

ORIGINAL ARTICLE

Inheritance of litter size at birth in farmed arctic foxes (*Alopex lagopus*, Canidae, Carnivora)

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Natural populations of the arctic fox (*Alopex lagopus*, Canidae, Carnivora) differ drastically in their reproductive strategy. Coastal foxes, which depend on stable food resources, produce litters of moderate size. Inland foxes feed on small rodents, whose populations are characterized by cycling fluctuation. In the years with low food supply, inland fox populations have a very low rate of reproduction. In the years with high food supply, they undergo a population explosion. To gain insight into the genetic basis of the reproductive strategy of this species, we performed complex segregation analysis of the litter size in the extended pedigree of the farmed arctic foxes involving 20 665 interrelated animals. Complex segregation analysis was performed using a mixed model assuming that the trait was under control of a major gene and a large number of

additive genetic and random factors. To check the significance of any major gene effect, we used Elston–Stewart transmission probability test. Our analysis demonstrated that the inheritance of this trait can be described within the frameworks of a major gene model with recessive control of low litter size. This model was also supported by the pattern of its familial segregation and by comparison of the distributions observed in the population and that expected under our model. We suggest that a system of balanced polymorphism for litter size in the farmed population might have been established in natural populations of arctic foxes as a result of adaptation to the drastic fluctuations in prey availability.

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Introduction

Arctic fox (*Alopex lagopus*, Canidae, Carnivora) provide a very interesting model for studies in evolution and genetic control of life history traits in animals. Natural populations of this species inhabiting coastal and inland areas depend on different resources and differ drastically in their reproductive strategy. Coastal foxes feed on sea birds, fish, seals and marine invertebrates (Hersteinsson and Macdonald, 1996). There is little fluctuation in the availability of these resources from year to year. Every year, the coastal foxes produce litters of moderate size. Conversely, the inland foxes depend on small rodents (mainly voles and lemmings), whose populations are characterized by cyclic fluctuation (Angerbjörn *et al.*, 1999). In the years with low food supply, inland fox populations demonstrate a very low rate of reproduction, if any. In the years when the prey species are abundant, the female inland foxes are able to produce up to 16–18 offspring. The mean litter size and the coefficient of variation are, on average, 1.5-fold higher

in the inland populations (Tannerfeldt and Angerbjörn, 1996, 1998; Elmhagen *et al.*, 2000).

Analysis of inheritance of litter size in the arctic fox may give insight into evolution and diversification of the reproductive strategy of this species. However, studies in quantitative genetics of natural populations set difficult problems. Genetic analysis requires the trait measurements on many individuals of known parentage. Natural populations rarely provide this opportunity, although recently several new methods of paternity testing have been developed and applied to the field studies for analysis of heritability of life history traits (Slate *et al.*, 1999; Kruuk *et al.*, 2000; Merila and Sheldon, 2000; Kingsolver *et al.*, 2001). Another problem is that natural populations are always under the strong influence of many random and systematic environmental effects. It is impossible to control the environmental variables in the field and therefore it is hard to assess the genetic architecture of the traits. These problems can be addressed in a breeding experiment under controlled conditions (Aulchenko *et al.*, 1998, 2002; Bacigalupe *et al.*, 2004; Carter *et al.*, 2004; Nespolo *et al.*, 2005). Weigensberg and Roff (1996) demonstrated that laboratory estimates of heritability provide reasonable estimations of both the magnitude and the significance of heritability in nature.

In this study, we carried out complex segregation analysis of the litter size in the extended pedigree of the

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farmed arctic foxes using a mixed model assuming that the trait was under control of a major gene and a large number of additive genetic and random factors. Recent studies have demonstrated the efficiency of this method for analysis of quantitative and qualitative traits of mammals (Janss *et al.*, 1997; Aulchenko *et al.*, 1998, 2002; Axenovich *et al.*, 2004; Maki *et al.*, 2004).

Materials and methods

This study is based on the breeding records of arctic foxes of the blue veil breed maintained at the Puskinsky fur farm (Moscow district, Russia).

