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Distinguishing Fetal and Maternal Genetic Effects on Variation in Birth Weight

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Abstract. In an attempt to uncover the causes of variation in birth weight for 13,970 offspring of MZ and DZ twins, several models were tested. Mean squares from nested analysis of variance were analysed with respect to fetal and maternal effects on variation in birth weight. The major part of the total variation in birth weight was found to be due to effects of genes. The contribution of fetal genes was larger than the contribution of maternal genes. About 11% of the variation could be attributed to effects of interactions between fetal and maternal genes. However, in this data set, the interaction variance could not be distinguished from variance due to fetal dominance or to effects of common environment of sibs.

Key words: Interaction variance, Fetal genes, Maternal genes, Birth weight, Common environment

INTRODUCTION

Birth weight is a complex and important variable to study with the methods of quantitative genetics. The variation in birth weight may be influenced by effects of fetal genes, maternal genes or environmental factors.

Various methods may be employed in order to explain the observed variation. Penrose [7] and Robson [8] interpreted correlation coefficients between family members in the light of genetic and environmental effects, and concluded that fetal genes are of little importance in explaining the variation. Nance et al [6], using the MZ half-sib method [5], also demonstrated a larger maternal than fetal effect.

We have attempted to evaluate these findings by studying a larger body of birth weight data from Norway. The method used is to a large extent similar to the approach of Nance and Corey [5], but the data set includes offspring of DZ twins in addition to offspring of MZ twins.

An attempt was made to include effects of interactions of fetal and maternal genes in the models. Interactions of fetal and maternal genes would appear as variation that depend on the joint action of fetal and maternal genes, unexplainable by additive effects of genes. These effects would only be present if specific maternal genes interact with specific fetal genes. Immunological incompatibility reactions are examples of such interaction effects.

MATERIALS AND METHODS

Subjects

The sample consists of 13,970 offspring of twins from a population-based panel of like-sexed twins born between 1915 and 1960 [4]. Birth weights of offspring were obtained by record linkage with the Norwegian Medical Birth Registry [1]. Only birth weights of singleborn infants who survived the first four weeks of life were included. A fuller account of the data together with a more complete analysis of fetal and maternal effects including the effects of X-linked genes, Y-linked genes and cytoplasmic effects has been presented [3].

Models and Data Analysis

The analysis is based on nested analysis of variance in the four family types (offspring of male MZ twins, female MZ twins, male MZ twins, and female DZ twins). Mean squares are functions of variance components (σ^2_A, σ^2_B, σ^2_W) and coefficients (B1, B2, and A) depending on the number of offspring in the families. The variance components can be expressed as sums of genetic and environmental parameters (Table 1). The variance within sibships (σ^2_W) is equal in all families. In families of MZ twins, σ^2_A reflects the covariance of half sibs, and σ^2_B the covariance of sibs minus the covariance of half sibs. In families of DZ twins, the σ^2_A reflects the covariance of cousins and σ^2_B the covariance of sibs minus the covariance of cousins.

The following assumption are made: 1) random mating is present, and 2) genes and environments do not covary or interact. The birth weight (BWx) of subject X can be expressed as:

$$BWx = Gx + Gmx + Gx \cdot mx + Ex,$$

where Gx is the deviation due to fetal genetic effects, Gmx the deviation due to maternal genetic effects, Gx • mx the deviation due to interaction effects, and Ex the deviation due to environmental effects. Similarly, the birth weight (BWy) of subject Y can be expressed as

$$BWy = Gy + Gmy + Gy \cdot my + Ey.$$

The covariance between the birth weights of subjects X and Y is then:

$$Cov(BWx, BWy) = Cov(Gx, Gy) + Cov(Gmx, Gmy) + Cov(Gx, Gmy) + Cov(Gy, Gmx) + Cov(Gx \cdot mx, Gy \cdot my) + Cov(Ex, Ey).$$

