INBREEDING AND EFFECTIVE POPULATION SIZE IN SIXTEEN CONTROL POPULATIONS OF MICE OF DIFFERENT ORIGINS

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SUMMARY

The realized rate of inbreeding and effective population size ($\bar{N}e$) were studied in eight control populations of mice of different origins each maintained in two environments. The main populations were kept under a controlled environment with 25 single pair matings for 70 generations. One replicate from each population kept in an environmentally uncontrolled laboratory with 15 single pair matings. One male and one female were selected for breeding from each family and used in a cyclical mating system. The realized inbreeding coefficient showed a repeating pattern of rises and falls over generations. The realized $\bar{N}e$'s were 33.7% to 65.5% smaller than the expected in different populations. Unequal contribution of different families to the next generation resulted in the variance of family size being larger than zero in almost all generations in all the populations. The genetically heterogeneous populations had smaller variance of family size and larger $\bar{N}e$ in both environments compared with those which had longer history of inbreeding.

INTRODUCTION

Rate of increase in inbreeding and effective population size under any mating plan are functions of fitness traits, and are affected by genetic and environmental factors. In populations of laboratory animals, even when the number of progeny per parent is intended to be constant, not all the families contribute equally to the next generation. Variations in fertility, mortality and sex ratio contribute to the variation in the number of progeny per parent. Published work on the breeding structure and effective population size of several large size contemporary populations of laboratory mammals maintained over a large number of generations are limited. The degree of agreement between the observed and expected effective population sizes in various populations used in this study will provide some information on the impact of original genetic heterogeneity of the populations and environmental factors on the effective population size.

MATERIALS AND METHODS

Four inbred lines of mice; A/J, RFM, DBA/1 and C57-BR/cd, which will be referred to as A, R, D, and C respectively, were mated reciprocally and six crossbred groups; RC, RA, DA, DR, AC, and CD were generated, but only AC and CD survived. The progeny of the 2-way crosses were reciprocally crossed again and were called generation zero of population IC. Four non-inbred strains of mice; Q, JH (10 pairs each), NB and XL (15 pairs each) were obtained from the Institute of Animal Genetics, Edinburgh,

Table 1. Some information about the main populations

Population	Pairing date first generation	Number of generations studied	Method of generating population	Inbreeding Coeff. Initial	Final
QL	1961/272†	72	non-inbred	0.0	0.4850
LX	1961/272	73	non-inbred	0.0	0.5832
NB	1961/272	73	non-inbred	0.0	0.7022
JH	1961/272	‡	non-inbred	‡	‡
OC	1962/240	69	QL*LX*NB*JH	0.0241	0.4407
AC	1962/260	69	A*C ¶	0.5000	0.7533
CD	1962/260	69	C*D ¶	0.5000	0.7894
IC	1962/240	69	A*C*D*R ¶	0.2500	0.6014
GL	1962/323	67	IC*OC	0.0709	0.2229

† Day one is January first.
‡ Population became extinct at generation 3.
¶ A, R, D and C are A/J, RFM, DBA/1 and C57-BR/cd inbred lines respectively.

Scotland, and were maintained as straightbreds. The JH showed some infertility and young mortality, and could not be continued more than 3 generations. The XL and Q were called LX and QL respectively. The 4-way crossbred progeny of the non-inbred strains were designated as generation zero of population OC. Population GL was formed by reciprocal crossing of the OC and IC. The populations were maintained from 1961 to 1979 (67 to 73 generations, Table 1). One replication from each of the 8 main populations was sampled between 1964 to 1966 by taking 15 pairs of mice from each population. Each replicate will be identified by adding the letter "R" to the name of the main population (Table 2)

All the main populations were kept in an environmentally controlled laboratory with 22±1° C temperature and 45±5 % relative humidity. The replicates were maintained in a poorly heated, poorly air conditioned building. Maximum temperature in this building, which fluctuated with outside temperature, was around 30° C, and minimum occasionally reached the freezing point. The mice were fed a pelleted mouse breeder ration *ad libitum* throughout the course of the study. Matings were made every 91 days, and only the first parity litters were used for breeding in so far as possible. All the main populations, except the GL, were maintained with 25 single pair mating per generation. The GL was maintained with a breeding sample of 49 males each mated to two females until generation 24 and with 50 males each mated to 2 females in each generation thereafter. The replicates were all raised with 15 single pair mating per generation. One male and one female were selected from each litter as the parents for the next generation. The foundation pairs were given family number from one to n. The son was given

