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Patterns of molecular genetic variation among cat breeds

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Abstract

Genetic variation in cat breeds was assessed utilizing a panel of short tandem repeat (STR) loci genotyped in 38 cat breeds and 284 single-nucleotide polymorphisms (SNPs) genotyped in 24 breeds. Population structure in cat breeds generally reflects their recent ancestry and absence of strong breed barriers between some breeds. There is a wide range in the robustness of population definition, from breeds demonstrating high definition to breeds with as little as a third of their genetic variation partitioning into a single population. Utilizing the STRUCTURE algorithm, there was no clear demarcation of the number of population subdivisions; 16 breeds could not be resolved into independent populations, the consequence of outcrossing in established breeds to recently developed breeds with common ancestry. These 16 breeds were divided into 6 populations. Ninety-six percent of cats in a sample set of 1040 were correctly assigned to their classified breed or breed group/population. Average breed STR heterozygosities ranged from moderate (0.53; Havana, Korat) to high (0.85; Norwegian Forest Cat, Manx). Most of the variation in cat breeds was observed within a breed population (83.7%), versus 16.3% of the variation observed between populations. The hierarchical relationships of cat breeds is poorly defined as demonstrated by phylogenetic trees generated from both STR and SNP data, though phylogeographic grouping of breeds derived completely or in part from Southeast Asian ancestors was apparent.

Keywords: Domestic cat; Cat breeds; STRUCTURE algorithm; STRs; SNPs; Population subdivision

The domestic cat, *Felis catus,* is one of the most recently evolved members of the Felidae, a family that has generated some of the most charismatic mammalian species in a rapid radiation over the past 11 million years [1]. The cat has played a significant role in human history, inspiring extremes of emotional response in humans from reverence in ancient Egyptian periods to fear and loathing in the Middle Ages. Numbering approximately 88.3 million in the United States alone, the domestic cat has become the most popular household pet [2].

The development of most domestic animal breeds has been the consequence of artificial selection of phenotypic variants, which largely improved the animal's utility to humankind. In contrast, cat breeds have arisen from the selection of visible traits prized by humans for aesthetic qualities. Cat breeds represent recent lineages that exhibit different combinations of coat color, patterning, texture, and hair length combined with other desirable traits [3]. Variants in genes underlying some of the phenotypes under selection, including *MLPH* (*dilute*), *TYR* (*siamese*, *burmese*), *TYRP1* (*chocolate, cinnamon*), *ASIP* (black), and *long hair*, have recently been elucidated [4–7,28]. Over 120 breeds have been recognized historically, many of which are extinct or no longer maintained [3]. In the United States, 57 breeds are currently recognized by the two largest cat registries, the Cat Fanciers' Association (CFA) (www.cfainc.org) and The International Cat Association (TICA) (www.TICA.org).

The objective of this study was to utilize short tandem repeat (STRs) and single-nucleotide polymorphisms (SNPs) to characterize genetic variation within and between breeds, assess

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genetic distinctiveness between breeds, and relate these phylogenetic and population data to the history of cat breeds.

Results

We have previously described a panel of highly polymorphic tetranucleotide repeat STR loci, selected for their informativeness in cat breeds, to be utilized in the forensic analysis of domestic cat specimens [8]. A population genetic database of 38 cat breeds was generated by genotyping the panel in a sample set of 1040 individuals (M. Menotti-Raymond et al., manuscript in preparation). Approximately 27 individuals represented each breed. We have utilized this data set to examine population substructure within the major cat breeds. A Bayesian model-based clustering algorithm, STRUCTURE [9], which identifies (K) genetically distinct subpopulations on the basis of patterns of allele frequencies, was utilized. The log likelihood of the number of subpopulations (K) is determined by the algorithm, which is considered optimal at the point at which log likelihood values start to plateau.

Steadily increasing values were observed for log likelihoods from $K=2$ to 22 subpopulations (Fig. 1). However, there was no distinct point at which the log likelihoods started to plateau between K of 22 and 28 (Fig. 1). Beyond a K of 22, nine subpopulations were composed of multiple breeds (Table 1). Each of these nine populations was examined as an independent data set in additional STRUCTURE runs to determine if there were support for any further substructure. Eight additional breeds were supported as independent subpopulations as a result of these analyses (Table 1). Sixteen breeds could not be resolved into independent subpopulations (Table 1).

The STRUCTURE algorithm additionally provides an estimation of the proportion of an individual's genome (Q) that originates from each of the K subpopulations [9] (Fig. 2) (Supplementary Tables 1a–1x). For each breed group, the average Q value was determined for individuals in the group to their breed classification. A wide range in the strength/robustness of population definition was observed, from breeds with high definition exhibiting an average Q of 88% of their genetic variation assigned to a single population (Havana, Abyssinian) to breeds with as little as a third of their genetic variation assigned to a single population (Selkirk Rex, Manx) (Table 2). Twenty-eight of the 38 breeds (74%) demonstrate less than 80% of their genome assigned to a single population. Although 17% ($n=137$) of the 1040 breed individuals demonstrated less than 50% of their genetic profile apportioned to their breed/population group, an individual rarely (4%) showed higher genetic apportionment to a breed/population group other than its own (Fig. 2) (Supplementary Tables 1a–1w). The majority of these admixed individuals showed evidence of a mixed genetic heritage from multiple populations (Supplementary Tables 1a–1w). Outbred cats (cats that are not a breed cat) in the sample set demonstrate assignment to multiple groups with no suggestion of population substructure (Fig. 2) (Supplementary Table 1x).