The founders of this breed were imported from Norway in 1959 (319 females, 79 males), 1964 (108 females, 40 males) and 1970 (40 females, 50 males). The breeding records used in this study contained data on the size of litters produced between 1985 and 1989 in 1936 crosses involving 833 females and 160 males. Litter size was scored at birth. Backward analysis of the records allowed us to reconstruct a complete pedigree of the breeding animals. The resulting pedigree involved 20 665 interrelated animals. The pedigree covered up to 12 generations and had a very complex structure. It contained multiple crosses and numerous loops; some lineages were inbred. However, the average inbreeding coefficient in the population was very low ($F=0.002$). The founders of this pedigree were 342 females and 91 males, whose origin was impossible to trace back.

Methods

Segregation analysis: Complex segregation analysis was performed using a mixed model of a major gene and a large number of additive genetic and random factors (Morton and MacLean, 1974). Three mathematical components form the basis of complex segregation analysis: the penetrance function, the gene frequency distribution and the transmission probabilities distribution. The effects of the model components are considered to be independent of each other. Thus, under the mixed model, the value of the quantitative trait y_i of some i th individual may be expressed as

$$y_i = \mu(g_i) + G_i + e_i$$

where $\mu(g_i)$ is the major gene effect, G_i is the impact polygenic factors, and e_i is the random effect.

It is assumed that the random effects are distributed normally with mean zero and variance σ_e^2 .

Assuming a diallelic (A_1 and A_2) autosomal major gene, the contribution of the major genic component may be described through means $\mu(g)$ defined for each major genotype $g = A_1A_1$, A_1A_2 and A_2A_2 . The frequency distribution of major genotypes in a population can be described by the population frequency of A_1 allele (q) under the assumption of panmixia and Hardy–Weinberg equilibrium.

For each triplet of major genotypes g , g_d and g_s , the model provides the probability $\Pr(g/g_d, g_s)$ of parents with genotypes g_d and g_s to have an offspring with genotype g . In the case of a diallelic major gene, this probability distribution is described via three transmission probabilities $\tau(g)$, that is, the probabilities of transfer of allele A_1 to offspring from a parent with genotype A_1A_1 , A_1A_2 or A_2A_2 . When Mendelian transmission of a

gene is valid, the $\tau(g)$ values are 1, 0.5 and 0 for A_1A_1 , A_1A_2 and A_2A_2 , respectively.

The distribution of the polygene in a pedigree consisting of N members follows the N -variate normal distribution with mean zero and the variance–covariance matrix, which is determined by the variance of polygene in population (σ_g^2) and the coefficients of kinship within pairs of individuals in the pedigree (Fisher, 1918; Lange *et al.*, 1976).

Thus, in our study, the mixed model of inheritance was expressed via parameters (q , $\mu(A_1A_1)$, $\mu(A_1A_2)$, $\mu(A_2A_2)$, $\tau(A_1A_1)$, $\tau(A_1A_2)$, $\tau(A_2A_2)$, σ_g^2 and σ_e^2).

The estimates of genetic parameters were obtained using the maximum likelihood method (Kendall and Stewart, 1951). Hypotheses were tested by the likelihood ratio test in a hierarchical manner. Twice the negative of the natural logarithm of the likelihood ratio is distributed approximately as χ^2 with degrees of freedom equal to the difference in number of independent parameters of the two models under comparison (Neyman and Pearson, 1928).

To check the major gene hypothesis, we compared three genetic models:

- (1) mixed Mendelian model: the transmission probabilities of the major gene are fixed at Mendelian values and all other parameters are estimated,
- (2) unrestricted model: all parameters, including transmission probabilities are estimated and
- (3) environmental model: implemented by fixing the transmission probabilities $\tau(A_1A_1) = \tau(A_1A_2) = \tau(A_2A_2) = q$.

According to Elston and Stewart (1971), the major gene hypothesis is accepted if:

- model (2) is significantly better than model (3),
- model (1) does not differ significantly from model (2).