Table 2. Some information about the replicate populations

Pop.	Pairing date first generation	Generation of main population sampled	Number of generation Studied	Inbreeding Coef. Initial	Inbreeding Coef. Final
QL-R	1964/328	13	59	0.2123	0.6456
LX-R	1966/354	22	50	0.3427	0.7762
NB-R	1966/018	17	54	0.3343	0.8216
OC-R	1964/328	9	59	0.1195	0.5887
AC-R	1966/258	17	51	0.6075	0.8553
CD-R	1966/096	15	53	0.6476	0.8617
IC-R	1966/257	17	42	0.4076	0.7711
GL-R	1966/362	17	50	0.1289	0.5379

the family number of his sire, while his mate came from another family varying systematically in different generations. Males of the r-th family in generation 1, 2, . . t' within each cycle (t'=n-1) mated with females belonging to families r+1, r+2, . . r+t' to produce generations 2, 3, . . t'+1=1, respectively. Each cycle took n-1 generation. The mating pattern was disrupted in some generations, mainly due to failure of a litter to provide the required healthy progeny or sire and/or dam infertility and death.

The coefficient of inbreeding for all the individuals (N=217,982) was computed by the method of coancestry. The realized effective population size over the course of the study for each population ($\bar{N}e$) was computed by the formula $(1-1/2\bar{N}e)^t = \Pi(1-1/2Ne_i)$, where t is the number of generations and Ne_i is the effective population size in each generation calculated from the relationships $Ne_i=1/2\Delta F_i$. All the calculations regarding the observed rate of inbreeding and effective population size were performed on the individuals selected for breeding at each generation. The mean and variance of the progeny number selected for breeding from each family were computed for each generation, and their means were calculated over all generations for each population. The formula $Ne=(N'\bar{k}-2)/(\bar{k}-1+\sigma^2_k/\bar{k})$, where N' is the number of grandparents and k is the number of gametes contributed by them (Kimura and Crow, 1963), was used to compute the effective population size, and the results were compared with those computed from the pedigree.

RESULTS AND DISCUSSION

The average inbreeding coefficients of each population showed a repeating pattern of rises and falls by generations, which was due to the systematic movement of females among the male families. The peaks in inbreeding coefficient appeared after each 12 and 7 generations in the main and replicate populations respectively, as expected from the theory (Farid *et al.*, 1986). The patterns were clear and regular in most of the populations,

but it was irregular in some of the populations which frequently encountered severe fertility problems, leading to the disruption of the mating system in some generations.

The inbreeding coefficients of the populations in the first and the last generations are shown in Tables 1 and 2, and the estimates of the realized $\bar{N}e$ of the populations are presented in Table 3. The realized rates of inbreeding in the populations were much faster than what were expected based on the planned population sizes and mating system. This was partly due to the fact that most of the populations had been started with a small number of mice (10 or 15 pairs) and the population numbers had been intentionally kept below 25 pairs during the early generations (the size of breeding segment of the replicates was 15 pairs from the first generation). Thus, the $\bar{N}e$'s in the main populations were computed starting from those generations in which the number of the breeding individuals was raised to be 25 pairs. The GL was not included in this comparison. The percentages of deviation of the realized $\bar{N}e$ from the expected values (the expected values were 97.3 and 57.9 for the main and replicate populations respectively; Farid *et al.*, 1986) are presented in Table 3. The $\bar{N}e$'s in the GL-R, OC, OC-R, QL and QL-R showed the least amount of deviation (<37.5%) from the expected. The $\bar{N}e$'s in the crosses between the inbred lines, and the LX showed almost similar deviations from the expected within each environment. The $\bar{N}e$'s in the NB and NB-R populations showed the highest deviations from the expected (65.5%). The results showed a fairly good agreement between the main and replicate populations in their ranking order for the deviation between the observed and expected $\bar{N}e$'s within each environment.

The differences between the realized and expected $\bar{N}e$'s were due to the unequal number of progeny per parents and also disruptions in the planned mating system (i.e. heram mating, raising second parity litters, overlapping generations). The variance of family size measures the degree of the differential contribution of different families to the next generation. The number of generations in which all the families contributed exactly two individuals to the next generation ($\sigma^2_k=0$) was indeed very small, ranging between zero to 5 in different populations (Table 3). The mean and standard deviation of the variance of family size per generation for both sexes combined in more than half of the populations were more than 2 (Table 3), which is the variance of family size under random mating. The number of breeding individuals in a large portion of the generations in most of the populations was maintained as planned, but the number of individuals available for selection was occasionally below the desired number in some generations, resulting in disruption of the planned mating system. The QL, QL-R, OC, OC-R, GL and GL-R did not have any fertility problems and so the number of breeding individuals was maintained as planned, and thus differences between the realized and expected $\bar{N}e$ were entirely due to the unequal number of progeny per parent in these populations.

