An Alternative Model for Additive and Cytoplasmic Genetic and Maternal Effects on Lactation

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ABSTRACT

Results from a recent study that presented evidence suggesting a lack of cytoplasmic inheritance of lactation traits were reexamined using a model that included effects of additive genotype, cytoplasmic genotype, their interaction, and maternal influences. Under this model, equivalent estimates of heritability from daughter-dam and granddaughter-granddam regression that exceed those from paternal half-sib correlation were consistent with the presence of cytoplasmic inheritance. A definitive answer to the question of cytoplasmic inheritance of lactation traits awaits a designed experiment, likely employing transfer of identical nuclei into varying cytoplasmic backgrounds.

INTRODUCTION

The mitochondrial genome of the bovine encodes sequences for two ribosomal ribonucleic acids, 22 transfer ribonucleic acids, and approximately 13 protein-encoding structural genes whose products play an important role in cell metabolism (1). Although the mitochondrial genome is not completely characterized, one structural gene is known to code for cytochrome b, and others code subunits of cytochrome oxidase and ATP synthase (1, 7). Since these enzymes are involved in milk synthesis, the proportion of variation in lactational traits accounted for by these genes has been a debated topic. Estimates of heritability of milk yield from daughter-dam (D.D) regression have generally exceeded those from paternal half-sib (PHS) correlation (5, 13, 15). Bell et al. (4) presented evidence that suggested this difference may be due in part to inheritance of cytoplasmic factors, as such factors would be strictly maternally inherited. Differences between maternal lines accounted for 2.0, 1.8, 1.8, and 3.5% of the variation in milk yield, milk fat yield, FCM yield, and milk fat percent in a study by Bell et al. (4) and 5.6, 4.8, 6.2, 10.1, and 12.5% of the variation in milk yield, fat percent, protein percent, fat plus protein, and milk returns in the study by Huizinga et al. (8). In both cases the authors attributed the variation to cytoplasmic genes, although Huizinga et al. (8) conceded the possibility of a contribution from other noncytoplasmic maternal effects. However, Kennedy (9) has conducted simulation studies that indicated that differences between female lines detected by the models used by Bell et al. (4) may have been the result of genetic drift rather than mitochondrial genes. Most recently, Reed and Van Vleck (11) suggested that field data indicated a lack of evidence of cytoplasmic inheritance. Under their model of inheritance, granddaughter-granddam regression (GD.GD) was expected to give higher estimates of heritability relative to D.D. regression because of the greater contribution of cytoplasmic inheritance to the estimate. Their results indicated no difference between these estimates of heritability, as did an earlier study by Van Vleck and Bradford (14). Consequently, they concluded that contribution of cytoplasmic genes to total variation in lactation traits was insignificant. A genetic model is proposed herein which can explain the discrepancy between PHS and D.D. estimates of heritability yet countenance both similar estimates of heritability from D.D and GD.GD regression and the existence of heritable cytoplasmic effects on lactation traits, a conclusion different from that reached by Reed and Van Vleck (11).

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MATERIALS AND METHODS

The path diagram in Figure 1 constitutes the model. It can also be described by the following linear model:

$$P = h_N A + h_C C + iI + mP' + eE \quad [1]$$

where:

- P = phenotype of an individual,
- h_N = correlation of phenotype and additive nuclear genotype in constant cytoplasmic genetic background,
- A = additive genotype attributable to nuclear genes,
- h_C = correlation of phenotype and cytoplasmic genotype in constant additive nuclear genetic background,
- C = cytoplasmic genotype,
- i = correlation of the joint interaction of additive and cytoplasmic genotypes with phenotype,
- I = joint interaction of additive nuclear and cytoplasmic genotypes,
- P′ = dam's phenotype,
- m = coefficient for influence of dam's phenotype on daughter's phenotype,
- E = random environmental effects (assumed independent and identically distributed), and
- e = coefficient for influence of random environmental effects.

However, I can be partitioned similarly:

$$I = nA + cC + sS \quad [2]$$

where:

- n = correlation of average contribution of additive nuclear genotype to interaction in varying cytoplasmic genetic background,
- c = correlation of average contribution of cytoplasmic genotype to interaction in varying additive nuclear genetic background,
- S = residual specific interaction in addition to and independent from paths labeled n and c, and
- s = correlation of residual specific interactions and total interaction.

