



On the origin of a domesticated species: identifying the parent population of Russian silver foxes (*Vulpes vulpes*)

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The foxes at Novosibirsk, Russia, are the only population of domesticated foxes in the world. These domesticated foxes originated from farm-bred silver foxes (*Vulpes vulpes*), whose genetic source is unknown. In the present study, we examined the origin of the domesticated strain of foxes and two other farm-bred fox populations (aggressive and unselected) maintained in Novosibirsk. To identify the phylogenetic origin of these populations we sequenced two regions of mitochondrial DNA, cytochrome *b* and D-loop, from 24 Novosibirsk foxes (eight foxes from each population) and compared them with corresponding sequences of native red foxes from Europe, Asia, Alaska and Western Canada, Eastern Canada, and the Western Mountains of the USA. We identified seven cytochrome *b*–D-loop haplotypes in Novosibirsk populations, four of which were previously observed in Eastern Canada. The three remaining haplotypes differed by one or two base change from the most common haplotype in Eastern Canada. Φ_{ST} analysis showed significant differentiation between Novosibirsk populations and red fox populations from all geographic regions except Eastern Canada. No haplotypes of Eurasian origin were identified in the Novosibirsk populations. These results are consistent with historical records indicating that the original breeding stock of farm-bred foxes originated from Prince Edward Island, Canada. Mitochondrial DNA data together with historical records indicate two stages in the selection of domesticated foxes: the first includes captive breeding for approximately 50 years with unconscious selection for behaviour; the second corresponds to > 50 years of additional intensive selection for tame behaviour. © 2011 The Linnean Society of London, *Biological Journal of the Linnean Society*, 2011, 103, 168–175.

ADDITIONAL KEYWORDS: domestication – mitochondrial DNA – phylogeography – red fox – tameness.

INTRODUCTION

Uncovering the origin of domesticated species is a subject of wide interest, and has numerous practical implications in fields such as agriculture and evolutionary biology (Diamond, 1999). Identification of the progenitor stock and comparison with the domesti-

cated form allows analysis of the genetic, physiological, morphological, and behavioural impacts of domestication (Trut, 1999). An experimental population of domesticated silver foxes, *Vulpes vulpes*, a colour variant of the red fox, has been developed and maintained at the Institute of Cytology and Genetics of the Russian Academy of Sciences (ICG) in Novosibirsk since 1959 (Trut, 1999). These animals were domesticated from farm bred foxes whose wild source is unknown.

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The red fox has the widest geographic distribution of all *Carnivora* species, occurring naturally throughout the Northern Hemisphere; in North Africa, Europe, Asia, and North America and, via introduction in Australia (Macdonald & Reynolds, 2004). Since the early 20th Century, the red fox has also become a common fur-farm animal in North America and Eurasia.

Red fox fur farming was pioneered on Prince Edward Island (PEI) in Southeastern Canada, beginning in the 1890s (Westwood, 1989). Most of the original breeding stock for the fur farming industry originated from PEI, and included locally caught foxes supplemented with those imported from southern Alaska (Balcom, 1916; Laut, 1921). Fur farmers on PEI primarily raised the silver/black colour variant of red foxes, which had the greatest economic value and were subsequently used to stock fur farms in many areas of North America and Eurasia (Petersen, 1914; Westwood 1989; Nes, Einarsson & Lohi, 1988). Given the high price of PEI foxes, it is possible that silver foxes from other indigenous populations were used to supplement breeding stock.

In Russia, fox farming started in the early 20th Century (Generozhov, 1916; Zhaharov, 1995). Small farms that maintained a few breeding pairs of local foxes or foxes captured in other regions of Russia were organized in different geographical regions, from European Russia (West of the Ural Mountains) through to Yakutia in the East (Zhaharov, 1995; Bespyatih, 2009). In the 1920s, a population of Canadian foxes and foxes of Canadian descent were imported to Russia and Baltic countries (Vahrameyev & Belyaev, 1948; Bespyatih, 2009). After World War II, fox farming grew into a large industry in the former Soviet Union; among the 505 000 pelts produced worldwide in 1990, 359 000 were produced in the USSR (Bespyatih, 2009). The importation of Canadian foxes to the USSR was not well documented in the literature, although most reliable publications state that the Russian commercial silver fox population is mostly of Canadian descent (Vahrameyev & Belyaev, 1948). There are also records that indicate an introduction of local foxes into the commercial breeding stock. A unique coat colour variant 'Огневка Вятская' ('Ognevka Vyatskaya') was developed by breeding foxes with a bright red coat colour from the Kamchatka Peninsula to the standard farm-bred silver foxes (Vohmyanin, 1981; Bespyatih, 2009).