Covariance terms between interaction effects and main effects have been omitted. Cov(Gx, Gy) is some fraction of the fetal genetic variance, depending on the relationship between X and Y. In Table 1, variances due to additivity (Va) and dominance (Vd) are included. Cov(Gmx,Gmy) is some fraction of the maternal genetic variance, and only the additive variance (Vma) have been included in Table 1. The Cov(Gx, Gmy) and Cov(Gy, Gmx) will be equal in size in this data set, but will only be different from zero if the same genes (or closely linked genes in linkage disequilibrium) have effects both through the mother and through the fetus. In the present data set, which includes covariances of sibs, half sibs and cousins, the expectations for the sum of Cov(Gx,Gmy) and Cov(Gy, Gmx) will equal the expectations for the additive maternal genetic variance, and have therefore not been included in Table 1.

Veb (Table 1) originates from environmental effects that are shared by sibs. Vew is the variance due to enviromental effects that differ for sibs. The expectations for Va, Vd, Vma, Veb and Vew are equal to the ones given by Nance and Corey [5], with the addition of expectations for offspring of DZ twins.

The interaction variance, cov(Gx • mx, Gy • my), will appear in the covariance of maternally related subjects. If only single genes are considered, the expectation for this term in any covariance of birth weight for two infants is equal to the product between two probabilities: 1) The probability of both being exposed to the maternal gene in question and 2) The probability of sharing the fetal gene involved in the interaction. In Table 1, the interaction variance has been named Va • ma. It is assumed that the genes that interact are on independently segregating loci. If the interacting genes were on the same locus, one would have to employ conditional probabilities for deriving the expectations. The sharing of the fetal genes involved in the interaction, would in that case depend on the

Table 1 - Nested Analysis of Variance for Birth Weights of Offspring of MZ Twins: Expectations of fetal genetic (Va, Vd), maternal genetic (Vma), genetic interaction (Va • ma, Vpa • ma) and environmental (Veb, Vew) variances for variance components (σ^2_A, σ^2_B, and σ^2_W)

Twin family type	Variance component	Va	Vd	Vma	Va • ma	Vpa • ma	Veb	Vew
MZ Male	σ^2_A	1/4	0	0	0	0	0	0
MZ Male	σ^2_B	1/4	1/4	1	1/2	1/2	1	0
MZ Female	σ^2_A	1/4	0	1	1/4	0	0	0
MZ Female	σ^2_B	1/4	1/4	0	1/4	1/2	1	0
DZ Male	σ^2_A	1/8	0	0	0	0	0	0
DZ Male	σ^2_B	3/8	1/4	1	1/2	1/2	1	0
DZ Female	σ^2_A	1/8	0	1/2	1/16	0	0	0
DZ Female	σ^2_B	3/8	1/4	1/2	7/16	1/2	1	0
All	σ^2_W	1/2	3/4	0	1/2	1/2	0	1

Table 2 - Nested Analysis of Variance for Birth Weights of Offspring of Twins: Observed mean squares among twin families (MSa), between sibships within families (MSb) and within sibships (MSw)

Twin family type	Observed mean square		df	Coefficients	
				B_1/B_2	A
MZ Male	MSa	378353	1075	1.6489	2.4509
MZ Male	MSb	290882	531	1.6261	
MZ Female	MSa	418215	1265	1.5924	2.4306
MZ Female	MSb	229338	678	1.5659	
DZ Male	MSa	379253	1748	1.6346	2.3157
DZ Male	MSb	305906	753	1.5827	
DZ Female	MSa	378264	1758	1.6089	2.3890
DZ Female	MSb	279418	863	1.5904	
All	MSw	143796	5295		

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Table 3 - Nested Analysis of Variance for Birth Weights of Offspring of Twins: Estimates (±SE) of square roots of genetic (Va, Vd, Vma, Va • ma, and Vpa • ma) and environmental variances (Vew and Veb) from fitting models to observed mean squares

