Genet. Res., Camb. (1997), **69**, *pp.* 227–232. Printed in the United Kingdom © 1997 Cambridge University Press

The use of selection experiments for detecting quantitative trait loci

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(*Received 25 October 1996 and in revised form 17 January 1997 and 11 March 1997*)

Summary

Gene frequency changes following selection may reveal the existence of gene effects on the trait selected. Loci for the selected quantitative trait (SQTL) may thus be detected. Additionally, one can estimate the average effect (α) of a marker allele associated with an SQTL from the allele frequency change (Δq) due to selection of given intensity (i). In a sample of unrelated individuals, it is optimal to select the upper and lower 27% for generating Δq in order to estimate α. For a given number of individuals genotyped, this estimator is $0{\cdot}25i^2$ times more efficient than the classical estimator of α, based on the regression of the trait on the genotype at the marker locus. The method is extended to selection criteria using information from relatives, showing that combined selection considerably increases the efficiency of estimation for traits of low heritability. The method has been applied to the detection of SQTL in a selection experiment in which the trait selected was pig litter size averaged over the first four parities, with $i = 3$. Results for four genes are provided, one of which yielded a highly significant effect. The conditions required for valid application of the method are discussed, including selection experiments over several generations. Additional advantages of the method can be anticipated from determining gene frequencies on pooled samples of blood or DNA.

1. Introduction

Various methods are available for mapping quantitative trait loci (QTL) and for evaluating their effects, as shown by the abundant literature on the subject since the pioneer studies of Geldermann (1975) and Soller & Genizi (1978). The aim of this paper is to present how selection experiments can be used for the same purposes, in an approach akin to selective genotyping. An illustration is provided using the hyperprolific line of pigs developed by the INRA (Legault & Gruand, 1976).

2. The method and its application

(i) *Estimators of average gene effect*

The method is based on the well-known fact that a gene frequency change in a population in the course of time is an indicator of selection acting on the gene. But the null hypothesis of genetic drift as an explanation for the change in gene frequency has to be excluded before a conclusion can be reached. A statistical test of this hypothesis has been devised by Fisher & Ford (1947). The test was later 'rediscovered' and applied to experimental populations of *Drosophila* (Yardley *et al*., 1977). The same test may be applied to gene frequency changes in selection experiments and thus constitutes a means of detecting loci involved in the selected quantitative trait (SQTL). The Fisher–Ford test can be completed by a test of linear trends of gene frequency in selected lines over time, as significant trends may be detected even though overall gene frequency changes do not significantly depart from drift alone (Schaffer *et al*., 1977). Table 1 shows the application of such a test to a maize selection experiment. Among the eight loci monitored in this experiment, three have been chosen in Table 1 to illustrate either changes in the same direction in both lines (*PGM*), or changes in opposite directions (*MDH*), or significant change only in one line (*GLU*).

Additionally, when a marker gene is associated with an SQTL, the average effect (α) of alleles at the SQTL can also be estimated, provided the marker gene and

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https://doi.org/10.1017/S0016672397002802 Published online by Cambridge University Press

Table 1. *Changes of allelic frequencies over* 10 *generations of selection for grain yield in maize*

Locus	Line	Frequency of the most frequent allele				Test of linear trend
		Generation 0	Generation 4	Generation 7 (or 8)	Generation 10	
PGM	J	0·85	0·85	1·00	1·00	**
	I	0·64	0·94	0·95	0·96	**
MDH	J	0·64	0·20	0·20	0·20	**
	I	0·74	0·97	1·00	1·00	***
GLU	J	0·57	0·69	0·89	0·90	*
	I	0·06	0·16	0·09	0·07	NS

From Stuber *et al.* (1980).
NS, non-significant; * $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$.