We have previously mentioned that the pedigree under analysis contained many loops. The computation of exact likelihoods for a large pedigree with multiple loops is unaffordable in terms of computing power. Several methods to approximate likelihood have, therefore, been developed (Guo and Thompson, 1994; Stricker *et al.*, 1995, 1996; Wang *et al.*, 1996). We used the approximation approach under which the loops were cut-extended by introducing artificial phenocopies of some individuals in a pedigree (breakers), then the likelihood was computed conditional on the likelihood of the phenocopies (Stricker *et al.*, 1996; Wang *et al.*, 1996).

The computation of the exact likelihood of the extended pedigrees under the mixed model is feasible only in the case when the major gene component is excluded from the model (Hasstedt, 1991; Sham, 1998). To calculate the likelihood of the extended pedigrees under a complete mixed model, some approximation methods have been developed (Hasstedt, 1982, 1991; Fernando *et al.*, 1994; Lange, 1997). We used hypergeometric approximation (Cannings *et al.*, 1978; Lange, 1997).

If complex segregation analysis results in a simple genetic model (recessive or dominant), it is possible to run classical segregation analysis of siblings. Using the parameters coming from complex segregation analysis, we represented litter size as a dichotomous trait: large vs small. If small litter size is recessive, then the majority of

the parents producing at least one daughter with small litter size must be heterozygous. We selected the families with at least one daughter that produced small litters and calculated the expected number of such daughters in these families using the following equation:

$$\hat{m}_s = \frac{pm_s}{1 - (1 - p)^s} \quad (1)$$

where p is segregation ratio equal to 0.25 under the recessive model; s is the number of daughters and n_s is the sum of daughters in all families of s size. Under the recessive model, the observed and expected number of daughters having small and large litter size was compared using the χ^2 test.

Model of balanced polymorphism: To model a system of balanced polymorphism for litter size in a natural population of arctic foxes, we used parameters that resulted from the complex segregation analysis of the farmed population. We supposed that two alleles A_1 and A_2 were present in a population living in a regularly fluctuating environment. Females A_1A_1 and A_1A_2 produced large litters (m_1) every year, and females A_2A_2 produced small litters (m_2). Following the data of Frafjord (1993), Kaikusalo and Angerbjörn (1995) and Angerbjörn *et al.* (1995, 2001), we supposed that the prey have a population peak every 4 years. In years with low food supply, the survival rate of the small litters produced by A_2A_2 mothers was assumed to be k -times higher than that of large litters produced by A_1A_1 and A_1A_2 mothers. In the years when the prey was abundant, the offspring of all mothers were given an equal chance of surviving ($k = 1$).

The frequency of A_2 in a generation i was calculated iteratively as

$$q_i = q_{i-1} \frac{m_1 - q_{i-1}(m_1 - km_2)}{m_1 - q_{i-1}^2(m_1 - km_2)} \quad (2)$$

starting from an initial q_0 .

Software: Analysis of variance and regressions was carried out using the SYSTAT.10 package.

We used the MAN_QTL software for complex segregation analysis of quantitative traits under the mixed model, LOOP_EDGE software for breaking loops and selection of optimal set of breakers, and the computer program RECODE_PED.pl for checking the incompatibilities of pedigree structure. These programs were developed in the Institute of Cytology and Genetics and were available at <http://mga.bionet.nsc.ru>.

Results

Definition of phenotype: Litter size can be considered as a female trait (Falconer, 1989) or a combined phenotype depending on both breeding partners (Aulchenko *et al.*, 1998). We estimated the effects of female and male partners on the litter size produced in each cross. The female effect was significant ($F = 2.142$, $df_1 = 832$, $df_2 = 1102$, $P < 0.001$), whereas the male effect was negligible ($F = 1.040$, $df_1 = 159$, $df_2 = 1775$, $P = 0.365$). Therefore, we can consider litter size as a female trait.

