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Genetic Control of Metabolism: Heritability Estimates of Enzyme Activities in Random-Bred Mice

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Summary. Heritability estimates were determined in the random-bred Q population of mice for seven enzymes, liver weight and body weight. The estimates were calculated by son-on-father regression at 10 weeks of age by mating Q strain males to inbred CBA females. Instead of using all the fathers and sons to calculate the heritability, families of the highest and lowest fathers were chosen as suggested by Hill (1970). The heritability of body weight was in general agreement with previous published data (0.40). The estimate for liver weight was higher (0.71*) and liver alkaline phosphatase was significant (0.52*). The estimates for the other enzymes were not significantly different from zero (plasma alkaline phosphatase, −0.12; lactate dehydrogenase, −0.34; pyruvate kinase, 0.29; alcohol dehydrogenase, −0.10; hexokinase, −0.10; malate dehydrogenase, −0.20).

Introduction

Most genetic studies of enzyme activities in the mouse, have been concerned with structural loci coding for enzymes, or with regulatory genes having a major effect on activity (review Paigen 1971). If enzyme activity is influenced by many genes at other loci, and since activity may be measured, it can also be studied as a metric character by the techniques of quantitative genetics.

Yuhas *et al.* (1967) and Nayudu and Moog (1967) have estimated the heritability of the specific activity of some enzymes using inbred strains of mice (h^2=0.3 to 0.7, av. 0.5). These estimates will, however, not be comparable to the additive genetic variance determined from random-bred mice (Falconer, 1960). Roderick (1960) has estimated a realised heritability for cholinesterase activity from a selection experiment. He obtained very different values between the two lines of rats selected upwards (0.13 and 0.58) and the two lines selected downwards (1.31 and 1.39).

The object of the work reported here was to investigate the quantitative genetic variation of enzyme activity in a random breeding population of mice (Q stock, Land and Falconer 1969) by estimating heritability from the regression of son-on-father, using inbred mothers. Seven enzymes and liver weight were measured and body weight was included as a comparison with published data. Only one was significantly different from zero. The heritability of body weight was in agreement with previously published work.

Abbreviations used. BW, body weight; LW, liver weight; PAP, plasma alkaline phosphatase (EC 3.1.3.1); LAP, liver alkaline phosphatase (EC 3.1.3.1); LDH, lactate dehydrogenase (EC 1.1.1.27/28); PK, pyruvate kinase (EC 2.7.1.40); ADH, alcohol dehydrogenase (EC 1.1.1.2); HK, hexokinase (EC 2.7.1.1); MDH, malate dehydrogenase (EC 1.1.1.37).

Methods

(i) *Animals and Chemicals*

The Q mice used as fathers were kindly supplied by Professor D. S. Falconer from his random breeding control population, which has been described (Land and Falconer 1969). The CBA mothers were obtained from Dr. Festing of the M. R. C. Laboratory Animal Centre, Carshalton. Unless otherwise stated all chemicals were obtained from Sigma.

(ii) *The characters: Body weight, liver weight and the assays for the activity of the seven enzymes*

Both fathers and their sons were analysed at 10 weeks of age. The techniques for the preparation of liver homogenates and erythrocyte lysates and the determination of the activity of the seven enzymes have been reported in detail elsewhere (Bulfield and Moore, 1974).

The extracts were tested for deterioration of the enzymes using a comparison of fresh and frozen CBA extracts. The enzymes chosen for analysis were those where no deterioration had taken place during storage. For each enzyme the fathers were all assayed on one day and the offspring all on one day. This will remove any bias due to possible daily variation within a group. The activity of each enzyme was determined five times on each animal and the mean of these values was used in the heritability calculation.

Activities are expressed as μmoles/min/gm of liver at 30 °C.

(iii) *Heritability estimates by parent-offspring regression*

Twenty-one males from the Q population were each mated to two inbred CBA females, and the Q fathers and their sons were all killed at exactly 10 weeks of age. The sons were all housed under identical conditions and sampled randomly. The heritability (and its standard error) of each character was calculated from the regression of son on father. This is equivalent to the intra sire regression of daughter on dam (Falconer 1960) where the heritability is twice the regression coefficient and the standard error of the heritability is twice the standard error of the regression.

Instead of using all the fathers and sons to calculate the heritability, families of the highest and lowest fathers

Table 1. *Means of the measurements of the nine characters on all the Q strain fathers (n = 21). Data also for the highest and lowest groups of fathers and their sons*

	Number of measurements per animal	Range of fathers	Average** coefficient of variation within animals	Means of fathers		Means of sons of fathers from	
				High group (n = 4)	Low group (n = 4)	High group (n = 12)	Low group (n = 12)
Body weight (gms)	1	32.20—24.64	—	31.05	25.51	26.05	24.62
Liver weight (gms)	1	1.90— 1.30	—	1.83	1.40	1.65	1.48
Enzymes:-							
PAP	3	18.31— 8.66*	—	18.11	9.47	16.40	16.67
LAP	3	9.34— 0.60*	—	8.13	0.98	6.35	4.65
LDH	5	153.0 —49.6+	2.76	125.7	70.2	101.9	110.5
PK	5	31.85—10.17+	2.26	24.07	11.49	25.09	24.03
ADH	5	.5873—.2881+	2.85	0.4408	0.3039	0.4422	0.4610
HK	5	.2650—.1368+	1.50	0.2340	0.1427	0.1979	0.2043
MDH	5	13.96— 9.12+	2.04	12.56	9.98	10.51	10.85

* King-Armstrong Units at 37 °C
+ μmoles/min/gm liver at 30 °C
** each enzyme assay was determined five times on each animal so coefficient of variation given represents of the repeatability of the technique.

were chosen as suggested by Hill (1970). The 21 fathers were killed and all the nine characters were determined on each. Then, for each character separately values were determined for three sons from each of the four highest and four lowest fathers (Hill, 1970).

