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The genetic basis of response in mouse lines divergently selected for body weight or fat content. II. The contribution of genes with a large effect

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Summary

Gene action underlying selection responses has been studied using crossbreeding. Maximum likelihood based segregation analysis has been presented for analysing backcross data for the presence of genes with a large effect. Two sets of divergently selected lines (P-lines for body weight and F-lines for fat content) were reciprocally crossed and the F_1s were crossed to the high and low lines to produce all possible backcrosses. Earlier analysis had shown that the difference in body weight at 10 weeks ($n = 595$) between the high and low P-lines was largely (75–80%) explained by autosomal, additive genes with the remainder explained by additive genes on the X chromosome. Maximum likelihood segregation analysis suggested the presence of a major effect on the X chromosome, but as there was only one round of recombination between the X chromosomes in the forming of the backcrosses, linked genes on the X chromosome could have acted together to give the appearance of a single major gene. The difference in fat content between the F-lines ($n = 578$) could be explained by autosomal genes of largely additive effect. Segregation analysis suggested the presence of a major gene with complete dominance, but this was attributed to a relationship between the mean and the variance: transformation of the data resulted in only polygenic additive genes being of importance. This study concluded that maximum likelihood based analysis and crosses between selected lines provide a powerful means for studying the gene action underlying responses to selection.

1. Introduction

An underlying assumption of many quantitative genetic analyses in plant and animal breeding studies is the additive infinitesimal model. Under this model it is assumed that genetic variance in the trait in question is controlled by an infinite number of unlinked, autosomal genes of infinitely small, additive effect. Although this model is obviously unrealistic, it can often provide reasonable predictions of progress under artificial selection for a limited number of generations. In longer term selection experiments, however, it is sometimes possible to show that the infinitesimal model is inadequate. For example, the genetic variance may change to a greater extent than would be expected due to the effects of inbreeding and linkage disequilibrium (Meyer & Hill 1991; Beniwal *et al.* 1992).

The difficulty in highlighting failures of the infinitesimal model is inherent in the analyses usually performed – it is intrinsically difficult to separate the effects of dominance, common family environment, maternal environment, major genes, etc., from those of additive genes of small effect (polygenes) using data from pedigree populations. The problem lies both in the computational difficulty of estimating a number of parameters simultaneously and in the power available with limited data to estimate separately parameters which have a similar influence on the variance/covariance structure. Although residual maximum likelihood (REML) methods are now being extended, to allow, for example, the estimation of maternal effects or dominance (Meyer, 1989), the methods are computationally demanding and the problem of limited power remains.

An alternative approach for the study of the gene action is the use of crossbreeding. Where the lines crossed have been selected, crossbreeding studies can be used to indicate the gene action that has contributed to the selection response. With a sufficient range of crosses, a model-fitting approach can be used to

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explore the data for evidence of the presence of a variety of gene actions. Because the information comes from the comparison of means of crosses with markedly different expectations, the method is much more powerful for the interpretation of gene action than the analysis of second order statistics.

Crossbreeding between lines of mice which have undergone long-term selection for components of growth is used. In a preliminary study (Hastings & Veerkamp, 1993) the means of the crosses provided information on the mode of action (additive, dominance, sex-linked or autosomal, mitochondrial or Y chromosomal) of any genes. In this study, variance and higher moments of the crosses are used to ascertain whether single genes of large effect may have contributed to line differences. Segregation analysis (Elston & Stewart, 1973) provided the evidence to discriminate between polygenic and monogenic gene action.

2. Materials and methods

Data: Lines of mice have been divergently selected for (i) body weight (P lines) and (ii) fat content (F lines). A comprehensive description of the data analysed here has been given by Hastings & Veerkamp (1993). Briefly, the P lines were selected high and low for 20 generations on the basis of estimated lean mass in the males at 10 weeks of age, followed by a further 10 generations of selection on 10-week-body-weight in both sexes. In the 30th generation animals from the high and the low lines were crossed to produce both reciprocal F_1 crosses. F_1 animals were crossed to animals from generation 31 to produce all possible backcrosses (see Table 1). Body weight at 10 weeks of age was recorded for all animals.