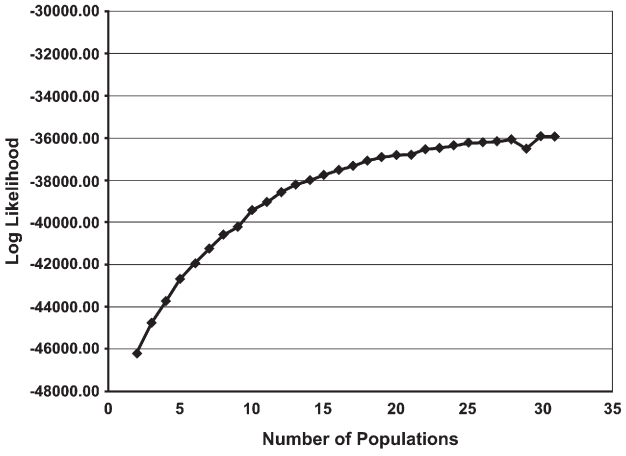

Fig. 1. Log likelihoods for values of K (2–32) in 1040 individuals registered in 38 cat breeds.

Table 1
Populations identified in STRUCTURE

1. Abyssinian/Somali
2. American Shorthair/American Wirehair
3. Balinese/Javanese/Colorpoint Shorthair/Oriental Shorthair/Siamese
4. Bengal
5. Birman
6. Bobtail
7. Bombay
8. British Shorthair/Scottish Fold
9. Burmese/Tonkinese
10. Chartreux
11. Cornish Rex
12. Devon Rex
13. Egyptian Mau
14. Exotic/Himalayan/Persian
15. Havana
16. Korat
17. Maine Coon Cat
18. Manx
19. Norwegian Forest Cat
20. Ocicat
21. Ragdoll
22. Russian Blue
23. Selkirk rex
24. Singapura
25. Sphynx
26. Turkish Angora
27. Turkish Van

The American curl breed failed to partition as a group.

Cat breeds exhibited average STR heterozygosities ranging from 0.53 (Havana, Korat breeds) to 0.85 (Norwegian Forest Cat, Manx breeds) (Table 2), though, of note, these loci were selected for high polymorphism to be utilized in genetic individualization of domestic cat samples. Outbred domestic cats exhibited an STR average heterozygosity of 0.85 (Table 2). Breeds that were more highly structured often exhibited lower heterozygosity values for the STR set, though the correlation was weak ($r^2=0.55$).

An analysis of molecular variance (AMOVA) demonstrated moderate Fst values among cat breeds, from a high of 0.53 to a low of 0.0 (Table 3). The average pairwise Fst value observed in cat breeds is 0.17, with most of the variation in cat breeds observed within a breed population (83.7%), versus 16.3% of the variation observed between populations (Table 3).

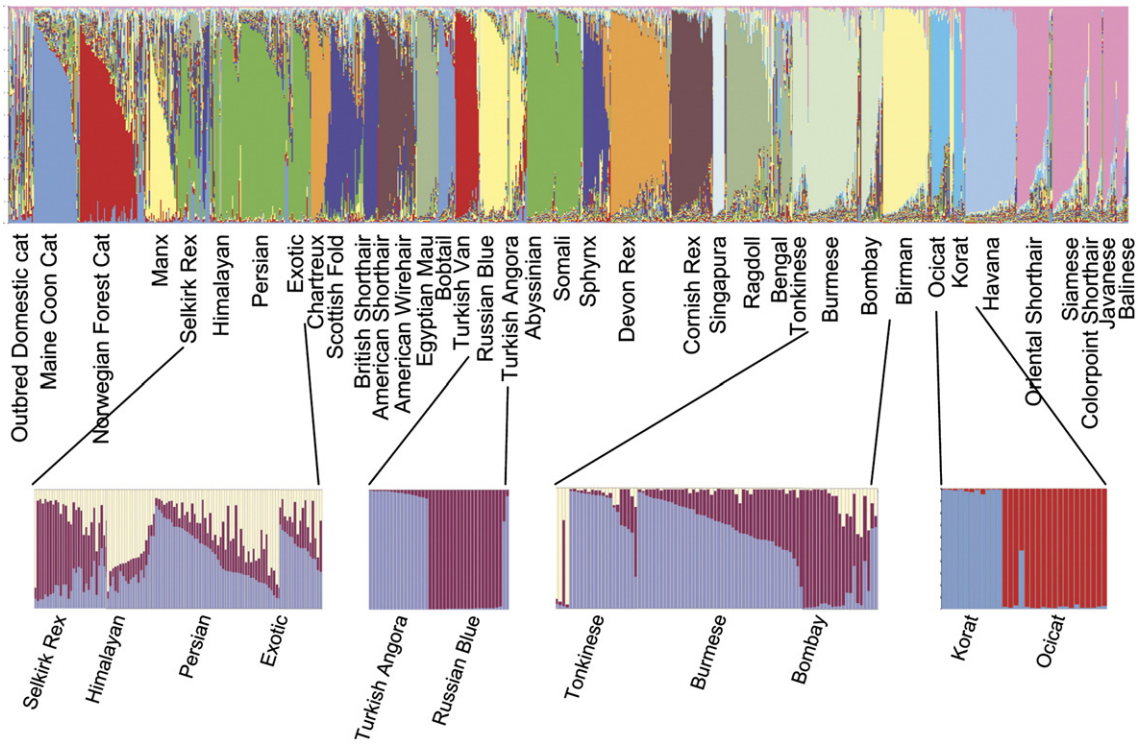

Fig. 2. Histogram demonstrating the proportion of each individual's genome that originated from each of 22 populations.

