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Original Article

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Missing history of a modern domesticate: Historical demographics and genetic diversity in farm-bred red fox populations

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Abstract

The first record of captive-bred red foxes (*Vulpes vulpes*) dates to 1896 when a breeding enterprise emerged in the provinces of Atlantic Canada. Because its domestication happened during recent history, the red fox offers a unique opportunity to examine the genetic diversity of an emerging domesticated species in the context of documented historical and economic influences. In particular, the historical record suggests that North American and Eurasian farm-bred populations likely experienced different demographic trajectories. Here, we focus on the likely impacts of founder effects and genetic drift given historical trends in fox farming on North American and Eurasian farms. A total of 15 mitochondrial haplotypes were identified in 369 foxes from 10 farm populations that we genotyped (n = 161) or that were previously published. All haplotypes are endemic to North America. Although most haplotypes were consistent with eastern Canadian ancestry, a small number of foxes carried haplotypes typically found in Alaska and other regions of western North America. The presence of these haplotypes supports historical reports of wild foxes outside of Atlantic Canada being introduced into the breeding stock. These putative Alaskan and Western haplotypes were more frequently identified in Eurasian farms compared to North American farms, consistent with historical documentation suggesting that Eurasian economic and breeding practices were likely to maintain low-frequency haplotypes more effectively than in North America. Contextualizing inter- vs. intra-farm genetic diversity alongside the historical record is critical to understanding the origins of this emerging domesticate and the relationships between wild and farm-bred fox populations.

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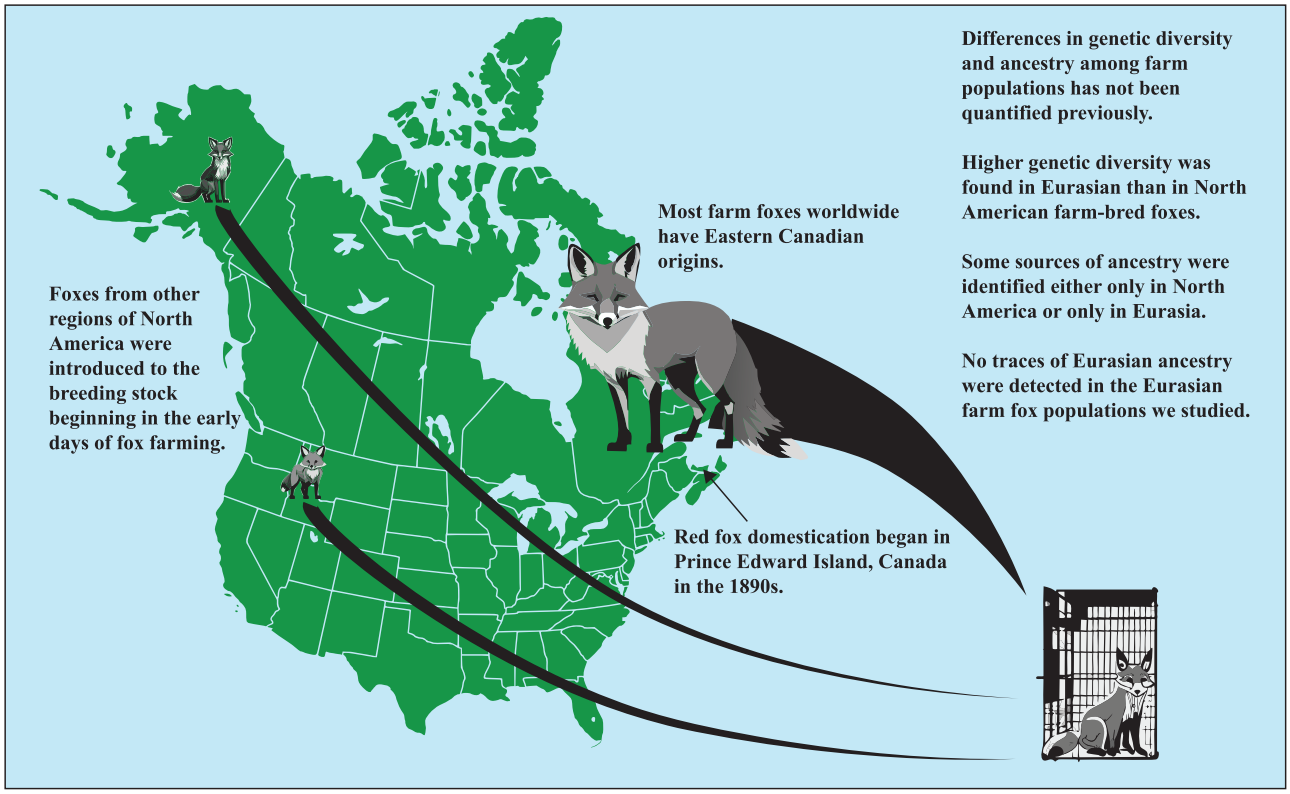
Graphical Abstract



Introduction

Animal domestication was a watershed event in human history. Domesticated dogs are thought to have emerged during the Upper Paleolithic (Zeder et al. 2006; Germonpré et al. 2009; Larson et al. 2012; Thalmann et al. 2013; Drake et al. 2015; Pendleton et al. 2018), and early evidence of other domesticates such sheep, pig, cow, and cat appeared in the archeozoological record at the beginning of the early Neolithic (Diamond 2002; Driscoll et al. 2009; Vigne 2011). Given that most domestication events date to prehistory, with only a rare few, like rabbit domestication, occurring in antiquity (Irving-Pease et al. 2018), little is known about the processes or circumstances underlying the domestication of most species. Likewise, ancestral wild populations are typically difficult to identify and likely no longer intact.

Therefore, many genetic studies of domesticates aim to reconstruct the history of the species based on genetic patterns identified in samples from archaeological or paleontological sources and in present-day populations. Domestication is often thought of as a two-part process. The first component is selection for animals that breed successfully under human control, or "natural selection in captivity" (Price 2002). The second component is explicit artificial selection, where traits of interest are propagated. A retrospective analysis cannot isolate these two phases chronologically or resolve when different regions of the genome were under selection, limiting our ability to study the selective mechanisms that drive the domestication process itself.

However, in one notable case, a species in the process of being domesticated offers an opportunity to simultaneously examine individuals at different stages of the process of domestication, from wild to captive breeding to domesticated. The domestication of the red fox (*Vulpes vulpes*) began only recently, with the first successful captive-bred colony of red foxes established in 1896 in Prince Edward Island (PEI), Canada (Laut 1921). The economic motivations for fox breeding are well known. At the turn of the 20th century, red fox pelts were a valuable commodity. The market value varied with coat color, and the rare silver pelts were the most valuable (Dearborn 1915; Laut 1921; Ashbrook 1923). Captive breeding of foxes was an economically appealing concept not because foxes were difficult to trap, but because the silver coat color was a rare phenotype in wild foxes (Dearborn 1915), it is now known to have a recessive mode of inheritance and be caused by recessive mutations in either the agouti gene or *MC1R* gene (Våge et al. 1997, 2003). However, the red fox was not easy to breed in captivity: early aspiring fox breeders met many challenges attempting to breed fur foxes (Jesse 2020), especially the fact that vixens would destroy their own young when stressed (Jones 1914; Laut 1921). Therefore, significant selective pressure was likely exerted on red foxes in captivity via natural selection.