Farm-bred foxes usually show fear or a fear-aggressive response to humans. Experimental domestication of farm-bred foxes was started by Dmitry Belyaev and Lyudmila Trut at the Institute of Cytology and Genetics of the Russian Academy of Sciences, in Novosibirsk, Russia, in the late 1950s. This experiment, known as 'the farm-fox experiment', has been

reviewed in several publications (Trut, 1999, 2001; Trut, Oskina & Kharlamova, 2009). Belyaev and Trut visited multiple farms across the former Soviet Union and identified a subset of commercial foxes that showed less fearful and aggressive responses to humans. These 130 foxes were brought to the experimental farm at the ICG and became the founders of the experimental population. Selection of foxes for tame behaviour was strict, with less than 10% of foxes bred to produce the next generation. At the same time, deliberate efforts were made to avoid inbreeding. A relatively low inbreeding level (0.02–0.07) has been maintained over the course of the project (Trut, 1999; Kukekova *et al.*, 2004). The current tame fox population comprises over 300 breeding animals that show friendly responses to humans similar to that of domestic dogs (<http://cbsu.tc.cornell.edu/ccgr/behaviour/Index.htm>; Trut, 1999, 2001; Kukekova *et al.*, 2008; Trut *et al.*, 2004, 2009).

In the 1970s, the ICG also started selection for an aggressive strain of foxes. Because there is deliberate selection on commercial farms against animals that show aggressive responses to humans, selection of the aggressive strain at ICG aimed to preserve this behaviour. Fifty farm-bred silver foxes with the most aggressive responses to humans were selected from several fox farms and used as founders of the aggressive population. The current aggressive population comprises approximately 130 breeding foxes that are aggressive and difficult to handle (Kukekova *et al.*, 2004, 2008; Trut *et al.*, 2009). The third fox population (unselected for behaviour) maintained at ICG originated from several commercial fox farms, some of which were the same source farms of the founders for the tame and aggressive strains.

The genetic origin of Russian farm-bred foxes has never been investigated at the molecular level. Such analysis would provide information about the history of the population and the gene pool or pools from which they stem. This information would be particularly important for studies aiming to identify regions of the fox genome implicated in fox domestication.

A recent analysis of two mitochondrial DNA regions found that red fox populations in Northern Eurasia and North America are divided into two distinct clades estimated to have diverged approximately 400 Kya (Aubry *et al.*, 2009). The Holarctic clade extends from Europe to Asia and across the Bering Strait into Alaska and Western Canada, whereas the Nearctic clade is restricted to North America (Fig. 1). These clades of foxes were separated during the Pleistocene in disjunct glacial refugia. Within the Holarctic clade, there is division into two subclades separated by the Bering Sea; one predominating in Alaska and Western Canada, the other in Eurasia. The Nearctic

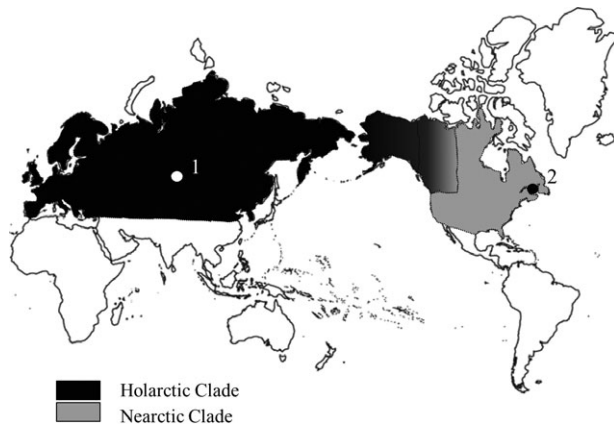


Figure 1. Clade breakdown of red fox lineages in Northern Eurasia and North America based on data obtained from Aubry *et al.* (2009). The Nearctic clade is restricted to North America, whereas the Holarctic clade stretches from Europe, through Northern Asia, into Alaska and Western Canada. The zone of contact between Nearctic and Holarctic lineages in Western Canada is indicated. Point 1 is Novosibirsk, Russia; point 2 is Prince Edward Island, Canada.

clade is subdivided into three subclades, with the Mountain subclade predominating in the Western Mountains of the USA, and the Eastern subclade dominating in Eastern Canada, whereas the Widespread subclade is older and more widely dispersed (Aubry *et al.*, 2009). This phylogenetic framework can be used to determine the geographic source of populations of unknown origin.