the SQTL are in strong linkage disequilibrium and so tightly linked that no recombination occurs (in case of loose linkage, a biased estimate would be obtained). One can then use the relationship which exists, under conditions detailed by Kimura & Crow (1978), between α and the gene frequency change (Δq) generated by truncation selection on the individual phenotype, for a given selection intensity (i). This had previously been suggested by Hill (1971, p. 308). From the equation $\Delta q = iq(1-q)\alpha$, α being expressed in phenotypic standard deviation units of the trait selected, one can derive an estimator of α:

$$\hat{\alpha}_s = \Delta q/[iq(1-q)]. \quad (1)$$

In applying this estimator to the situations described below, its sampling variance will be compared with the direct estimator of α, as obtained by regressing the trait on marker genotype using the classical definition of α (e.g. Falconer, 1989, p. 120). This estimator, termed $\hat{\alpha}_b$, has the sampling variance of a regression coefficient, i.e. $V(\hat{\alpha}_b) = 1/[2nq(1-q)]$ approximately, for a sample of n unrelated individuals drawn at random from a population in Hardy–Weinberg equilibrium with gene frequency q (see Smith, 1967).

Equation (1) can be generalized to the case of any selection criterion whose accuracy relative to individual phenotype is ρ/h, where ρ is the accuracy of the selection criterion (i.e. correlation between breeding value and selection criterion) and h^2 the heritability of the trait considered. A general expression for the estimator (1) then is

$$\hat{\alpha}_s = [\Delta q/(iq(1-q))]h/\rho. \quad (2)$$

(ii) *Application to samples selected from a population*

Starting from a sample of unrelated individuals, a selection intensity i applied to a given trait produces a change of gene frequency, from which the average effect of the gene on the trait can be estimated using (1). Given subsamples of sizes n_1 and n_2 for the selected and unselected samples respectively, one has

$$V(\Delta q) = q(1-q)\left(\frac{1}{2n_1}+\frac{1}{2n_2}\right)$$

and

$$V(\hat{\alpha}_s) = \left(\frac{1}{2n_1}+\frac{1}{2n_2}\right)/i^2\, q(1-q). \quad (3)$$

For an equal size of selected and unselected samples and a total number n of individuals genotyped, $n_1 = n_2 = n/2$, (3) becomes: $V(\hat{\alpha}_s) = 2/ni^2\, q(1-q)$. The efficiency of the estimator (1) relative to the regression estimator is equal to the inverse ratio of their sampling variances:

$$V(\hat{\alpha}_b)/V(\hat{\alpha}_s) = i^2/4. \quad (4)$$

When an equal proportion p is selected at both ends of the distribution of a sample of S individuals, i.e. $n_1 = n_2 = n/2 = Sp$, and i is defined as twice the selection intensity applied in each direction, (3) becomes

$$V(\hat{\alpha}_s) = 1/Spi^2\, q(1-q). \quad (5)$$

This variance is minimal when pi^2 is maximal, which corresponds to $p = 0{\cdot}27$ for a normally distributed trait (see Hill, 1971, p. 300, who shows that this value of p also minimizes the sampling variance of the estimate of realized heritability in a divergent selection experiment). With such an optimal proportion selected, the selection estimator (1) is thus 1·5 times as efficient ($i^2/4 = 2{\cdot}45^2/4 = 1{\cdot}5$) as the regression estimator for a given number n of individuals typed.

The method can be extended to samples subdivided into families, which allow either family, within-family or combined selection, and α_s is then estimated by (2) using the appropriate accuracy ρ, as for instance Keightley & Bulfield (1993) did for within-family selection. The efficiency of estimator (2) is to be compared with the regression estimator applying in such a case. As suggested by Lande & Thompson (1990, appendix II), this regression may be estimated separately and independently using family means or individual deviations from family means, and the two estimates may be pooled using the inverse of their sampling variances as weights. Assuming a sample of n individuals subdivided into v families of size s, i.e. $n = vs$, r and t being the kinship and phenotypic correlation coefficients between family members respectively, $T = t+(1-t)/s$ and $R = 2r+(1-2r)/s$,

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Table 2. *Efficiency of QTL evaluation* (*in* %) *through various methods of selection with equal selection intensity and equal numbers genotyped, expressed relative to a regression estimator applied to a sample of same family structure. The baseline 100 corresponds to the efficiency of mass selection relative to a regression estimator on a sample of unrelated animals*

t	0·10 0·05	0·50 0·25	0·90 0·45
Family selection	147 (450) 120 (158)	60 (50) 26 (25)	9 (6) 11 (1)
Within-family selection	25 (50) 68 (75)	40 (50) 74 (75)	48 (50) 74 (75)
Combined selection	173 (500) 188 (233)	100 (100) 100 (100)	58 (56) 86 (76)