The F lines were selected on fat content at 10 weeks to generation 20 and subsequently on the ratio of dry body weight to wet body weight at 14 weeks, a trait highly correlated with fat content (Hastings & Hill, 1989). Crosses between high and low line animals in the 40th generation were used to produce both reciprocal F_1 crosses (Table 1). F_1 animals were crossed to high and low line animals of generation 41 to produce all possible backcrosses. Fat content was measured in F_1 and backcross animals and in high and low line animals of the 41st and the 42nd generations (contemporaries of the F_1 and backcrosses, respectively), but no records were available from the animals in the 40th generation.

The dependent variates in this study were: (i) P line crosses: body weight at 10 weeks of age and its square root were analysed. This transformation was used to make the variances within each cross type independent of their means. (ii) F line crosses: mice were weighted at 14 weeks of age, dried and then weighed again. The ratio of dry weight to body weight was used as predictor or fat content. The variances within each cross type were related with their means and log(ratio-24) was found to be the best transformation, using a weighted regression of the variances on the means, to remove this association.

Segregation analysis: Elston & Stewart (1973) describe a method for maximum likelihood segregation analysis for the detection of a major gene segregating in crosses between inbred lines. Underlying assumptions of their method are that the distribution within each genotype of the major gene is normal, that environmental variances within each major genotype are equal and that the high and low lines are homozygous for alternative alleles at a major gene. The natural logarithm of the likelihood for the model used (adapted from Elston & Stewart, 1973) is:

$$L = -N\ln(\sqrt{2\pi}) - N\ln(\sigma) + \sum_{i=1}^{n_{cross}}\sum_{j=0}^{n_{sex}}\sum_{k=1}^{n_{ij}}\ln\sum_{l=1}^{n_{genoij}}\left(P_{transijl} \times \exp\left(\frac{(-\chi_{ijk} - \underline{\mu} - geno_{ijl} - fixed_{ijk})^2}{2\underline{\sigma}^2}\right)\right)$$

$$geno_{ijl} = \sum_{m=1}^{n_{gene}}(g_{mijl} \times \underline{GENE}_m)$$

$$fixed_{ijk} = lit_{ijk} \times \underline{LITTER} - j \times \underline{SEX} - \sum_{p=1}^{n_{fixed}}(fix_{ijkp} \times \underline{FIX}_p)$$

L = Log-likelihood; N = total numbers of animals (595 or 578); n_{sex} = number of sex classes (2); n_{ij} = number of animals of the ith cross of the jth sex (Table 1: 10–58); n_{cross} = number of crosses (i = 1, 12); n_{genoij} = number of genotypes expected for cross ij (Table 2: 1, 2 or 4); fix_{ijkp} = incidence of pth fixed effect to ijkth animal; lit_{ijk} = littersize of ijkth animal; n_{fixed} = number fixed effects levels; g_{mijl} = expectation of $\underline{GENE}_m$ in the ijlth genotype (Table 2); $P_{transijl}$ = transmitting probability for lth genotype (Table 2); X_{ijk} = observed weight of the kth mouse of the ijth group; $\underline{\sigma}$ = estimate for the intra-genotype standard deviation; $\underline{\mu}$ = estimate for the mean; $\underline{GENE}_m$ = estimate for the mth gene effect; $\underline{LITTER}$ = estimate for regression on litter size; $\underline{SEX}$ = estimate for absolute sex difference (males j = 1; females j = 0); $\underline{FIX}_p$ = estimate for pth fixed effect level (e.g. dry batch).