A phylogenetic analysis of composite STR genotypes was used to examine breed relationships. A neighbor-joining tree constructed utilizing distance matrices generated from the proportion of shared alleles (Dps) is presented in Fig. 3 [10]. Many of the breed relationships observed in the neighbor-joining tree were supported in the STRUCTURE analysis (Fig. 2). Breeds derived completely or in part from Southeast Asian ancestors, including Korat, Birman, Tonkinese, Burmese, Havana, Bombay, Singapura, Siamese, Oriental Shorthair, Colorpoint Shorthair, Javanese, and Balinese, clustered together with strong bootstrap support identifying two independent clades. The nine subpopulations identified in STRUCTURE that were composed of multiple breeds (Table 1) were recognized as clades in the neighbor-joining tree, most with relatively robust bootstrap values. These populations are composed of breeds that share a common ancestry or are currently allowed to be interbred [11] (Table 2). The hierarchical branching order of the different breeds was generally unresolved, providing little evidence that one breed was "older" than the rest (Fig. 2).

Genetic diversity was additionally examined in cat breeds utilizing a group of 284 SNPs identified as heterozygous in *Cinnamon*, an Abyssinian cat whose genome was recently sequenced at two fold equivalents [12]. Selected SNPs are located in 10 regions spanning blocks of approximately 600 kb identified on nine autosomes and the X chromosome [12]. The 284 SNP sites were genotyped in 77 cats representing 24 breeds ($n=1$–5 unrelated individuals) (Supplementary Tables 2a–2j). The number of variable SNP sites of 284 observed per breed was highly variable (Table 2), from a high of 72 SNPs observed in the American Shorthair ($n=4$) and Egyptian Mau ($n=5$) to a low of 9 SNPs observed in the Devon Rex. An average of 37 SNPs were identified per breed.

The SNP genotypes were used to generate a maximum likelihood tree of the 74 individual breed cats (Fig. 4). Most of the individuals clustered with other members of their breed group, with the exception of the British Shorthair/Scottish Fold, which were intermixed with one another. Differences were observed in the extent of monophyly in the different breeds, with some of the more recently established breeds showing more departures from monophyly. As observed with the phylogenetic tree generated from STR data, the hierarchical branching order of the different breeds was generally unresolved, providing little evidence that one breed has been established as an isolated population longer than the rest. Individuals of Southeast Asian origin (Siamese, Burmese, Havana, Birman) clustered together, as was observed with the STR-generated phylogeny. Several breed relationships that were supported in the neighbor-joining tree included the British shorthair/Scottish Fold, Sphynx/Devon Rex associations and clustering of two breeds of Middle Eastern origin (Turkish Van and Turkish angora).

Discussion

We have recently reported on a Fertile Crescent origin for the domestication of *F. catus* from the Near Eastern wildcat, *Felis lybica*, based on patterns of molecular genetic variation in mitochondrial DNA and 36 STR loci in a sample set of 851 individuals [13]. Domestication of the cat likely occurred in conjunction with the storage of grain stocks, which attracted rodent pests, in a developing agrarian society. Cats subsequently became common in Europe and Asia by the 10th century, as a

Table 2
Cat breed population statistics and histories

Cat breed	STR data set (*n*)	Origin [a]	Date(s) of origin [a]	Outcrosses allowed [b]	Breed classification [c]	H_e (STR)	Average Q [d]	SNP data set (*n*)	No. SNP sites	Average pairwise *p* distance
Abyssinian	29	Ethiopia	1860s		Established	0.62	0.88	3	36	0.112
American Curl	9	Domestic mutation introduced into ASH	1980s	ASH	Variant ASH	0.82			ND	
American Shorthair	26	U.S. domestic population	1900		Established	0.77	0.70	4	72	0.150
American Wirehair	9	Domestic mutation introduced into ASH	1966	ASH	Variant ASH	0.75	0.48		ND	
Balinese	11	USA	1940s [e]	SIA	Variant SIA	0.58	0.77		ND	
Bengal	13	USA	1963		Hybrid	0.80	0.45		ND	
Birman	43	Burma, with outcrosses	1930s [e]		Established	0.60	0.86	3	41	0.109
Bombay	21	ASH and BUR cross	1958	Sable Burmese or black ASH	Hybrid	0.72	0.65		ND	
British Shorthair	13	UK	1870s [e]		Established	0.66	0.82	3	37	0.106
Burmese	50	Thailand	1350–1767		Established	0.69	0.80	3	31	0.072
Chartreux	21	France, with outcrosses to BSH	14th cent.	Outcrossed to BSH (blues) to reestablish breed after WWI	Established	0.74	0.64	5	28	0.042
Colorpoint Shorthair	14	USA, UK	1947	SIA (until 2019)	Variant SIA	0.70	0.77		ND	
Cornish Rex	41	Mutation in UK domestic population with outcrosses to SIA and other breeds	1950		Established	0.71	0.81	2	14	0.096
Devon Rex	57	Mutation in UK domestic population with early outcrosses to ASH and other breeds	1960	ASH, BSH (until 2013)	Established	0.66	0.78	2	9	0.07
Egyptian Mau	21	Egypt	Early [f]		Established	0.70	0.82	5	72	0.01
Exotic	18	USA	1966	PER	Variant PER	0.75	0.77		ND	
Havana	49	Originated from crosses between OSH and other domestics	1951		Established	0.55	0.89	2	13	0.074
Himalayan	19	USA, UK	1950s/1920s	PER, EXO	Variant PER	0.71	0.76			
Bobtail	16	Japan	5th–10th cent.		Natural breed	0.76	0.74	4	45	
Javanese	13	UK, USA	1960s	BAL, CSH, SIA	Variant OSH	0.68	0.75		ND	
Korat	11	Thailand	1350–1767		Natural breed	0.55	0.62		ND	
Maine Coon Cat	43	New England, USA	1860s		Established	0.79	0.70	4	39	0.09
Manx	29	UK, Isle of Man	Early [f]		Natural breed	0.84	0.39	4	56	0.13
Norwegian Forest Cat	67	Norway	Early [f]		Natural breed	0.84	0.52	4	42	0.094
Ocicat	19	Cross between ABY and SIA	1964	ABY (until 2015)	Hybrid	0.65	0.70	2	18	0.138
Oriental Shorthair	33	UK	1950s	SIA, CSH	Variant SIA	0.74	0.70		ND	
Persian	51	Iran	Early [f]		Established	0.77	0.73	4	50	0.103
Ragdoll	43	U.S. domestic population with crosses to other breeds	1960s		Established	0.76	0.69	4	59	0.135
Russian Blue	23	Russia	Late 1800s		Established	0.71	0.76	2	15	0.086
Scottish Fold	41	Mutation in British domestic population with crosses to BSH, ASH, and PER	1961	ASH, BSH	Mutation/ hybrid	0.81	0.46	2	15	0.105
Selkirk Rex	28	Mutation in U.S. domestic population with crosses to PER, ASH, and BSH	1987	PER, EXO (until 2010) BSH (until 2015)	Mutation/ hybrid	0.77	0.32	1	ND	
Siamese	34	Thailand	1350–1767		Established	0.64	0.75	5	57	0.082
Singapura	14	Small founding population of cats of SE Asian origin	1971		Established	0.57	0.84		ND	