Results

All the measurements made on the Q strain fathers (frequency distributions shown in fig. 1) have been tabulated showing means, coefficients of variations within animals. The data are arranged to show the means of the fathers of the highest and lowest groups and those of their sons (table 1). If there were major gene effects segregating in the Q population for any of the characters studied, this would be expected to show as gross clumping of the data displayed in fig. 1. No gross clumping can be observed.

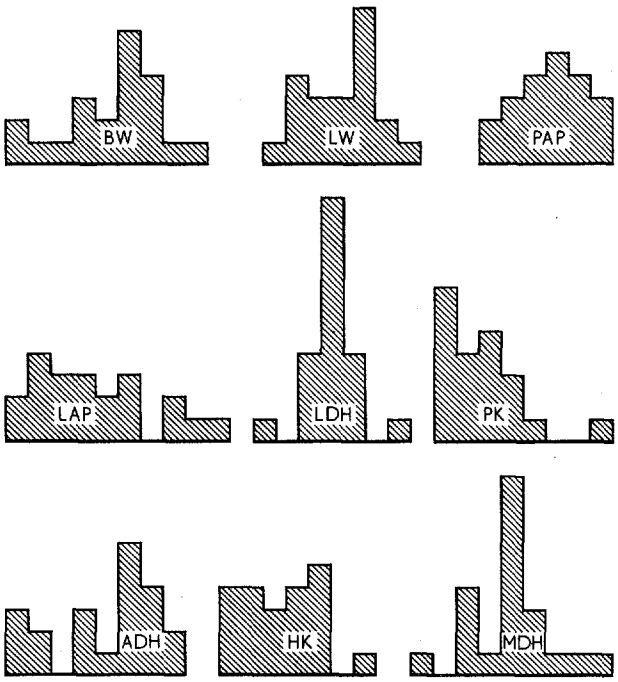

Fig. 1. Frequency distributions of the nine characters on the Q strain fathers (n — 21)

The data in table 1 form the basis of the parent offspring regression and the calculation of heritabilities, their standard errors and their significance (table 2).

Table 2. *Heritability estimates (h^2) of the nine characters with standard errors (S. E.) and levels of significance (P)*

Character	h^2	S. E.	P	Character	h^2	S. E.	P
BW	0.40	0.25	N. S.	LDH	—0.34	0.22	N. S.
LW	0.71	0.24	0.05	PK	0.29	0.29	N. S.
PAP	—0.12	0.40	N. S.	ADH	—0.10	0.32	N. S.
LAP	0.52	0.22	0.05	HK	—0.10	0.44	N. S.
				MDH	—0.21	0.42	N. S.

From table 2 it may be seen that the heritability estimates of the activity of six enzymes are low, and not significantly different from zero, and one (LAP 0.52*) is significant. The estimates for liver weight (0.71*) and 10 week body weight (0.40) are fairly high.

Discussion

The heritability of enzyme activity in a random breeding population gives an estimate of the proportion of the phenotypic character which is additively genetic. This could include variation from segregation at the structural locus and regulating loci for the enzyme (Paigen, 1971). It is probable that there are no genes with major effects segregating in this population for any of the enzymes studied as

there is no gross clumping of activity measurements in the Q strain mice used as fathers (fig. 1).

Although the heritability of the activity of only one enzyme is significantly positive, the generally large standard errors introduce an element of caution in placing too much reliance on these estimates. The heritability of 10 week body weight (0.40) is however similar to that previously determined on this population for 8 week body weight (0.34) by Monteiro and Falconer (1966). The use of inbred CBA mothers in the present experiment to estimate the heritability might bias it is there is a concentration of dominant or recessive alleles in the CBA's. This dominance, however, should be randomly distributed over the seven enzyme characters measured and would not be expected to bias all the heritability estimates in the same direction.

These heritability estimates of enzyme activity are lower than previously published ones determined by different designs and breeding systems (0.3 to 0.7, mean 0.5). The heritabilities of Yuhas *et al.* (1967) and Nayudu and Moog (1967) were estimated from data from inbred strains. These estimates would not be expected to agree with those calculated on random-bred mice.

Whitney, McClearn and DeFries (1970) have discussed in detail the influence of different experimental designs and breeding systems on the size of the heritability estimate of a physiological character. They found that when the heritability of alcohol preference in mice was estimated from data on F_1's and F_2's by crossing a pair of very different inbred strains (the "classical analysis") they obtained values of 0.18 to 0.35, depending on the method of calculation. They then determined the heritability by parent-offspring regression in a heterogenous population, formed by crossing 8 inbred strains, randomly mated. By this method they obtained a much lower heritability (-0.02 ± 0.13) not significantly different from zero.

Roderick (1960) obtained a realised heritability of cholinesterase activity, in rats, of 0.13 and 0.58 for two lines selected upwards and 1.31 and 1.39 for two lines selected downwards; an overall average of 0.78. However, the extremely high heritability downwards and the rather short duration of response to selection (4–6 generations) suggest fixation of a few pairs of alleles with major effects on cholinesterase activity.

Although the data from inbred strains indicate that the heritability of enzyme activity is fairly high (av. 0.5), the data from random-bred mice presented in this paper indicate much lower values (av. −0.06). If this observation can be generally confirmed then the additive genetic components of variance for enzyme activity are therefore small compared with such characters as body weight (0.40) and liver weight (0.71). This low heritability would then have to be reconciled with the widespread existence of electrophoretic enzyme variants in natural populations and the existence of many mechanisms for regulating enzyme synthesis by genetic (Paigen, 1971) or hormonal and environmental means (review Rechcigl, 1971).

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