The possible genotypes for each cross, the transmission probabilities (P_{trans}) for each genotype and the expectations (g_{mijl}) for polygenic and monogenic gene action in each cross are given in Table 2. The transmission probability is the probability that an animal has a particular genotype for the major gene given the allele frequency in that cross. The absolute difference between sexes was estimated by $\underline{SEX}$, the interaction between the gene effects and sex were estimated by inclusion of an extra genetic component for the males that has zero expectation for the females. Analyses of the P-lines included generation

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Table 1. *Description of the crosses, the generation of the parents and the number of male and female records per cross*

	P-line			F-line		
Cross[1]	Sire × dam	Females	Males	Sire × dam	Females	Males
H × H	30 × 30	58	43	40 × 40	28	28
				41 × 41	19	15
L × L	30 × 30	41	41	40 × 40	28	26
				41 × 41	20	18
L × H	31 × 31	22	19	40 × 40	33	50
H × L	31 × 31	30	31	40 × 40	25	10
H × (LH)	31 × F1	19	20	41 × F1	15	15
H × (HL)	31 × F1	25	23	41 × F1	15	17
(LH) × H	F1 × 31	17	19	F1 × 41	20	18
(HL) × H	F1 × 31	15	14	F1 × 41	18	16
L × (LH)	31 × F1	20	19	41 × F1	17	19
L × (HL)	31 × F1	20	20	41 × F1	20	18
(LH) × L	F1 × 31	20	20	F1 × 41	17	16
(HL) × L	F1 × 31	21	18	F1 × 41	18	19

[1] Genotype of the male parent given first.

Table 2. *The expectations (g_{mijl}) for the fitted polygenic (poly) and monogenic (mono) effects, the transmitting probabilities (P_{trans}) and the possible genotypes for each cross. Each possible genotype is enclosed by brackets.*

	F-cross					P-cross						
Cross[1]	P_{trans}	Poly A[2]	Mono A	Poly D	Mono D	P_{trans}	Poly A	Mono A	Poly As female	Poly As male	Mono As female	Mono As male
H × H	1	(1	1	0	0)	1	(1	1	1	1	1	1)
L × L	1	(−1	−1	0	0)	1	(−1	−1	−1	−1	−1	−1)
L × H	1	(0	0	1	1)	1	(0	0	0	1	0	1)
H × L	1	(0	0	1	1)	1	(0	0	0	−1	0	−1)
H × (LH)	1/2	(0·5	1	0·5	0)	1/4	(0·5	1	0·5	0	1	1)
and	1/2	(0·5	0	0·5	1)	1/4	(0·5	0	0·5	0	0	−1)
H × (HL)						1/4	(0·5	1	0·5	0	0	−1)
						1/4	(0·5	0	0·5	0	1	1)
(LH) × H	1/2	(0·5	1	0·5	0)	1/2	(0·5	1	1	1	1	1)
	1/2	(0·5	0	0·5	1)	1/2	(0·5	0	1	1	1	1)
(HL) × H	1/2	(0·5	1	0·5	0)	1/2	(0·5	1	0	1	0	1)
	1/2	(0·5	0	0·5	1)	1/2	(0·5	0	0	1	0	1)
L × (LH)	1/2	(−0·5	−1	0·5	0)	1/4	(−0·5	−1	−0·5	0	−1	−1)
and	1/2	(−0·5	0	0·5	1)	1/4	(−0·5	0	−0·5	0	0	1)
L × (HL)						1/4	(−0·5	−1	−0·5	0	0	1)
						1/4	(−0·5	0	−0·5	0	−1	−1)
(LH) × L	1/2	(−0·5	−1	0·5	0)	1/2	(−0·5	−1	0	−1	0	−1)
	1/2	(−0·5	0	0·5	1)	1/2	(−0·5	0	0	−1	0	−1)
(HL) × L	1/2	(−0·5	−1	0·5	0)	1/2	(−0·5	−1	−1	−1	−1	−1)
	1/2	(−0·5	0	0·5	1)	1/2	(−0·5	0	−1	−1	−1	−1)

[1] Genotype of the male parent given first.
[2] Abbreviations: A = direct additive autosomal; D = direct dominance autosomal; As = direct additive sex-linked.