The recent timeline of red fox domestication is especially interesting because the red fox is such an important model in domestication. Though even today, conventional commercially bred farm-fox populations do not show the docile behavior typical of most domesticated species, a long-running experimental breeding program at the Institute for Cytology and Genetics (ICG) bred genetically tame behavior into a farm-fox population through artificial selection for tameability, with the trait reaching fixation after around 50 generations of breeding (Trut et al. 2009).

Therefore, while this species may not fit the same behavioral profile of domesticates bred over thousands of years, different

populations of the species occupy different positions on the continuum of domestication. Farm-bred fox populations that have adapted to reproducing under human control do not show the full behavioral profile of domestication, offering a striking contrast to the ICG's experimentally bred "tame" population whose behavior is often called "dog-like". Because this initial domestication effort occurred during recorded history, information is available about early breeding practices and their motivations. Additionally, the short time frame of the history of the domestication process means that wild progenitor populations can be pursued and identified, either in their modern incarnations or in museum specimens (e.g. Lounsberry et al. 2017; Black et al. 2018).

However, to date, full advantage has not been taken of these available resources. The first study to examine the genetic ancestry of farm foxes compared the ICG's foxes to modern wild populations to assess their geographic origin (Statham et al. 2011). Subsequently, many studies have analyzed mitochondrial deoxyribonucleic acid (mtDNA) from specific farm-bred populations along with local wild populations to infer patterns in admixture between farm-bred and wild foxes, including farm-bred populations in Newfoundland (Atlantic Canada) (Lounsberry et al. 2017), Wisconsin (north-central United States of America) (Black et al. 2018), Wielkopolska (western Poland) (Zatoń-Dobrowolska et al. 2019), and southeastern Poland (Horecka et al. 2017). A full temporospatial view of farm-bred foxes, including both the historical documentation about farm-breeding practices and the genetics of geographically distinct modern farm-bred populations, has not been attempted. In order to leverage the full potential of this model of domestication, it is necessary to understand the origins and structure of farm-bred populations. Here, we thus dive in primary sources to gain a historical perspective on the origins and spread of fox farming around the world in the early 20th century. Then, using these insights, we compare genetic ancestry and diversity across several fox farms in North America and Eurasia. The combined historical and genetic context will allow us to gain a broader perspective on the history of fox domestication, the evolutionary context of the ICG's tame population, and the intellectual value of this species for probing the genetic basis of domestication.

Historical documentation of fox farming

It is well established that Prince Edward Island (PEI) and surrounding regions in Atlantic Canada, especially the nearby island of Newfoundland, played a fundamental role in the early days of fox farming. However, historical records suggest that farm-bred fox populations were likely developed with stock from many sources. Many documents report that the success of pioneers of the fox industry in PEI prompted the development of fox ranches in other Canadian provinces and in Alaska in the early 1900s (Forester and Forester 1973). Worldwide farm populations were established at different points in history, with the practice spreading outwards from PEI into the rest of Atlantic Canada and the US state of Maine by 1908 (Osgood 1908) and into mainland Canada and Alaska by 1917 (Dearborn 1917). The farm-fox industry in Canada and the US rapidly expanded throughout the early 20th century, and breeding stock was exported to Eurasia beginning in the 1910s–1920s (The Globe 1919; New York Times 1926; Vahrameyev and Belyaev 1948; Forester and Forester 1973).

The historical record suggests that these emerging enterprises outside of Atlantic Canada likely introduced new diversity to the farm-fox gene pool. Due to the high cost of purchasing breeding stock in the early 1900s, aspiring breeders were incentivized to raid fox dens for kits (Carroll 1914; New York Times 1914) or trap adult foxes to sell as breeders (Laut 1921). Such introgression events were reported in Ontario, Quebec, and Maine (Balcom 1916) as well as New Hampshire (The Washington Post 1908), Yukon (New York Times 1914), and Alaska (Laut 1921; Forester and Forester 1973). Later, after interest in fox breeding was piqued in Eurasian countries, reports of similar efforts came from Scandinavia (Forester and Forester 1973; Nes et al. 1988), Great Britain (Campbell 1924), and the USSR (Parkalov 2011). Some of the wild-caught foxes from other locations were likely later mixed into the PEI stock. For example, the largest Alaskan fox farm was moved to PEI in 1914 (Hodgson 1947). Therefore, historical records suggest that diversity within the farm-bred population would be expected to shift over time as fox farming grew and spread and trade patterns shifted. Founders of different farm-bred populations worldwide may therefore have been sampled from different pools of genetic diversity depending on when they were established.

History also suggests that farmed fox population sizes have likely been unstable. The fur industry boomed from the turn of the century until the 1930s, but around the time that World War II (WWII) began, fox fur sales began to falter in North America. Compared to 150K pelts harvested in the US in 1933 (Redington 1933) and over 250K in 1939 (Sixteenth Census of the United States (1940) Agriculture, United States Government Printing Office 1942), as of 1951, Canada and the United States each produced only about 40K pelts (Kharlamov et al. 2017). The Canadian National Silver Fox Breeders Association is credited with encouraging farmers to hold onto enough breeding stock (Fox Farming in Canada 1980) during this time to allow for a moderate recovery of the industry in the 1960s and 1970s (Alexander 1962; Taylor 1968a, 1968b). All the same, by 1973, the United States had only 45 active fox farms and produced only 6.6K pelts in total ("1974 Census of Agriculture", United States Government Printing Office 1977) (Fig. 1). Similarly, only 54 fox farms were active in Canada by the mid-1970s (Fox Farming in Canada 1980). Thus, the history of fox farming suggests that an initial period of rapid expansion was followed by a period of contraction, with limited subsequent recovery. From an evolutionary perspective, this boom-then-bust trend would be expected to exacerbate the effects of genetic drift.

Further complicating the picture, the intensity of these population swings likely varied with geography. Some of the social forces driving the mid-century decline in the North American fur farming industry were not as prevalent in Eurasia. For example, though in North America WWII heralded a permanent shift in the fox fur industry, Soviet fox fur production quickly recovered, with a drop from almost 20K pelts produced in 1940 to 11K in 1945 followed by growth to 85K by 1963 (Kharlamov et al. 2017) and 400K by 1971 (Parkalov 2011). The government-supported Soviet fur industry remained strong up until the 1990s (Balakirev and Tinaeva 2001). Therefore, population sizes on fur farms in the USSR/Russia likely remained larger and more robust during the 20th century than their competitors in North America. These different trajectories are likely to affect the genetic diversity of farm-bred populations today.