Because the majority of females produced several litters, it seemed reasonable to define the phenotype as

average litter size. However, the length of the reproductive life of each female was determined by the breeders. This decision was made based upon the fur quality of the offspring and reproductive performance of a female in the previous breeding season. Figure 1 shows that the females left for the next breeding season had significantly larger litter size than the females excluded from reproduction after the breeding season. This means that the females producing smaller litters in any one breeding season had a lower chance of being allowed to breed again. To minimize this effect on the results of segregation analysis, we excluded the last scored litter of each female from further consideration. All females producing only one litter were assigned in genetic analysis as having an unknown phenotype. The number of phenotyped females was thus reduced to 529.

Next, we tested the effects of the parity number, the year and year \times parity interactions. The effects of the year and year \times parity interactions were not significant ($F = 1.386$, $df_1 = 3$, $df_2 = 1078$, $P = 0.246$, and $F = 1.493$, $df_1 = 15$, $df_2 = 1078$, $P = 0.1$, correspondingly), whereas the parity effect was highly significant ($F = 6.627$, $df_1 = 5$, $df_2 = 1078$, $P \ll 0.001$). Because this effect was nonlinear, we used the following logarithmic transformation to remove it: $y = x - 2.171 \cdot \log(n) + 1.165 \cdot \log^2(n)$, where x is measured litter size and n is the parity number.

The trait transformed in such a way did not show an effect of parity ($F = 0.439$, $df_1 = 5$, $df_2 = 1096$, $P = 0.821$). In our further analysis of inheritance, we define the litter size phenotype of each female as the mean transformed litter size produced in all breeding seasons but the last one.

Segregation analysis: Table 1 shows the results of segregation analysis of the litter size under different models. These results might be interpreted as evidence for the major gene control of the trait because (i) the Mendelian and unrestricted models do not differ significantly from each other ($\chi^2 = 5.4$, $df = 3$, $P > 0.15$) and (ii) the environmental model differs significantly from the unrestricted model ($\chi^2 = 7.86$, $df = 3$, $P < 0.05$).

We tried to simplify the Mendelian model assuming a dominant effect of the A_1 or A_2 allele. Table 1 shows that the model with the dominant effect of the A_1 allele does not differ significantly from either the Mendelian ($\chi^2 = 1.20$, $df = 1$, $P > 0.25$) or the unrestricted model

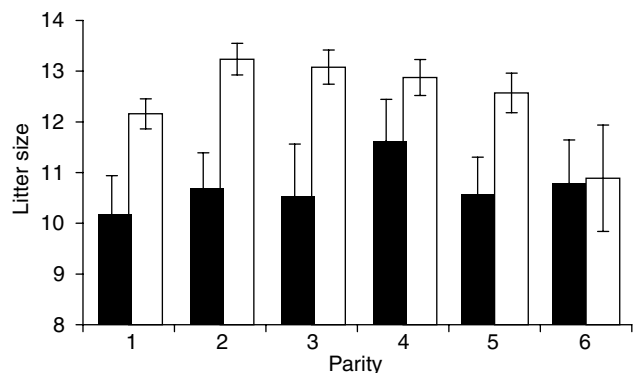


Figure 1 Mean (\pm s.d.) litter size in the females excluded from reproduction after the breeding season (filled) and the females left for the next breeding (blank).

Table 1 Results of complex segregation analysis of litter size in arctic foxes under different models of inheritance

Parameter	Model			
	Unrestricted	Environmental	Mendelian	Dominant effect of A_1
q	0.63	0.81	0.76	0.73
$\tau(A_1A_1)$	0.84	0.81 ^a	1.00 ^b	1.00 ^b
$\tau(A_1A_2)$	1.00	0.81 ^a	0.50 ^b	0.50 ^b
$\tau(A_2A_2)$	0.00	0.81 ^a	0.00 ^b	0.00 ^b
$\mu(A_1A_1)$	12.71	11.60	11.63	12.33
$\mu(A_1A_2)$	11.50	13.58	13.43	12.33 ^a
$\mu(A_2A_2)$	8.75	7.45	8.00	8.61
σ_G^2	0.04	0.67	0.11	0.24
σ_e^2	4.38	3.12	3.58	4.29
–LH	703.92	707.85	706.62	707.22
χ^2 (df) ^c		7.86(3)	5.40(3)	6.60(4)
P -value		<0.05	>0.15	>0.17