(three levels: parental crosses, F1 and BC) and litter size as a linear covariate. Analyses of F-lines included a fixed effect for generation with two levels (the F_1 crosses with contemporary generation 41 and the back crosses with contemporary generation 42) and litter size as a linear covariate. Dry weights were obtained in 9 different batches across the different crosses, so batch was included as fixed effect in the analysis of the F-lines. Using the routine E04JAF, a quasi-Newton algorithm for finding a maximum of a function (Numerical Algorithms Group, 1988), L was optimised by changing the underlined variables in the model and using information on the other variables in the model.

The first model contained only the polygenic effects that were identified by Hastings and Veerkamp (1993)

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as significantly greater than zero in their REML analyses. Subsequently, models with both polygenic and monogenic effects were compared with the basic polygenic model. The significance of the improvement in the model obtained by the inclusion of monogenic effects was tested using the likelihood-ratio test, i.e. the likelihood's of nested models were compared using the test statistic (TS) $= 2 \times (\log_e(L_1) - (\log_e(L_2))$, where the likelihood L_1 had m parameters estimated and the likelihood L_2 had n parameters estimated ($m > n$), then under the null hypothesis TS is distributed as χ^2 with $(m-n)$ degrees of freedom (Wilks 1938).

3. Results

The relationship between the cross means and the cross variances is shown in Figure 1 for the F-crosses. Transformation removed the initial strong correlation between the means and variances.

The results of the segregation are given in Table 3. For weight at 10 weeks, both transformed and untransformed, a significant improvement in the likelihood was found when the monogenic sex-linked effect (Model 3) was included in Model 1. Inclusion of the monogenic sex-linked effect greatly reduced the estimate of the polygenic sex-linked effect. The monogenic effect explained all of the sex-linked effect in females and around two thirds of the total sex-linked effect in males. There was no evidence for a autosomal monogenic effect for body weight at 10 weeks (Model 2).

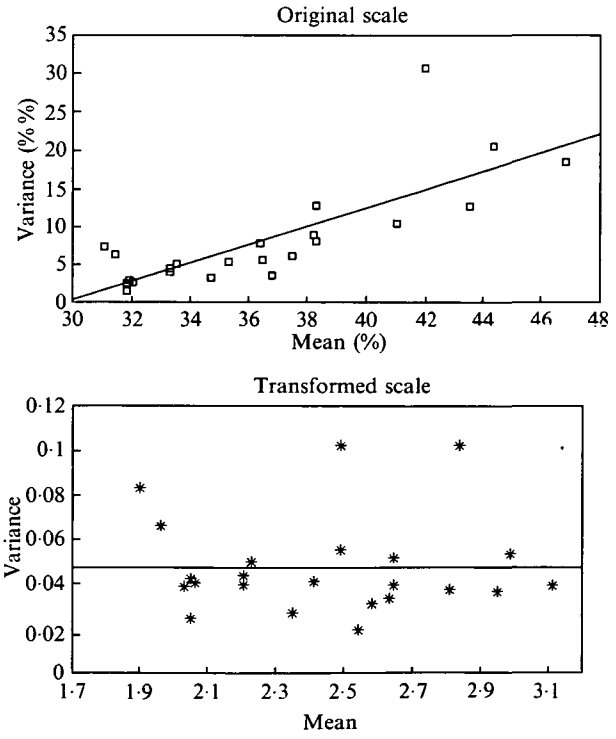

Fig. 1. Relationships between cross means and the variances of the F-crosses, before and after transformation.

Including separate additive and dominance autosomal monogenic effects did not result in a significant improvement in the fit of the model for percentage dry weight to body weight, but when both additive and dominance autosomal monogenic effects were included (Model 4), the likelihood improved significantly. The estimated monogenic additive effect was approximately twice the size in males than it was in females (explaining approximately 34% and 19% of the autosomal additive effect in males and females, respectively) and was completely recessive for the increasing allele. Inclusion of monogenic effects did not result in an improved model for the transformed data.