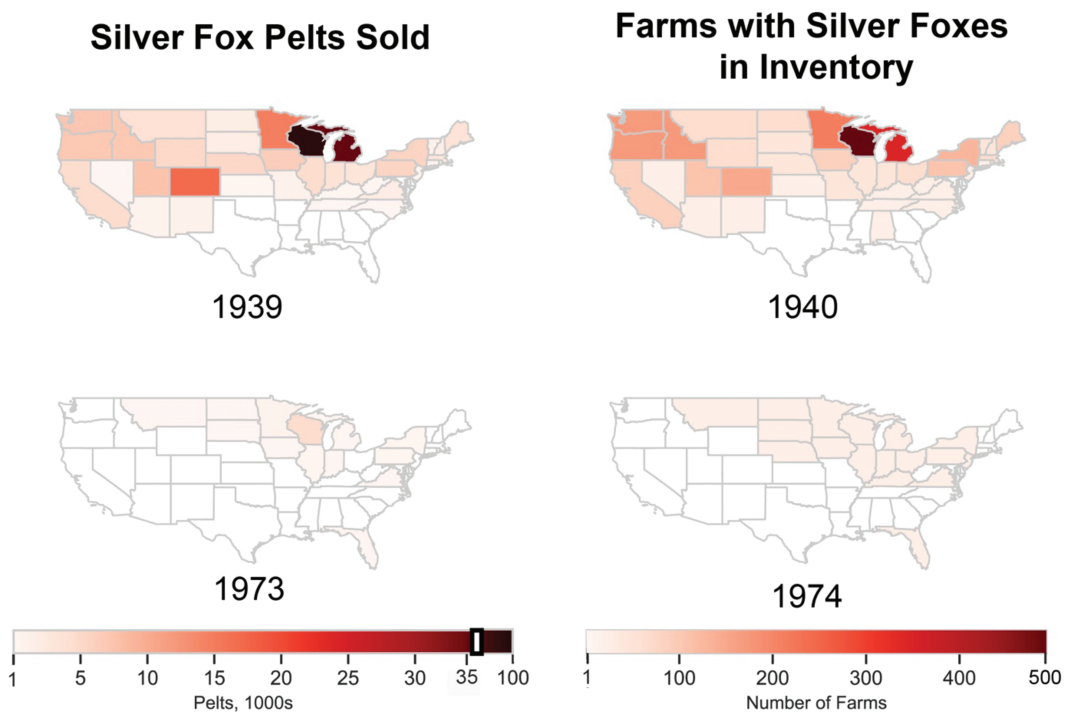


Fig. 1. Choropleths visualizing shifts in the fox farming industry in the United States between 1939 and 1973. The agricultural census surveyed fox farming twice (Sixteenth Census of the United States Agriculture 1940, Census of Agriculture 1974), and the data collected in each census is visualized. Only states belonging to the continental United States were included in the census.

Patterns in farm-fox genetics

To date, genetic studies involving farm-bred red foxes have typically focused on the question of whether Atlantic Canada is the dominant source of ancestry for farm-bred populations or whether local admixture is present (Statham et al. 2011, 2012; Horecka et al. 2017; Lounsberry et al. 2017; Black et al. 2018; Zatoń-Dobrowolska et al. 2019). All have agreed that Atlantic Canada dominates the genetic ancestry of modern farm-bred fox populations. In fact, farm-bred foxes in all cases have been found to carry almost exclusively North American mtDNA haplotypes, with the only report of Eurasian haplotypes coming from three foxes on a Norwegian farm (Statham et al. 2012).

Red fox mtDNA phylogeography makes it possible to delve more precisely into the origin of mtDNA haplotypes. North American mtDNA haplotypes follow distinct phylogenetic patterns that were shaped by vicariance during the Illinoian through Wisconsinan glaciations, resulting in two major clades: Nearctic, which is endemic to North America, and Holarctic, which is found in both Eurasia and North America (Aubry et al. 2009). The Nearctic clade can be further divided into three major subclades, Eastern, Widespread, and Mountain (Aubry et al. 2009). Haplotypes endemic to Atlantic Canada belong to the Eastern subclade (Aubry et al. 2009). Therefore, Eastern subclade haplotypes are expected to dominate in farm-bred fox populations based on the known history of fox farming.

However, the historical record also suggests that the genetic makeup of the founding population associated with individual fox farms would vary with time and geography. mtDNA haplotypes from other Nearctic subclades and from the Holarctic clade have been reported at low frequency in several modern fox farm populations (Statham et al. 2011, 2012; Lounsberry et al. 2017; Black et al. 2018; Zatoń-Dobrowolska et al. 2019). These haplotypes are consistent with historical accounts of introductions of foxes outside of Atlantic Canada to the breeding population. At the same time, this story is complicated by the long history of anthropogenic translocations, where red foxes have been relocated to new environments by people for purposes that likely include hunting, fur farming, and even companionship (e.g. Lewis et al. 1998; Sacks et al. 2010; Kasprowicz et al. 2015).

The timing of major geopolitical events such as the world wars suggests that differences between farm-bred populations would be especially pronounced at the continent level. Differences in the stability of population sizes are also expected to affect genetic diversity, with genetic drift having a stronger effect on populations that experienced more dramatic size fluctuations. Once again, the historical record suggests that these trajectories also differed between Eurasia and North America. Differences in founders and population size are expected to leave genetic signatures that may be detectable in modern-day farm-bred populations.

To date, little is known about variation in genetic ancestry and diversity in different farm fox populations. Prior studies have analyzed mtDNA haplotypes in farm-bred foxes, but these studies have focused on farms in a single region (Horecka et al. 2017) or pooled data from multiple farms (Statham et al. 2012). However, a focused analysis of farm-fox diversity is necessary for efforts to leverage this modern domesticate to understand the process of domestication. Here, we collect all farm fox haplotypes published (to our knowledge) and compare their mtDNA diversity to newly sequenced haplotypes from fox farms chosen strategically based on historical documentation. The result is the first intercontinental perspective on genetic diversity in farm-bred foxes, allowing us to

compare farms in four countries (Canada, the United States, Poland, and Russia).

Methods

In addition to haplotypes identified in the literature, tissue samples were obtained from red foxes on farms (Table 1) and in the wild (Table 2) in locations across North America and Eurasia. Molecular analyses were conducted at two laboratories (the University of Illinois at Urbana-Champaign and the University of California, Davis) within the United States, with laboratory-specific procedures described in the Supplementary Methods. In broad terms, both labs extracted DNA from blood, tissue hair, or feces samples and amplified segments of the cytochrome b (CytB) gene (354 bp) and the mitochondrial control region within the hypervariable D-loop (approximately 343 bp) with PCR using the primers RF14724 and RF15149 (Perrine et al. 2007) and VVDL1 and VVDL6 (Aubry et al. 2009), respectively. PCR products were purified and sequenced using Sanger technology. Sequences were queried against previously identified sequences using the NCBI's nucleotide/nucleotide BLAST tool (blastn) (https://blast.ncbi.nlm.nih.gov/Blast.cgi). If the query sequence aligned to a known sequence with an identity of 100%, it was considered a match, and the individual was assigned the haplotype from the BLAST result. If no match was identified, the spectrograph was reexamined to confirm the call, and the individual was considered to have a novel haplotype.

Sequences corresponding to the reference haplotypes identified in this study and other studies of farm-bred and wild fox populations (Statham et al. 2011; Lounsberry et al. 2017; Black et al. 2018; Zatoń-Dobrowolska et al. 2019) (Table 1) were then downloaded from NCBI's nucleotide database. For each of the two regions analyzed, all haplotypes observed were loaded into MEGA X (Kumar et al. 2018) and aligned using MUSCLE (Edgar 2004) using the default parameters. Sequences were trimmed so that all haplotypes were the same length (354 bp for cytochrome b and 339 bp for the D-loop, 693 bp total), which did not remove any segregating sites except in the case of two sequences identified in Black et al.

Table 1. Farm-bred red fox sample sources.