Abbreviations: q , allele A_1 frequency; $\tau(A_1A_1)$, $\tau(A_1A_2)$, $\tau(A_2A_2)$, transmission probabilities; $\mu(A_1A_1)$, $\mu(A_1A_2)$, $\mu(A_2A_2)$, major genotype means; σ_G^2 , additive polygene variance; σ_e^2 , environmental variance; LH, logarithm of likelihood; P , significant level of likelihood ratio test.

The major gene hypothesis is accepted if unrestricted model is significantly better than environmental one ($P < 0.05$) and Mendelian model does not differ significantly from unrestricted one ($P > 0.05$).

^aParameter value is constrained to equal preceding parameter value and is not estimated in this model.

^bParameter value is fixed.

^cLikelihood-ratio χ^2 (upper bound on degrees of freedom) testing the null hypothesis of no difference from the unrestricted model.

($\chi^2 = 6.60$, $df = 4$, $P > 0.15$). The model with the dominant effect of the A_2 allele differs from the Mendelian and unrestricted models ($\chi^2 = 5.94$, $df = 1$, $P < 0.025$ and $\chi^2 = 11.34$, $df = 4$, $P < 0.025$, respectively). Therefore, we may consider the Mendelian model with the dominant effect of the A_1 allele and the recessive effect of the A_2 allele as the most parsimonious model for inheritance of the litter size.

Within the framework of this model, the frequency of the recessive allele of the major gene (A_2) controlling small litter size in the population was estimated at 0.27. The mean litter size $\mu(g)$, produced by females of major genotypes A_1A_1 and A_1A_2 , was estimated as 12.33, and by genotype A_2A_2 as 8.61. This gave us an estimate of variance of the litter size, determined by the major gene polymorphism, equal to 0.93. The variance determined by polygenic and random effects were estimated as $\sigma_G^2 = 0.24$ and $\sigma_e^2 = 4.29$ (Table 1). The contribution of genetic variation in phenotypic variance of the litter size (i.e. heritability in a broad sense) in the population studied was estimated at 0.22.

We calculated the expected distribution of the trait as a mixture of two normal distributions with means and variances coming from Table 1. The mixing parameter was defined as genotype probabilities corresponding to the estimated frequencies of the alleles. We found no significant difference between the expected and observed distributions ($\chi^2 = 10.33$, $df = 12$, $P > 0.6$). This resemblance can be interpreted as indirect evidence in favour of our genetic model.

We analysed segregation of the litter size within the families with at least one daughter that produced small litters. Table 2 shows that the observed distributions of daughters having small and large litter sizes did not differ significantly from that expected under a recessive model ($\chi^2 = 2.7$, $df = 5$, $P = 0.214$). This supports our hypothesis that small litter size is inherited as a recessive trait in the farmed fox population under the study.

Table 2 Testing of recessive model of litter size segregation in the families with at least one daughter producing small litters

No. of daughters	No. of families	Small LS ^a		Large LS		χ^2
		Observed	Expected ^b	Observed	Expected	
2	12	16	13.7	8	10.3	0.9
3	12	14	15.6	22	20.4	0.3
4	4	5	5.9	11	10.1	0.2
5	1	2	1.6	3	3.4	0.1
6	1	1	1.8	5	4.2	0.5
7	1	1	2.0	6	5.0	0.7
Total		39	40.6	55	53.4	2.7

^aTransformed litter size <11.

^bExpected number of daughters was estimated via formula (1).

