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The ascent of cat breeds: Genetic evaluations of breeds and worldwide random-bred populations

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Abstract

The diaspora of the modern cat was traced with microsatellite markers from the presumed site of domestication to distant regions of the world. Genetic data were derived from over 1100 individuals, representing 17 random-bred populations from five continents and 22 breeds. The Mediterranean was reconfirmed to be the probable site of domestication. Genetic diversity has remained broad throughout the world, with distinct genetic clustering in the Mediterranean basin, Europe/America, Asia and Africa. However, Asian cats appeared to have separated early and expanded in relative isolation. Most breeds were derived from indigenous cats of their purported regions of origin. However, the Persian and Japanese bobtail were more aligned with European/American than with Mediterranean basin or Asian clusters. Three recently derived breeds were not distinct from their parental breeds of origin. Pure breeding was associated with a loss of genetic diversity; however, this loss did not correlate with breed popularity or age.

Keywords: Breeds; Cat; Diversity; Domestication; Genetic; *Felis*; Origins; Phylogeography; Phylogenetics; Structure

The domestic cat (*Felis catus,* Linneas 1758) is prolific and cosmopolitan, occupying most habitable corners of the world. Archeological evidence suggests the domestication of the cat occurred in the Near East approximately 9000–10,000 years ago [1]. However, the initiation of domestication probably began thousands of years earlier as humans and ancestral cats became progressively more interdependent [2]. The domestication process likely began during the period when humans ceased following wild herds of animals and adopted more agricultural lifestyles, particularly in the Fertile Crescent [3]. This change occurred 10,000–11,000 years ago and was made possible by the domestication of certain wild grains and grasses [4]. The human/cat relationship was beneficial for the control of crop-destroying rodents, which had also joined their evolutionary fate to human civilization. Although many cats eventually became pets, the modern cat is not fully domesticated in the classic sense. Modern cats remain self-sufficient if need be, maintaining keen hunting skills even when provided food and exhibiting a spectrum of behaviors ranging from untamable to highly affectionate pets [5,6].

Cats spread to virtually all parts of the Old World, probably along trade routes between ancient civilizations. Despite their rapid spread, cats have remained amazingly similar to their wild felid ancestors (*Felis silvestris* subspp.) in form and function [2,6]. The progenitor species of domestic cats remained compatible with

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Table 1
Genetic variation of cat breeds, random-bred populations, and wildcats

Population	N	F_{IS}	H_O	H_E	Avg. allelic richness	Avg. No. alleles/locus	Alleles/locus range
Abyssinian	40	0.13	0.45	0.52	2.44	4.29	2–7
American shorthair	13	0.09	0.57	0.63	2.90	4.59	2–7
Birman	28	0.10	0.43	0.48	2.31	3.82	1–6
British shorthair	28	0.11	0.56	0.63	2.96	5.82	2–9
Burmese	25	0.22	0.40	0.51	2.51	4.44	1–9
Chartreux	30	0.08	0.57	0.61	2.81	4.62	1–8
Egyptian mau	19	0.23	0.49	0.63	2.86	4.56	2–7
Exotic shorthair	40	0.12	0.55	0.63	2.96	5.91	2–10
Havana brown	11	0.13	0.41	0.46	2.28	3.03	1–6
Japanese bobtail	32	0.12	0.60	0.67	3.14	5.97	3–12
Korat	39	0.02	0.56	0.57	2.62	4.44	1–8
Maine coon	31	0.13	0.58	0.66	3.08	6.00	2–11
Norwegian forest	10	0.13	0.61	0.70	3.29	4.82	2–11
Persian	33	0.19	0.51	0.62	2.90	5.68	3–9
Russian blue	25	0.09	0.46	0.50	2.40	3.79	2–6
Siamese	32	0.10	0.47	0.52	2.47	4.06	1–8
Siberian	19	0.05	0.69	0.73	3.45	6.65	3–12
Singapura	24	0.12	0.34	0.38	1.98	2.82	1–5
Sokoke	14	0.07	0.41	0.44	2.14	2.82	1–6
Sphynx	27	0.10	0.58	0.64	3.00	5.59	1–9
Turkish Angora	14	0.15	0.56	0.66	3.08	5.21	2–10
Turkish Van	21	0.18	0.49	0.59	2.71	4.62	1–8
Breed average	**25**	**0.12**	**0.51**	**0.58**	**2.74**	**4.71**	
Total/range	**555**	**0.02–0.23**	**0.34–0.69**	**0.38–0.73**	**1.98–3.45**	**2.82–6.65**	**1–12**
Brazil	26	0.08	0.66	0.71	3.40	6.82	2–13
Hawaii, USA	54	0.10	0.63	0.69	3.32	7.87	3–13
New York, USA	35	0.12	0.62	0.69	3.36	7.60	3–14
Texas, USA	30	0.10	0.66	0.72	3.50	7.18	3–12
Germany	45	0.14	0.62	0.70	3.41	8.39	2–15
Finland	32	0.08	0.61	0.65	3.22	7.00	2–13
Italy	47	0.1	0.67	0.72	3.56	7.8	3–14
Turkey	70	0.11	0.68	0.76	3.70	10.39	6–18
Israel	47	0.10	0.70	0.76	3.71	8.97	5–16
Egypt	27	0.11	0.68	0.74	3.67	8.26	4–17
Tunisia	17	0.04	0.68	0.69	3.38	6.45	2–12
Kenya	33	0.13	0.59	0.65	3.17	5.46	2–11
Sri Lanka	24	0.07	0.70	0.74	3.56	7.26	3–14
Singapore	29	0.10	0.65	0.71	3.47	7.68	3–14
Vietnam	20	0.08	0.63	0.66	3.27	6.42	2–12
Henan (China)	20	0.05	0.63	0.64	3.16	6.32	3–12
Korea	40	0.06	0.62	0.65	3.16	7.37	3–16
Random-bred avg.	**35**	**0.09**	**0.65**	**0.70**	**3.41**	**7.48**	
Total/range	**596**	**0.04–0.14**	**0.59–0.70**	**0.64–0.76**	**3.16–3.71**	**5.46–10.39**	**2–18**
Felis silvestris caffra	10	0.30	0.57	0.76	3.98	6.55	2–10
F. s. tristami	5	0.11	0.60	0.49	2.41	2.60	1–4
F. s. silvestris	10	0.47	0.43	0.71	3.70	5.24	3–11
Wildcat average	**8**	**0.29**	**0.53**	**0.65**	**3.36**	**4.80**	
Total/range	**25**	**0.11–0.49**	**0.43–0.60**	**0.49–0.76**	**2.41–3.98**	**2.60–6.55**	**1–11**

