Theor. Appl. Genet. 58, 49-53 (1980)

Establishment of Equilibrium for the Dominant Lethal Gene for Manx Taillessness in Cats

S. Adalsteinsson
The Agricultural Research Institute, Animal Production Department, Keldnaholt, Reykjavík (Iceland)

Summary. An account is given of a model by which the dominant gene for Manx taillessness in cats is maintained at a stable equilibrium value in cat populations in spite of the homozygous condition being lethal. The model assumes that *M*-carrying sperm have a selective advantage during fertilization, and that *M*-carrying chromatids are selectively retained at the second maturation division. Estimates of fertilization parameters differed significantly from the value 0.5, which is the expected value if selective fertilization is absent.

Key words: Cats – Taillessness – Selective fertilization – Equilibrium

Introduction

Manx taillessness in cats is believed to have arisen by mutation among domestic cats on the Isle of Man, where the first mention of this condition has been traced back to 1835 (Todd et al. 1979). It was shown by Suomalainen (1956) that Manx taillessness was due to an autosomal dominant allele with full penetrance and variable expressivity, and that this allele in the homozygous condition was lethal. The same conclusion was reached by Todd (1961, 1964).

Basrur and De Forest (1979) showed that when tailless females were mated to tailless males, some grossly distorted foetuses occurred in the uterus during early gestation together with apparently normal tailless and normal tailed foetuses. The abnormal foetuses all showed similar malformations of the central nervous system, which included local overgrowth of tissue in both the brain and spinal cord. These authors postulated that 'the basic underlying mechanism for the Manx condition may be similar to that postulated for Brachyuric mice, i.e. the presence of defective cell surface antigens'.

Todd et al. (1979) reported that the manx allele showed a frequency of 0.163 on the Isle of Man. Such a high frequency can only be maintained by relatively strong selection for the lethal allele. It was suggested by Todd et al. (1979) that this selection consisted of human preference for tailless cats under the prevailing conditions on the Isle of Man.

An alternative explanation is offered in this paper. It is suggested that selective fertilization with *M*-carrying sperm occurs, and that the *M*-carrying chromatid is selectively retained at the second maturation division in eggs which are fertilized by *m*-carrying sperm.

The result of this selective fertilization should be measurable in terms of disturbed segregation ratios and should also result in a stable frequency of the M-allele higher than zero. It should be noted in this connection that Bateman (1960) found selective fertilization and selective sperm penetration to be associated with certain abnormal alleles at the *T*-locus in the mouse, which is responsible for taillessness in that species.

Material and Methods

A model which describes selective fertilization in terms of two parameters, u and v, is shown in Table 1. According to this model the parameter u measures the probability of fertilization of an egg with an *M*-carrying sperm while 1-u is the probability of fertilization with an *m*-carrying sperm. The parameter u can only be measured in matings where *M*- and *m*-carrying sperm compete with each other on equal footing, i.e., in matings where the male is of genotype *Mm*. In a similar way, v measures the probability in eggs fertilized by *m*-carrying sperm that an *M*-carrying chromatid of the egg is retained at the second maturation division and that the *m*-carrying chromatid is expelled in the second polar body, while 1-v is the probability that the *m*-carrying chromatid is retained.

Table 2 shows in the uppermost part (a) the expected combinations of the alleles from sire and dam in the three matings *Mm* × *Mm*, *Mm* × *mm* and *mm* × *Mm*, measured in terms of the fertilization parameters u and v. In part (b) of Table 2 are shown the expected ratios of the three progeny genotypes *MM*, *Mm* and *mm*

0040-5752/80/0058/0049/$ 1.00

Table 1. Model for selective fertilization in Manx cats

Probability of	Parameters in model	Normal situation
Fertilization by *M*-carrying sperm	u	0.5
Fertilization by *m*-carrying sperm	1-u	0.5
Sum	1	1.0
Retention of *M*-carrying chromatid in egg[a]	v	0.5
Retention of *m*-carrying chromatid in egg[a]	1-v	0.5
Sum	1	1.0

[a] For eggs fertilized by *m*-carrying sperm

Table 2. Expected combinations of alleles (a) total frequencies of genotypes (b) frequencies of genotypes alive (c), and symbols for observed numbers (d)