Table 2 (*continued*)

Cat breed	STR data set (*n*)	Origin [a]	Date(s) of origin [a]	Outcrosses allowed [b]	Breed classification [c]	H_e (STR)	Average Q [d]	SNP data set (*n*)	No. SNP sites	Average pairwise *p* distance
Somali	24	USA, Canada	1967		Variant ABY	0.66	0.84		ND	
Sphynx	26	Domestic mutations with crosses to DRE and ASH	1966	DRE, ASH (until 2010)	Mutation	0.78	0.62	3	38	0.105
Tonkinese	19	Cross between BUR and SIA	1950s		Hybrid	0.71	0.70		ND	
Turkish Angora	17	Turkey	Early [f]		Natural breed	0.81	0.41	3	35	0.107
Turkish Van	28	Turkey	Early [f]		Natural breed	0.76	0.66	3	24	0.067
Average						0.71	0.69	77	36.8	0.099
Complete breed set	1040					0.87			284	0.21
Outbred cats	24					0.85		19	101	0.145

ABY, Abyssinian; ASH, American Shorthair; BAL, Balinese; BSH, British Shorthair; BUR, Burmese; CSH, Colorpoint Shorthair; DRE, Devon Rex; EXO, Exotic; OSH, Oriental Shorthair; PER, Persian; SIA, Siamese; UK, United Kingdom. ND, not determined.

[a] From Vella and Robinson [3].

[b] www.cfa.org., www.tica.org, outcrosses are allowed to the breeds listed until the date in parentheses.

[c] Natural breed, newer breeds that have originated in specific geographic regions; good representatives of breed still to be found in their native state as pets, barn cats, feral cats. Established breed, breeds that have evolved through selective breeding to a state approaching the goals as set by their standards. Mutation breed, breeds that typically differ from one of the older established breeds on the basis of a single allele introduced by outcross. Hybrid breed, breeds that have been developed by means of deliberate crosses between two or more existing breeds.

[d] Average genetic apportionment to a single population [9].

[e] Date of breed recognition; derived from natural population.

[f] Early, prior to 1800.

consequence of their dispersal throughout Europe by Roman legions, and were ultimately transported around the world on the major land and sea trade routes.

The majority of the cat breeds recognized today have experienced a very short history [3], numbering only in the hundreds of years for the oldest breeds (Table 2). Twenty-two of the 38 breeds (58%) in this study have received breed recognition only within the past 100 years [3,11]. Modern cat breeds have been established in multiple ways. Natural breeds arose in specific geographic regions that experienced some degree of isolation, which resulted in fixation of alleles for distinctive morphological traits of the breed. Representatives of these breeds can still be found in their native state as pets, barn cats, or even feral cats (Norwegian forest cat) (Table 2). "Established breeds" have evolved through selective breeding of natural breeds to a state approaching the goals set by their standards (i.e., Persian) (Table 2). "Variant breeds" typically differ from one of the older established breeds on the basis of a single allele introduced by outcross, followed by backcross to establish the trait (i.e., the Himalayan is a variant of the Persian, generated from crosses with the Siamese to introduce the "pointed" phenotype [5,6]) (Table 2). "Mutation breeds" typically differ from one of the older established breeds or from the general domestic feline population on the basis of spontaneous mutation in a single gene locus (Scottish fold, American curl). "Hybrid breeds" have been developed by means of deliberate crosses between two (or occasionally more) existing breeds. Unlike dog breeds, breed barriers are not as strictly defined in cats and outcrosses are permissible between some breeds of very recent origin (Table 2) [3] (http://www.cfainc.org/), a position that breed clubs have taken to reduce the potential of inbreeding problems and to allow for the introduction of new phenotypic characteristics.

Despite their relatively short history, cat breeds demonstrate quite a remarkable degree of population substructure. Twenty-seven population clusters were identified based on STRUCTURE analyses, with 6 of the clusters composed of multiple breeds (Table 1). The multibreed clusters were an entirely expected finding, given that within these clusters strong breed barriers have not been established. Either the breeds share very recent common ancestry (<50 years) with other breeds within the population or breeding is currently allowed between the more recently "derived" breeds and the breeds that contributed to the founder breed pool (see Table 2).