Model of balanced polymorphism: We used parameters resulting from complex segregation analysis of the farmed population (Table 1) to model a system of balanced polymorphism for litter size in a population living in a regularly fluctuating environment described by equation (2). We supposed that females A_1A_1 and A_1A_2 produced 12 offspring every year, and females A_2A_2 produced eight offspring and analysed the dynamics of the frequency of the allele A_2 (q_i) under various initial q_0 and differences in the survival rate of small and large litters (k). Figure 2 shows that the dynamics of the frequency of the allele A_2 is critically dependent on the k value. When the chance of surviving in the years of poor food supply was twice as high in small litters ($k = 2$), allele A_2 became fixed very rapidly under all initial frequencies. Alternatively, when k was 1.5, the frequency of the allele controlling small litter size decreased gradually, although it did not reach zero during 400 generations. An intermediate k value of 1.7 resulted in establishment of a stable polymorphism with equal allele frequencies.

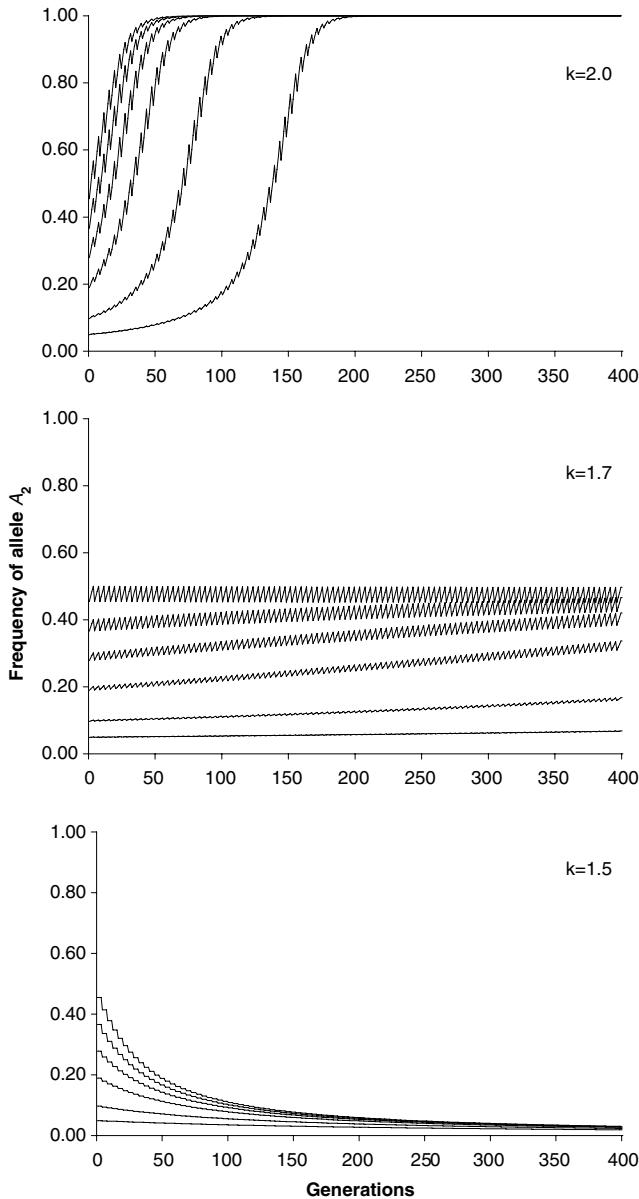


Figure 2 Dynamics of the frequency of recessive allele A_2 , controlling small litter size, over the generations under the assumption that survival of small litters in the years with low food supply is k -times higher than the survival of large litters (Equation (2)).

Discussion

Our analysis has demonstrated that inheritance of litter size in the arctic fox population bred at the Pushkinsky fur farm can be described within the frameworks of a major gene model. This model is based upon the results of complex segregation analysis and was also supported by the pattern of its familial segregation and by the comparison of observed and expected distributions of the trait in the population.