The primary aim of the present study was to determine the genetic source of the Novosibirsk Silver Foxes, which may be descendant from indigenous Russian foxes, and/or from animals of more distant origins. Second, we examined the mitochondrial genetic diversity of this population which has been divided into three closed breeding units since the 1970s. These aims were addressed by comparing the genetic sequence data of Novosibirsk silver foxes with that of native red fox populations in Northern Eurasia and North America.

MATERIAL AND METHODS

SAMPLES

Three fox populations: tame, aggressive, and unselected for behaviour are maintained at the experimental farm of the ICG at the Russian Academy of Sciences, in Novosibirsk, Russia. Using pedigree information, we selected eight foxes from each population that do not have mothers or grandmothers in common for population genetic analysis (Novosibirsk total, $N = 24$). Animal care and use at the ICG is in

compliance with Russian law regarding laboratory animals.

LABORATORY PROCEDURES

We extracted DNA from blood samples collected from the Novosibirsk populations using the Qiagen Maxi Blood kit. We amplified the 5' region of the cytochrome *b* gene using primer pair RF14724 and RF15149 (Perrine *et al.*, 2007), and the D-loop using primer pair VVDL1 and VVDL6 (Aubry *et al.*, 2009). Polymerase chain reaction products were purified and sequenced as described previously (Perrine *et al.*, 2007; Aubry *et al.*, 2009; Sacks *et al.*, 2010).

STATISTICAL ANALYSIS

To assess geographic origins we compared haplotypes obtained in the present study with previously published reference sequences from putative source populations. These data included 354-bp cytochrome *b* ($N = 220$) and 342-bp D-loop ($N = 174$) haplotypes from Europe (Germany, Italy, Spain, and Sweden), Asia (China, Mongolia, and Eastern Siberia), Alaska and Western Canada, Eastern Canada (Manitoba, Newfoundland and Labrador, Ontario, and Quebec), and the Western Mountains of the USA (Cascade Range, Sierra Nevada, and Rocky Mountains) (Perrine *et al.*, 2007; Aubry *et al.*, 2009). Additionally, we included all homologous portions of sequences from all published Eurasian haplotypes (Fratini *et al.*, 1998; Inoue *et al.*, 2007) and those available in GenBank to evaluate possible Eurasian ancestry.

We estimated haplotype diversity (h) and nucleotide diversity (π) (Nei, 1987) using ARLEQUIN, version 3.1 (Excoffier, Laval & Schneider, 2005) and DNASP, version 4.50 (Rozas *et al.*, 2003). Relationships among haplotypes were determined using a median-joining network (Bandelt, Forster & Röhl, 1999) within NETWORK 4.2.0.1 (<http://www.fluxus-engineering.com>). We estimated the extent of genetic differentiation among populations using Φ_{ST} (Nei & Li, 1979) in ARLEQUIN, version 3.1. This statistic is similar to F_{ST} but takes into account the divergence between haplotype sequences. Statistical significance ($\alpha = 0.05$) was determined based on 1000 permutations, and then corrected for multiple tests using the sequential Bonferroni method (Rice, 1989).

RESULTS

We identified four distinct cytochrome *b* haplotypes in the Novosibirsk population, three of which had previously been identified in native populations of Eastern Canada (Table 1, Fig. 2). We identified seven distinct D-loop haplotypes, two of which (haplotypes 85 and 86) were novel (EMBL/GenBank/