Country	Population type	Tissue	Number of samples analyzed[b]	Source
Canada				
Newfoundland	Commercial	Skin	92	Lounsberry et al. (2017)
USA				
Iowa	Commercial	Skin	10	Present
Nebraska	Commercial	Skin	60	Present
Wisconsin	Commercial	Hair	44	Black et al. (2018)
Poland				
Southeastern Poland	Commercial	Blood	60	Present
Wielkopolska	Commercial	Tongue	48	Zatoń-Dobrowolska et al. (2019)
Russia				
Moscow	Commercial	Blood	10	Present
Novosibirsk	Experimental (Conventional)	Blood	17; 8	Present; Statham et al. (2011)
Novosibirsk	Experimental (Tame)	Blood	15; 8	Present; Statham et al. (2011)
Novosibirsk	Experimental (Aggressive)	Blood	15; 8	Present; Statham et al. (2011)
Novosibirsk	Experimental (Aggressive × Tame Hybrid)[a]	Blood	1	Present

Red fox samples collected from each farm-bred population. Some haplotypes were experimentally determined in the present study, while others were extracted from the literature and included in the present analyses. When results from the literature were included in analyses, the reference for the source is specified in the "Source" column. Sample numbers from multiple sources are separated by a semicolon, as are the sources.
[a]Because this hybrid fox's mother was aggressive, he is counted as a member of the aggressive population for the purposes of mtDNA inheritance in this study.
[b]When samples that were sequenced in the current study were used together with published data from the same population, the number of former and latter samples is listed.

Table 2. Wild red fox sample sources.

Location	Tissue analyzed	Number of samples	Source
Newfoundland, Canada	Skin or tongue	103	Lounsberry et al. (2017); Present
Alaska, USA	Bone	50	Aubry et al. (2009)
Wisconsin, USA	Tissue or dentin	125	Black et al. (2018); Present
Western USA	Tissue, blood, hair, and feces	800	Quinn et al. (2019, 2022)
Vermont, USA	Tissue	26	Kasprowicz et al. (2015)

Haplotypes from several wild populations were included in the analyses. Some haplotypes were experimentally determined in the present study, while others were reported in publications and reanalyzed in the present analyses. When results from the literature were included in analyses, the reference for the source is provided.

(2018): 84a (relative only to 84) and 12a (relative only to 12). Therefore, for all analyses, 84a and 84 were collapsed into a single haplotype, as were 12a and 12. The alignments were then exported in multi-FASTA format.

A Python script was developed to concatenate cytochrome b and D-loop haplotypes. The cytochrome b and D-loop haplotype names were concatenated with a dash (-) to create a joint haplotype name (e.g. F-17). The joint haplotypes were analyzed in R (https://www.r-project.org) using pegas version 0.12-1 (Paradis 2010) that was modified to use not only single nucleotide polymorphisms but also insertions and deletions to compute the distance between two haplotypes.

To characterize within-population diversity, the effective number of haplotypes and haplotype richness rarified to the minimum sample size were calculated following the procedure previously described (Rando et al. 2017). The effective number of haplotypes represents the number of haplotypes that would be required at equal frequency to result in the amount of diversity observed in the sample. The haplotype richness allows for cross-population comparison by adjusting the number of haplotypes observed in each population to account for small sample sizes in some populations (here, the minimum number of observations was $n = 10$ in the Iowa and Moscow populations). Tajima's D was calculated per farm population. A multi-FASTA was generated for each containing the joint haplotypes observed in that population. The files were then read into R as DNABin files using the function fasta2DNAbin from the package adegenet (Jombart 2008) and each was then analyzed using the function tajima.test from the package pegas. The estimated parameters D and pval.beta (the P-value if D is rescaled and assumed to follow a beta distribution) were reported for each population. Finally, the distribution of Nearctic and Holarctic haplotypes observed on Eurasian versus North American farms was evaluated using a hypergeometric test.

Results

Of the 188 farm-bred fox samples sequenced for this study, 161 were assigned both cytochrome b and D-loop haplotypes. All sequences matched known haplotypes in the NCBI Genbank nucleotide database, with one exception: a novel D-loop haplotype was identified in the ICG's conventional farm-bred population. It differed by one substitution from D-loop haplotype 17 (m.45T > C) and is referred to here as D-loop haplotype 279, represented by the joint haplotype F-279. This sequence has been deposited in the NCBI Genbank nucleotide database under accession number OL310496.

A total of 15 joint mtDNA haplotypes was identified across the ten farm-bred populations sequenced here and reported elsewhere (Supplementary Table 1). In the haplotype network depicting the relationship among farmed foxes (Fig. 2), most haplotypes sampled on farms formed a star-like cluster around the most frequent haplotype, F-17. The haplotypes F-17, F-79, and F-9 that were identified in historical samples from wild 19th-century Newfoundland (Lounsberry et al. 2017), which is geographically close to PEI and was also an early contributor to the fox farming industry, all fall within this star cluster. When mtDNA haplotypes from farmed foxes were visualized in a network alongside those of wild North American red foxes (Fig. 3), most of the farm-fox haplotypes clustered with the Eastern subclade within the Nearctic clade (Supplementary Table 1). Some of the farm-fox haplotypes in this cluster have also been reported in the wild in Vermont, Wisconsin, and the Western United States (Aubry et al. 2009; Kasprowicz et al. 2015; Black et al. 2018; Quinn et al. 2019, 2022). These haplotypes are therefore likely to be endemic to eastern North America and to Atlantic Canada, in line with the known origin of fox farming.

As expected, some haplotypes identified on farms did not belong to the Eastern subclade associated with ancestry in Atlantic Canada. These haplotypes included Nearctic haplotypes A-63 [widespread subclade per (Statham et al. 2012)], A-67 [widespread subclade per (Aubry et al. 2009)], and O-24 [mountain subclade per (Statham et al. 2012)], as well as the Holarctic haplotype G-73 (Alaskan subclade per Statham et al. 2012). A-67 was observed in both North American and Eurasian farm populations ((Zatoń-Dobrowolska et al. 2019) and the present analysis), while A-63 and G-73 were observed in Eurasian farm populations only (Statham et al. 2011, 2012) and O-24 in North American farm populations only (Lounsberry et al. 2017; Black et al. 2018). O-24 has also been reported in several North American wild populations, specifically in western states including Washington, Montana, Nevada, and California (Black et al. 2018; Quinn et al. 2019, 2022). Additionally, G-73 has been reported in the wild in Alaska (Aubry 2009).

The effective number of haplotypes and the rarified haplotype richness revealed variable diversity among individual farm populations. The least diverse population was the farm in Iowa (United States), where one mitochondrial haplotype was observed among the ten individuals sampled. However, even though a much larger number of individuals was sampled from the farm in Newfoundland (Canada), the effective number of haplotypes and rarified haplotype richness were not much higher. On the other side of the spectrum, the most diverse farm population was the ICG's conventional population, followed by the commercial farms sampled in Wielkopolska (western Poland) and Wisconsin (United States). Though our investigation of historical records identified Wisconsin, with its deep history of fox farming (Fig. 1), as potentially less affected by genetic drift than regions where the fox farming industry was weaker, this actually may not be the explanation for why this particular farm was more diverse. After sharing the results with the owner, we learned that the fox population at this particular farm was founded less than 10 years ago and its breeding stock was established with foxes purchased from several different Midwestern farms. Therefore, while it may give a more complete view of haplotypes found in the Upper Midwest and environs, its diversity would not be comparable to farms that have been maintaining mostly consistent genetic pools for decades or longer, such as the ICG and commercial farms with longer histories.