N, sample size; F_{IS}, average inbreeding coefficient of an individual relative to its subpopulation; H_O, observed heterozygosity; H_E, expected heterozygosity; Avg. allelic richness, expected number of alleles in a sample of three diploid individuals, averaged over all loci.

human agriculture. Gene flow between feral and tame modern cats, and between modern cats and their wild subspecies [7–10], has not negatively impacted the role of cats as the principal small carnivore in human-dominated ecosystems. In fact, having a feral pool of modern cats surrounding the periphery of villages and farms may have been advantageous for the control of pests and associated zoonotic diseases. Therefore, the impetus to change cats to suit certain human needs was much less than for the other domesticated species and breed development for cats lagged considerably. Although reasons to change the basic form and function of the cat were not as compelling as for other species, nonetheless, certain types of cats were artificially selected in various regions of the world. Interestingly, this “breed selection” was often based on aesthetics and involved simple traits of coat color, color patterns, etc. and less noticeably form or function. Cats did not lend themselves to become herders, workers of the hunt, or guardians, but their grace and beauty have always been obvious.

The small subset of domestic cats that have undergone intensive artificial selection is the pedigreed (purebred) cats, which were bred to maintain or alter purely aesthetic traits. Of the 41 breeds recognized by the Cat Fanciers' Association (CFA) [11], 16 "natural breeds" are thought to be regional variants that predate the cat fancy [12]. The remaining breeds were developed over the past 50 years and are usually defined as simple, single-gene variants derived from the natural breeds. This is in stark contrast to most other domesticated species that have undergone millennia of intense selection for complex behavioral, performance, or production traits involving complex gene interactions [13].

A recent phylogenetic study concludes that the domestic cat is the product of a single domestication event in the Near East [14]; however, dispersal patterns of the cat since that initial domestication event have not yet been studied. The objectives of the present paper are threefold. The first is to trace the journey of the modern cat through the ancient world and to the Americas, thereby supporting origins of domestication. The second objective is to measure any changes in genetic diversity that may have occurred during the movement of cats from the Fertile Crescent. The third objective is to measure any loss of genetic diversity that might be ascribed to the development of older (foundation) or more contemporary breeds. Genetic data, reported herein, are derived from over 1100 cats, representing 17 populations of random-bred cats dispersed over five regions (Europe, Mediterranean, Asia, Africa, Americas), as well as 22 recognized breeds, including both foundation and several modern breeds (Table 1). Highly polymorphic microsatellite markers [15] were used to determine genetic relationships of cat breeds, geographical origins, and the levels of genetic loss due to inbreeding.

Results

Phylogeographical structure of domestic cats

A Bayesian analysis of random-bred cat populations using the software STRUCTURE [16] elucidated the phylogeography of the domestic cat. The clustering patterns were examined with ancestral groups (K) set between 2 and 4. The first split ($K=2$) separated Asian and East African cats from all other populations (Fig. 1a). The Mediterranean basin populations were separated from the European populations at $K=3$. East African cats formed a separate and distinct cluster at $K=4$. The result of the $K=4$ analysis clearly delineated four genetic clusters of cats, corresponding to Europe, the Mediterranean basin, East Africa, and Asia.

We next included cat breeds in the Bayesian analyses to determine the most basal relationships among all cat breeds and all random-bred cat populations. At $K=2$, 4 of 5 Asian random-bred cat populations grouped with 6 of 7 Asian breeds with posterior probabilities of 75–85%; this grouping of 10 populations was also distinct from all other cat populations (Fig. 1b). At $K=3$, the groupings were refined into a Southeast Asian cluster, a Western European cluster, and a cluster that included all other cats from the Mediterranean basin, East Africa, and Northern Asia. Cats from Singapore were an admixture of cats of Asian and European origins. American random-bred cats grouped with random-bred cats from Western Europe. Italian cats appeared to be an admixture of European and Mediterranean stock. Southeast Asian breeds clustered with the feral populations from Vietnam. Of the Asian breeds, only the Japanese Bobtail grouped strongly with Western cats, albeit with some Asian influence. The two breeds that originated in the United States (Maine Coon and American Shorthair) clustered with the seven Western European breeds. The Persian breed unexpectedly clustered with cats from Western Europe. The Sokoke, an indigenous African breed, was closely related to random-bred cats from Kenya.

