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Gametic imprinting effects on rate and composition of pig growth

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Abstract Genetic improvement schemes in livestock are based on the assumption that the expression of relevant genes is independent of parent of origin. Until now no evidence has been found to reject this assumption. The present study on three purebred pig populations, however, shows that a significant proportion of the phenotypic variance in backfat thickness (5–7%) can be explained by genes subject to paternal imprinting. The implication is that there are genes affecting backfat that are expressed only when derived from the paternal gamete. Paternal imprinted effects explained 1–4% of the phenotypic variation for growth rate. Maternal imprinted effects were heavily confounded with heritable maternal environmental effects. When modelled separately, these effects explained 2–5% and 3–4% of the phenotypic variance in backfat thickness and growth rate, respectively. Gametic imprinting may have consequences for the optimization of breeding programmes, especially in crossbreeding systems with specialized sire and dam lines.

Key words Variance components · Gametic imprinting Growth · Pigs

Introduction

For estimation of breeding values of candidates for selection and prediction of genetic trend in livestock improvement programmes, genes are generally assumed to be expressed independent of parental origin, i.e. it is irrelevant whether genes are transmitted via the paternal or the maternal gamete. When cytoplasmatic effects and relevant genes on the sex chromosomes are disregarded, the genetic effect for an animal can be written as the average parental genetic effect, together with a term to account for Mendelian sampling (Falconer 1989).

Experiments in mice with pronuclear transplantation failed to create progeny from parents of the same sex (reviewed by Surani et al. 1984), suggesting that the assumption of equal parental contribution might not always hold. Evidence for unequal parental contribution has come recently from crossbreeding studies with transgenic mice (Reik et al. 1987; Sapienza et al. 1987; Barlow et al. 1991; DeChiara et al. 1991) in which it was found that the expression of a gene can be blocked by methylation and that the degree of methylation can depend on the origin of the gene. This phenomenon is referred to as genomic or gametic "imprinting". Until now, research on gametic imprinting has been restricted to experiments with transgenic laboratory animals and studies on genetic diseases in humans (reviews by Reik 1989 and Hall 1990). No proof is available on the relevance of effects of gametic imprinting on quantitative traits in livestock improvement schemes.

The aim of the study presented here is to quantify gametic imprinting effects in pig breeding populations. For this purpose, data from one Dutch and two Australian purebred populations were analysed with statistical models including paternal or maternal imprinted genetic effects. Attention was also given to heritable maternal environmental effects because of the expected confounding between these effects and maternal imprinted effects.

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Material and methods

Data

One data set consisted of records on Yorkshire animals of a Dutch breeding company; the other two were derived from a Large White

and a Landrace population at a private breeding enterprise in Australia. The Dutch data set will be referred to as DY (Dutch Yorkshire); the Australian data sets will be referred to as LW (Large White) and LR (Landrace). Traits analysed were average lifetime daily gain (ADG) and ultrasonically measured backfat thickness (BF). The animals were evaluated at approximately 23 (LW and LR) or 26 weeks of age (DY).

Data on DY performance were collected from 1983 to 1991; data on LW and LR were recorded from 1982 to 1992. All data were checked for extreme values (greater than 3 standard deviations from the mean), but no data had to be excluded. The structures of the data sets are given in Table 1.

Statistical analysis

The following general mixed model was used for analysing the two traits:

$$y = Xb + Za + Lm + Qc + e$$

where

- y: vector of observations
- b: vector of fixed effects
- a: vector of random additive genetic animal effects
- m: vector of random parental effects
- c: vector of random effects of common litter environment
- e: vector of random residual effects
- X: incidence matrix for fixed effects
- Z: incidence matrix for additive genetic animal effects
- L: incidence matrix for parental effects
- Q: incidence matrix for common litter effects

Common litter environment (c) refers to the component that creates extra covariance between full sibs (litter mates) as a result of simultaneously sharing the same environment (mother and pen) at a young age. Fixed effects in the model were contemporary group and sex. Contemporary groups were defined as 2-month periods within each year, and assignment to these groups was based on date of birth. For BF, final test weight was added to the model as a covariate.

As a reference, the data sets were first analysed without the parental effect (m) in the above mixed model. Thereafter, three alternative analyses were performed, which included for the parental effect: (1) paternal gametic imprinted effect, (2) maternal gametic imprinted effect or (3) heritable maternal environmental effect. It was assumed that the paternal environmental effects could not play a role because the sires were only involved at mating. The heritable maternal environmental effect represents uterine environment and nursing ability as provided by the dam.