Tajima's D was calculated as a negative value in every population except two Russian populations, the commercial farm in Moscow and the ICG's aggressive population. However, Tajima's D was significant only in the Canadian farm population, where the negative value of D suggests the population has experienced an expansion in population size. The hypergeometric test suggested that Holarctic haplotypes were enriched in the Eurasian farm populations by 2.21-fold ($P = 0.008$).

Finally, comparing the haplotype frequency spectra of Eurasian versus North American farms (Fig. 4; Supplementary Table 3) revealed that low-frequency haplotypes are common

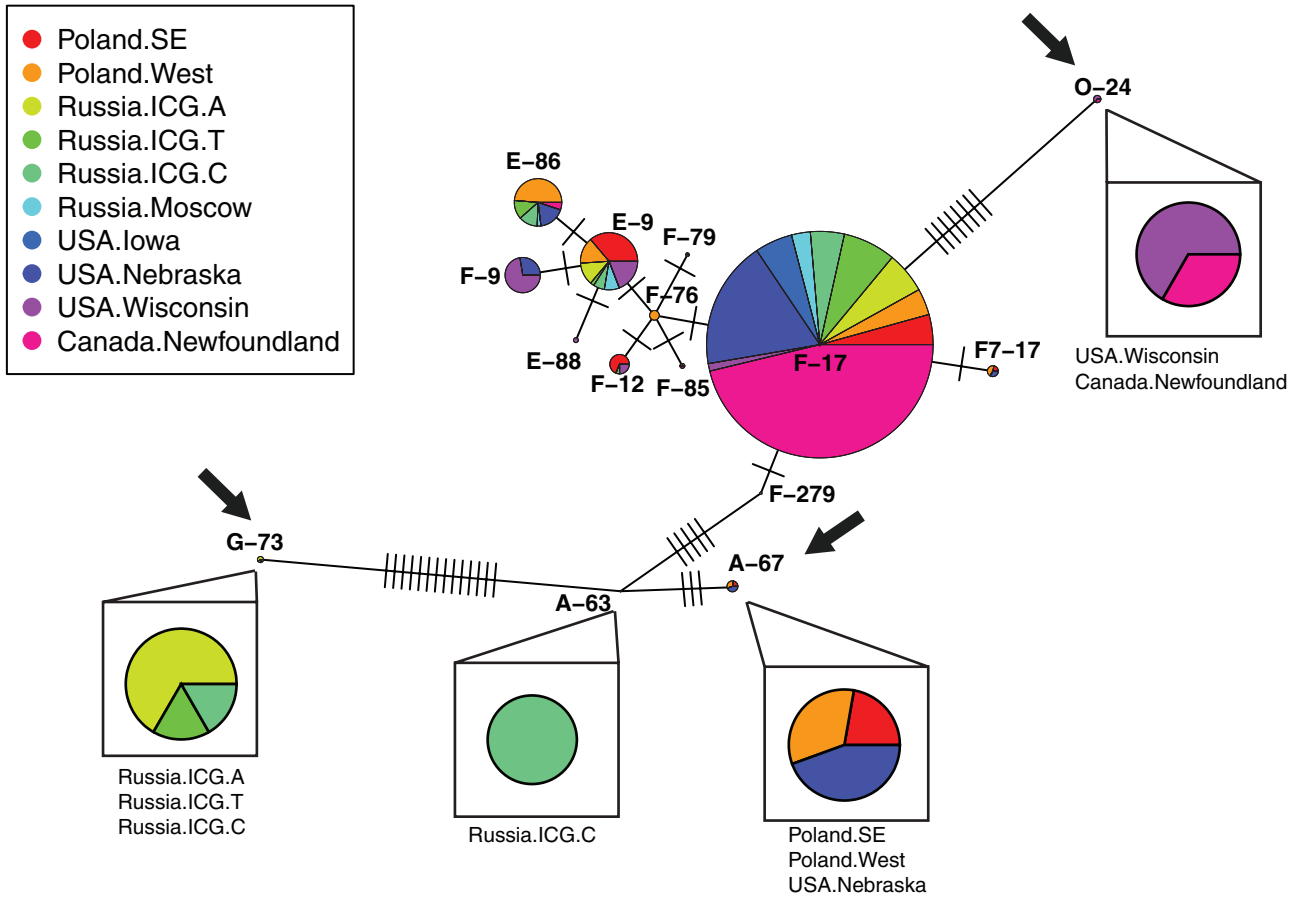


Fig. 2. mtDNA haplotype network of farm-bred foxes. Each node represents a haplotype identified in at least one farm-bred fox. Nodes are scaled according to the number of individuals carrying the haplotype and colored according to the relative frequency in each population. Step mutations are indicated by hatch marks. Areas of the network that fall outside of the Eastern subclade of the Nearctic clade are indicated with arrows, and the populations each haplotype was identified in are explicitly called out below each magnifier box. The ICG's farm is subdivided into three populations, corresponding to individual lines: A = aggressive, T = tame, and C = conventional. This network includes both novel sequences and data published elsewhere (Statham et al. 2011; Lounsberry et al. 2017; Black et al. 2018; Zatoń-Dobrowolska et al. 2019) (Supplementary Table 1).

in both populations, but North American farms have a single very high-frequency haplotype (F-17) and only one haplotype of intermediate frequency (F-9). In contrast, several intermediate-frequency haplotypes were found across the Eurasian farms. This pattern suggests that, as expected, the North American farm-bred population has lost genetic diversity, consistent with a bottleneck, as indicated by the dearth of intermediate haplotypes. This pattern is also apparent in the haplotype network (Figs. 2 and 3).

Discussion

Here we evaluated mtDNA diversity on modern red fox farms in the context of historical documentation about the process of red fox domestication, performing a comparative analysis involving 369 farm-fox mtDNA amplicons collected from ten populations on eight farms, some of which were presented here for the first time and others of which were extracted from the literature (Statham et al. 2011; Lounsberry et al. 2017; Black et al. 2018; Zatoń-Dobrowolska et al. 2019). In line with the hypotheses suggested by primary historical sources, our genetic analysis revealed different demographic patterns in North America and Eurasia. Together, these results suggest patchiness in the distribution of genetic ancestry among worldwide farm-bred fox populations, consistent with the complex history of fox farming throughout the 20th century. Our findings allow us to support six conclusions based on a consilience of historical and genetic supporting evidence.

Eastern North America is the dominant source of modern farm-fox ancestry

In total, 15 haplotypes were observed in farm-bred foxes. Of the 15 haplotypes, 11 belonged to the Eastern subclade of the Nearctic clade (Supplementary Table 1), consistent with a large proportion of ancestry originating in eastern Canada. Haplotypes from the Eastern subclade formed a dense region of the haplotype network (Fig. 2); in total, 94% of foxes genotyped on farms carried a haplotype from the Eastern subclade, supporting Eastern North America as the dominant source of farm-fox ancestry. Moreover, half (50.4%) of the farm-bred foxes sequenced carried a single mtDNA haplotype from this subclade, F-17, while an additional 43.6% of foxes carried a closely related haplotype. F-17 was the most common haplotype observed in seven of the ten farm populations, with frequencies ranging from 5% (Wisconsin) to 100% (Iowa) (Supplementary Table 1). In line with the conclusions of prior genetic studies about individual populations (Statham et al. 2011; Lounsberry et al. 2017; Black et al. 2018), our findings support Eastern North America as the dominant source of farm foxes overall.