We constructed neighbor-joining trees to provide additional confirmation of the genetic structure, as well as an alternative way to represent the phylogeographical patterns. Both Cavalli-Sforza's chord measure [17] and Nei's genetic distance [18] gave similar results. The tree produced by chord measure (Fig. 2) had stronger support, as indicated by bootstrap values greater than 50%, and differentiated the Asian cluster from all other cats. In addition, East African, Mediterranean, and European clusters each formed monophyletic clades. This phylogeographical structure was also supported by factorial correspondence analysis (FCA) (Figs. 3 and S1). Cats from the rim of the Arabian Sea, Sri Lanka and Abyssinians, bridged the European and Asian groups. While Asian populations were highly dispersed, the Western European cats formed a tight cluster.

Genetic diversity within the domestic cat

Genetic differentiation was determined by analysis of molecular variance (AMOVA) [19] for cat populations from Europe (including the Americas), East Africa, the Mediterranean and East Asia (Table S1). The American samples were included with the European populations, as no domestic cats were indigenous to the Americas. The greatest genetic diversity was found in cats from the Mediterranean (500 alleles across all markers). Asian cats had substantially fewer alleles (418 across all markers). The Mediterranean cats also had 41 private alleles, compared to 14 private alleles among Asian cats (Table S2).

Genetic structure of cat breeds

Bayesian clustering was used to examine the genetic relationships among breeds. A range of cluster numbers was examined, with 20 chosen as the most appropriate. This method separated the cats into inferred clusters corresponding to their breed designation (Fig. 1c) and with a purported accuracy of 95% [20]. Cats from 14 breeds were assigned to distinct clusters by this statistical analysis. The separation of 8 breeds, 4 pairs, was not consistent. Singapura and Burmese, Havana Brown and Siamese, Korat and Birman, and Exotic Shorthair and Persian could not be distinguished as distinct breeds. However, these 4 breed pairs could be unequivocally differentiated when analyzed independent of other breeds (data not shown). Two geographically related breeds, the Turkish Angora and the Turkish Van,