4. Discussion

In this study we have used crossbreeding between selected lines to provide information on the gene action underlying the responses to selection, with likelihood based analyses used to estimate the magnitude of different genetic effects. Residual maximum likelihood was used in the companion study to analyse factors contributing to differences between the cross means (Hastings & Veerkamp, 1993). This resulted in only the important gene effects being left over for the more computational demanding segregation analysis in this study.

Less computational demanding methods for the detection of possible genes with a large effects were presented by Fain (1978) and Karlin *et al.* (1981). Fain (1978) regressed the logarithme of the variance on the mean of the sibships and significance of different models (linear, quadratic or combined) indicated the presence or absence of different major locus models. This method was based on the expectation that in an F3 population where a major gene is segregating a relationship is expected between the phenotype mean of a sibship and the within-sib variance. Although these test characteristics were designed to work on a randomly bred population, they can be adapted for backcross data. Karlin *et al.* (1981) introduced three classes of structured exploratory analysis (midparental pairwise correlation coefficient, major gene index and the offspring between parents function) to identify presence of major genes. Their specified outlines should indicate sporadic, polygenic and major gene effects. Veerkamp (1991) used these tests on the P-line backcross data, but could not find evidence of a major gene segregating, presumably because both methods (Fain 1978; Karlin et al. 1981) are not very powerful (Le Roy, 1989).

In this study, maximum likelihood segregation analysis showed no significant improvement when an autosomal monogenic effect was included in the model, but the likelihood for body weight and transformed body weight improved significantly when a sex-linked monogenic effect was fitted. However, one should be cautious in attributing this effect to a

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Table 3. *Segregation analysis results: four different models were fitted for each of the four traits. The test statistic (T. S.) after inclusion of an extra monogenic effect (model 2, 3 and 4 against model 1) and estimates for the intra-genotype standard deviation (σ), the mean (μ), regression on litter size (LITTER), the absolute sex difference (SEX) and estimates for polygenic and monogenic gene effects ($GENE_m$), poly and mono respectively, are presented*

	Body weight (g)				Transformed body weight			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
T.S.	0	2·1	8·4**	8·4**	0	1·6	7·2**	7·4**
σ	3·0	2·9	2·8	2·8	0·8	0·8	0·8	0·8
μ	31·4	31·4	31·4	31·4	18·0	18·0	18·0	18·0
LITTER	−0·4	−0·4	−0·4	−0·4	−0·1	−0·1	−0·1	−0·1
SEX (male–female)	5·5	5·4	5·4	5·4	1·5	1·5	1·5	1·5
poly A[1] female	9·0	7·8	9·0	9·0	2·7	2·1	2·7	2·2
poly A male	9·4	6·8	9·5	9·5	2·6	2·0	2·6	2·6
poly As female	2·4	2·4	−0·1	−0·1	0·7	0·7	−0·2	−0·1
poly As male	3·3	3·3	1·1	1·2	0·9	0·9	0·4	0·3
mono A female	—	1·1	—	0·0	—	0·6	—	0·5
mono A male	—	2·6	—	0·0	—	0·6	—	0·0
mono As female	—	—	2·5	2·5	—	—	0·9	0·8
mono As male	—	—	2·1	2·1	—	—	0·5	0·6
	Fat (%)				Transformed fat			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
T.S.	0	0·3	0·3	19·7***	0	0	0	1·2
σ	2·8	2·8	2·8	2·6	0·20	0·20	0·20	0·20
μ	39·8	39·8	39·8	39·8	1·53	1·53	1·53	1·53
LITTER	−0·2	−0·2	−0·2	−0·2	−0·02	−0·02	−0·02	−0·02
SEX (male–female)	1·2	1·2	1·2	1·2	0·04	0·04	0·04	0·04
poly A female	6·5	6·5	6·5	5·3	0·54	0·54	0·54	0·58
poly A male	8·2	9·6	8·2	5·4	0·63	0·63	0·63	0·73
poly D female	−3·0	−3·0	−3·0	−1·8	−0·09	−0·09	−0·09	−0·14
poly D male	−1·4	1·4	−2·9	1·2	0·10	0·10	0·10	0·00
mono A female	—	0·0	—	1·3	—	0·00	—	−0·05
mono A male	—	−1·5	—	2·7	—	0·00	—	−0·10
mono D female	—	—	0·0	−1·3	—	—	0·00	0·05
mono D male	—	—	1·5	−2·7	—	—	0·00	0·10