The partitioning of I into a general interactive additive effect, general interactive cytoplasmic effect, and specific interactive effect is analogous to the partitioning of heterosis into general and specific combining abilities. After substituting for I:

$$P = (h_N + ni)A + (h_C + ci)C + sS + mP' + eE \quad [3]$$

The terms A, C, S, P′, and E are considered as standardized variables; as such, they are devia-

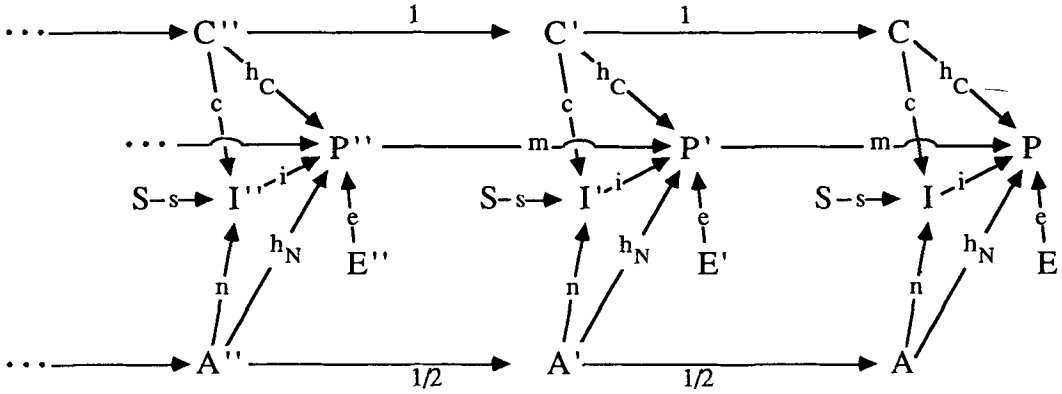

Figure 1. Path diagram illustrating the influence of cytoplasmic genotype (C), additive genotype (A), interaction of cytoplasmic and additive genes (I), interaction effects specific to unique combinations of additive and cytoplasmic genes (S), ancestors' phenotypes (P′, P″, . . .), and random environmental effects (E) on an individual's phenotype (P). Primes indicate ancestral factors, and lower case letters are path coefficients relating the various factors.

tions from mean values divided by their associated standard deviations. Thus, they have means of 0 and variances of 1. The model expressed by [1] is similar to one proposed by Falconer (6) to describe the association of litter size of dam and daughter in mice, with the addition of cytoplasmic inheritance. The coefficient m represents both maternal genetic and maternal environmental effects. Examples of such effects would be the influence of dam's performance on daughter's development in utero, e.g., genetic or environmental influences on dam's nutrition in turn might positively affect both dam's lactational performance and daughter's prenatal development and subsequent lactational performance, or the influence of a manager's expectation for the offspring's performance based on dam's performance. Falconer's model (6) is extended to include effects of cytoplasmic genes, which are assumed to be strictly maternally inherited. Because cytoplasmic genes would be expected to be passed intact from one female generation to the next, the path coefficient for this path is unity in the absence of mutation. The term $(h_N + ni)$ is the square root of narrow-sense heritability as estimated by paternal half-sib correlation. The usual additive effect on phenotype has been partitioned into an independent effect of nuclear genes and an average interaction of those genes with cytoplasmic genes. Cytoplasmic effects are similarly partitioned.

Covariances between random environmental effects (E) and other parameters in the model are assumed to be zero. Similarly, covariance between residual specific interaction (S) and other terms is zero. Covariance between additive and cytoplasmic genetic effects is zero, the relationship between these being described by the interaction term, I, in the path diagram. All other covariances are permitted. Correlations between relatives can be determined from the linear model (Appendix) or by tracing the appropriate paths of the diagram (Figure 1) using Wright's method (16) with the following results for dam and daughter (P.P′) and granddam and granddaughter (P.P″):

$$r_{P.P'} = (h_N + ni)^2 \left(\frac{1}{2 - m}\right) + (h_C + ci)^2 \left(\frac{1}{1 - m}\right) + m \qquad [4]$$

$$r_{P.P''} = (h_N + ni)^2 \left(\frac{1 + 2m}{2(2 - m)}\right) + (h_C + ci)^2 \left(\frac{1 + m}{1 - m}\right) + m^2 \qquad [5]$$

Correlation between PHS is not influenced by maternal effects and is $\frac{1}{4}(h_N + ni)^2$. Correlation and regression are equivalent when path analysis with standardized variables is considered. Conversion of daughter-dam correlation to D.D. could be accomplished by multiplying the correlation by the ration $\sigma_p/\sigma_{p'}$, where both phenotypic standard deviations are expressed on the original scale (10). Regressions of D.D and GD.GD are multiplied by 2 and 4, respectively, to arrive at estimates of heritability.

Hypothetical values for $(h_N + ni)^2$, $(h_C + ci)^2$, and m were substituted into equations [4] and [5] to examine the effects of maternal and cytoplasmic factors on D.D and GD.GD regression estimates of heritability. Narrow-sense heritability, $(h_N + ni)^2$, of milk yield was assumed to be .25 on the basis of PHS correlation estimates (5, 14, 15). Values of .02, .04, and .08 were considered for cytoplasmic heritability, $(h_C + ci)^2$, covering most of the range reported by Bell et al. (4) and Huizinga et al. (8). The maternal effect coefficient, m, was assigned values of 0, .02, .04, and .08.

