2}{\sqrt{2pq(d_1 + d_2)^2 + 2(d_1 - d_2)^2}} = -\rho_{ADM}.
\]

A graph of \( \rho_{ADM} \) as a function of \( d_z \), with other parameter values fixed, is shown in Figure 3. Note that when imprinting causes heterozygotes to be more like homzygotes for the maternally derived allele (i.e., complete or partial paternal inactivation, \( d_z < d_i \)), then \( \rho_{ADM} \) is negative: female additive and dominance deviations are negatively correlated.

**Resemblance between relatives:** We can now calculate various correlations between relatives in terms of the above components of variance, comparing the expressions with the standard, Mendelian formulas. Take, for instance, the covariance between the genotypic values of fathers and their offspring assuming random mating, \( \sigma_{OPm} \). We follow the treatment of Falconer and Mackay (1996) for an unimprinted locus, considering deviations from the population mean. Since the mean genotypic deviation of offspring is, by definition, one-half the breeding value of the father, we want to find the covariance between \( G (= A_m + D) \) and \( \frac{1}{2}A_m \), which, by elementary statistical theory, is \( \frac{1}{2}(\sigma_A^2 + \sigma_{ADm}) \). This result can also be derived from first principles, with the help of Tables 2 and 3, as follows:

\[
\sigma_{OPm} = E[OP_m] - E[O]E[P_m]
\]

\[
= a(ap^2 + dp^2q) + d_1(a^2p^2q + d_1/2pq^2 + d_1/2pq^2) + d_2(a^2p^2q + d_2/2pq^2 + d_2/2pq^2) - a^2p^2q - aq^2 - \mu^2
\]

\[
= \frac{1}{2}(\sigma_A^2 + \sigma_{ADm}).
\]

Hence, the regression coefficient of mean offspring phenotypes plotted against that of their fathers is given by \( \beta_{OPm} = (\sigma_A^2 + \sigma_{ADm})/2\sigma_A^2 \), in which \( \sigma_A^2 = \sigma_D^2 + \sigma_{AD}^2 \) is the (total) phenotypic variance of the population and \( \sigma_D^2 \) is the so-called environmental variance. In deriving this formula, we assume \( \sigma_D^2 \) to be the same for males and females; if it is not, then the regression must be calculated for sons and daughters separately and the latter multiplied by the ratio of the square root of the total variance, \( \sigma_n \), in males to that in females (Falconer and Mackay 1996). If these two adjusted regression coefficients are similar, they can be averaged to give \( \beta_{OPm} \).

Similarly, the covariance between maternal and offspring genotypic values is given by

\[
\sigma_{OPf} = E[OP_f] - E[O]E[P_f]
\]

\[
= \frac{1}{2}(\sigma_{A_m}^2 + \sigma_{ADm})
\]

and the regression of offspring against mothers is

\[\beta_{OPf} = (\sigma_{A_m}^2 + \sigma_{ADm})/2\sigma_{A_m}^2 \text{. Graphs of } \beta_{OPm} \text{ and } \beta_{OPf} \text{ as functions of } d_z \text{ for two different values of } d_i \text{ are shown in Figure 4. Also shown is the standard parent-offspring regression coefficient (i.e., assuming no imprinting), } \beta_{OP}, \text{ which is not the mean of the two imprinting values.}

Interpreting differences between \( \beta_{OPm} \) and \( \beta_{OPf} \) is problematic, however, since if the latter is larger it may be due to a maternal effect rather than imprinting. This problem can be alleviated somewhat if the correlation among half-sibs is also calculated. The covariance of half-sibs can be found by the same logic as above. Remembering that the covariance among offspring who share a mother but not a father is the variance of the genotypic means of those half-sib groups and that these means are one-half the breeding values of the mothers, we have that the covariance is one-quarter the mothers’ additive variance:

\[
\sigma_{HSPf} = \frac{1}{2}\sigma_{A_m}^2.
\]

Hence, the correlation among half-sibs who share a mother is \( \rho_{HSPf} = \sigma_{A_m}^2/4\sigma_{A_m}^2 \). Similarly, the covariance among half-sibs who share a father is \( \sigma_{HSPf} = \frac{1}{2}\sigma_{A_m}^2 \) and the correlation is \( \rho_{HSPm} = \sigma_{A_m}^2/4\sigma_{A_m}^2 \).

This latter value should be unaffected by maternal effects provided mating has been at random (Roff 1997).
and we can use it and the regression of offspring against their fathers to obtain an equation for $\sigma_{\text{adm}}^2$:

$$\sigma_{\text{adm}}^2 = 2(\beta_{\text{opm}} - 2\beta_{\text{pom}})\sigma_1^2.$$  

(18)

If this value (or equivalently, the simpler $\beta_{\text{opm}} - 2\beta_{\text{pom}}$) is not zero, there is evidence of imprinting. Hence, in principle, we can use the standard estimates of regression ($h_{\text{pm}}$) and correlation ($r_{\text{pm}}$) to obtain a test statistic that is nonzero when imprinting occurs:

$$c = h_{\text{pm}}^2 - 2r_{\text{pm}}^2.$$  

(19)

Moreover, provided $-a \leq d_1, d_2 \leq a$, the sign of $c$ is the same as that of $d_1 - d_2$.