The ‘broad sense heritability’ (i.e. a contribution of genotype into phenotypic variation) of litter size estimated in our study was similar to the estimates obtained in farmed populations of the arctic fox in Poland by Wierzbicki (2004). Apparently, such polymorphism is

also present in other farmed populations of arctic foxes. Nordrum (1994) demonstrated a negative effect of inbreeding of fecundity of Norwegian-farmed populations. Although inbreeding depression may be caused by various genetic mechanisms, the main effect of inbreeding is an increase in the frequency of recessive homozygotes.

The main target of selection in farmed arctic foxes is fur quality, although selection for high fecundity is usually employed in fur-breeding farms (Milovanov, 2001). This might cause a reduction in the additive polygenic component of genetic variability for fecundity in farmed populations. However, if the small litter size is a recessive trait and effective size of farmed population is large, the major gene polymorphism would remain in such a population for many generations despite selection against recessive homozygotes.

This major gene polymorphism in the farmed populations of the arctic foxes was apparently derived from the natural populations. Arctic fox have been bred in captivity since 1920s, that is, about 30–40 generations. The founders of modern breeds were taken from various local populations (Nes *et al.*, 1987; Nordrum, 1994). The blue veil breed used in this study has been derived from the Norwegian breed called Nordic blue fox (Milovanov, 2001), which originated in 1920s from animals trapped on the islands of Svalbard, Jan Mayen and Greenland. At early stages of the breeding history, Alaskan arctic foxes were also involved in crossing (Nes *et al.*, 1987; Frafjord, 1993; Nordrum, 1994). Thus, we may suppose that both coastal and inland foxes contributed to the farmed gene pool.

These populations might have been polymorphic or polytypic for different alleles. As we mentioned in the introduction, coastal and inland populations of the arctic fox employ different reproductive strategies (Frafjord, 1993; Tannerfeldt and Angerbjörn, 1998). Coastal foxes, which produce relatively small litters every year, have apparently lost the capacity to produce very large litters. This could have happened very rapidly because, according to our model, a dominant gene largely controls litter size. The populations of inland foxes, which cannot reproduce successfully every year but have larger litter size, might have fixed the dominant allele. Thus, we may suppose that the farmed foxes inherited the alleles for small and large litter size from coastal and inland populations, respectively.

Alternatively, and more interestingly, they might inherit both alleles from the inland foxes providing that a system of balanced genetic polymorphism of litter size was maintained in the natural populations. The results of experimental and theoretical studies demonstrate that balanced genetic polymorphism may appear and be maintained in a population living in a spatially and temporally fluctuating environment (Timofeeff-Ressovsky, 1940; Ellner and Sasaki, 1996; Moorcroft *et al.*, 1996; Turelli *et al.*, 2001). Using a simple two allele model, we demonstrated that a balanced polymorphism for genes controlling litter size may be maintained in a population under following conditions: (1) fluctuations in resource availability are regular in period and magnitude and (2) variation in litter size at birth does not depend on resource availability.

Results of field studies in natural populations of arctic fox allow us to check the validity of these assumptions. It

has been shown that the fluctuations of prey were rather regular (Angerbjörn *et al.*, 2001). No correlation has been found between the number of placental scars (i.e. number of embryos) on one hand and food availability and female condition on other hand (Macpherson, 1969; Tannerfeldt and Angerbjörn, 1998). However, the litter size at weaning and young cub survival positively correlated with prey abundance (Macpherson, 1969). Angerbjörn *et al.* (1995) demonstrated in a long-term field experiment that litter sizes were larger at dens supplemented with food. This shows that food availability affects the survival rate of the young cubs rather than litter size at birth. Tannerfeldt and Angerbjörn (1998) considered several hypotheses explaining variation in litter size in natural populations of arctic foxes. They suggested the combined effects of the immediate resource level and the resource predictability determine litter size. The inland foxes may, therefore, employ a jackpot strategy. Our model shows that this strategy is evolutionary stable when it is employed by certain genotypes within a population rather than all of its members. A major gene polymorphism for litter size may be considered to be the result of adaptation to a drastic fluctuation of prey availability.

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