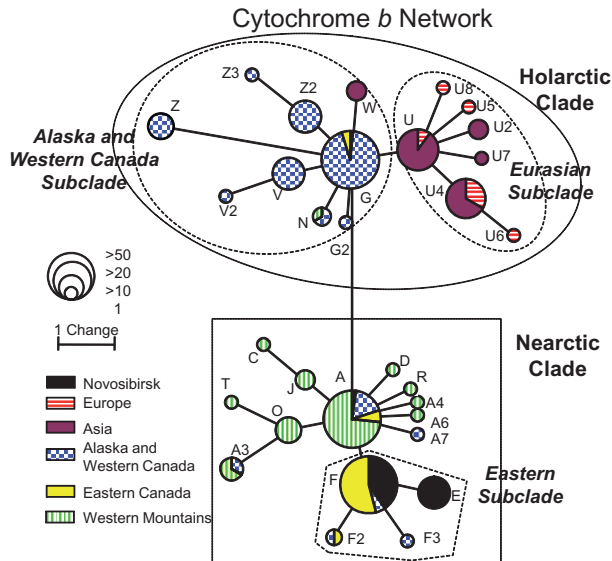


Figure 2. Cytochrome *b* median-joining network based on 354 bp for 24 Novosibirsk and 220 native North American and Eurasian red fox specimens. Branch lengths are proportional to the number of substitutions, and circle sizes are proportional to the number of individuals represented. Clades are indicated by dotted lines and subclades by dashed lines.

DDBJ nucleotide database accession no. HM461967-8; Table 1). The cytochrome *b* and D-loop data, when taken together, gave seven composite haplotypes (Table 2).

PHYLOGENETIC ANALYSIS

Most (92%; 22 of 24) Novosibirsk red foxes had haplotypes belonging to the Eastern subclade, within the

Nearctic clade, which predominates in Eastern Canada (Table 2). One haplotype in particular, F-17 (i.e. cytochrome *b* haplotype F, and D-loop haplotype 17), composed half of the sample and occurred in all three Novosibirsk populations. This haplotype has previously been identified in Newfoundland and Labrador, in Eastern Canada (Aubry *et al.*, 2009). Haplotype F-12 was previously found in Manitoba, Canada. Other Eastern subclade haplotypes identified in the Novosibirsk population differed by either one base (E-9, F-85) or two bases (E-86) from the most common haplotype in Eastern Canada. Haplotype G-73, part of the Holarctic clade, was previously found in several different Canadian provinces and territories from the Yukon in Western Canada through to Quebec in the East. Haplotype A-63, part of the Widespread subclade (within the Nearctic clade), has also been found at relatively high prevalence in many of the same areas. We found no Eurasian haplotypes, or haplotypes that clustered with Eurasian haplotypes, among the Novosibirsk red foxes.

Pairwise Φ_{ST} values based on both the cytochrome *b* and D-loop datasets indicated that the Novosibirsk population was not significantly differentiated from the Eastern Canada population, although it was significantly and substantially differentiated from all other populations (Table 3).

The Novosibirsk population as a whole had haplotype (*h*) and nucleotide (π) diversities slightly lower, although on the same order of magnitude, as most of the native reference populations (Table 4). When individual lines of Novosibirsk foxes were considered, the aggressive line had the lowest level of diversity. None of the Novosibirsk lines were significantly differentiated (based on Φ_{ST} or F_{ST}) from each other.

Table 1. Occurrence of four cytochrome *b* haplotypes (354 bp) and seven D-loop haplotypes (342 bp) among foxes from Novosibirsk and their prevalence in native red fox populations in North America and Northern Eurasia

Population	Cytochrome <i>b</i> haplotype					D-loop haplotype							
	<i>n</i>	A	E	F	G	<i>n</i>	9	12	17	63	73	85	86
Novosibirsk: Aggressive	8	–	1	7	–	8	1	–	6	–	–	1	–
Novosibirsk: Tame	8	–	2	5	1	8	1	–	4	–	1	1	1
Novosibirsk: Unselected	8	1	4	3	–	8	1	1	2	1	–	–	3
Europe	6	–	–	–	–	8	–	–	–	–	–	–	–
Asia	21	–	–	–	–	13	–	–	–	–	–	–	–
Alaska, Western Canada	112	–	–	2	59	77	3	1	–	3	14	–	–
Eastern Canada	26	3	–	19	2	26	8	2	5	5	1	–	–
Western Mountains	55	31	–	–	–	50	–	–	–	–	–	–	–

Europe consists of Germany, Italy, Spain, and Sweden.

Asia consists of China, Mongolia, and Russia.

Eastern Canada consists of Manitoba, Newfoundland, Ontario, and Quebec.

Western Mountains consists of populations from the western Mountains of the USA, the Rocky Mountains, the Sierra Nevada, and Cascade Range.