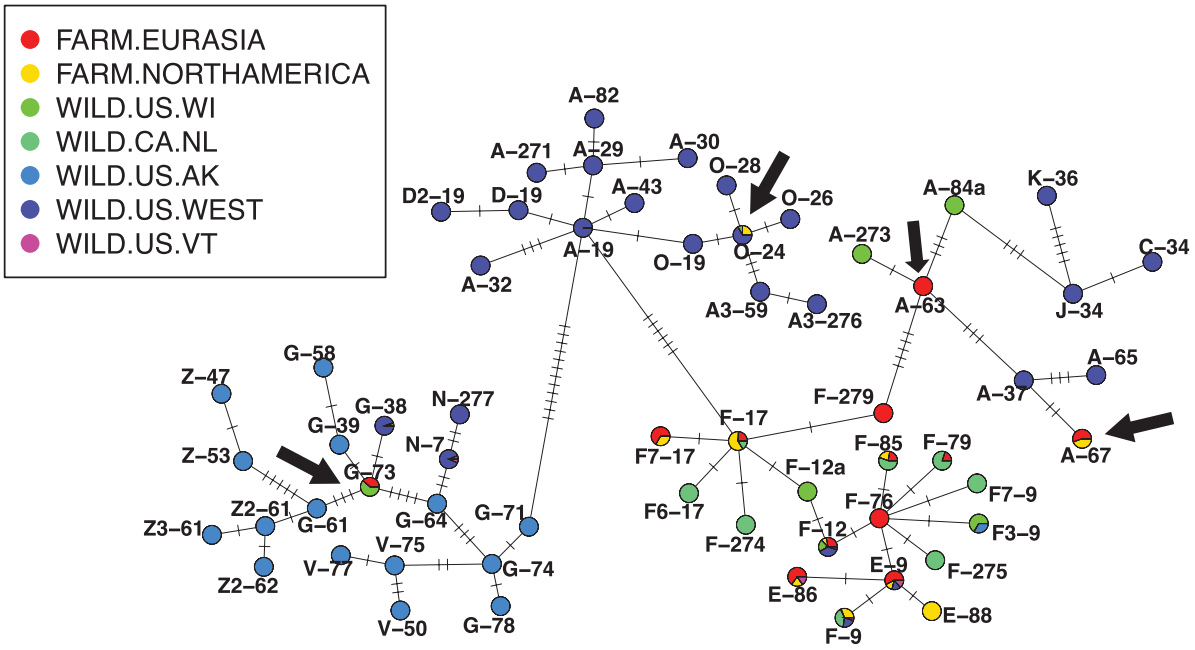


Fig. 3. Network of mtDNA haplotypes found in wild and farm-bred foxes. Each node represents a haplotype identified in at least one fox. Nodes are not scaled by frequency but are colored according to the relative frequency in each population. Step-mutations are indicated by hatch marks. Haplotypes from farm-bred foxes are aggregated at the continent level. Data from several external sources that sampled wild fox populations is included (Aubry et al. 2009; Kasprowicz et al. 2015; Lounsberry et al. 2017; Black et al. 2018; Quinn et al. 2019, 2022). Data from wild populations was not filtered to remove non-native haplotypes; this figure is intended to facilitate the comparison of data collected across multiple studies. As in Fig. 2, arrows call out the regions of the network corresponding to non-Eastern subclade haplotypes were identified on farms.

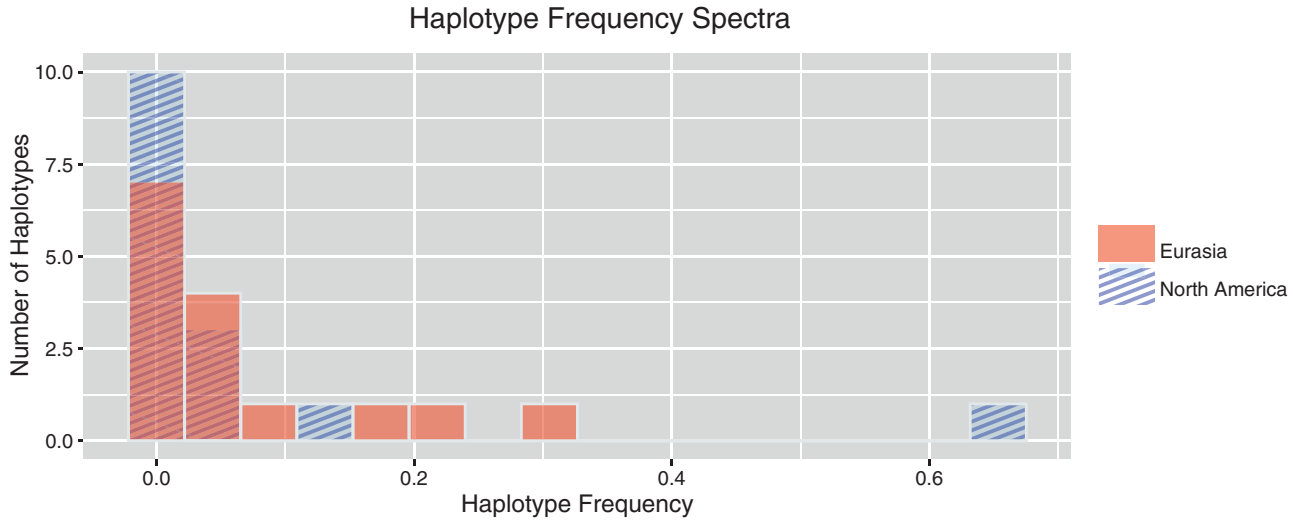


Fig. 4. Haplotype frequency spectra from North American and Eurasian farms. Haplotype frequencies were compared based on the joint CytB and D-loop mtDNA haplotypes. North American farms had an excess of very rare and very common haplotypes relative to Eurasia (Supplementary Table 3). The bar furthest to the right corresponds to F-17, which was found in over 65% of North American farm-bred foxes.

Newfoundland also played a major role in farm-fox ancestry

While PEI is widely accepted as the birthplace of fox farming historically, in genetic studies, other regions of Eastern Canada, especially Newfoundland, have often been used to represent the birthplace of the fox farming industry (e.g. Statham et al. 2012; Lounsberry et al. 2017). Newfoundland also played an early, major role in the industry (Osgood 1908; Carroll 1914). However, despite their geographic proximity, the Atlantic Canadian islands of PEI and Newfoundland have different histories and potentially distinct populations of red foxes. PEI and Newfoundland have likely been separated since the last glacial maximum, and Newfoundland, which is 240 km further from the mainland than PEI, is believed to have acquired its mammalian inhabitants primarily through over-water dispersal (Dodds 1983). Consistent with these distinct histories, PEI has at least 25 endemic terrestrial mammalian species (Sobey 2007), which are a superset of Newfoundland's 13 (Strong and Leroux 2014). However, Newfoundand's wild red fox population has been much better characterized in

Table 3. Metrics of diversity in farm-bred populations.