**TABLE 3**

<table>
<thead>
<tr>
<th>Father’s genotypic value</th>
<th>Offspring’s genotypic value</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a$</td>
<td>$a$</td>
<td>$p^2(\frac{1}{2}pq + \frac{1}{2}pq + q^2) = p^2$</td>
</tr>
<tr>
<td>$a$</td>
<td>$d_1$</td>
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</tr>
<tr>
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<td>$0$</td>
</tr>
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The significance of the value of $c$ obtained from an experiment can be deduced by considering the sampling distributions of $h_{\text{pm}}$ and $r_{\text{pm}}$. For instance, if $n$ offspring from each of $N$ families are used in assessing the regression of offspring means on their fathers and $\tau$ is the correlation among offspring within families, the variance of $h_{\text{pm}}$ is approximately

$$\sigma_1^2 = \frac{1 + (n - 1)\tau}{nN}.$$  

(20)

(FALCONER and MACKAY 1996). Similarly, the variance of $r_{\text{pm}}$ is given by

$$\sigma_2^2 = \frac{2(1 + (n - 1)r_{\text{pm}})^2(1 - r_{\text{pm}})^2}{n(n - 1)(N - 1)}.$$  

(21)

Hence, the variance of $c$ is, approximately,

$$\sigma_{\text{adm}}^2 = \sigma_1^2 + 4\sigma_2^2 - 4\sigma_b,$$  

(22)

in which $\sigma_b$ is the covariance between $h_{\text{pm}}$ and $r_{\text{pm}}$. An approximate test for significance (i.e., testing the null hypothesis that the true value for $c$ is zero) is thus given by seeing if the interval $c \pm 2\sigma_{\text{adm}}$ includes zero or not.

Unfortunately, although simulations show that values of $c$ are very close to normally distributed, this test probably lacks sufficient power to be useful in many situations. For example, under the null hypothesis of no imprinting ($d_1 = d_2 = d$), the smallest standard errors arose when there was no environmental variance (i.e., $\sigma_1^2 = \sigma_2^2$) and when the two alleles were equally frequent ($p = q = 0.5$). When $d$ was in the range 0.0–0.25, the variances of $c$ values estimated from 100 fathers and two half-sib offspring were $\sim0.03$, which correspond to confidence intervals for $\sigma_{\text{adm}}$ of $\pm0.35$, approximately. For $\sigma_{\text{adm}}$ to be significant, we would require the genotypic means of the reciprocal heterozygotes to be quite
different: $d_1 = -0.5$ and $d_2 = 0.5$ (and hence $\sigma_{A\text{dm}} = -0.375$), for instance. If the environmental variance was not negligible—$\sigma^2_\epsilon = 1$, for example—then the confidence interval increased to the extent that no $\beta$ values were able to be significant for this size data set.

**DISCUSSION**

At a genomically imprinted locus, the maternal and paternal copies are differentially expressed. Hence, the mean phenotypes of reciprocal heterozygotes, identical under the rules of standard Mendelian expression, need no longer be the same. We show that this loss of symmetry destroys much of the simplicity that occurs in the standard single-locus models of quantitative genetics and their well-known measures of genetic variance and resemblances among relatives. Under imprinting, breeding values and additive genetic variances are different for males and females. Although male and female dominance deviations are also different, dominance genetic variances for males and females are identical. Breeding values and dominance deviations are no longer uncorrelated, which means that the genetic variance cannot be partitioned into the usual additive and dominance variances.

Under imprinting, offspring will more closely resemble the parent that does not downregulate expression in the genes it transmits. In the case of Igf-2, for instance, the maternal copy is silenced in a large number of fetal tissues and so offspring phenotypes resulting from Igf-2 expression should be more similar to those of fathers than those of mothers. Sakatani et al.’s (2001) estimate of the mean ratio of maternal to paternal human IGF-2 expression of 0.102 suggests that, if we assume additive contributions from each gene copy, plausible parameter values for the genotypic values in our model are $a = 1$, $d_1 = -0.8$, and $d_2 = 0.8$. If two equally frequent alleles were present and the environmental variance is given by $\sigma^2_\epsilon = 1$, for example, the regression of offspring against their fathers is

$$\beta_{opm} = \frac{\sigma^2_A + \sigma_{A\text{dm}}}{2(\sigma^2_c + \sigma^2_\epsilon)} = \frac{1.62 + (-0.72)}{2(0.82 + 1)} = 0.247. \quad (23)$$

whereas, assuming no maternal effects, the regression of offspring against their mothers is

$$\beta_{opf} = \frac{\sigma^2_A + \sigma_{A\text{dm}}}{2(\sigma^2_c + \sigma^2_\epsilon)} = \frac{0.02 + 0.08}{2(0.82 + 1)} = 0.027, \quad (24)$$