Allele from		Mating		
Sire	Dam	*Mm* ♂ × *Mm* ♀	*Mm* ♂ × *mm* ♀	*mm* ♂ × *Mm* ♀
(a)				
M	*M*	0.5 u	...	...
M	*m*	0.5 u	u	...
m	*M*	(1-u) v	...	v
m	*m*	(1-u) (1-v)	1-u	1-v
Sum		1	1	1
Genotype of progeny		Frequency		
(b)				
MM		0.5 u (die)	...	...
Mm		0.5 u + v-uv	u	v
mm		(1-u) (1-v)	1-u	1-v
Sum alive		(2-u)/2	1	1
(c)				
Alive progeny	*Mm*	(u + 2v-2uv)/(2-u)	u	v
	mm	2(1-u) (1-v)/(2-u)	1-u	1-v
Sum		1	1	1
(d)				
Observed numbers	*Mm*	n_1	n_3	n_5
	mm	n_2	n_4	n_6
Sum		N_1	N_2	N_3

in terms of u and v. All *MM* genotypes die, and the sum of the born genotypes from the *Mm* × *Mm* mating is therefore below unity. In part (c) of Table 2 are shown the expected ratios of *Mm* and *mm* progeny based on live born progeny only, and in the bottom part of Table 2 are shown the symbols for observed numbers of *Mm* and *mm* progeny from the three matings.

The expected ratios of viable progeny of genotypes *Mm* and *mm* in part (c) of Table 2 were used as basic class probabilities when forming a likelihood product from which the parameters u and v were estimated by the method of maximum likelihood (Bailey 1961).

The observed numbers from which the maximum likelihood estimates of the parameters, $\hat{u}$ and $\hat{v}$, were obtained, are from several different sources in the literature, as seen in Table 3.

From the logarithms of the likelihood function, the first and second derivatives were obtained. The variance-covariance matrix of the parameter estimates was obtained as the inverse of the negative expectations of the second derivatives. This matrix was used to obtain intermediate adjustments of the estimated values of u and v. The estimation of u and v was carried out by iteration, where guessed initial values of u and v, u_0 and v_0 were inserted into the first derivatives of the logarithm of the likelihood function. The resulting values were multiplied by the variance-covariance matrix mentioned above and the products added to the first guessed values of u_0 and v_0, giving the improved values u_1 and v_1. These improved values of u and v were again inserted into the first derivatives, and new results obtained. These were used to calculate new improvements in u and v, and so on, until the improvements had become practically zero.

The likelihood function, the first derivatives of the logarithms of the likelihood function and the negative expectations of the second derivatives of the likelihood function are shown in Appendix I.

Results

The final values of the estimated parameters u and v were as follows.

u ± s.e. (u) = 0.580 ± 0.041; (t = 1.94), and

v ± s.e. (v) = 0.565 ± 0.034; (t = 1.90).

When the deviations of u and v from the expected value 0.5 are tested by a one-sided t-test, both are significant ($P < 0.05$.).

The numerical values of the expected ratios of live *Mm* and *mm* progeny from the four possible inter se matings of *Mm* and *mm* genotypes are shown in Table 4. In the same table are also shown the expected frequencies of the matings in terms of p, the frequency of *M*, and q, the frequency of *m*, in a given cat population. It can be seen from Table 4 that the expected ratios of progeny from an inter se mating of tailless parents are 0.743 *Mm* and 0.257 *mm* progeny. These ratios are far removed from the basic ratios 0.667 *Mm* and 0.333 *mm* progeny which are expected when all homozygotes die and no selection favours the heterozygotes.

The expected numerical ratios in Table 4 have been used to calculate expected numbers of *Mm* and *mm* progeny for each type of mating. Expected numbers of *Mm* and *mm* progeny have also been calculated under the assump-

tion of the ratios 0.667 *Mm* and 0.333 *mm* from the *Mm* X *Mm* matings and 0.5 *Mm* and 0.5 *mm* progeny from both the other matings. The observed numbers of the two types of progeny as well as the expected numbers for the two above possibilities are shown in Table 5. It is seen from Table 5 that the expected numbers, which are obtained under the assumption that selective fertilization is operative, are very similar to the observed numbers for all matings. This is also borne out by the χ^2-values where the observed numbers differ significantly from expectation

Table 3. Observed numbers of *Mm* and *mm* progeny from three different types of matings

Mating	Offspring			Reference
	Mm	*mm*	Total	
Mm ♂ X *Mm* ♀	65	28	93	Suomalainen (1956)
	88	27	115	Todd (1961)
	9	3	12	Todd (1964)
Sum	162	58	220	
Mm ♂ X *mm* ♀	21	19	40	Suomalainen (1956)
	15	12	27	Todd (1961)
	17	6	23	Wilson (see Todd 1961)
Sum	53	37	90	
mm ♂ X *Mm* ♀	36	27	63	Todd (1961)
	30	22	52	Anthony and Kennel (see Todd 1961)
	13	10	23	Todd (1964)
Sum	79	59	138	