Farm population	Number of individuals assigned haplotypes	Eastern subclade (%)	Observed number of haplotypes	Effective number of haplotypes	Rarified haplotype richness	Tajima's *D* (*P*-value)
Poland-SE	40	95	5	3.3	3.8	−0.955 (ns)
Poland-West	48	94	6	4.2	4.7	−0.534 (ns)
Russia-ICG	69	90	9	3.4	4.5	−0.667 (ns)
Russia-ICG-A	23	83	5	3.0	3.8	0.456 (ns)
Russia-ICG-T	22	95	5	2.2	3.3	−1.62 (0.090)
Russia-ICG-C	24	92	8	4.6	5.4	−1.69 (0.074)
Russia-Moscow	10	100	3	2.4	3	0.850 (ns)
USA-Iowa	10	100	1	1	1	N/A
USA-Nebraska	56	93	5	2.4	3.6	−0.974 (ns)
USA-Wisconsin	44	91	6	3.4	4.3	−0.991 (ns)
Canada-Newfoundland	92	98	4	1.1	1.6	−2.052 (0.017)

The number of individuals assigned haplotypes, as well as the percentage of individuals carrying haplotypes from the Eastern subclade are provided, along with the total number of haplotypes observed across all individuals in each population. The effective number of haplotypes and rarified haplotype richness are metrics that allow for comparisons across populations. The effective number of haplotypes indicates the number of haplotypes needed for the same level of pairwise diversity if all haplotypes were at equal frequency. The rarified haplotype richness estimates the number of haplotypes that would be observed if all populations were sampled at the same n as the smallest sample size (here, $n = 10$). Tajima's D is provided as well as any associated P values < 0.10.

terms of genetic ancestry [e.g. 159 modern samples analyzed by Langille et al. (2014) and 79 modern plus 12 historical samples analyzed by Lounsberry et al. (2017); with 22 red fox D-loop haplotypes from PEI in Langille et al. (2014) being the only source we were able to identify].

The dominance of the haplotype F-17 clearly supports the documented origins of fox farming in Atlantic Canada. Here and in other studies (Langille et al. 2014; Lounsberry et al. 2017), this haplotype has been found in roughly 35% to 40% of wild foxes in Newfoundland. It was also found in 3 of 8 (37.5%) museum specimens collected in Newfoundland prior to fox domestication (Lounsberry et al. 2017). Three other haplotypes (F-9, F-79, and F-85) that were reported previously at low and intermediate frequencies in farm-bred foxes were also found in the wild foxes sampled in Newfoundland here and previously (Langille et al. 2014; Lounsberry et al. 2017). In total, 60% of farm-fox haplotypes observed were endemic to Newfoundland (Supplementary Table 1).

In contrast, limited information is available about foxes living on PEI. The only study to evaluate their mtDNA ancestry characterized D-loop haplotypes in modern wild-caught foxes (Langille et al. 2014). Of the 24 foxes sampled, 22 carried D-loop haplotype 76. F-76 has been observed only on one farm: it made up 17% of farm-fox haplotypes observed in western Poland (Zatoń-Dobrowolska et al. 2019). The F-76 haplotype has not been observed in the wild in Newfoundland here (Table 2) or elsewhere (Langille et al. 2014; Lounsberry et al. 2017). Of the remaining two foxes captured on PEI, one carried haplotype 17 and the other haplotype 9 (Langille et al. 2014), which are also found in Newfoundland. Therefore, the dominant haplotype in modern PEI was found only on one Eurasian farm, while the haplotypes that are dominant in Newfoundland today are also dominant in farm-bred populations, generally.

Therefore, these patterns indicate that PEI and Newfoundland may both have left their mark on modern farmed fox populations. A gap remains in the literature surrounding the haplotypes present on PEI at the time that foxes were captured for the original breeding efforts in the 1890s. Analysis of historical PEI samples would provide valuable information for understanding the impact the island has on modern populations.

Rare genetic ancestry supports reports of introductions in historical records

Haplotypes from other subclades and clades were also identified on farms. These haplotypes were associated with the Widespread (A-63 and A-67) and Mountain (O-24) subclades of the Nearctic clade, as well as the Alaskan subclade of the Holarctic clade (G-73). We once again found no evidence of introgression from Eurasian wild populations despite historical reports of this practice. Genetic evidence for such introgression has been reported only once, when (Statham et al. 2012) identified a European mtDNA haplotype in Norwegian farm-bred foxes.

Instead, these haplotypes provide genetic support for farm fox ancestry in central and western North America (Aubry et al. 2009). A-67 was found in a historical population in British Columbia, and A-63 has been identified in Alberta, Manitoba, and the Northwest Territories (Aubry et al. 2009). O-24 is endemic to the regions surrounding the Cascade Mountains of Washington state in western North America (Aubry et al. 2009; Statham et al. 2012; Akins et al. 2018). Finally, G-73 is closely related to haplotypes endemic to Alaska (Fig. 3) and was found to be historically widespread from Yukon to British Columbia and Alberta, south to the Sierra Nevada (Sacks et al. 2010), and as far east as Quebec.

Thus, the genetic evidence supports historical records indicating that foxes in the western regions of Canada and the United States were captured to establish breeding programs. The Widespread haplotypes identified and Holarctic haplotype G-73 are consistent with historical reports of approximately 800 foxes in captivity in what is now the Yukon as early as 1914 (New York Times 1914). Holarctic haplotype G-73 could have been introduced into the breeding stock in any of several regions known to have taken an active role in fox farming early in its history, though Alaska in particular played a major role in the earliest days of the fox farming industry. While O-24 is not associated with one of

the early industry leaders, historical documents suggest that fox farming likely began in or near the Cascade Mountains early in the history of fox farming, sometime between 1908 (Osgood 1908) and 1915 (Dearborn 1915). In summary, however, these haplotypes provide clear evidence that regions outside of Atlantic Canada have had longstanding impacts on the genetic ancestry of farm-bred foxes.

Rare haplotypes are more common on Eurasian farms

Comparing mtDNA haplotype diversity among farms revealed that the Eurasian fox farms were more diverse than those in North America. Of the four farms with the lowest effective number of haplotypes, three were in North America (Table 3). Likewise, three of the four farms with the highest effective number of haplotypes were in Eurasia. A similar pattern was observed in haplotype richness.

Several haplotypes were associated exclusively or primarily with Eurasian farms. G-73, the only haplotype observed from the Holarctic clade, was observed in all three of the ICG's experimental populations (Table 1; Statham et al. 2011) but not in any other farm-bred populations. From the Widespread subclade A-63 was observed only in the ICG's conventional population (Statham et al. 2011, 2012; Quinn et al. 2019, 2022), while haplotype A-67 was previously reported in Poland (Zatoń-Dobrowolska et al. 2019), and, in the present study, it was observed in a different region of Poland and in Nebraska, USA. Although Nebraska is located in North America, this farm introduced breeding stock from Norway in the early 2000s (J. Smeal, Heartland Blends, personal communication, 25 February 2007). Exportation of Norwegian farm foxes back to North America has been documented from 1990 onwards (Lounsberry et al. 2017). Therefore, it is possible that these haplotypes were lost in North American farm populations prior to recent re-introductions.

Combining historical and genetic information thus makes it possible to fill in some of the missing history of these haplotypes. In light of the historical records, our findings suggest that many such haplotypes may have been preserved in Eurasia due to more stable population sizes while being lost or becoming very rare in North American farm-bred populations. Additional sampling of farms in North America with pedigree information could help to establish the extent to which these Widespread subclade haplotypes have been maintained on farms in North America and to strengthen our understanding of translocations.