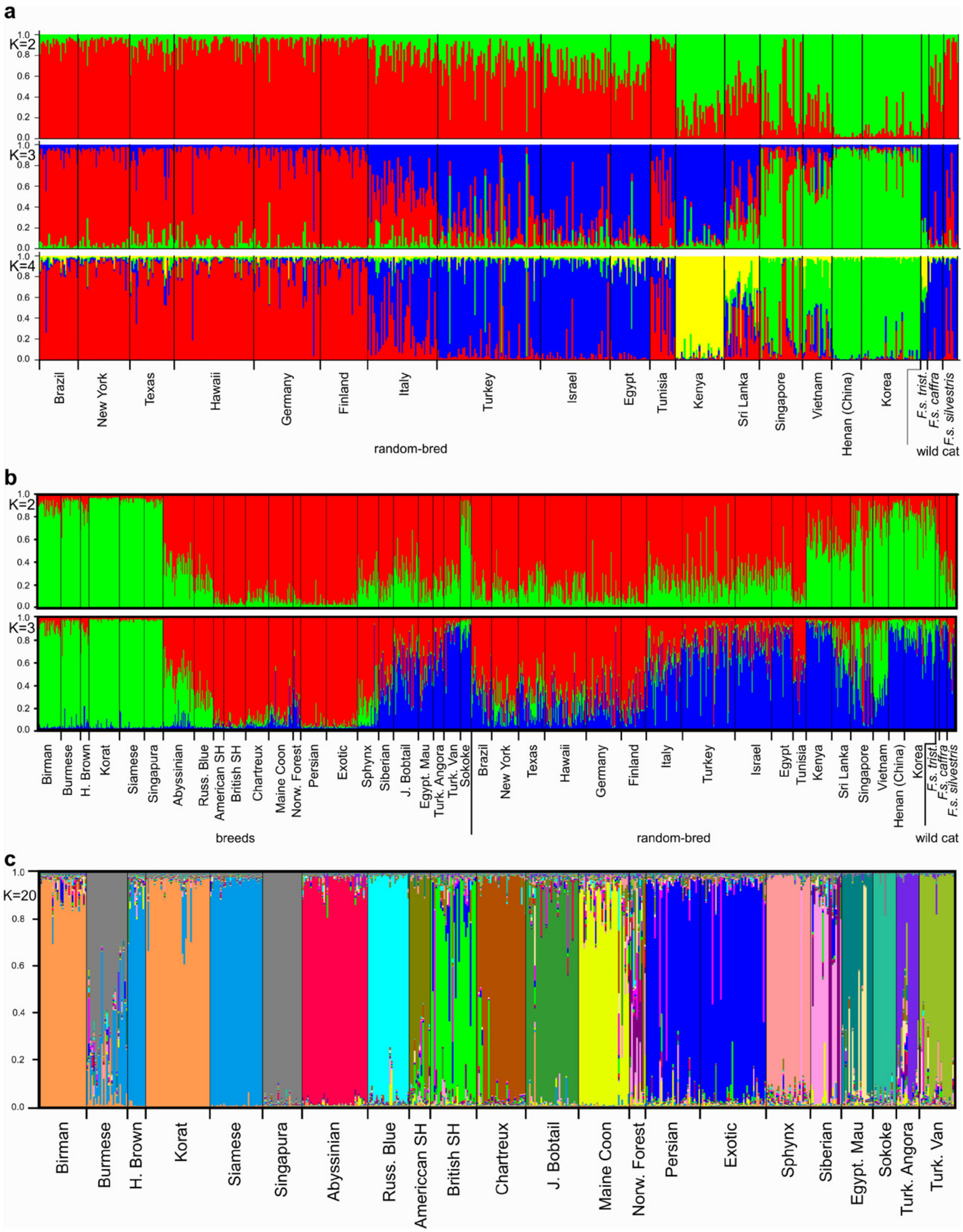

Fig. 1. Bayesian analysis of cat breeds and populations. The colors correspond to predicted genetic clusters: Western Europe (red), Mediterranean basin (blue), Asia/Southeast Asia (green), and East Africa (yellow). Each column represents an individual cat. The *y* axis represents the proportion of iterations that an individual is assigned to the given cluster. (a) The first three basal separations of random-bred cats and wildcats. (b) (Top) The first basal separation of all populations ($K=2$). Asian breeds, the Sokoke, and Asian random-bred populations (green) are clearly distinguished from all other cats. (Bottom) Analysis of all populations ($K=3$). African/Mediterranean/Asian cats (blue) separate from Southeast Asian (green) and European (red) populations. (c) Twenty-two cat breeds ($K=20$). Three pairs, Havana browns and Siamese, Persians and exotics, and Burmese and Singapura, are not genetically differentiated. Burmese appear to share origins with Siamese and Korats. Korats and Birmans also appear to be strongly related. Persians and Siberians show within-breed heterogeneity.

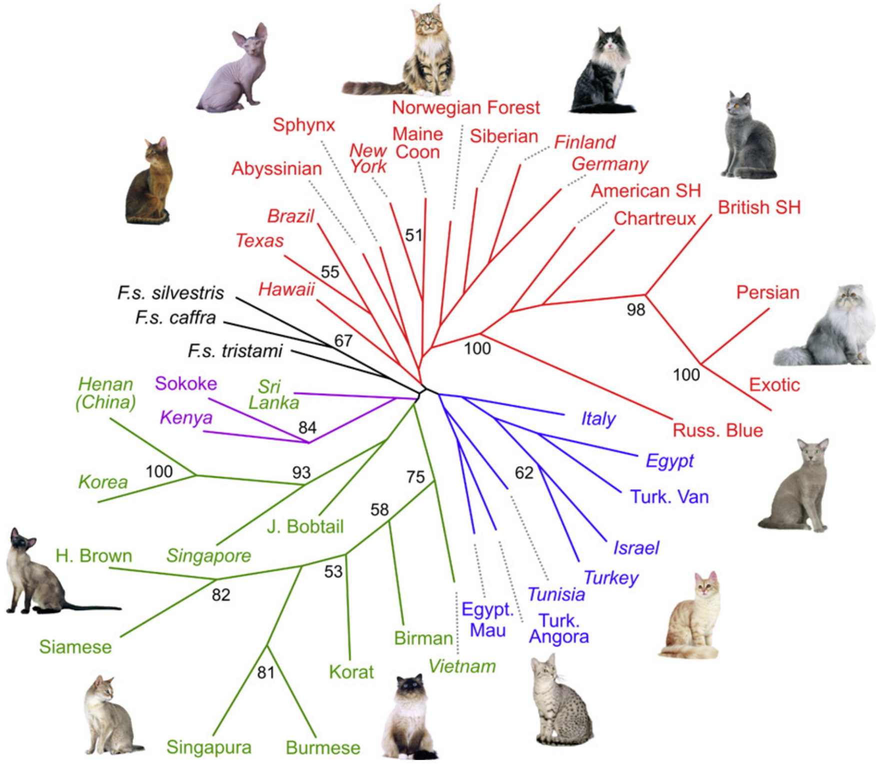

Fig. 2. Neighbor-joining tree of cat breeds and populations. The phylogenetic tree was constructed using Cavalli-Sforza's chord distance. Bootstrap values above 50% are presented on relationship nodes. Asian (green), Western European (red), East African (purple), Mediterranean basin (blue), and wildcat (black) populations form strongly supported monophyletic branches. European and African wildcats are closely related, whereas short branches of most all other populations indicate close relationships of these breeds and populations. Random-bred populations are indicated in italics, breeds are in standard font. Cat photographs courtesy of Royal Canin and Richard Katris of Chanan Photography.

were distinct from each other. Five breeds (British Shorthair, Exotic Shorthair, Norwegian Forest Cat, Persian, and Siberian) showed subdivisions within each breed, indicating multiple lineages.

Changes in genetic diversity with pure breeding

Cat breeds had less overall genetic diversity than random-bred cats, as evidenced by the relatively low within-population variance component (Table 2). The average heterozygosity for random-bred and purebred animals was 0.65 ± 0.03 and 0.51 ± 0.09, respectively (Fig. 4). Breeds such as the Burmese, Havana Brown, Singapura, and Sokoke had the lowest heterozygosity values, while Siberians had the highest among the breeds, which was comparable to random-bred cats. Average number of alleles per locus, average inbreeding coefficient (F_{IS}), and allelic richness followed a similar trend (Table 1, Fig. 4).