First line, full-sib families of size $s = 5$; second line, half-sib families of size $s = 50$; in brackets, families of infinite size.

the sampling variances are $T/[2vq(1-q)R]$ and $(1-T)/2(n-v)q(1-q)(1-R)$ for the between-family and within-family regressions respectively. The sampling variance of the combined estimator, being the inverse sum of the weights, is then obtained, replacing v by n/s, as:

$$V(\hat{\alpha}_b) = [1/2nq(1-q)]/[R/sT+(1-R)(1-1/s)/(1-T)].$$

The efficiency of the estimator (2) relative to the corresponding regression estimator then is

$$V(\hat{\alpha}_b)/V(\hat{\alpha}_s) = (i^2/4)(\rho^2/h^2)/[R/sT+(1-R)(1-1/s)/(1-T)], \quad (6)$$

with $\rho^2/h^2 = R^2/T, (1-R)^2/(1-T)$ or the sum of the two terms for family, within-family, or combined selection respectively. Table 2 presents examples of relative efficiencies in various situations. It can be seen that, except for high values of t, within-family selection is the least efficient method, at equal selection intensities, and that combined selection may considerably increase efficiency for traits of low heritability (provided common family environment is also low). It can be shown that in the case of large full-sib family sizes ($R = 0{\cdot}5$ and $T = t$), expression (6) under combined selection reduces to $i^2/8t$, or $i^2/4h^2$ if there is no common family environment ($t = 0{\cdot}5h^2$). In such a situation, if combined selection is optimized, i.e. $p = 0{\cdot}27$ in either direction, (6) reduces to $0{\cdot}75/t$ (or $1{\cdot}5/h^2$ if $t = 0{\cdot}5h^2$). Similarly, in the case of large half-sib family sizes ($R = 0{\cdot}25$ and $T = t = 0{\cdot}25h^2$), (6) reduces to $1+0{\cdot}5/h^2$. However, as the increase in $V(\Delta q)$ due to the family structure is not taken into account, those relative efficiencies are to be considered as slightly overestimated.

(iii) *Application to selection experiments*

The difference in gene frequency of interest is now between selected lines, or between a selected line and the base population. This difference implies a genetic drift component which has to be included in the sampling variance of Δq. This can be derived from the variance–covariance matrix of gene frequencies at each generation established by Fisher & Ford (1947), taking into account the number of individuals typed (n) and the number of breeding individuals, or effective size of the line (N). For a number g of generations, this $(g+1)\times(g+1)$ matrix is

$q(1-q)$

$$\begin{bmatrix} 1/2n & 0 & 0 & & 0 \\ 0 & 1/2n+1/2N & 1/2N & \dots & 1/2N \\ 0 & 1/2N & 1/2n+2/2N & \dots & \vdots \\ \vdots & \vdots & \vdots & & \vdots \\ 0 & 1/2N & \vdots & & 1/2n+g/2N \end{bmatrix}.$$

Consequently, the gene frequency difference between two divergent lines after g generations of selection Δq_g has a sampling variance equal to twice the last diagonal term of the above matrix, i.e. $2q(1-q)[(1/2n)+(g/2N)]$. The sampling variance of the change per generation Δq, assuming a proportion selected $p = N/n$ at each generation, can be derived as

$$V(\Delta q) = V(\Delta q_g/g) = q(1-q)(1+p/g)/npg. \quad (7)$$

It is worth noting that the same expression (7) was obtained by Hill (1971, p. 308) using a different approach, namely considering Δq as a correlated response to the selection on the quantitative trait.

The model used here to estimate α_s and its sampling variance assumes a moderate change in the quantity $q(1-q)$ over the g generations, implying an approximately linear change in q over time. An average value of q may then be used to estimate α_s and its sampling variance.

