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Separation of additive-genetic imprinting variance from additive-genetic maternal variance

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Maternal effects in mammals have been studied extensively and the importance especially for early development has long been recognized (e.g. Willham, 1972; Meyer, 1992; Roehe, 1993). In presence of genetic maternal effects the genotype of the mother has an influence on the phenotype of the offspring.

Genomic imprinting refers to an epigenetic marking of genes which are differentially expressed from the maternally and paternally inherited alleles. The first molecular evidence for imprinting in mammals was found in the middle of the 1980s. The molecular mechanism is a parent-specific methylation of DNA, established during gametogenesis. Many studies have shown that imprinting plays a role in aspects of development, cell proliferation, adult behavior and some diseases. Additionally there are results on imprinted QTL in pigs and poultry. IGF2 was identified as an important imprinted gene in pigs.

The first study on the importance of imprinted alleles was done by a variance-component approach (De Vries et al., 1994). In order to assess the relative importance of genomic imprinting for the genetic variation we applied a model including two random genetic effects for each animal. The model allows for paternal and maternal imprinting as well as of any combination of full and partial imprinting simultaneously. Active maternal effects in case of litter size or birth weight can lead to an undesirable mixture of imprinting variance for the direct effect and the maternal variance.

Therefore, we are interested in the relative portion of the additive genetic variance induced by imprinted genes relieved of maternal variances.

Theory

Gametic model

In general the model of analysis comprises fixed effects and, among possible additional random effects, two genetic effects, the direct effect and the maternal effect, per animal. Basically the model in matrix notation is

$$y = X\beta + Z_{dir}g_{dir} + Z_{mat}g_{mat} + e \qquad (1)$$

analogous to Willham (1972), where $Z_{dir}g_{dir}$ describes the direct genetic effect and $Z_{mat}g_{mat}$ stands for the maternal genetic effect, expressed as gametic effects. As already mentioned the direct genetic effect can be 'split' into a genetic effect as sire and a genetic effect as dam. Equally we do so for the maternal genetic effect. Thus the model in matrix notation becomes:

$$y = X\beta + \overbrace{Z_s g_s + Z_d g_d}^{\text{direct effect}} + \overbrace{Z_o g_o + Z_u g_u}^{\text{maternal effect}} + e \qquad (2)$$

where the assumptions on the covariance of random effects are

$$\mathrm{Var}\begin{bmatrix} a_s \\ a_d \\ a_o \\ a_u \\ e \end{bmatrix} = \begin{bmatrix} 1/2\,G\sigma_s^2 & 1/2\,G\sigma_{sd} & 1/2\,G\sigma_{so} & 1/2\,G\sigma_{su} & 0 \\ 1/2\,G\sigma_{sd} & 1/2\,G\sigma_d^2 & 1/2\,G\sigma_{do} & 1/2\,G\sigma_{du} & 0 \\ 1/2\,G\sigma_{so} & 1/2\,G\sigma_{do} & 1/2\,G\sigma_o^2 & 1/2\,G\sigma_{ou} & 0 \\ 1/2\,G\sigma_{su} & 1/2\,G\sigma_{du} & 1/2\,G\sigma_{ou} & 1/2\,G\sigma_u^2 & 0 \\ 0 & 0 & 0 & 0 & I\sigma_e^2 \end{bmatrix}. \qquad (3)$$