The analyses required inverses of variance-covariance matrices of the random effects. For additive genetic effects, this required the inverse of the numerator relationship matrix (A), constructed following the rules of Henderson (1976). For common litter environment and for the residual effect, no covariances were assumed between different levels of the effects.

To fit a heritable maternal effect, the inverse of the numerator relationship matrix (A) could again be used. The modelling of the variance-covariance structure for gametic imprinting was more complicated. The inverse of a matrix (A*) had to be derived including 'real' animals as well as their maternal or paternal-derived gametes. The rules for building this matrix are provided by Tier and Sölkner (1993) who treated gametes as homozygous diploid animals, thus allowing for their inclusion in the relationship matrix.

Univariate REML estimates of the parameters were obtained using the DFREML programmes of Meyer (1989). These programmes employ derivative-free algorithms (Graser et al. 1987) to avoid inversion of the coefficient matrix of the mixed model equations. The Simplex method (Nelder and Mead 1965) was used to locate the maximum of the log-likelihood (L). The variance of the function values, $-2\Delta \log (L)$, in the Simplex of less than 10^{-8} was taken as the convergence criterion. Standard errors of the estimated variance components were approximated by fitting a quadratic function to the likelihood surface (Meyer 1989).

A likelihood ratio test (Kendall and Stuart 1973) was performed for each of the parental effects. The test criterion used was the difference in maximized function values in the Simplex $[-2\Delta \log (L)]$ between a model with and without the parental effect, representing twice the reduction in log-likelihood. This statistic was assumed to have a chi-square distribution with one degree of freedom.

Table 1 Data size and structure for the three populations

	Population		
	DY	LW	LR
Numbers			
Records	10 454	13 672	13 265
Litters	2 139	2 979	2 765
Dams	1 302	684	745
Sires	381	202	208
Dam-offspring record pairs	1 001	484	546
Sire-offspring record pairs	270	126	151
Contemporary groups	52	57	57
Sex ratio for males/females with records	47/53	51/49	50/50

Table 2 Proportion of total variance explained (R^2 in%) by fixed effects (contemporary group and sex) and covariate, relative parts (%) of phenotypic variance estimated to be due to additive genetic effects (h^2) and common litter environmental effects (c^2), together with the estimated phenotypic standard deviation (σ_p) in a model without parental effects

Trait/Population		R^2	h^2	(SE)	c^2	(SE)	σ_p
ADG/	DY	21.1	19.2	(2.9)	23.3	(1.3)	53.7
	LW	42.2	20.7	(2.1)	16.7	(1.0)	53.0
	LR	39.8	23.8	(2.6)	16.6	(1.1)	53.1
BF/	DY	46.3	43.5	(3.2)	15.9	(1.1)	1.68
	LW	29.4	44.8	(2.9)	6.9	(0.7)	2.08
	LR	33.3	52.5	(2.8)	6.0	(0.7)	2.01

Results

Exclusion of the parental effect

Table 2 gives estimates of sources of variance in the model that did not include the parental effect. The R^2 values show that a large proportion of the total variation in average daily gain (ADG) and backfat thickness (BF) was explained by the fixed effects and/or the covariate (final test weight when analysing BF). The high R^2 for ADG in the two Australian populations (LW and LR) was primarily due to contemporary group effects (large seasonal influence). The high R^2 for BF in the DY population resulted mainly from the regression on final test weight, which accounted for 41% of the total variance in DY but only for 13% and 9% in LW and LR, respectively.

Heritablity estimates were approximately 20% and 45% for ADG and BF, respectively. The LR population had higher estimated genetic variation than DY and LW, but the differences in estimated heritabilities were relatively small. Less consistent were estimates for common litter environmental variance (c^2). In the DY population, this component was high for both ADG and BF. These high values

Table 3 Proportion (%) of total variance explained (R^2) by fixed effects (contemporary group and sex) and covariate, relative parts (%) of phenotypic variance estimated to be due to additive genetic effects (h^2), common litter environmental effects (c^2) and paternal gametic imprinted effects (m^2), together with twice the reduction in log-likelihood (-2Δ log L) due to including m^2 in the model and its associated probability (P) based on a chi-square distribution