Mountain subclade haplotypes were only found on North American farms

A different pattern was observed for the Mountain subclade haplotype O-24. This haplotype has been identified on farms in Newfoundland and Wisconsin (Lounsberry et al. 2017; Black et al. 2018) but not in Eurasia. Given that rare haplotypes in general are over-represented on Eurasian farms relative to North American farms likely due to different demographic trajectories, the fact that O-24 has not been identified in Eurasian farms is notable. This pattern raises the possibility that O-24 was introduced into the breeding stock after founders had already been exported to create Eurasian breeding populations.

Contemporary government reports about the spread of the industry suggest that fox farming in Washington likely began between 1908 (Osgood 1908) and 1915 (Dearborn 1915). Meanwhile, historical documents suggest that the North American epicenters of live fox export were, primarily, PEI and, secondarily, New York City (The Times of India 1925; New York Times 1926); as an illustration, in 1926, the first exchange between the United States and the U.S.S.R. of live silver foxes for live Russian sables was brokered by a Leo Frank, a New Yorker who owned a prominent PEI fur farm, acting in a diplomatic capacity (New York Times 1926). Therefore, one possibility is that O-24 and related haplotypes were geographically concentrated on farms in the western United States at the time Eurasian populations were founded via stock exported from eastern North America. Additionally, an early resource on fox farming (Dearborn 1917) notes that though the melanistic variant of silver-black was unusually common in the Cascade Mountains, the foxes in this region "had little to recommend them besides color" (p. 27) because they tended to be small with coarse fur. In contrast, foxes from Alaska, Yukon, and the Atlantic seaboard from Maine through Labrador were considered of the highest grade on the international market at the time that Eurasian farm-bred populations were founded (Dearborn 1917).

Translocations are challenging to identify

The complex history of anthropogenic influences on red fox populations makes it challenging to resolve the phylogeographic history of farm-bred foxes. For example, haplotypes from the dense cluster of Eastern subclade farm-fox haplotypes (Fig. 2) have been detected in wild populations in the Central and Western United States (Fig. 3) (Aubry et al. 2009; Statham et al. 2012; Kasprowicz et al. 2015; Sacks et al. 2016; Merson et al. 2017; Black et al. 2018). O-24 has also been identified in contemporary wild foxes in the American West and Midwest (e.g. Sacks et al. 2010; Black et al. 2018; Cross et al. 2018; Quinn et al. 2019, 2022). In general, the presence of these haplotypes outside their presumed native ranges is thought to be evidence of translocations caused by farm breeding (Statham et al. 2012; Sacks et al. 2016; Merson et al. 2017).

However, some Nearctic Eastern haplotypes that fall into the cluster most similar to wild populations in Eastern Canada are endemic to regions far beyond Atlantic Canada: for example, the CytB haplotype F was found in two historical samples collected in the wild in Wisconsin during the 1890s, one of which was assigned the common farm-fox D-loop haplotype 12 (Black et al. 2018). This pattern is consistent with the range of Eastern subclade haplotypes proposed by (Aubry et al. 2009). Given that Wisconsin was a secondary epicenter of fox farming after Atlantic Canada (Fig. 1), it is possible that some Eastern subclade haplotypes were introduced outside of Newfoundland and PEI. For example, haplotype F-12 was not found in the wild in this (Table 2) or prior (Langille et al. 2014; Lounsberry et al. 2017) studies of Atlantic Canada, but it is found on farms in Poland, Russia, and Wisconsin (United States) (Supplementary Table 1).

In some cases, haplotypes that have been interpreted as evidence of anthropogenic translocations via the fur industry have not, to date, actually been identified on farms. A-273, which has been identified in the western and midwestern United States, is one such example (e.g. Sacks et al.

2010, 2016; Black et al. 2018, 2021). This haplotype is closely related to haplotypes that have been observed on farms, but it has never been identified in a farm population itself. Holarctic haplotypes (e.g. G-38) also provide examples of this phenomenon (Statham et al. 2012). In such cases, these haplotypes serve as a physical manifestation of the missing history surrounding fox farming: the evidence strongly suggests that they were present in the past but they have not yet been identified in North American farm-bred populations. Whether they have now been lost entirely or whether they may be identified with additional sampling remains unknown. Despite our inability to reconstruct translocation events in detail, the results of the current study are in line with previous observations (Langille et al. 2014; Lounsberry et al. 2017; Black et al. 2018) that indicate a loss or near loss of haplotypes that were present in historical farm populations and their potential reintroduction to the wild before the drastic reduction of the farm-fox population in North America.

The missing history of domesticated foxes

Here, we examined the history of fox farming and characterized the genetic ancestry of modern farm-bred populations, allowing us to contextualize mtDNA haplotype diversity in modern farm-fox populations relative to historical patterns in fox breeding. This context is especially important today because the red fox is an emerging model for the genomics of domestication (Kukekova et al. 2018). In particular, the ICG's experimentally bred populations provide a unique model for behavior genetics. The red fox is also the quintessential model species used to support the theory of a domestication syndrome, or a suite of traits proposed to emerge through the process of domestication (Clutton-Brock 1992; Wilkins et al. 2014).

A recent critique questioned the relevance of the ICG's Russian Farm-Fox Experiment to exploring the genetics of domestication broadly and as evidence of the domestication syndrome (Lord et al. 2020). This perspective argued that a lack of diversity in the ICG's founding population could have allowed tame behavioral traits to dominate via drift rather than selection. However, the present analysis indicates that Eurasian farm populations, including the ICG's conventional line, likely lost less mtDNA diversity during the 20th century due to bottlenecks than farms in North America and then commercial farms broadly. Additionally, in our analyses, the ICG's population ranked well for all diversity metrics relative to other populations, even when the experimental lines were considered individually (Table 3). Therefore, we propose that the ICG's populations are, for some genetic markers, more representative of early farm-bred populations than many modern conventional domesticated populations are.

However, there are limitations to using mtDNA alone to fill in the history of fox domestication. mtDNA is inherited differently from the rest of the genome and can provide an incomplete picture of ancestry (Ishida et al. 2011; Cahill et al. 2015). Here, due to our reliance on mtDNA, we can speak only to the maternal lineages of farmed foxes. Future efforts to paint a more complete picture of genome-wide diversity by examining nuclear and Y-chromosomal patterns of diversity are still needed. A small pilot study that examined Y-chromosome microsatellite haplotypes in the ICG's farm-bred populations and in wild populations suggested that similar sources of ancestry, with eastern Canada predominant and other sources much rarer, may also characterize the Y-genome (Rando et al. 2017), but more work is needed.

This integrative approach to farm-bred fox diversity by combining historical records with genetic evidence underscores the complexity of the effects of anthropogenic environmental modifications on modern populations. By examining the genetic and historical evidence together, we reveal how geopolitical and regulatory policies may have shaped which fox populations were integrated into the breeding population, and thus which fox populations later introgressed with wild native populations. It is unlikely that we will ever be able to fully recover the missing history of farm-bred foxes, but the parallels between the historical and genetic record provide a more complete view of where mtDNA diversity in modern farm-bred populations may have originated. The red fox represents one of very few mammalian species domesticated in recent times, offering a unique opportunity to combine historical and biological research to arrive at a more complete picture of the forces shaping populations today.

Supplementary material

Supplementary material is available at *Journal of Heredity* online.

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Data availability

The code used for the analyses and to generate the networks is available at https://github.com/rando2/mtDNA-network. The novel D-loop haplotype has been deposited in the NCBI SRA under accession number OL310496.

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