Resulting in the following mixed model equations

$$\begin{bmatrix} X'X & X'Z_s & X'Z_d & X'Z_o & X'Z_u \\ Z'_sX & Z'_sZ_s + G^{-1}\alpha_1 & Z'_sZ_d + G^{-1}\alpha_2 & Z'_sZ_o + G^{-1}\alpha_3 & Z'_sZ_u + G^{-1}\alpha_4 \\ Z'_dX & Z'_dZ_s + G^{-1}\alpha_2 & Z'_dZ_d + G^{-1}\alpha_5 & Z'_dZ_o + G^{-1}\alpha_6 & Z'_dZ_u + G^{-1}\alpha_7 \\ Z'_oX & Z'_oZ_s + G^{-1}\alpha_3 & Z'_oZ_d + G^{-1}\alpha_6 & Z'_oZ_o + G^{-1}\alpha_8 & Z'_oZ_u + G^{-1}\alpha_9 \\ Z'_uX & Z'_uZ_s + G^{-1}\alpha_4 & Z'_uZ_d + G^{-1}\alpha_7 & Z'_uZ_o + G^{-1}\alpha_9 & Z'_uZ_u + G^{-1}\alpha_{10} \end{bmatrix} \begin{bmatrix} \tilde{\beta} \\ \hat{g}_s \\ \hat{g}_d \\ \hat{g}_o \\ \hat{g}_u \end{bmatrix} = \begin{bmatrix} X'y \\ Z'_sy \\ Z'_dy \\ Z'_oy \\ Z'_uy \end{bmatrix} \qquad (4)$$

where Y is the vector of observations, X is the design matrix for fixed effects with the corresponding vector β, Z_s and Z_d are the design matrices for random genetic effects with the vectors g_s and g_d for the gametic effects as sire and as dam, Z_o and Z_u are the design matrices for random genetic maternal effects with the vectors g_o and g_u. The variance components for the direct effect are the gametic effects σ_s^2 for the paternal one, σ_d^2 for the maternal one and σ_{sd} for their covariance. In the mixed model equation the variance components are represent by $\alpha_{(1,..,10)}$. Each α will be calculated as the quotient of the error and the corresponding (co-) variance component. The matrix G is the usual gametic relationship matrix.

In the analysis the hypothesis testing will be done with the S matrices from the extended *Mendelian* model (no imprinting, but maternal effects will assumed)

$$S = \begin{bmatrix} \sigma_g^2 & \sigma_g^2 & \sigma_{go} & \sigma_{gu} \\ \sigma_g^2 & \sigma_g^2 & \sigma_{go} & \sigma_{gu} \\ \sigma_{go} & \sigma_{go} & \sigma_o^2 & \sigma_{ou} \\ \sigma_{gu} & \sigma_{gu} & \sigma_{ou} & \sigma_u^2 \end{bmatrix} \qquad (5)$$

for the null hypothesis and from the extended imprinting model (maternal effects were assumed)

$$S = \begin{bmatrix} \sigma_s^2 & \sigma_{sd} & \sigma_{so} & \sigma_{su} \\ \sigma_{sd} & \sigma_s^2 & \sigma_{do} & \sigma_{du} \\ \sigma_{so} & \sigma_{do} & \sigma_o^2 & \sigma_{ou} \\ \sigma_{su} & \sigma_{du} & \sigma_{ou} & \sigma_u^2 \end{bmatrix} \quad (6)$$

for the alternative hypothesis.

Reduced model

Inheritance can be modelled by two random genetic effects per animal for the direct effect: one for the genetic effect as sire, i.e. half of the breeding value as sire and one for the genetic effect as dam, i.e. half of the breeding value as dam. Equally we do so for the maternal genetic effect. The model in matrix notation is

$$Y = X\beta + Z_s a_s + Z_d a_d + Z_u a_u + Z_o a_o + Z_s m + e \quad (7)$$

where Z describes the Mendelian sampling.