Under mass selection, the efficiency of $\hat{\alpha}_s$ relative to $\hat{\alpha}_b$ (the latter estimated from a sample of unrelated individuals), for the same number $2n$ of individuals genotyped, can then be obtained from (7), namely $V(\hat{\alpha}_b)/V(\hat{\alpha}_s) = i^2pg/(1+p/g)$, noting that i and p refer to the selection applied in each line. Table 3 shows how the efficiency of $\hat{\alpha}_s$ varies as a function of p and g, and

Table 3. *Relative efficiency of QTL evaluation in divergent mass selected lines for differing proportion selected* (p) *and number of generations of selection* (g) (*100 corresponds to the efficiency of the regression estimator with an equal number of individuals genotyped*)

	g						
p	1	2	3	4	5	…	10
0·50	21	51	82	113	145	…	303
0·40	27	62	99	136	173	…	359
0·30	31	70	110	150	190	…	391
0·20	33	71	110	149	188	…	384
0·10	28	59	89	120	151	…	305

https://doi.org/10.1017/S0016672397002802 Published online by Cambridge University Press

that an optimum value of p exists for each value of g. It can also be shown that efficiency is halved in the case of unidirectional selection, as divergence is halved and despite the halving of the drift variance (no control line being needed).

Other selection methods could also be considered and estimator (2) would apply. Equation (7) would then have to be modified to take into account the genetic drift generated by the corresponding selection method. In particular, within-family selection may considerably reduce genetic drift and therefore become a more attractive strategy than in the situations of Table 2.

3. Discussion

Several conditions must be met for a valid application of the methods described above. The link between selection and gene frequency change, justifying (1), assumes truncation selection is applied to the trait being analysed and not to any other trait, differences between genotypes at the SQTL are small relative to the phenotypic variance, and there is a normal distribution of environment and other gene effects within SQTL genotypes (e.g. Ollivier, 1981). The last condition, however, is not strictly needed, as shown by Kimura & Crow (1978). Crow & Kimura (1979) have shown that when selection is not strictly by truncation the change in gene frequency is reduced, with the consequence that (1) underestimates the real gene effect. Considerable deviation from truncation is, however, needed before substantial underestimation would occur.

When selection experiments are considered, additional conditions are required. Over a large number of generations gene frequency may change considerably, and the sampling variance of q has to be made independent of the mean value of q, for instance by the angular transformation used by Fisher & Ford (1947). The estimation of gene effects also implies constant fitnesses leading to linear trends in gene frequencies. Obviously, the longer the experiment the less likely it is that the assumptions underlying the model will be fulfilled. When large changes of gene frequencies are observed – which would also occur in one round of selection for major genes – the method would still detect SQTLs but would not provide reliable estimates of their effects. A more flexible approach is provided by the maximum likelihood estimation of adaptive values proposed by Dumouchel & Anderson (1968), as for instance applied by Keightley & Bulfield (1993) to a selection experiment on mice.

It should be emphasised that the method proposed can detect only markers showing strong linkage disequilibria with the SQTL. If linkage disequilibrium is initially weak, selection will become less and less effective in changing marker gene frequency. However, in such a situation, evaluations of $\hat{\alpha}$ and q in successive generations would in theory allow estimation of the initial average effects and linkage disequilibria.

We have compared our method with the classical regression estimator under the implicit assumption that individual typings are used in both cases. The possibility of determining allele frequencies directly on pooled samples of blood or DNA (Crooijmans *et al.*, 1996) would give an additional advantage to the use of selected individuals, and make it a highly valuable alternative, in terms of typing costs, to the regression approach of Lande & Thompson (1990) for marker-assisted selection. The two-step procedure they advocate to obtain unbiased effects of the markers chosen among a large set of markers would similarly apply here.