(**$P < 0·05$; ***$P < 0·01$). [1] Abbreviations see Table 2.

single major gene on the X chromosome. Recombination is only possible between X chromosomes from the high and low lines in the F_1 females, so many genes will stay together and linked polygenes will act like one single major gene. The rapid decrease in additive genetic variance after the initial generations of selection in the P-lines, revealed by Beniwal *et al.* (1992), does support the major gene hypothesis, but could also reflect the fixation of a section of the X chromosome carrying a number of genes. The analysis of Beniwal *et al.* (1992) were made under the assumption, however, that all the genetic variance was autosomally linked. A crossing scheme which allows for more recombination between the high and low X chromosome, for example, with the F_2 and subsequent generations, is needed to distinguish between a sex-linked major gene and sex-linked polygenes.

There was a strong relationship between means and variances in the crosses between the F-lines and transformation to remove this relationship changed the results of the analyses. Maximum likelihood segregation analysis found evidence for a major gene affecting fat percentage – an autosomal major gene with complete dominance is suggested (Females: AA = 1·3, Aa = −1·3, aa = −1·3; Males: AA = 2·7, Aa = −2·7, aa = −2·7). In the analysis of the transformed data the likelihood did not improve significantly when the monogenic effects were included. Transformation has removed evidence for a major gene effect. It seems likely that evidence for the major gene in the data prior to transformation is spurious, with a recessive major gene helping to explain the increase in the variance with the mean. In the presence of a major gene, transformation to equalise the variance of the high and low lines would not reduce the variance in the back crosses to the same level and so would not abolish all evidence for the presence of a major gene. In our analyses, however, after transformation the estimates for the major gene effect are too small to be of importance.

Elston (1984) extended his presented likelihoods (Elston & Stewart, 1973) to account for an en-

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vironmental correlation among litter mates. The method of segregation analysis used in this study ignored the correlation between animals within the same litter. Estimates for effects were similar in REML analyses accounting for correlation between litter mates (Hastings & Veerkamp 1993) and the polygenic model in the segregation analyses, thus it seems likely that the omission of the sire or litter effect from the segregation analyses has not greatly biased the results. Our segregation analysis also assumes that any major gene is fixed for alternative alleles in the two selection lines. Because of the long term selection for one trait in the parental lines, it is likely that any major gene with a large effect on the trait which was segregating in the founder population will have been fixed. In lines where selection has been less intense, or crosses are between outbred lines that have not been divergently selected, this may not be the case and therefore gene frequencies may also have to be estimated (Haley *et al.* 1993). Segregation analysis assumes homogeneous intra-genotype variances and normally distributed genotypes. In this study a transformation was used to make cross means independent of cross variances. After the transformation regression of the variances on the means was no longer significant (Figure 1). These results from the F-crosses illustrate that the assumption of homogeneous variance is critical and that non-homogeneous variances can suggest spurious major gene effects.

In this study crosses between selected lines provides a useful means for analysing gene action that underlies responses to selection. Such analyses should be considered to be preliminary to the analysis of the accumulated data within lines describing the responses to selection as the former analyses provide a relatively powerful means of determining what factors should be accounted for in the latter analyses. It may be appropriate to work towards methods which provide an integrated analysis of data from such lines, incorporating information on both responses to selection within lines and crosses between lines to give a unified picture of gene action.

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