Trait/Population		R^2	h^2	(SE)	c^2	(SE)	m^2	(SE)	-2Δ log L	P
ADG/	DY	21.1	17.4	(3.0)	23.0	(1.3)	1.3	(1.0)	2.0	>0.05
	LW	41.4	17.4	(2.1)	15.6	(1.0)	3.7	(1.1)	32.2	<0.001
	LR	39.0	18.8	(2.6)	15.8	(1.0)	4.2	(1.3)	23.5	<0.001
BF/	DY	45.4	36.5	(3.3)	14.0	(1.1)	6.6	(1.7)	29.7	<0.001
	LW	28.4	36.5	(3.1)	6.4	(0.7)	5.5	(1.6)	33.4	<0.001
	LR	32.5	44.0	(3.2)	5.5	(0.6)	5.7	(1.6)	35.2	<0.001

Table 4 Proportion (%) of total variance explained (R^2) by fixed effects (contemporary group and sex) and covariate, relative parts (%) of phenotypic variance estimated to be due to additive genetic effects (h^2), common litter environmental effects (c^2) and maternal gametic imprinted effects (m^2), together with twice the reduction in log-likelihood (-2Δ log L) due to including m^2 in the model and its associated probability (P) based on a chi-square distribution

Trait/Population		R^2	h^2	(SE.)	c^2	(SE)	m^2	(SE)	-2Δ log L	P
ADG/	DY	21.2	15.0	(2.8)	21.6	(1.4)	3.7	(1.5)	9.3	<0.01
	LW	42.6	14.0	(2.0)	15.1	(1.0)	4.3	(0.9)	44.8	<0.001
	LR	40.0	19.0	(2.6)	15.5	(1.0)	3.3	(1.1)	16.0	<0.001
BF/	DY	46.5	38.0	(3.3)	14.1	(1.1)	4.5	(1.5)	15.6	<0.001
	LW	29.8	40.5	(3.1)	6.5	(0.7)	2.1	(0.9)	12.4	<0.001
	LR	33.5	49.2	(3.0)	5.6	(0.7)	1.9	(0.9)	7.9	<0.01

might be explained by the testing procedure in this population, with most litter mates being penned together both before and after weaning.

Paternal gametic imprinting

In the present study paternal or maternal gametic imprinted effects were defined as the effects of genes expressed only when received from the paternal or maternal gamete, respectively. This means that imprinting is defined here as a positive phenomenon with respect to the expression of the genes involved.

Estimates of variance components in the model including the variance due to paternal gametic imprinting (m^2) are given in Table 3, which also gives test statistics for m^2 based on the likelihood ratio test. The paternal component was significant in two of the three populations for ADG. The estimates ranged between 1.3% and 4.2%. For BF, estimates were larger and more consistent (5.5–6.6%). For all three populations, m^2 for BF significantly deviated from zero ($P<0.001$). Comparison of Table 3 with Table 2 shows that inclusion of m^2 reduced estimates of h^2. Estimates for c^2 were only slightly decreased, whereas R^2 values were barely affected.

Maternal gametic imprinting

Results for the model including maternal gametic imprinted effects are presented in Table 4. The estimates of m^2 ranged between 1.9% and 4.5% and were significantly different from zero ($P<0.01$). Inclusion of m^2 considerably reduced h^2 estimates (Table 4 vs. Table 2), and also reduced estimates for c^2. In comparison to the additive genetic variance, the variances of maternal imprinted effects were high for ADG, but low for BF.

Maternal effects

Results from fitting heritable maternal effects (Table 5) closely followed those from fitting maternal imprinted effects (Table 4). This pattern is not surprising since both of these components contribute to covariance between maternal half-sibs.

The contributions of the variance components to the expected covariances between relatives are given in Table 6 and were derived from Falconer (1989) and Schaeffer et al. (1989). The last two columns demonstrate the strong confounding between maternal gametic imprinting and heritable maternal effects. The only difference is the coefficient for maternal half-sibs and full sibs, which is 1/2 for imprinting and 1 for maternal effects. This is due to Mendelian sampling of the imprinted genes during production of the gametes.

A comparison of Tables 4 and 5 shows that inclusion of heritable maternal effects instead of maternal imprinting affected the estimates of h^2 and c^2. Overall, c^2 was slightly lower, whereas h^2 was slightly higher. The reduced c^2 can be explained by the increased contribution of m^2 to the resemblance between full sibs (Table 6).