Resulting in the following mixed model equations

$$\begin{bmatrix} X'X & X'Z_m & X'Z_s & X'Z_d & X'Z_o & X'Z_u \\ Z'_m X & Z'_m Z_m + M^{-1}\lambda_m & Z'_m Z_s & Z'_m Z_d & Z'_m Z_o & Z'_m Z_u \\ Z'_s X & Z'_m Z_s & Z'_s Z_s + A^{-1}\alpha_1 & Z'_s Z_d + A^{-1}\alpha_2 & Z'_s Z_o + A^{-1}\alpha_3 & Z'_s Z_u + A^{-1}\alpha_4 \\ Z'_d X & Z'_m Z_d & Z'_d Z_s + A^{-1}\alpha_2 & Z'_d Z_d + A^{-1}\alpha_5 & Z'_d Z_o + A^{-1}\alpha_6 & Z'_d Z_u + A^{-1}\alpha_7 \\ Z'_o X & Z'_m Z_o & Z'_o Z_s + A^{-1}\alpha_3 & Z'_o Z_d + A^{-1}\alpha_6 & Z'_o Z_o + A^{-1}\alpha_8 & Z'_o Z_u + A^{-1}\alpha_9 \\ Z'_u X & Z'_m Z_u & Z'_u Z_s + A^{-1}\alpha_4 & Z'_u Z_d + A^{-1}\alpha_7 & Z'_u Z_o + A^{-1}\alpha_9 & Z'_u Z_u + A^{-1}\alpha_{10} \end{bmatrix} \begin{bmatrix} \tilde{\beta} \\ \hat{a}_m \\ \hat{a}_s \\ \hat{a}_d \\ \hat{a}_o \\ \hat{a}_u \end{bmatrix} = \begin{bmatrix} X'y \\ Z'_m y \\ Z'_s y \\ Z'_d y \\ Z'_o y \\ Z'_u y \end{bmatrix} \quad (8)$$

In terms of gametic variances the variance components for the genetic effects are $1/2\,\sigma_s^2$ for the paternal one, $1/2\,\sigma_d^2$ for the maternal one and $1/2\,\sigma_{sd}$ for their covariance. The matrix A is the usual numerator-relationship matrix. In exceptional cases the variance of the Mendelian sampling effects (no observation for the mother and only one progeny per mother) is a diagonal matrix, which is included in the error of the reduced model. In general M_i is block-diagonal covariance matrix and Mendelian sampling effects have to be estimated as separate random effects. A 2*2 block M_i has to be included for all animals i (1,…, n) who are mothers of progeny with an observation, have an own observation or both.

$$M_i = Var\begin{bmatrix} m_{i1} \\ m_{i2} \end{bmatrix} = 1/2\,\sigma_s^2\,(1 - F_{si}) \otimes \begin{bmatrix} 1/2\,\sigma^2_{ma,s} & 1/2\,\sigma_{madi,s} \\ 1/2\,\sigma_{madi,s} & 1/2\,\sigma^2_{di,s} \end{bmatrix} + 1/2\,\sigma_d^2\,(1 - F_{di}) \otimes \begin{bmatrix} 1/2\,\sigma^2_{ma,d} & 1/2\,\sigma_{madi,d} \\ 1/2\,\sigma_{madi,d} & 1/2\,\sigma^2_{di,d} \end{bmatrix}, \quad (9)$$

Where F_{si} and F_{di} are the inbreeding coefficient of the parents of the animal i. The pure imprinting variance for the direct effect can be expressed as the variance of the difference of the gametic effects as sire and as dam

$$\sigma_i^2 = \sigma_s^2 + \sigma_d^2 - 2\sigma_{sd} . \qquad (10)$$

The imprinting variance σ_i^2 is a part of the total additive genetic variance.

Discussion

The separation of imprinting variances of the direct trait and maternal variances is, in principle, possible. The disadvantage is the necessity to estimate of so many variance components, but for reproduction traits the separation of the genetic variances due to genomic imprinting and the heritable maternal effect make sense. The estimates of the imprinting variance for the maternal effect will be upper bounds, because the absolute separation is not possible. The results of the imprinting variances for the direct effect present the pure part of the additive genetic variance which is influenced by imprinting. When the variance components are established, use the reduced model for the estimation of breeding values, because it needs a lower number of equations. First results of an analysis of a large data set from a commercial pig population give hints that genomic imprinting seems to be responsible for notable differences in the number of piglets born alive.

Literature

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