Discussion

Genetics of the feline diaspora

Recently, strong evidence has suggested that cat domestication occurred in the Near Eastern part of the Fertile Crescent pursuant to agricultural development [14]. The Mediterranean basin has been previously suggested as the site for cat domestication based on archeological evidence [1,21]. Driscoll and colleagues [14] used mitochondrial sequence and microsatellite markers to elucidate the origin of cat domestication. Because microsatellite markers are a better indicator of more recent genetic diversity, this study focused on microsatellite markers to evaluate the more recent breed origins. Based on the present study, genetic diversity was not substantially decreased by the subsequent diaspora of modern cats from the Mediterranean to other areas of the ancient world. However, there were interesting regional differences in their genetic makeup. FCA, Bayesian clustering, and neighbor-joining phylogenetic trees divided all of the world's cats into four distinct groups: Asia, Mediterranean basin, Western Europe, and East Africa. American cats consistently grouped with cats from Western Europe, suggesting European settlers probably brought cats to the New World and the cat's time in America has been too brief for significant genetic differentiation.

Genetic diversity remained fairly uniform among various areas within the Mediterranean region. The constant movement of ships and caravans, as well as cats, in this key region of early civilization would have promoted a constant interchange of cats. Although Mediterranean cats tended to be genetically uniform, there were some interesting differences and relationships between certain areas within the Mediterranean region. Bayesian analysis indicated that Italian and Tunisian cats were an admixture of Western European and Mediterranean cats. This mixing supported the historical ties between Tunisia and Western European countries. Cats from Sri Lanka and Singapore

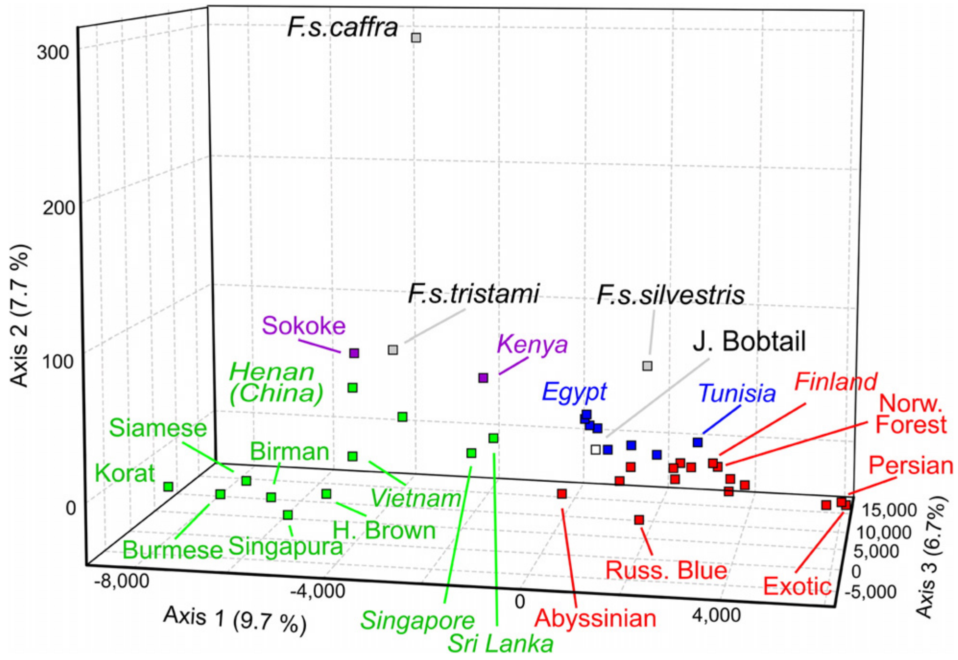

Fig. 3. Factorial correspondence analysis of cat breeds and populations. Squares represent population centers of the geographic regions Asia (green), Western Europe (red), Mediterranean basin (blue), East Africa (purple) and wildcats (black). The affinities of the Sokokes to the Asian populations, the Japanese bobtails to the Mediterranean and European cats, and the Tunisian cats to the European populations are apparent and are in agreement with the STRUCTURE results. Arabian wildcats (*F. s. tristami*) associate with East African populations, European (*F. s. silvestris*) with European populations and African wildcats (*F. s. caffra*) appear most distinct from all other groups. See Supplementary Fig. 1 for alternate views.

were an admixture of cats from Southeast Asia, Europe, and everywhere else when defined with $K=3$ (Fig. 1b). However, some Singapore cats did not appear to be hybrids, but rather a mixed sampling of genetically different cats. This may have been a relic of British colonialism or recent importation. According to the FCA (Fig. 3), Sri Lankan cats and the Abyssinian breed bridged cats of the East and West, perhaps resulting from maritime trade routes in the Arabian Sea or again from recent British colonialism. The most interesting difference involved the Asian cluster of cats, which was genetically distinct from cats of the Mediterranean basin, Western Europe, and Africa. This pattern of genetic diversity indicates that the first domestic cats reached the Far East relatively early, followed by a long period of relative isolation. This isolation may have been caused by the waxing and waning of trade between successions of great ancient empires. The Asian population was of further interest because it was internally segregated. Populations of cats from different parts of Asia (random bred and purebred) were more genetically divergent from one another than local populations within the Mediterranean basin or Western European clusters. This partitioning of genetic diversity within the Asian population was also corroborated by the longer branch lengths within the Asian clade on the phylogenetic tree (Fig. 2). This suggests not only that the Asian population was relatively isolated from the three other regional clusters, but also that cats within various regions of Asia were kept separate.