Cat breeds clearly display a wide range of genetic definition, a reflection of multiple contributing factors important in population dynamics, including longevity of the breed, founder effects, population bottlenecks—some of natural consequence and some imposed to standardize conformation, effective population size, temporary relaxed breed standards in newer breeds (Table 2), admixture, and the use of popular sires. For breeds that are well defined genetically (Abyssinian, Havana, Birman) up to ~90% of their genetic variation is assigned to a single population, while breeds that are less well defined exhibit as little as a third of their genetic variation to a single population (Table 2) (Supplementary Tables 1a–1x). Strong genetic definition as a breed is clearly influenced by the age of the breed, but breed-specific dynamics can influence this pattern profoundly, as two of the older breeds (Norwegian forest cat, Manx) demonstrated low genetic definition (as defined by breed averaged Q values, Table 2) (Supplementary Tables 1p and 1q), while a recently established breed in the United States (Singapura) generated from an extremely small founder population, exhibits a high degree of population substructure (Table 2) (Supplementary Table 1t). Additionally, many of the more recently established breeds demonstrate a high degree of admixture largely to breed(s) that

Table 3
Pairwise Fst values among cat breeds

	ABY	ACU	AMW	ANG	ASH	BAL	BEN	BIR	BOB	BOM	BSH	BUR	CHA	CRE	CSH	DRE	EXO	HAV	HIM	JAV
ABY	0.00																			
ACU	0.15	0.00																		
AMW	0.20	0.12	0.00																	
ANG	0.18	0.09	0.10	0.00																
ASH	0.19	0.12	0.02	0.11	0.00															
BAL	0.26	0.13	0.26	0.20	0.23	0.00														
BEN	0.19	0.07	0.11	0.10	0.10	0.14	0.00													
BIR	0.28	0.22	0.28	0.23	0.25	0.23	0.21	0.00												
BOB	0.18	0.10	0.14	0.12	0.11	0.18	0.12	0.20	0.00											
BOM	0.27	0.15	0.16	0.15	0.14	0.21	0.14	0.23	0.16	0.00										
BSH	0.28	0.19	0.12	0.15	0.11	0.32	0.20	0.34	0.18	0.21	0.00									
BUR	0.29	0.17	0.21	0.20	0.20	0.17	0.18	0.23	0.19	0.06	0.26	0.00								
CHA	0.19	0.11	0.12	0.13	0.12	0.22	0.15	0.26	0.12	0.17	0.13	0.20	0.00							
CRE	0.22	0.11	0.18	0.14	0.16	0.22	0.14	0.27	0.17	0.20	0.22	0.23	0.17	0.00						
CSH	0.21	0.11	0.22	0.15	0.19	0.05	0.11	0.18	0.12	0.16	0.25	0.16	0.18	0.15	0.00					
DRE	0.21	0.17	0.22	0.17	0.20	0.26	0.20	0.26	0.22	0.25	0.25	0.27	0.22	0.23	0.21	0.00				
EXO	0.20	0.12	0.07	0.10	0.10	0.22	0.12	0.25	0.12	0.17	0.11	0.21	0.11	0.17	0.17	0.23	0.00			
HAV	0.33	0.24	0.34	0.27	0.29	0.17	0.21	0.27	0.25	0.26	0.39	0.26	0.29	0.28	0.20	0.27	0.32	0.00		
HIM	0.20	0.11	0.09	0.10	0.10	0.24	0.11	0.27	0.15	0.16	0.14	0.21	0.13	0.16	0.19	0.22	0.04	0.29	0.00	
JAV	0.23	0.11	0.23	0.17	0.19	0.04	0.11	0.17	0.12	0.16	0.28	0.16	0.19	0.17	0.03	0.20	0.20	0.15	0.21	0.00
KOR	0.33	0.21	0.27	0.21	0.23	0.26	0.20	0.27	0.21	0.22	0.30	0.23	0.26	0.23	0.18	0.27	0.25	0.31	0.25	0.13
MAU	0.26	0.16	0.13	0.17	0.13	0.25	0.13	0.25	0.17	0.23	0.23	0.24	0.19	0.22	0.23	0.25	0.14	0.33	0.19	0.21
MAX	0.16	0.06	0.06	0.07	0.06	0.18	0.08	0.21	0.08	0.12	0.11	0.15	0.08	0.11	0.14	0.18	0.07	0.24	0.08	0.14
MCC	0.18	0.09	0.10	0.08	0.10	0.19	0.12	0.23	0.10	0.16	0.14	0.19	0.12	0.14	0.15	0.20	0.10	0.28	0.11	0.16
NFC	0.15	0.05	0.07	0.06	0.06	0.17	0.08	0.20	0.09	0.13	0.12	0.16	0.09	0.08	0.13	0.17	0.09	0.22	0.09	0.13
OCI	0.21	0.15	0.13	0.15	0.13	0.23	0.11	0.27	0.17	0.18	0.23	0.23	0.20	0.19	0.17	0.26	0.16	0.29	0.16	0.14
OSH	0.20	0.10	0.18	0.14	0.16	0.03	0.09	0.19	0.12	0.15	0.24	0.15	0.17	0.13	0.00	0.21	0.16	0.17	0.16	0.01
PER	0.18	0.11	0.08	0.09	0.09	0.22	0.12	0.25	0.12	0.15	0.09	0.20	0.11	0.15	0.17	0.21	0.00	0.29	0.03	0.20
RAG	0.21	0.07	0.13	0.10	0.14	0.17	0.12	0.21	0.12	0.14	0.16	0.16	0.13	0.16	0.14	0.20	0.11	0.25	0.11	0.14
RUS	0.23	0.13	0.17	0.11	0.16	0.23	0.15	0.27	0.17	0.22	0.24	0.24	0.20	0.20	0.20	0.23	0.18	0.31	0.18	0.20
SFO	0.16	0.08	0.05	0.07	0.05	0.19	0.09	0.22	0.10	0.12	0.07	0.17	0.08	0.14	0.15	0.17	0.04	0.26	0.06	0.16
SIA	0.25	0.16	0.26	0.18	0.23	0.04	0.14	0.20	0.18	0.18	0.30	0.16	0.22	0.20	0.04	0.22	0.23	0.16	0.23	0.03
SIG	0.28	0.20	0.24	0.21	0.21	0.28	0.21	0.33	0.24	0.16	0.30	0.21	0.24	0.23	0.23	0.32	0.25	0.35	0.24	0.23
SOM	0.03	0.13	0.19	0.17	0.18	0.24	0.17	0.28	0.18	0.25	0.26	0.27	0.17	0.21	0.21	0.22	0.18	0.33	0.17	0.22
SPH	0.20	0.09	0.13	0.10	0.12	0.20	0.12	0.22	0.15	0.17	0.19	0.21	0.15	0.15	0.17	0.09	0.13	0.24	0.13	0.14
SRE	0.17	0.07	0.07	0.09	0.08	0.19	0.11	0.22	0.09	0.15	0.10	0.18	0.09	0.13	0.14	0.19	0.04	0.28	0.08	0.14
TOK	0.27	0.14	0.21	0.18	0.19	0.15	0.15	0.22	0.17	0.10	0.27	0.05	0.20	0.19	0.12	0.24	0.20	0.25	0.20	0.09
VAN	0.23	0.12	0.15	0.10	0.13	0.22	0.14	0.23	0.14	0.18	0.21	0.20	0.16	0.17	0.17	0.23	0.17	0.25	0.18	0.17
FC	0.16	0.04	0.07	0.07	0.07	0.14	0.06	0.18	0.07	0.13	0.13	0.16	0.10	0.10	0.10	0.18	0.08	0.23	0.09	0.11