Table 5 Proportion (%) of total variance explained (R^2) by fixed effects (contemporary group and sex) and covariate, relative parts (%) of phenotypic variance estimated to be due to additive genetic effects (h^2), common litter environmental effects (c^2) and heritable maternal effects (m^2), together with twice the reduction in log-likelihood (-2Δ log L) due to including m^2 in the model and its associated probability (P) based on a chi-square distribution

Trait/Population		R^2	h^2	(SE)	c^2	(SE)	m^2	(SE)	-2Δ log L	P
ADG/	DY	21.2	16.1	(3.0)	21.2	(1.5)	3.6	(1.4)	9.6	<0.01
	LW	42.4	14.6	(2.1)	14.7	(1.9)	4.8	(1.0)	52.0	<0.001
	LR	39.7	19.7	(2.6)	15.2	(1.1)	3.5	(1.0)	19.3	<0.001
BF/	DY	46.1	40.4	(3.5)	13.5	(1.2)	4.3	(1.3)	17.6	<0.001
	LW	29.4	42.1	(3.2)	6.5	(0.7)	1.6	(0.7)	9.9	<0.01
	LR	33.3	50.7	(3.0)	5.6	(0.7)	1.5	(0.7)	6.6	<0.05

Table 6 Contributions of variance components to expected covariances between relatives (V_a additive genetic effect, V_c common litter environment, $V_{g,p}$ paternal imprinted gametic effect, $V_{g,m}$ maternal imprinted gametic effect, V_{hm} heritable maternal effect)

	Coefficients for contributions of variance components				
Relationship	V_a	V_c	$V_{g,p}$	$V_{g,m}$	V_{hm}
Paternal half sibs	1/4	0	1/2	0	0
Maternal half sibs	1/4	0	0	1/2	1
Full sibs	1/2	1	1/2	1/2	1
Sire-offspring	1/2	0	1/2	0	0
Dam-offspring	1/2	0	0	1/2	1/2

Discussion

Method

The Simplex method was used to locate the maximum of the likelihood surface. Meyer (1989) considers this approach robust when maximizing the likelihood with respect to several parameters. A pilot study using a few small simulated populations showed the estimation procedure to perform well, without local maxima problems.

An important assumption for the likelihood ratio test is that the test criterion, $-2\Delta \log L$, is distributed as chi-square. This assumption relies on a large sample theory (Kendall and Stuart 1973). Meyer and Hill (1992) studied confidence intervals of estimated parameters in simulated populations (3200 animals) and found a good agreement between observed and expected confidence intervals. The populations in this study are much larger, so the use of large sample theory is probably valid here.

Imprinted effects were fitted with the approach of Tier and Sölkner (1993). As a result, imprinted variance (V_i) was defined at the individual rather than the gametic level (V_g). Tier and Sölkner compared their method with the gametic level approach of Schaeffer et al. (1989). They demonstrated equivalence, but showed that $V_i = 0.5V_g$, because the breeding value (for imprinted gene effects) of an individual is defined as the average value of its paternal and maternal gametes. For the present study, this implies that under the gametic level approach, m^2 values (together with their SEs) in Tables 3 and 4 would be doubled.

Unfortunately, more than four random effects (including the residual) could not be simultaneously fitted. The best fit should be achieved with a model that includes paternal and maternal imprinted effects. From Table 6, the sum of the paternal and maternal imprinted gametic variances ($V_{g,p}+V_{g,m}$) appears difficult to separate from additive genetic variance. However, the use of parent-offspring covariances as well as of the covariance structures within grandparent families (differences between paternal and maternal grandparental effects) should make it possible to disentangle the variance components.

A simultaneous fit of maternal imprinting and heritable maternal effects would also have been informative. However, these two effects are strongly confounded (Table 6) and would be difficult to disentangle. Further problems with confounding would arise if maternal-direct genetic covariance would also be included in the model. The difficulty of confounding also holds for dominance and common litter environment because dominance variance contributes to the covariance among litter mates (full sibs).

The additive genetic and gametic imprinted effects were assumed to be controlled by many unlinked genes, each of a small effect (infinitesimal model). Hence, the genetic effects were considered to be normally distributed. It will be interesting to test these (or comparable) data sets for the existence of a major gene and to examine the likelihood of such a gene being subject to gametic imprinting.