RESULTS AND DISCUSSION

The influence of various maternal and cytoplasmic effects on heritability estimates is shown in Table 1. These hypothetical results are intended to be illustrative, not exhaustive. In the absence of maternal effects, GD.GD regression estimates of heritability would exceed those from D.D regression. However, appropriate combinations of maternal and cytoplasmic effects would result in comparable estimates of heritability from GD.GD and D.D. regression that exceed those from PHS correlation. Exact solutions of this nature can be determined by setting equation [4] equal to two times equation [5], substituting values for $(h_N + ni)^2$ and $(h_C + ci)^2$ or $(h_N + ni)^2$ and m, and solving for the third variable. Such a relationship has been observed on several occasions. Van Vleck and Bradford (14) reported estimates of heritability for milk yield of .448, .444, and .23 from D.D. and GD.GD regression and PHS correlation.

TABLE 1. Heritability estimates for various cytoplasmic and maternal effects.[1]

		Cytoplasmic heritability, $(h_C + ci)^2$					
		.02		.04		.08	
	PHS	D.D	GD GD	D.D	GD.GD	D.D	GD.GD
m = 0	.25	.29	.33	.33	.41	.41	.57
m = .02	.25	.33	.35	.37	.43	.46	.60
m = .04	.25	.38	.37	.42	.45	.50	.63
m = .08	.25	.46	.42	.51	.52	.59	.70

[1]Actual heritability, $(h_N + ni)^2$, assumed to be .25. D.D and GD.GD denote heritability estimates from daughter-dam and granddaughter-granddam regression.

Reed and Van Vleck (11) examined a larger data set and found estimates from D.D. and GD.GD regressions of .35 and .34 for milk yield. Reed and Van Vleck's (11) conclusion of no influence of cytoplasmic genes on lactation traits was correct assuming no maternal influence on lactation. As the model outlined demonstrates, an alternative to Reed and Van Vleck's (11) conclusion of a lack of evidence for cytoplasmic inheritance is that the various observations are all consistent with the presence of a positive maternal effect, cytoplasmic inheritance, and additive nuclear genetic effects.

The model used here, based on that formulated by Falconer (6), is simplistic yet provides an adequate illustration of the possible influence of noncytoplasmic maternal and cytoplasmic maternal effects. This model is unnecessarily restrictive; maternal genetic and maternal environmental effects on offspring are constrained to the same proportion as influenced the phenotype of the dam, and maternal genetic effects are limited to pleiotropic effects of genes, which influence lactation in the dam directly and subsequent lactation in the daughter indirectly. A more complicated model, such as that proposed by Riska et al. (12), which incorporated separate maternal genetic and persistent environmental effects, could have been used to account more adequately for sources of variation. However, Occam's Razor, the principle that assumptions introduced to explain a thing must not be multiplied beyond necessity, applies in this case. Use of the Riska et al. (12) model would have unnecessarily complicated the illustration without changing the results, since maternal genetic effects would have contributed equally to heritability estimates from D.D and GD.GD regression. In addition, the model used here differs in parameterization of the additive and interaction effects from that of Beavis et al. (3). The current model is more flexible, since interaction involves four separate terms (n, c, i, s), which can take either positive or negative values. Because the exact biological nature of the nuclear-cytoplasmic interaction has yet to be determined, neither mathematical model can be proved correct.

Resolution of the debate over the influence of cytoplasmic genes on lactational traits will not come from further examination of field data. Data presented by Reed and Van Vleck (11) can not be used to support conclusively or reject the existence of cytoplasmic effects on lactational traits. A more definitive answer will come from experiments involving nuclear transfer into embryonic cells of purported cytoplasmic diversity. Given recent technological developments (2), the impact of cytoplasmic inheritance may soon be resolved.

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APPENDIX

Derivation of Correlation Between Phenotype of Dam and Daughter

Because both phenotypes are expressed as standardized variables, the covariance will be equivalent to the correlation. Covariance between additive (A) and cytoplasmic (C) genotype is zero. Likewise, covariances of environmental effects (E) or specific A × C interaction effects (S) with other terms are zero.

$$\begin{aligned}\text{Cov}\,(P,P') &= \text{Cov}\,\{[(h_N + ni)A + (h_C + ci)C + sS + mP' + eE],\\ &\qquad [(h_N + ni)A' + (h_C + ci)C' + sS' + mP'' + eE']\}\end{aligned}$$

$$\begin{aligned}&= \text{Cov}\,\{(h_N + ni)A, (h_N + ni)A'\} + \text{Cov}\,\{(h_N + ni)A, mP''\}\\ &\quad + \text{Cov}\,\{(h_C + ci)C, (h_C + ci)C'\} + \text{Cov}\,\{(h_C + ci)C, mP''\}\\ &\quad + \text{Cov}\,\{mP', P'\}.\end{aligned}$$