	KOR	MAU	MAX	MCC	NFC	OCI	OSH	PER	RAG	RUS	SFO	SIA	SIG	SOM	SPH	SRE	TOK	VAN	FC
KOR	0.00																		
MAU	0.25	0.00																	
MAX	0.12	0.15	0.00																
MCC	0.16	0.19	0.08	0.00															
NFC	0.13	0.16	0.06	0.08	0.00														
OCI	0.23	0.23	0.11	0.15	0.12	0.00													
OSH	0.18	0.19	0.07	0.10	0.06	0.15	0.00												
PER	0.17	0.18	0.07	0.09	0.06	0.14	0.06	0.00											
RAG	0.16	0.17	0.08	0.10	0.07	0.14	0.08	0.08	0.00										
RUS	0.22	0.23	0.11	0.14	0.10	0.17	0.11	0.11	0.11	0.00									
SFO	0.15	0.17	0.07	0.09	0.06	0.14	0.06	0.06	0.07	0.11	0.00								
SIA	0.23	0.24	0.11	0.14	0.10	0.17	0.10	0.10	0.11	0.15	0.10	0.00							
SIG	0.30	0.31	0.15	0.18	0.14	0.21	0.14	0.14	0.15	0.19	0.14	0.18	0.00						
SOM	0.23	0.24	0.11	0.14	0.10	0.17	0.10	0.10	0.11	0.15	0.10	0.14	0.18	0.00					
SPH	0.19	0.20	0.09	0.11	0.08	0.15	0.08	0.08	0.09	0.13	0.08	0.11	0.16	0.11	0.00				
SRE	0.20	0.21	0.09	0.12	0.08	0.16	0.08	0.08	0.09	0.13	0.08	0.12	0.16	0.11	0.09	0.00			
TOK	0.24	0.25	0.12	0.15	0.11	0.18	0.11	0.11	0.12	0.16	0.11	0.15	0.19	0.14	0.12	0.13	0.00		
VAN	0.21	0.22	0.10	0.13	0.09	0.16	0.09	0.09	0.10	0.14	0.09	0.13	0.17	0.12	0.10	0.11	0.13	0.00	
FC	0.18	0.19	0.08	0.11	0.07	0.14	0.07	0.07	0.08	0.12	0.07	0.11	0.15	0.10	0.08	0.09	0.11	0.09	0.00

ABY, Abyssinian; ACU, American Curl; AMW, American Wirehair; ANG, Turkish Angora; ASH, American Shorthair; BAL, Balinese; BEN, Bengal; BIR, Birman; BOB, Bobtail; BOM, Bombay; BSH, British Shorthair; BUR, Burmese; CHA, Chartreux; CRE, Cornish Rex; CSH, Colorpoint Shorthair; DRE, Devon Rex; EXO, Exotic; HAV, Havana; HIM, Himalayan; JAV, Javanese; KOR, Korat; MAU, Egyptian Mau; MAX, Manx; MCC, Maine Coon Cat; NFC, Norwegian Forest Cat; OCI, Ocicat; OSH, Oriental Shorthair; PER, Persian; RAG, Ragdoll; RUS, Russian Blue; SFO, Scottish Fold; SIA, Siamese; SIG, Singapura; SOM, Somali; SPH, Sphynx; SRE, Selkirk Rex; TOK, Tonkinese; VAN, Turkish Van; FC, Outbred domestic cats.

are, or have been in the past, acceptable outcrosses for a limited period of time by the breed registries (Table 2) (Fig. 2). We still observed 96% of individuals assigned to their breed/population (Table 1). This indicates a high degree of population subdivision, though within individual breeds, a relatively high degree of genetic diversity can be observed.