4. An application to the INRA hyperprolific pig

The selection applied since 1973 on the prolificacy of French sows in order to establish a line of hyperprolific boars (Legault & Gruand, 1976) provides an example for application of the method described in this paper. The situation created is indeed equivalent to a highly

Table 4. *Estimation of the effects* ($\pm SE$) *of four genes on pig prolificacy*

Locus/allele	Allele frequency in the control (q)	Difference in frequency select–control (Δq)	Average effect of the allele (total no. born/litter)		
			α_s[a]	α_b[b]	Pooled estimate[c]
ESR/B	0·49	0·06	0·14 ± 0·17	0·48 ± 0·42	0·19 ± 0·16 NS
RARG/1	0·33	0·04	0·11 ± 0·18	0·14 ± 0·38	0·12 ± 0·17 NS
RBP4/2	0·57	0·01	0·02 ± 0·17	0·45 ± 0·43	0·08 ± 0·16 NS
MTNR1A/1	0·15	0·16	0·75 ± 0·24	Not estimable	0·75 ± 0·24**

ESR, oestrogen receptor; RARG, retinoic acid receptor-gamma; RBP4, retinol-binding protein 4; MTNR1A, melatonin receptor 1A; Δq, α_s and α_b defined in text. NS, non-significant; ** $P < 0{\cdot}01$.

[a] Sample sizes: $n_1 = 47$, $n_2 = 55$.

[b] Sample size: $n = 27$.

[c] α_s and α_b weighted by the inverses of their sampling variances (except for MTNR1A).

https://doi.org/10.1017/S0016672397002802 Published online by Cambridge University Press

selected sample of individuals, the trait selected being pig litter size averaged over the first four sow parities ($\rho/h = 1{\cdot}66$ and SD = 3, as given by Legault *et al.*, 1996) and the selection intensity $i = 3$. Two samples, of respective sizes $n_1 = 55$ (select) and $n_2 = 47$ (control), were gathered as described by Legault *et al.* (1996). The hyperprolific and control lines were genotyped for the oestrogen receptor (ESR), retinoic acid receptor-gamma (RARG), retinol-binding protein 4 (RBP4) and melatonin receptor 1A (MTNR1A) genes by methods previously described (Rothschild *et al.*, 1996; Messer *et al.*, 1996*a*, *b*, 1997). The favourable allele of ESR has been significantly associated with increased litter size in the Meishan and Large White breeds of pig (Rothschild *et al.*, 1996). RARG and RBP4 are strong candidate genes for little size based upon their expression during the critical elongation stage of pregnancy.

Gene frequencies at the four loci were compared between the two samples in order to estimate α_s, and α_b was also directly estimated on a subsample of 27 unselected sows, except for MTNR1A, due to the extremely low frequency of the favourable allele and the lack of homozygotes for that allele. The two estimates being independent, they were pooled using inverses of the sampling variances as weights. The results, given in Table 4, show that statistical significance is obtained only for MTNR1A. It can also be noted that α_s is smaller than α_b in the three comparisons made. Sampling variation may explain the differences, given the large standard errors for α_b. However, a deviation from strict truncation, given that the number of parities included in the selection criterion has been variable, or selection for other traits, given that the control sample is not genetically contemporary to the selected one, may also be possible explanations for underestimations of α_s in this situation. It should be noted that variable, and usually larger, effects of the ESR locus have been shown in different genetic backgrounds, e.g. from 0·6 to 1·2 piglets in first parity estimated by Rothschild *et al.* (1996), showing that linkage disequilibrium states around ESR may differ in various pig populations. As to the response of 1·4 piglets per litter estimated in our hyperprolific line by Bidanel *et al.* (1994), clearly the markers examined in Table 4 can only explain a small part of it. Further markers would therefore be worth investigating on the same samples.

5. Conclusion

The advantages of selective genotyping have been pointed out by several authors (e.g. Lander & Botstein, 1989; Soller, 1990). The method described in this paper provides an additional illustration of this principle. Recently, a selection experiment in mice has allowed creation of a map of QTL for body weight, based on marker frequency divergence observed after 21 generations of selection on approximately only 120 individuals typed (Keightley *et al.*, 1996). The feasibility of similar experiments on farm animals is, however, questionable in view of the other methods (e.g. crosses) available for the detection of QTL. It can be recommended only that steps such as DNA banking be taken for following marker frequency changes when a selection experiment is started. More generally, performance recording in most farm animal species offers the possibility of very intense selection which could usefully be exploited for detecting markers of interest for genetic improvement.

This is journal paper no. J-17107 of the Iowa Agriculture and Home Economics Experiment Station, Ames, Iowa project no. 3148.

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