		Square roots of									
Model		Va	Vma	Vew	Va • ma	Vpa • ma	Veb	Vd	χ^2	df	P
1	Est	507.3		124.0					14.14	7	0.049
	SE	7.4		22.6							
2	Est	436.7	182.0	221.2					3.18	6	0.787
	SE	24.5	28.0	26.2							
3	Est	410.0	166.8	207.1	183.8				2.44	5	0.786
	SE	40.7	36.0	32.8	103.9						
4	Est	390.8	194.2	228.9		172.0			2.23	5	0.816
	SE	44.2	27.9	26.1		63.9					
5	Est	401.8	190.5	231.6		135.9	52.2		2.12	4	0.714
	SE	45.4	29.1	>5000		>10,000	>10,000				
6	Est	397.0	191.1	196.4		123.9		156.8	2.18	4	0.702
	SE	47.3	28.3	>10,000		>10,000		>10,000			

sharing of the maternal genes that are active in the interaction. However, if one assumes that interactions only involve the fetal genes that are of paternal origin, then, under random mating, the presence of the fetal genes will be independent of the presence of the maternal genes. In this case, the interaction variance may also be attributed to interactions of fetal and maternal genes at the same locus. This variance (Vpa • ma in Table 1) will only be found in the covariances of relatives who are related both through their mothers and their fathers (sibs, double first cousins).

Model fitting was performed with the aid of the computer program LISREL IV [2]. The program gives estimates of the square roots (± SE) of the variances, and a χ^2- value to test the fit of the model to the data.

RESULTS

The mean birth weight for the 13,970 offspring was 3524 g (range 730-5775 g). The variance was 272484. The distribution deviates only slightly from the normal one (skewness: -0.274).

Table 2 gives the mean squares, obtained from nested analysis of variance. To these data, a series of models were fitted. It was decided to always include Vew in the models. This component includes errors of measurement and recording. A model of Va + Vew did not fit the data. Table 3 (Model 1) gives the estimates (± SE) of the square roots of the genetic (Va) and environmental variance (Vew). Also models with Vew + Veb alone ($\chi^2 = 117.74$, 7 df, $P < 0.01$) or with Vew + Vma alone ($\chi^2 = 105.23$, 7 df, $P < 0.01$) did not fit the data. However, a good fit was found for Vew + Va + Vma (Model 2).

Adding Va • ma (Model 3) lowered the χ^2 insignificantly. In Model 4, Vpa • ma was included. The effect of including Vpa • ma together with either Veb or Vd in this data set is shown in Models 5 and 6. The large standard errors of the estimates indicate that Vpa • ma is confounded with Veb and Vew in Model 5, and with Vd and Vew in Model 6. Addition of other parameters to the model did not significantly change the size of the estimates of Va or Vma. Table 4 gives the magnitude of Va, Vma, Vew and Vpa • ma relative to the total variation in birth weight based on Model 4. However, the statistical evidence in favor of this model over Model 2 is marginal, and Vpa • ma could equally well be substituted with Vd or Veb. Conservatively, one may conclude from Model 2 that 70% of the variation is due to effects of fetal genes, 12% to effects of maternal genes and 18% to effects of random environment.

Table 4 - Components of the Total Variation in Birth Weight Based on Model 4 in Table 3: Va is the variance due to fetal genes, Vma the variance due to maternal genes, Vpa • ma the interaction variance and Vew is environmental variance

Variance component	Estimate	Percent of total
Va	152725	56
Vma	37714	14
Vpa • ma	29584	11
Vew	52395	19
Total	272418	100

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DISCUSSION

A large effect of fetal genes and a smaller effect of maternal genes on the variance in birth weight was found in this study. Together, genes appeared to account for about 80% of the variance in the population examined.

It is theoretically possible that specific interactions between maternal and fetal genes may cause variation in birth weight. In the absence of laboratory tests to detect interactions, the biometric approach is a simple and inexpensive method to search for such effects. In the present study, the interaction variance could not explain more than 11% of the total variance, and it could not be distinguished from effects of dominance or common environment. Further biometric research on interaction effects may lead to improved study design and to estimates on the sample sizes necessary for detection of effects. The possibility of interactions between maternal and fetal genes as causes of pregnancy related diseases, be it maternal (hyperemesis, preeclampsia) or fetal (intrauterine growth retardation), warrants further study.

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