Table 2
AMOVA of cat breeds and random-bred populations

Sample	Variance components (%)		
	Within populations	Among populations within regions	Among regions
Breeds	61	24	15
Random bred	86	6	8
Combined	73	18	9

Genetic variation across random-bred and purebred populations

The substructuring of populations is important for parentage analyses, forensic applications, individual matching, and disease studies. Random-bred cats have the largest within-population variance, consistent with their larger population sizes, freedom to migrate, and no artificial selection. However, the various breeds of cats exhibit the largest among population variance, reflecting their distinctness. The within-population variance component of random-bred cats was 86%, compared to 93–95% in humans [22], suggesting that individual cat populations are less genetically variable than human populations. Purebred cats, with a within-population variance component of only 61%, were less genetically variable than the random-bred populations, which was also reflected in the estimates of average heterozygosity. The average heterozygosity of the breeds was 10% lower than that of the random-bred populations (Fig. 4), which in turn was 10% lower than the average for human populations. Worldwide human populations range from 0.50 to 0.78 in average heterozygosity, most being above 0.70. The among-populations between-regions variance of cat populations was approximately twice that seen in humans (6% in cats, 2.5% in humans) as was the among-regions variance (8% in cats, 3.6–4.3% in humans).

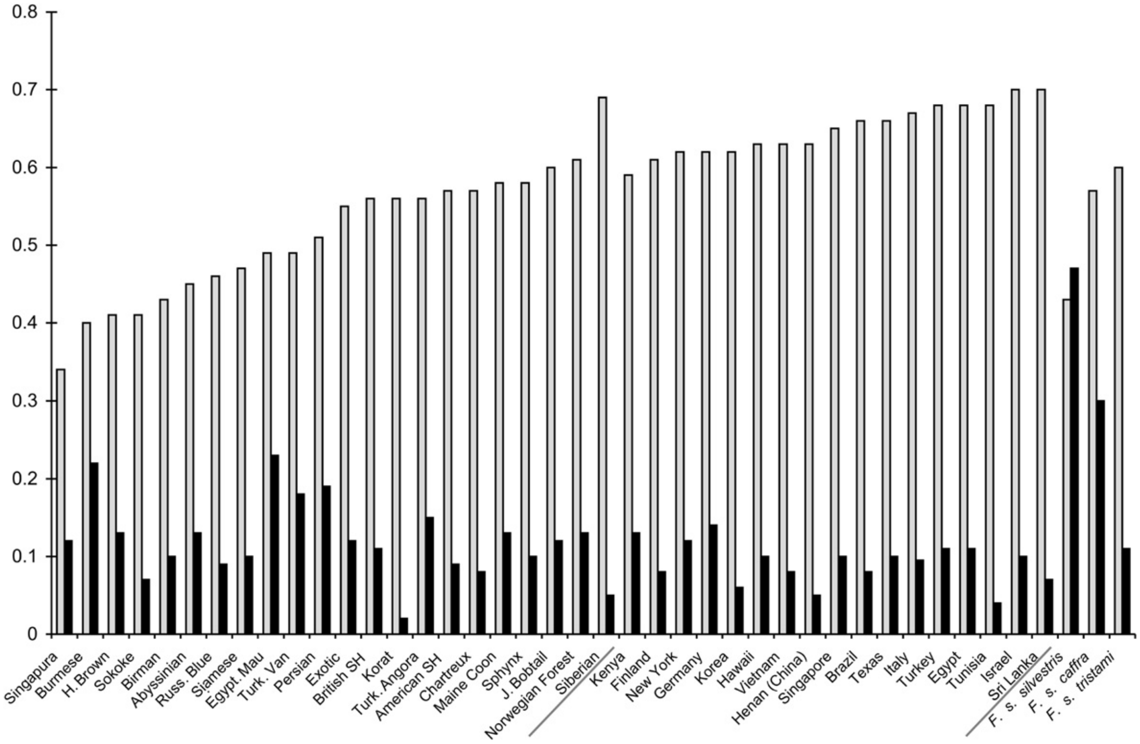

Fig. 4. Genetic diversity indices of breeds, random-bred populations, and wildcats. Light bars represent observed heterozygosity (H_O) and dark bars represent the inbreeding coefficient (F_{IS}). Populations are listed in ascending order of heterozygosity, breeds are on the left, random-bred populations in the middle, and wildcat populations to the right. The *y* axis represents the proportion of heterozygosity or inbreeding coefficient.

This increase suggests that cat populations are more genetically isolated due to geography than human populations. The large among-populations (24%) and among-regions (15%) variance of the breeds is likely a result of the intensive artificial selection and isolation imposed by breeding practices. The Burmese and Singapura breeds have the lowest heterozygosity and the highest F_{IS} of any breed, reflecting the most intense inbreeding (Fig. 4). The newest CFA breed, the Siberian, had the highest variation, comparable to random-bred populations. This indicates that it was derived from a broad foundation stock. The Sphynx, which is a derivative of the Devon Rex breed, also had high genetic diversity. Given these results, Burmese and Singapura breeders should be concerned about genetic diversity, while Siberian breeders should be encouraged to retain existing diversity as their breed becomes more established. Similar to the conservation efforts in captive exotic felid populations, genetic analyses, breed histories, and population dynamics could be used to develop breed management or survival programs to maintain genetic variation within the breed gene pool for an extended period of time. In addition, these regional differences in the genetic variation of cats suggest that the genetic markers used in cat DNA profiling should be tested in the diverse populations to validate their efficiency.

Genetic structure and origins of cat breeds

We have demonstrated that genetic diversity following domestication was regionalized in areas of the ancient world and even within localities within those regions. Some differences could be explained by isolation, while others were best explained by interchanges of animals between clusters and localities. All of these differences involved human activities, but were probably not strictly intentional. However, intentional changes in the genetics of cats ultimately occurred during the development of breeds.