Table 3. The realized effective population size ($\bar{N}e$), % deviation of realized and expected† $\bar{N}e$'s (%Dev.), number of generations in which variance of family size was zero(No. $\sigma^2_k=0$), and mean and standard deviation of variance of family size per generation (σ^2_k)

Pop.	$\bar{N}e$	%Dev.‡	No. $\sigma^2_k=0$ M	F	M+F	σ^2_k Mean	SD
QL	53.47	-33.7	2	2	0	1.887	5.556
QL-R	36.56	-37.5	3	2	2	1.406	.837
LX	41.38	-49.1	0	0	0	3.075	5.673
LX-R	22.99	-60.9	1	1	1	2.928	2.108
NB	29.97	-65.6	0	0	0	4.305	4.704
NB-R	20.75	-65.5	1	1	1	3.067	2.964
OC	61.33	-36.6	1	2	2	1.303	1.096
OC-R	38.35	-34.8	6	5	5	1.286	1.154
AC	48.37	-48.9	0	0	0	2.316	2.699
AC-R	25.31	-56.6	2	2	2	2.734	2.021
CD	39.58	-49.2	0	0	0	2.670	2.891
CD-R	28.04	-52.2	3	4	3	2.409	2.142
IC	54.05	-40.7	3	2	1	1.771	1.883
IC-R	21.81	-62.7	2	1	1	2.682	3.114
GL	184.96						
GL††			8	3	2	1.012	1.330
GL¶			0	0	0	.853	.659
GL-R	38.90	-33.7	8	4	4	1.179	1.164

† The expected effective population sizes were 97.3 and 57.9 for the main and replicate populations respectively.
‡ Computed over those generations of the main populations in which the intended number of breeding individuals was 25 pairs
†† Computed from the male families
¶ Computed from the female families

The ratio of the effective population size computed from the formula $\bar{N}e_1=(N'\bar{k}-2)/(\bar{k}-1+\sigma^2_k/\bar{k})$ over that computed from $\bar{N}e_2=2N-2$ would be unity if all the families had equal contribution to the next generation ($\sigma^2_k=0$). The deviation of this ratio from unity measures the combined effects of unequal contribution of different families to the next generation and disruptions in the original mating plan. The ratios of $\bar{N}e_1/\bar{N}e_2$ were maximum in the populations which did not have fertility problems (GL-R, OC, OC-R, QL, QL-R), ranging between 0.60 to 0.64 (Table 4). These values indicate that the variance of family size reduced the effective population size by about 40% in these populations. This ratio was smaller (between 0.53 to 0.09) in the other populations due to the combined effects of non-zero variance of family size and violation in the mating system.

Table 4. The effective population size computed from the formula $\bar{N}e_1=(N'\bar{k}-2)/(\bar{k}-1+\sigma^2_k/\bar{k})$, and its ratios over $\bar{N}e_2=2N-2$ and that computed from the pedigree ($\bar{N}e_3$)

Pop.	$\bar{N}e_1$	$\bar{N}e_1/\bar{N}e_2$	$\bar{N}e_1/\bar{N}e_3$	Pop.	$\bar{N}e_1$	$\bar{N}e_1/\bar{N}e_2$	$\bar{N}e_1/\bar{N}e_3$
QL	55.48	.63	1.04	QL-R	33.96	.60	.93
LX	34.85	.38	.84	LX-R	11.38	.22	.50
NB	26.36	.30	.88	NB-R	15.08	.30	.73
OC	58.18	.61	.95	OC-R	36.33	.64	.95
AC	43.99	.50	.91	AC-R	19.04	.35	.75
CD	36.89	.43	.93	CD-R	26.42	.47	.94
IC	50.39	.53	.93	IC-R	4.07	.09	.19
GL	----	---	---	GL-R	36.43	.64	.94

The results showed that the genetic structure of a population plays a major role in its ability to maintain the $\bar{N}e$ close to the census number of breeding individuals. The larger the genetic heterogeneity, or shorter the inbreeding history of a population, the smaller the variance of family size and the closer the realized and expected $\bar{N}e$'s under any mating plan and environmrntal condition. This conclusion is based on the fact that the populations ranked fairly similar for all the parameters studied in both environments, and that the rate of inbreeding and variance of family size were generally smaller and the effective population size was larger in the OC, OC-R, GL-R, QL and QL-R compared with the other populations of comparable size. The OC and GL had crossbred origin, and therefore were genetically heterogeneous. The QL and QL-R were similar to the above two populations with respect to all the parameters studied, possibly because QL originated from crosses between several non-inbred strains (Falconer, 1973).

The ratio of $\bar{N}e_1$ over the effective population size computed from the pedigree ($\bar{N}e_3$) indicates how accurately the effective population size, and therefore the rate of inbreeding, could be computed without using the pedigree. The estimates (Table 4) indicated that this ratio was larger than 0.9 in many of the populations, even in some populations such as CD in which occasionally the original mating system was disrupted. Frequent violation of the underlying assumptions upon which the formula was developed, resulted in weaker agreement, as expected.

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