Population distinctiveness as quantified by an AMOVA demonstrates that by far the greatest amount of genetic variation is observed within breeds (83.7%) versus 16.3% of the variation observed between breeds (Table 3). In human populations, 93–95% of genetic variation is observed within populations [14]. Dog breeds in contrast exhibit far greater breed definition, as a consequence of strong breed barriers, with an average genetic distance between breeds estimated at Fst=0.33 [15].

A moderate level of resolution is observed with regard to the hierarchical relationships of cat breeds, demonstrated by phylogenetic trees generated from both STR and SNP data. The STR- and SNP-generated trees additionally demonstrate phylogeographic partitioning of breeds derived completely or in part from Southeast Asian ancestors, as well as the relationships of breeds sharing common ancestry. However, there is little evidence of which breeds are ancestral or were established first (Fig. 3). The concordance of these data sets likely reflects the recent ancestry of most of the breeds. An expanded set of STRs (n=22), genotyped in a smaller data set of individuals representing all of the major breeds (n=213, 28 breeds) [7], did not demonstrate higher definition trees (Supplementary Fig. 1), suggesting that our findings are a reflection of the recent ancestry of the breeds as opposed to a lack of resolution. The analyses of Driscoll et al.

KOR	MAU	MAX	MCC	NFC	OCI	OSH	PER	RAG	RUS	SFO	SIA	SIG	SOM	SPH	SRE	TOK	VAN	FC
0.00																		
0.29	0.00																	
0.21	0.12	0.00																
0.20	0.12	0.08	0.00															
0.17	0.13	0.04	0.05	0.00														
0.25	0.21	0.14	0.18	0.13	0.00													
0.15	0.20	0.12	0.14	0.11	0.13	0.00												
0.23	0.15	0.06	0.09	0.08	0.16	0.16	0.00											
0.21	0.18	0.09	0.10	0.08	0.19	0.13	0.10	0.00										
0.28	0.23	0.12	0.16	0.11	0.21	0.17	0.18	0.16	0.00									
0.20	0.13	0.05	0.09	0.05	0.10	0.14	0.03	0.10	0.15	0.00								
0.22	0.27	0.18	0.20	0.16	0.21	0.04	0.22	0.17	0.25	0.19	0.00							
0.31	0.30	0.18	0.21	0.17	0.27	0.20	0.22	0.20	0.29	0.18	0.25	0.00						
0.32	0.23	0.14	0.17	0.14	0.23	0.20	0.16	0.19	0.20	0.15	0.25	0.23	0.00					
0.20	0.17	0.08	0.13	0.09	0.19	0.14	0.13	0.14	0.17	0.10	0.19	0.24	0.17	0.00				
0.22	0.12	0.04	0.06	0.05	0.14	0.13	0.04	0.08	0.16	0.04	0.20	0.21	0.14	0.11	0.00			
0.21	0.24	0.14	0.18	0.15	0.21	0.11	0.19	0.14	0.22	0.15	0.13	0.20	0.25	0.18	0.17	0.00		
0.25	0.19	0.09	0.11	0.08	0.21	0.17	0.17	0.13	0.15	0.13	0.21	0.24	0.21	0.14	0.13	0.19	0.00	
0.18	0.10	0.03	0.06	0.04	0.13	0.09	0.08	0.08	0.13	0.06	0.15	0.17	0.14	0.09	0.05	0.13	0.10	0.00

[12], which examined the origins of the domestic cat utilizing 36 STR loci, included 108 breed cats representing 38 of the major cat breeds in a phylogenetic data set of 851 domestic cats and their wild progenitors. These data provided no strong support for the relative relationships among cat breeds.

As a consequence of small effective population sizes, founder effects, and population bottlenecks, cat breeds have become repositories of spontaneous mutations causative of hereditary disease. Over 200 hereditary diseases have been reported in cat populations, many with homologous counterparts in humans [12]. In conjunction with the 2× whole genome sequencing of the cat, SNP analyses examined linkage disequilibrium in 24 cat breeds in 10 sequence blocks, each spanning approximately 600 kb [12]. The level of homozygosity observed was used to estimate that 45,000 equivalently spaced SNP variants would be required for a linkage disequilibrium/haplotype-based association genome search of a complex heritable disease within cat breeds [12].

Linkage disequilibrium (LD) mapping in dog breeds has recently become a powerful tool for identification of genes associated with breed-specific phenotypes [16], including hereditary pathologies [17–20]. Whereas LD mapping has demonstrated its effectiveness in identifying a region linked to disease phenotype, the extent of the region in LD can stretch over megabases [21], including a large number of genes. In the cat breeds examined, LD was observed to decay roughly threefold faster [11] than in the dog breeds previously examined [20]. A knowledge of breed relationships in dogs has had important application in identifying other breeds that may share an allele for a disease phenotype by common descent and have