Table 2. Occurrence of seven combined cytochrome *b* and D-loop haplotypes (696 bp) among foxes from Novosibirsk, indicating the clade/subclade to which the haplotypes belong

Population	Total	A-63 Nea* Wide†	E-9 Nea East	E-86 Nea East	F-12 Nea East	F-17 Nea East	F-85 Nea East	G-73 Hol Alas
Novosibirsk: Aggressive	8	–	1	–	–	6	1	–
Novosibirsk: Tame	8	–	1	1	–	4	1	1
Novosibirsk: Unselected	8	1	1	3	1	2	–	–
Novosibirsk	24	1	3	4	1	12	2	1

*Nea, Nearctic clade; Hol, Holarctic clade.
†Wide, Widespread subclade of North America; East, Eastern subclade of North America; Alas, Alaska and Western Canada subclade. The Widespread subclade and the Eastern subclade are both part of the Nearctic clade. The Alaska and Western Canada subclade is part of the Holarctic clade.

Table 3. Pairwise Φ_{ST} values between Novosibirsk and native red fox populations in North America and Northern Eurasia

Population	Europe	Asia	Alaska†	Eastern‡	Mountains§
Novosibirsk cytochrome <i>b</i>	0.86*	0.84*	0.68*	0.05	0.50*
Novosibirsk D-loop	0.73*	0.62*	0.54*	0.03	0.58*

Values in the first row are based on the cytochrome *b* dataset, values in the second row on the D-loop dataset. Asterisks indicate statistical significance ($P < 0.05$) based on sequential Bonferroni correction for multiple tests (Rice, 1989).
†Alaska and Western Canada.
‡Eastern Canada (Manitoba, Newfoundland and Labrador, Ontario, and Quebec).
§The western mountains of the USA (Cascade Range, Sierra Nevada, and Rocky Mountains).

Table 4. Within-population statistics for Novosibirsk and native red fox populations in North America and Northern Eurasia based on mitochondrial cytochrome *b* and D-loop datasets

Population	Cytochrome <i>b</i>				D-loop			
	<i>n</i>	Number of haplotypes	<i>h</i>	π	<i>n</i>	Number of haplotypes	<i>h</i>	π
Novosibirsk: Aggressive	8	2	0.25	0.0007	8	3	0.46	0.0020
Novosibirsk: Tame	8	3	0.61	0.0047	8	5	0.78	0.0088
Novosibirsk: Unselected	8	3	0.68	0.0023	8	5	0.86	0.0076
Novosibirsk	24	4	0.54	0.0026	24	7	0.73	0.0070
Europe	6	4	0.80	0.0034	8	6	0.89	0.0109
Asia	21	5	0.74	0.0032	13	5	0.73	0.0132
Alaska, Western Canada	112	13	0.69	0.0055	78	23	0.91	0.0136
Eastern Canada	26	5	0.46	0.0032	26	7	0.83	0.0096
Western Mountains	55	11	0.61	0.0027	50	16	0.85	0.0110

DISCUSSION

IDENTIFYING THE PARENT POPULATION OF
RUSSIAN SILVER FOXES

The present analysis clearly and unambiguously identifies Eastern Canada as the primarily, if not sole, source of ancestry for the farm-bred red fox populations maintained in Novosibirsk, Russia. Four of the seven combined cytochrome *b*/D-loop haplotypes found had previously been identified in Eastern Canada, including in samples collected in the 1800s before the advent of fur farming (Aubry *et al.*, 2009). The remaining haplotypes were all part of the eastern subclade and were closely related to the most common haplotype in Eastern Canada. No Eurasian haplotypes were identified in the Novosibirsk population, and pairwise Φ_{ST} analysis showed significant differentiation between Novosibirsk populations and red fox populations from all geographic regions studied except Eastern Canada.

These findings are consistent with historical records indicating that the red fox fur farming industry in Russia and elsewhere traces back to the first successful fur farms in Southeastern Canada (Petersen, 1914; Balcom, 1916; Laut, 1921; Vahramyev & Belyaev, 1948; Westwood 1989). Furthermore, because the coat-colour genes associated with silver morphs are indigenous to North America, it is to be expected that at least some of the ancestry of the Novosibirsk foxes was North American. It is noteworthy that we found no Eurasian haplotypes in the Novosibirsk population given that indigenous Russian red foxes were used to supplement fur-farm stock in some areas (e.g. for particular crosses; Vohmyanin, 1981; Bespyatih, 2009). Although our findings suggest Novosibirsk matriline descend directly from North American founders, the use of biparentally inherited nuclear markers or Y chromosome markers will be necessary to determine if male Eurasian red foxes have contributed to the Novosibirsk gene pool.