Table 4. Numerical values of expected ratios of *Mm* and *mm* progeny from individual matings, and expected frequencies of each mating under assumption of a random mating system

Mating	Expected ratios of progeny		Expected freq. of mating	Expected frequency of progeny	
	Mm	*mm*		*Mm*	*mm*
Mm ♂ X *Mm* ♀	0.743	0.257	$4p^2q^2/d$[a]	$2.97p^2q^2/d$	$1.03p^2q^2/d$
Mm ♂ X *mm* ♀	0.580	0.420	$2pq^3/d$	$1.16pq^3/d$	$0.84pq^3/d$
mm ♂ X *Mm* ♀	0.565	0.435	$2pq^3/d$	$1.13pq^3/d$	$0.87pq^3/d$
mm ♂ X *mm* ♀	0.000	1.000	q^4/d	0	q^4/d

[a] d = divisor = $(1-p^2)^2$

Table 5. Expected numbers of *Mm* and *mm* progeny from each type of mating when selective fertilization is absent and present, together with observed numbers

Mating	Selective fertilization				Observed numbers		Total
	absent		present				
	Mm	*mm*	*Mm*	*mm*	*Mm*	*mm*	
Mm ♂ X *Mm* ♀	146.7	73.3	163.4	56.6	162	58	220
Mm ♂ X *mm* ♀	45.0	45.0	52.2	37.8	53	37	90
mm ♂ X *Mm* ♀	69.0	69.0	77.9	60.1	79	59	138

when no selective fertilization is postulated, ($\chi^2_3 = 10.54$; $P < 0.05$), but by bringing selective fertilization into the picture, the discrepancies are small and non-significant ($\chi^2_1 = 0.11$; $P < 0.10$). The difference $-\chi^2_2 = 10.43$ ($P < 0.01$) shows that almost all the deviations of the observed numbers have been explained by the two parameters u and v.

The expected ratios of mating types shown in Table 4, together with the expected frequency of *Mm* and *mm* progeny, are functions of both the fertilization parameters, u and v as well as p and q, the frequencies of the genes *M* and *m* in a random mating population. It can be shown that the sum of all *Mm* progeny in Table 4 and p, the frequency of *M* are as follows in generation i and i + 1.

Sum *Mm* progeny $= p_i\,(0.682p_i + 2.29)/(1 + p_i)^2$

and $p_i + 1 = \frac{1}{2}p_i\,(0.682p_i + 2.29)/(1 + p_i)^2$.

The change in p_i from one generation to the next can be found by starting with a value of p_i between 0 and 1 and then calculating the value of $p_i + 1$ as half the frequency of the *Mm*-progeny in generation i.

The above formulae yield $p = 0.083$ as an equilibrium value. If a mutation of *m* to *M* occurred in a population of 5000 individuals the initial frequency of *M*, p_0, is 0.0001, and it would take nearly 120 generations to reach the equilibrium value from this starting point.

Discussion

The high frequency of the dominant lethal allele *M*, for taillessness in cats on the Isle of Man has been explained by human preference for taillessness in cats (Todd et al. 1979). The hypothesis put forward in the present paper is that to a large extent the gene *M* takes care of itself by having a selective advantage during fertilization.

The latter hypothesis has been tested by using all available data on segregation ratios of tailless and normal cats in experimental or controlled matings, and by estimating parameters which measure the deviations of the observed ratios from those expected under the assumption of normal segregation and complete elimination of *MM* homozygotes.

The estimated parameters, u and v, are significantly different from their expected values of 0.5, and the deviations of the segregation results from expectation can be fully accounted for by the deviations of the estimated parameters from 0.5.

The parameter values, when used to calculate the expected equilibrium value of p, the frequency of *M*, lead to an equilibrium value of $p = 0.083$. The high value of $p = 0.163$, reported by Todd et al. (1979) is about twice as high as the estimated equilibrium value. The parameters for selective fertilization estimated on the basis of unrelated segregation data can thus explain a substantial proportion of the *M*-alleles on the Isle of Man, but other factors seem to have been at work as well. It is thus reasonable to assume that both human preference and selective fertilization play a role in the high frequency of *M* on the Isle of Man. It should further be borne in mind that the equilibrium value of 0.083 found in the present study is calculated from data which have been obtained in a situation of controlled breeding for only one generation. The Isle of Man value of 0.163 is that observed after the cat population had been exposed to perhaps more than a century and a half of intense selective pressure by man for the Manx phenotype. The two situations are thus hardly comparable, and the difference between the two equilibrium values should therefore not be overemphasized.

No previous reports on selective fertilization in cats have been traced, but Bateman (1960) showed that selective fertilization was active in connection with certain alleles for taillessness in the mouse. Adalsteinsson (1970) found that selective fertilization seemed to be present in connection with certain colour alleles at the *A*-locus in sheep.