The covariances between A and mP'' and between C and mP'' expand into infinite series:

$$\begin{aligned}\text{Cov}\,\{(h_N + ni)A, mP''\} &= m\,\text{Cov}\,\{(h_N + ni)A, (h_N + ni)A''\}\\ &\quad + m\,\text{Cov}\,\{(h_N + ni)A, mP'''\}\end{aligned}$$

$$\begin{aligned}&= m\,\text{Cov}\,\{(h_N + ni)A, (h_N + ni)A''\}\\ &\quad + m^2\,\text{Cov}\,\{(h_N + ni)A, (h_N + ni)A'''\}\\ &\quad + m^3\,\text{Cov}\,\{(h_N + ni)A, (h_N + ni)A''''\}\\ &\quad + \ldots\end{aligned}$$

$$\begin{aligned}\text{Cov}\,\{(h_C + ci)C, mP''\} &= m\,\text{Cov}\,\{(h_C + ci)C, (h_C + ci)C''\}\\ &\quad + m\,\text{Cov}\,\{(h_C + ci)C, mP'''\}\end{aligned}$$

$$\begin{aligned}&= m\,\text{Cov}\,\{(h_C + ci)C, (h_C + ci)C''\}\\ &\quad + m^2\,\text{Cov}\,\{(h_C + ci)C, (h_C + ci)C'''\}\\ &\quad + m^3\,\text{Cov}\,\{(h_C + ci)C, (h_C + ci)C''''\}\\ &\quad + \ldots\end{aligned}$$

Covariance between A and A' is 1/2, covariance between A and A'' is 1/4, etc. The covariance between C and other C terms, regardless how far removed, is 1. Covariance between P' and P' is 1. Thus, the covariance (correlation) between daughter and dam can be described as follows;

$$\text{Cov}(P,P') = \frac{1}{2}(h_N + ni)^2 \sum_{n=0}^{\infty}(m/2)^n + (h_C + ci)^2 \sum_{n=0}^{\infty}(m)^n + m$$

A geometric series of the form $\sum_{n=0}^{\infty} r^n$ converges if $|r| < 1$ and equals $\frac{1}{1-r}$.

Therefore, $\text{Cov}(P,P') = (h_N + ni)^2 \frac{1}{2-m} + (h_C + ci)^2 \frac{1}{1-m} + m$

Derivation of Correlation Between Daughter and Granddam Using the Linear Model

$$\begin{aligned}\text{Cov}(P,P'') = \text{Cov}\ &\{[(h_N + ni)A + (h_C + ci)C + sS + mP' + eE],\\ &[(h_N + ni)A'' + (h_C + ci)C'' + sS'' + mP''' + eE'']\}\end{aligned}$$

$$\begin{aligned}= \text{Cov}\ &\{(h_N + ni)A, (h_N + ni)A''\} + \text{Cov}\ \{(h_N + ni)A, mP'''\}\\ &+ \text{Cov}\ \{(h_C + ci)C, (h_C + ci)C''\} + \text{Cov}\ \{(h_C + ci)C, mP'''\}\\ &+ \text{Cov}\ \{mP', P''\}.\end{aligned}$$

$$\begin{aligned}= (h_N + ni)^2 &[\text{Cov}(A, A'') + m\ \text{Cov}(A, A''')\\ &+ m^2\ \text{Cov}(A, A'''') + m^3\ \text{Cov}(A, A''''') + \ldots]\\ &+ (h_C + ci)^2 [\text{Cov}(C, C'') + m\ \text{Cov}(C, C''')\\ &+ m^2\ \text{Cov}(C, C'''') + m^3\ \text{Cov}(C, C''''') + \ldots]\\ &+ m\ \text{Cov}(P', P'').\end{aligned}$$

Cov (P', P'') was determined in the first part of this appendix. After substituting this in and expressing terms in A and C as infinite series, the result is:

$$\begin{aligned}\text{Cov}(P,P'') = &\frac{1}{4}(h_N + ni)^2 \sum_{n=0}^{\infty}(m/2)^n + (h_C + ci)^2 \sum_{n=0}^{\infty}(m)^n\\ &+ m\left[(h_N + ni)^2 \frac{1}{2-m} + (h_C + ci)^2 \frac{1}{1-m} + m\right]\\ = &\frac{(h_N + ni)^2}{2(2-m)} + \frac{2m(h_N + ni)^2}{2(2-m)} + \frac{(h_C + ci)^2}{(1-m)} + \frac{m(h_C + ci)^2}{(1-m)} + m^2\\ = &(h_N + ni)^2 \frac{1+2m}{2(2-m)} + (h_C + ci)^2 \frac{1+m}{1-m} + m^2.\end{aligned}$$