Unlike breeds of domestic horses, dogs, cattle, sheep, etc., some of which are thousands of years old, most cat breeds were developed within the past 150 years, mainly in Europe and the United States [12]. Although documentation for nearly 80 cat breeds exists, the largest cat fancy association recognizes only 41 breeds [23,24]. The Persian, Russian Blue, Siamese, and Angora were among the first cat breeds registered by cat associations. The CFA designates 16 cat breeds as “natural” or “foundation.” Fifteen of the foundation breeds are included in this study, lacking only the Manx, the tailless breed of cat that was developed on the Isle of Man.

Purebred cats had similar structuring to the random-bred cats of their regions. The Southeast Asian breeds, including Birman, Burmese, Havana Brown, Korat, Siamese, and Singapura, form a grouping that is distinct and at the opposite end of the genetic spectrum from the Western breeds, as depicted by the FCA. The Abyssinians and Japanese Bobtails were exceptions and possessed genetic markers common to both Southeast Asian and Western breeds. This indicates that cats from both Asia and Europe were used to create these breeds.

Each of the foundation breeds was genetically distinguishable with 95% accuracy from the others. One of the oldest recognized cat breeds, the Persian, has been used in the development of several other breeds. Crossbreeding with Persian cats is often used to produce a more brachycephalic head type. The Exotic Shorthair is essentially a shorthaired variant of the Persian, which is demonstrated by the complete clustering of these two breeds as one group. The most dolichocephalic breed, the Siamese, has also been used to create numerous other breeds, including Colorpoints, Orientals, Havana Browns, and longhaired breed variants. Although listed as different, most of these derived breeds vary by only a single gene variant, such as hair length, color patterns, or fur coloration; thus, these derived breeds will likely be inseparable as distinct breeds, as was shown with the Havana Brown and Siamese. The Burmese and Singapura grouping proved to be an additional example of recent breed derivations. The close associations of the Persian and Exotic, the Siamese and Havana Brown, and the Burmese and Singapura resulted in the highest branch supports in the neighbor-joining tree and the inability to separate members of each pair by the genetic markers used in this study. However, it is important to remember that most breeds have a written/oral history in addition to a genetic fingerprint. Cat breeding folklore contends that both Burmese and Singapura are indigenous to ancient Burma. Folklore also suggests that Burmese cats from the United States were taken to Singapore, purposely bred with native cats, and then later returned to the United States as the new breed Singapura. Havana Browns are considered a separate breed in the United States; however, European cat breed associations consider them only a color variant of Siamese.

These data show that most, but not all, foundation or modern breeds appeared to have originated from random-bred cats of the purported region of origin. The Southeast Asian breeds were strongly associated with the random-bred cats from Vietnam, China, Korea, and Singapore. The Siberian is one of the newest cat breeds from Russia and is actively under development. Random-bred cats from Russia were not available, but the Siberian had strong associations with cats from the nearby countries of Germany and Finland. Turkish Vans grouped with regional random-bred cats from Turkey, Israel, and Egypt. Likewise, cats from the Kenyan islands of Lamu and Pate group with the Sokoke breed, which was developed in Kenya. The Kenyan islands and the mainland were accessed via shipping routes in the Arabian Sea, allowing exchange between India, the Near East, the Arabian Peninsula, and Africa. All other breeds and random-bred populations form a network of closely related and less distinctive cats of Western European grouping. Surprisingly, the Persian breed was not genetically associated with random-bred cat populations from the Near East, but grouped with random bred cats of Western Europe. The Persian is perhaps the oldest recognized cat breed and has undergone selection for an extreme phenotype, which likely involved complex gene interaction. Even though the early Persian cat may have in fact originated from ancient Persia, the modern Persian cat has lost its phylogeographical signature. Similarly, the Japanese Bobtail does not appear to hail from its stated origins of Japan. Although cats were not indigenous to Japan, they migrated to the islands as part of Asian trade routes hundreds of years ago. Introduced as a breed in the United States in 1968, Japanese Bobtails from the United States appear to have been influenced more in their gene pool by European cats than by Asian cats. Egyptian Maus also appear to be on the verge of losing their historical origins via genetic influences from Europe. Overall, these results indicate that both the random-bred and the breed populations group in a manner largely concordant with geography. Breed histories, for the most part, appear to be accurate.

This study reconfirmed that the Mediterranean was the likely site of domestication of the modern cat. Genetically distinguishable clusters of cats were found in the Mediterranean, Europe, Asia, and Africa. North American cats were closely linked to European cats. The Asian cluster was genetically unique, indicating that it became isolated following its introduction. Genetic diversity remained surprisingly broad among cats from various parts of the world. Genetic data demonstrated that most, but not all, foundation breeds originated from indigenous cats of the regions of purported origin and that this was associated with some loss of diversity. Researchers should recognize the relative recent development of the breeds, which influences linkage disequilibrium and the power of association studies. This study also provides a warning to modern cat fanciers that breed development must be done slowly and with the maintenance of a broad genetic base. Over 20 deleterious genetic disorders have been recognized in modern cats, and all have been identified in pure breeds. The elucidated genetic relationships of the cat breeds can be used by cat breeders to develop more efficient breed management plans.