With respect to paternal effects, paternal environment is expected to be negligible since sires were involved only at mating. Thus, the estimated paternal effect in Table 3 was labelled as a gametic imprinting effect. However, whether or not all other possible sources of variance can be ruled out is not clear. Wilken et al. (1992) in a reciprocal crossbreeding study using embryo transfer found a breed of sire effects to be significant for backfat thickness and longissimus muscle area. This is in agreement with the significant paternal effect found in the present study. However, these authors speculated that these effects might be related to genes on the Y chromosome because the breed of sire effects were significant only in barrows and not in gilts. Another explanation for their results, however, would be an interaction of sex with imprinted genes. Their reciprocal differences may also have been due to sampling, resulting in the observed differences between sire and dam groups of one or both breeds.

Results

The results in Table 2, in which imprinting and additive maternal effects were not included, agree well with estimates found in the literature. Recent reviews and estimates based on models without imprinting have been given by Hofer et al. (1992) and Lo et al. (1992).

No estimates for the parental effects fitted in this study have been found in the literature. Support for the relevance of imprinting effects on growth characteristics comes from transgenic studies in mice and from studies on genetic disorders in humans. DeChiara et al. (1990) demonstrated the important role of the mouse insulin-like growth factor II (IGF-II) gene in embryonic growth. DeChiara et al. (1991) showed this gene to be subject to parental imprinting. Barlow et al. (1991) found imprinting in the IGF-II receptor gene.

Supporting studies in humans concern the deletion of a portion of the long arm of chromosome 15 (15q11-q13). A paternal deletion has been found to produce obesity and other developmental defects, a disorder referred to as the Prader-Willi syndrome (Nicholls et al. 1989). A maternal deletion results in a totally different syndrome, referred to as the Angelman syndrome (Malcolm et al. 1991), that involves mental retardation and proneness to seizures, but not obesity. The differences between these two syndromes illustrate the possibility of paternal imprinting for genes influencing fat deposition (obesity).

Consequences

Most pig breeding organizations use an index combining ADG and BF. Assuming that the inter-trait correlation at the level of imprinted gene effects is close to the phenotypic correlation, the relative size of the imprinting variance (m^2) of an index will be in between the m^2 estimates of the component traits.

The presence of imprinting effects will have several consequences. In most populations, additive genetic variance components for growth and carcass traits will have been overestimated. The bias can be considerable, particularly when the estimates are based on half-sib covariance, because for this type of family relationship the contribution of the imprinted gametic effects are twice that of additive genetic effects (Table 6). As shown in the appendix, selection for imprinted genes is about 50% less efficient than selection for non-imprinted genes. Consequently, imprinting will contribute to lower than expected selection responses in genetic improvement schemes. When the commercial product is based on a cross-breeding system with specialized sire and dam lines (as is done in pig production), selection in sire lines should account for paternal gametic imprinted genes, and selection in dam lines should account for maternal imprinted genes.

Conclusions

A significant proportion of the phenotypic variance in backfat thickness (5–7%) could be explained by genes subject to paternal gametic imprinting. For growth rate, the estimates ranged from 1% to 4%. At this stage, whether maternal imprinted genes or genes controlling maternal performance are responsible for the maternal effects found in this study is not clear, but these effects explained 2–5% and 3–4% of the phenotypic variance in backfat thickness and growth rate, respectively. The existence of gametic imprinting has consequences for the optimization of breeding programmes, particularly for systems with specialized sire and dam lines.

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Appendix

Efficiency of selection under models with additive genetic and imprinting effects

Assume a population with selection on phenotypic performance in males and females. In situation 1, a complete additive genetic model is assumed. In situation 2, a model is assumed with part of the relevant genes being subject to paternal gametic imprinting. Let h^2 be additive genetic variance (relative to the phenotypic variance), and g_p^2 be variance due to paternal (or maternal) gametic imprinted genes. The ratio of expected response (R) to selection differential (S) is equal to the regression of offspring performance on the average performance of the parents (mid-parent value) (Falconer 1989).

In situation 1, the covariance of offspring with each of the two parents, and thus also with the mid-parent value is equal to $0.5\ h^2$. The variance of mid-parent values is equal to half of the phenotypic variance. Hence, the regression of offspring on mid-parent value is equal to h^2 (Falconer 1989, p. 153). The expected response from each round of selection then is given by

$$R=h^2\ S$$

In situation 2, the covariance of offspring with sire is $h^2+0.5\ g_p^2$, whereas the covariance with dam is $0.5\ h^2$. This means that the regression of offspring on mid-parent value is $h^2+0.5\ g_p^2$, and thus expected response is given by

$$R=(h^2+0.5\ g_p^2)S$$

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