GENETIC DIVERSITY

Our findings indicate that the efforts to avoid inbreeding at Novosibirsk were largely successful. The genetic diversity of the Novosibirsk population as a whole is substantially higher than that of farmed arctic foxes (*Vulpes lagopus*) from Norway, Sweden, and Finland where only a single D-loop haplotype was identified in a sample of 41 individuals (Norén *et al.*, 2005). Interestingly, in a parallel situation to the Novosibirsk populations, the haplotype found in these farmed arctic foxes was not found in wild native Fennoscandian populations and likely came from a distant geographic source population. The genetic

diversity of the Novosibirsk population was similar to that of the wild Eastern Canadian source population (Table 4), covering a vast geographic area spanning four Canadian provinces [Manitoba, Newfoundland and Labrador, Ontario, Quebec, (Aubry *et al.*, 2009)]. Within individual lines, two haplotypes (A-63 and F-12) were restricted to the unselected population and one (G-73) was restricted to the tame. The absence of unique haplotypes in the aggressive population, along with the lower haplotype and nucleotide diversities, reflects the smaller number of founders and smaller total number of individuals maintained in this line. Considering the relatively small size ($N < 1000$ breeding animals), and the number of years since they became closed breeding units, a considerable degree of mitochondrial genetic diversity has been maintained in the Novosibirsk populations.

The present study indicates the common ancestry of all Novosibirsk fox populations. Two combined cytochrome *b* and D-loop haplotypes, F-17 and E-9, were found in all three Novosibirsk populations, making up over half of all individuals sampled. In addition, three of the cytochrome *b* haplotypes (E, F, and G) found in the Novosibirsk populations were also found in a recently established red fox population likely stemming from farmed animals in southern California (Perrine *et al.*, 2007; Sacks *et al.*, 2010). The results of our analyses suggest that farm-bred foxes maintained in Novosibirsk descend from the foxes that were bred in captivity for over 100 years.

FURTHER GENETIC ANALYSIS

With the growth of genomic technologies and reduction of sequencing cost, it appears reasonable to expect that the red fox genome sequence and single nucleotide polymorphism (SNP) map will become available in the next few years. These resources will allow phylogenetic analysis of fox populations with nuclear gene markers and analysis of genetic divergence between the tame and aggressive fox strains. Genome-wide association mapping across dog breeds has successfully been used for identification of loci and genes for breed specific traits (Jones *et al.*, 2008; Chase *et al.*, 2009; Akey *et al.*, 2010; Boyko *et al.*, 2010). SNP analysis of the dog and wolf-like wild canids identified regions in the dog genome demonstrating signatures of positive selection of dogs from wolves (vonHoldt *et al.*, 2010). Similar analysis can be applied to identify selective sweeps in the fox genome produced by long-term farm-breeding. The genome-wide association mapping of tame and aggressive strains maintained in Novosibirsk and pedigrees produced by cross-breeding of the two strains (Kukekova *et al.*, 2010) will facilitate the identification of genomic regions implicated in these behavioural phenotypes.

CONCLUSIONS

Identification of the origin of the Novosibirsk fox populations and estimation of the populations' ages allows a better understanding of the selection process that led to the development of the tame, dog-like Novosibirsk foxes. Mitochondrial DNA data together with historical records indicate two stages in the selection of domesticated foxes: an initial period of approximately 50 years of captive breeding in fur farms with conscious selection for fur quality and unconscious selection for behaviour, followed by an additional 50 years of intensive selection for tame behaviour carried out at the ICG in Novosibirsk since 1959 (Trut, 1999, 2001). Understanding the phylogeographic origins of experimental populations is critical. Failure to do so can lead to spurious conclusions about selection. For example, in a biometric study of aortic branches in red foxes, native Polish red foxes were compared with Polish fur farmed foxes and significant differences were found between farmed and wild groups (Nowicki, 2005). This differentiation was attributed to the effects of captive breeding, without knowledge of the potential confounding effects of the considerable phylogenetic differentiation found in the present study. Understanding the history of this population will be highly advantageous for ongoing studies focused on the identification of genetic loci and genes implicated in domesticated behaviour in foxes and other species.

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