Materials and methods

Sample collection and DNA isolation

Our dataset consisted of 22 cat breeds, including 15 of 16 supposed foundation breeds, 2 breeds under development, Siberian and Sokoke, and 5 more recently developed breeds, including Exotic Shorthair, Havana Brown, Japanese Bobtail, Singapura, and Sphynx (Table 1). We obtained DNA samples of most breeds at cat shows and by request from cat owners in the United States. Korat, Turkish Angora, Turkish Van, and Siberian samples were acquired from the United States and Europe because these breeds have the same standards between continents. We reviewed pedigrees to ensure that no first-degree relatives were included in the study and that a majority of cats did not share common grandparents. The random-bred cats included feral cats that have no feeding or housing assistance from humans, random-bred cats that have had some influence by humans, and cats owned and cared for by humans but that are not of a specific breed. For random-bred populations, we did not include littermates or both parents and their kittens. We used sterile cytological brushes to noninvasively obtain buccal (cheek) cells and the QIAmp DNA mini kit (Qiagen, Valencia, CA, USA) to extract the DNA. Samples from Kenya and U.S. random-bred populations were provided as blood or tissue, and we extracted the DNA using standard phenol/chloroform [25]. African wildcat (*F. s. caffra*) [10] and European wildcat (*F. s. silvestris*) [26] DNA samples were provided from previous studies. The Arabian wildcats (*F. s. tristami*) were collected in Israel. We used the Replig-G kit (Qiagen) to augment in part the wildcat DNA samples by multistrand-displacement whole-genome amplification.

Genotyping

Thirty-eight microsatellites were genotyped in 1176 cats representing 22 breeds, 17 random-bred and 3 wild populations (Table 1). On average, each random-bred and purebred population was represented by 35 and 25 cats, respectively, ranging from 10 to 70 for the domestic cats. For wildcat populations 5 to 10 samples were genotyped. The microsatellite markers were chosen based on the criteria of high heterozygosity, high polymorphism information content, and wide chromosomal distribution of at least 100 cM from the closest neighbor [27]. The primer sequence of marker FCA80 contained mismatches compared to publicly available sequence and was substituted by an updated version, FCA80B, which interrogates the same microsatellite (forward, 5′-AGCAAAGAGGT-GAAGCAAGA; reverse, 5′-TTCCCTCCTCCGTGTATGTA). Genotyping PCR was carried out on MJ gradient thermal cyclers (Bio-Rad, Hercules, CA, USA) with Taq polymerase and buffer supplied by ABgene (Rochester, NY, USA). Ten to 25 ng DNA was analyzed in a reaction mix consisting of 1× PCR buffer, 0.01% BSA, 0.25 M betaine, 2.0 mM $MgCl_2$, 0.25 units Taq, 200 μM dNTPs, and 0.02 μM each primer. Forward primers were fluorescently labeled with 6-FAM, NED, PET, or VIC dyes (Applied Biosystems, Foster City, CA, USA). Microsatellites were multiplexed into groups of four or five markers during PCR. The thermal cycling program was carried out as follows: 5 min at 95 °C initial denaturation; 35 cycles of 1 min at 95 °C, 1 min at 58 °C, 1 min at 72 °C; followed by a 30-min final extension at 72 °C. We employed an ABI 3730 (Applied Biosystems) DNA analyzer to perform the fragment separation and we visualized the results using STRand [28].

Population structure analyses

The structure of all sampled populations was determined by FCA (GENETIX 4.05) [29] and by Bayesian clustering (STRUCTURE) [16]. The multidimensional FCA was performed under default settings. In each Bayesian clustering analysis, 1,000,000 iterations were carried out after a 10,000-iteration burn-in under the admixture model. The entire dataset, including the breeds, random-bred cats, and wildcats, was analyzed to obtain basal relationships for $K=2$ and $K=3$. Analyses of only random-bred populations ($K=2$ to $K=4$) were performed to clarify phylogeographical relationships. Ten runs each at $K=16$ to $K=26$ were performed on the breed dataset. The estimated log-probability of the data for a given value of K in the range of interest displayed a flat trend (data not shown). This suggests that STRUCTURE was unable to determine which number of inferred ancestral populations in the biologically significant range (those surrounding 22) was the most probable. We therefore chose $K=20$ as the best fit because, at that value, the genetic clusters formed by the analysis most closely corresponded to supposed breeds. Assignment testing was performed using the Bayesian methods of Rannala and Mountain [30], as implemented by GENECLASS2 [20].

Tree building

Phylogenetic trees were constructed with the entire dataset (PHYLIP) [31]. A series of components was employed in the following order: Seqboot, Genedist, Neighbor, and Consense. We used Genedist to produce both Nei's genetic distance and Cavalli-Sforza's chord measure outfiles so that two different trees were produced under these two distance measures. In each case, the trees were bootstrapped with 1000 iterations to assess confidence. We used TreeView [32] to visualize the resulting trees.

AMOVA

To quantify the degree of regional differentiation, we performed an AMOVA [19] in three parts: breeds only, random-bred populations only, and the combined dataset, which did not include wildcats (Arlequin) [33]. The populations were divided into four groups corresponding to their geographical origins as shown in Supplementary Table 3. The *a priori* geographical origins of Abyssinians and Sri Lankan cats, as well as their placement in the FCA and STRUCTURE analyses, were unclear; thus, they were not included in the AMOVA.

Population parameters

We calculated population-based allele numbers, ranges, and observed and expected heterozygosities (H_O and H_E, respectively) using GENALEX [34]. We used Arlequin to calculate F_{IS}. Allelic richness, a measure of allele number standardized for sample size, was also calculated using Fstat [35]. Locus-specific parameters are presented in Supplementary Table 2.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ygeno.2007.10.009.

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