We can contrast these values with various hypothetical nonimprinting examples, again assuming $a = 1$, two equally frequent alleles ($p = q = 0.5$), and an environmental variance, $\sigma^2_\epsilon$, of 1, but enforcing $d_1 = d_2 = d$. When $d = 0$,

$$\beta_{opf} = \frac{\sigma^2_A + \sigma_{A\text{dm}}}{2(\sigma^2_c + \sigma^2_\epsilon)} = \frac{0.5}{2(0.5 + 1)} = 0.167, \quad (25)$$

whereas $d = 0.8$ gives $\beta_{opf} = 0.379$. The former ($d = 0$) example shows that the effect of imprinting that has the same mean genotypic value for heterozygotes is to increase the regression of offspring against the parental sex that does not downregulate the genes it passes on. The latter ($d = 0.8$) example shows, however, that if one sex begins to downregulate those genes, both regressions will decrease.

The derivations above do not apply to X-linked genes, of course. Ironically, however, the situation for sex-linked loci has been the subject of previous work. In marsupials (and eutherian placentas), dosage compensation is effected by condensation of the paternally derived X chromosome (Graves 1996), which amounts functionally to imprinting. In contrast, X-inactivation in placental mammals is random with respect to parental origin in embryonic cell lineages, which causes female eutherians to be mosaics for their active X chromosomes. Such modifications have been incorporated into the standard X-linked models (James 1973; Grossman and Eisen 1989; Lynch and Walsh 1998). There are no obvious parallels between these models and those described above, however. Covariances between the breeding values and dominance deviations do not disappear in the autosomal imprinting model; even with com-
plicate paternal inactivation (\(d_1 = a\) and \(d_2 = -a\)), for
instance, \(\sigma_{\text{ADm}} = -4a^2 pq\) (although \(\sigma_{\text{ADm}} = 0\)). In sex-linked models, however, these covariances are always zero.

In principle, the nonzero correlation between breeding values and dominance deviations under imprinting may be used to test if imprinted loci are influencing a trait of interest. Continuing our numerical example above, the correlation among half-sibs sharing a father is

\[
\rho_{\text{HSM}} = \frac{\sigma_{\text{HSM}}^2}{4(\sigma_1^2 + \sigma_2^2)} = \frac{1.62}{4(0.82 + 1.00)} = 0.223, \quad (26)
\]

and we can recover the value of \(\sigma_{\text{ADm}}\) (−0.72) from Equation 18:

\[
\sigma_{\text{ADm}} = 2(\beta_{\text{OPm}} - 2\rho_{\text{HSM}})\sigma_1^2 = 2(0.247 - 2 \cdot 0.223)\sigma_1^2 = -0.724. \quad (27)
\]

Unfortunately, the large standard error of this estimate of \(\sigma_{\text{ADm}}\) limits its use as a practical statistical test for the presence of imprinting. Only in cases with large data sets and large differences in the genotypic values of the reciprocal heterozygotes will a 95% confidence interval exclude zero, the value under the null hypothesis of standard expression. Again using the illustrative numbers above, 1000 simulations showed that, when obtaining both the regression and correlation estimates from families of two half-sibs of 100 fathers, 95% of the estimates of \(\sigma_{\text{ADm}}\) fell in the range from −2.136 to 0.625. Using 500 families sufficiently reduced this interval to (−1.378, −0.156).

Of course, the model developed above is extremely simple in many ways. Most importantly, (i) it is concerned with a single locus only and so can ignore the complicating effects of epistasis; (ii) it assumes that there is no genotype by environment (\(G \times E\)) interaction; and (iii) it avoids dealing with maternal effects. All of these aspects limit the direct applicability of the model. The extension to several additive loci is presumably straightforward, however; see Hill and Keightley (1988) for a model of multiple, additive loci in which imprinting causes complete inactivation of one copy of each gene at the imprinted loci, e.g., \(d_1 = -a\) and \(d_2 = a\).

The importance of these limitations becomes apparent when we recall that many imprinted loci have effects on fetal growth (Bartolomei and Tilghman 1997) and this suite of phenotypes is clearly influenced by genes at several loci and maternal effects, not to mention probable \(G \times E\) interactions. Nevertheless, incorporating the full range of features found in quantitative genetic models is not the objective of this article; rather, we aim to show how genomic imprinting requires the rederivation of even the simplest concepts in quantitative genetics. We suggest that such considerations will need to be built into more complex models of specific interest (e.g., those concerned with mammalian birthweight).

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**LITERATURE CITED**