The findings by Basrur and DeForest (1979) that the lethal action of the *M* gene is connected with malformations of the central nervous system may be of importance in this connection, and may provide a link between the selective fertilization found in mice, cats and sheep. Pigment-producing melanocytes originate in the neural crest and it is conceivable that mutant alleles which affect tissues of neural crest origin have one or more features in common which enhance selective fertilization.

It has been pointed out by one of the reviewers of this paper that the aberrant segregation ratios shown in Table 3 could have arisen through increased viability of *Mm* zygotes irrespective of the genotype of the parents. This hypothesis has been examined, and the maximum likelihood estimates of ratios of *Mm* offspring under this hypothesis are 0.747 for *Mm* × *Mm* matings and 0.596 for *Mm* × *mm* matings, or quite similar to the ratios obtained from the author's model. The differential viability model would, however, be expected to lead to either an increase in litter size when *Mm* progeny occurred in the litter, or an increased mortality of *mm* offspring to counterbalance the excess of heterozygotes. The differential viability model will therefore not necessarily lead to a simpler or a more realistic situation. The data in Table 3 do not permit discrimination between the two models.

Appendix I

Likelihood function:

$$e^L \propto \{(u + 2v - 2uv)/(2 - u)\}^{n_1} \cdot$$

$$\cdot \{2(1 - u)(1 - v)/(2 - u)\}^{n_2} \cdot$$

$$\cdot u^{n_3}\,(1 - u)^{n_4}\,v^{n_5}\,(1 - v)^{n_6}$$

First derivatives of the logarithms of the likelihood function:

$$S_1 = \frac{dL}{du} = \frac{n_1\,(1-2v)}{u+2v-2uv} + \frac{n_1+n_2}{2-u} - \frac{n_2+n_4}{1-u} + \frac{n_3}{u}$$

$$S_2 = \frac{dL}{dv} = \frac{2n_1\,(1-u)}{u+2v-2uv} - \frac{n_2+n_6}{1-v} + \frac{n_5}{v}$$

Negative expectations of the second derivatives of the likelihood function:

$$-E\left(\frac{d^2L}{du^2}\right) = N_1\left\{\frac{(u-v)^2}{(u+2v-2uv)(2-u)} - \frac{1}{(2-u)^2} + \frac{2(1-v)}{(1-u)(2-u)}\right\} + \frac{N_2}{u(1-u)}$$

$$-E\left(\frac{d^2L}{dudv}\right) = 2N_1\left\{\frac{(u-v)^2}{(u+2v-2uv)(2-u)}\right\}$$

$$-E\left(\frac{d^2L}{dv^2}\right) = 2N_1\left\{\frac{2(u-v)^2}{(u+2v-2uv)(2-u)} + \frac{1-u}{(1-v)(2-u)}\right\} + \frac{N_3}{v(1-v)}$$

Literature

Adalsteinsson, S. (1970): Colour inheritance in Icelandic sheep and relation between colour, fertility and fertilization. J. agric. Res. Iceland **2** (1), 3-135

Bailey, N.T.J. (1961): Introduction to the Mathematical Theory of Genetic Linkage. Oxford: Oxford Univers. Press

Basrur, P.K.; DeForest, M.E. (1979): Embryological impact of the Manx gene. Proc. First Intern. Conference of Domestic Cat Population Genetics and Ecology, Siracusa (Sicily), Italy. Carnivore Genetics Newsletter **3** (10), 378-384

Bateman, N. (1960); Selective fertilization at the T-locus. Genet. Res. **1**, 226-238

Suomalainen, E. (1956): Hännättömyyden periytymissuhteista kissalla (The inheritance of taillessness in the cat). In: Novant'anni delle Leggi Mendeliane (Ed. Gedda L.), pp. 219-234. Rome: Istituto Gregorio Mendel

Todd, N.B. (1961): The inheritance of taillessness in Manx cats. J. Hered. **52**, 228-232

Todd, N.B. (1964): The Manx factor in domestic cats. J. Hered. **55**, 225-230

Todd, N.B.; Garrad, L.S.; Blumenberg, B. (1979): Mutant allele frequencies in domestic cats of the Isle of Man. Proc. First Intern. Conference of Domestic Cat Population Genetics and Ecology, Siracusa (Sicily), Italy. Carnivore Genetics Newsletter **3** (10), 388-407.

Received February 20, 1980
Communicated by D. Van Vleek

Dr. S. Adalsteinsson
The Agricultural Research Institute,
Animal Production Department,
Keldnaholt, 110 Reykjavik (Iceland)