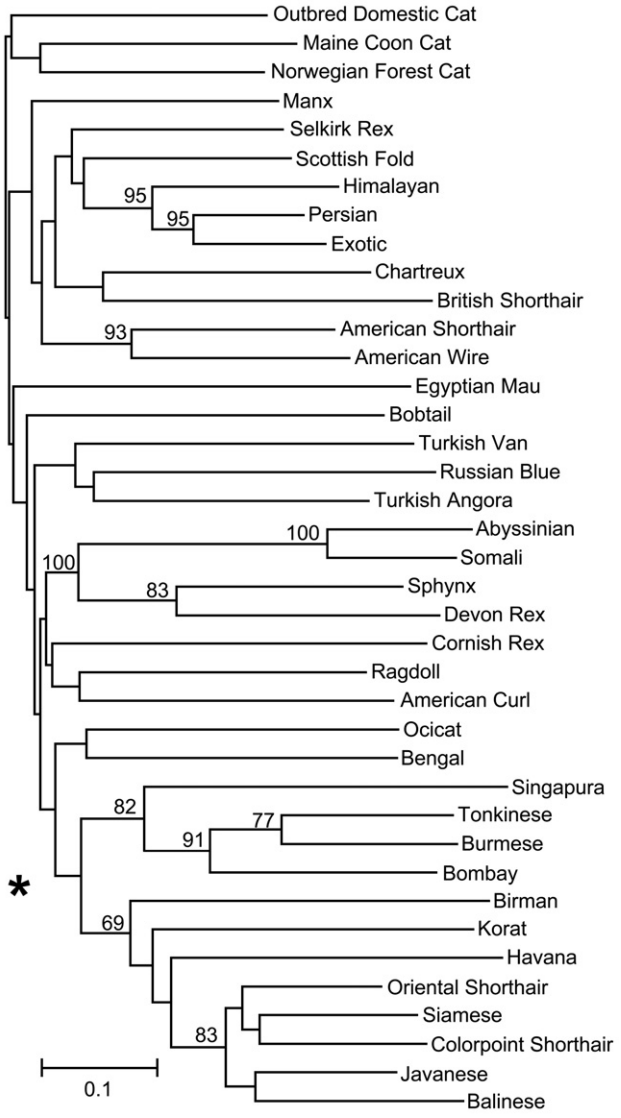

Fig. 3. Phylogenetic neighbor-joining tree of individuals from 38 cat breeds based on distance matrices generated from proportion of shared alleles algorithm (Dps) from composite genotypes. Bootstrap support for branches supported in more than 60% of 100 replicates is indicated. The asterisk identifies a group of breeds that was derived completely or in part from Southeast Asian ancestors.

utility in fine mapping [21]. The first LD mapping in the cat identified the causative mutations for chocolate and cinnamon coat colors at the *TYRP1* locus [5]. SNP discovery on a genome-wide scale across major cat breeds, currently planned as part of the 7× whole genome sequencing of the domestic cat, will become a valuable genomic resource for LD mapping in cat breeds. An understanding of cat breed relationships will further empower this strategy in characterizing mutations causative of hereditary disease in the domestic cat.

Materials and methods

Cat breed sample collection

Blood and/or buccal swab samples of 1040 individuals representing 38 cat breeds recognized by the CFA or TICA were obtained from cat breeders (n=611) through request for samples in directed mailings or contact with cat breeders at cat shows organized by CFA or TICA. Pedigrees were examined for approximately 60% of the sample set to determine if individuals were related. The identities of individual owners are withheld at the request for anonymity from many of the participants. Additional samples were part of the Laboratory of Genomic Diversity's DNA stock collection of felid samples [22]. The sample set consisted of individuals of the following breeds: 29 Abyssinian, 24 Somali, 9 American curl, 9 American wirehair, 26 American shorthair, 11 Balinese, 13 Bengal, 43 Birman, 16 Bobtail, 21 Bombay, 13 British Shorthair, 50 Burmese, 21 Chartreux, 14 Colorpoint Shorthair, 41 Cornish Rex, 57 Devon Rex, 18 Exotic, 49 Havana, 13 Javanese, 11 Korat, 21 Egyptian Mau, 19 Himalayan, 29 Manx, 43 Maine Coon Cat, 67 Norwegian Forest Cat, 19 Ocicat, 33 Oriental Shorthair, 51 Persian, 43 Ragdoll, 23 Russian Blue, 41 Scottish Fold, 34 Siamese, 14 Singapura, 24 Somali, 26 Sphynx, 28 Selkirk Rex, 19 Tonkinese, 17 Turkish Angora, 28 Turkish Van. Pedigrees were requested from cat breeders to reduce the probability of including related individuals in this study. Blood samples from 24 outbred domestic cats were obtained from the NIH cat colony, which originated from individuals obtained from Liberty Labs (Waverly, NY, USA).

Sample set for the SNP study

Seventy-seven individuals from each of 24 cat breeds were used for SNP discovery, including 3 Abyssinian, 4 American Shorthair, 3 Birman, 3 British Shorthair, 3 Burmese, 5 Chartreux, 2 Cornish Rex, 2 Devon Rex, 5 Egyptian Mau, 2 Havana, 4 Bobtail, 4 Maine Coon Cat, 4 Manx, 4 Norwegian Forest Cat, 2 Ocicat, 4 Persian, 4 Ragdoll, 2 Russian Blue, 2 Scottish Fold, 1 Selkirk Rex, 5 Siamese, 3 Sphynx, 3 Turkish Angora, 3 Turkish Van. Of these 77 individuals, 74 were included in the STR data set.

DNA extraction

DNA was extracted from blood and buccal samples using Qiagen QiAmp DNA Blood Midi and Mini Extraction Kits following the manufacturer's suggested protocols. DNA was quantified using a Hoefer DyNA Quant 200 Flurometer (Amersham BioSciences). A proportion of each sample was diluted to a standard concentration of 2.5 ng/μl with sterile distilled water (Quality Biological).

Amplification of STR loci and electrophoresis of samples

The STRs were PCR amplified and electrophoresed as a single multiplex of 11 loci using fluorescently labeled primers as described in [8].

SNP genotyping

Primer selection and genotyping was performed on the Sequenom HME platform as previously described [23]. Primers and probes were designed in a multiplex format with a minimum of one SNP per pool and an optimum of five SNPs using SpectroDESIGNER software (Sequenom, San Diego, CA) (Supplementary Table 3). Only SNPs with a call rate of at least 75% were included in the analysis.

Fst estimates

Fst estimates among breeds were estimated from the STR data as in [24].

STR population and phylogenetic analyses

Population structure was examined using the Bayesian clustering program STRUCTURE, version 2 [9] (http://pritch.bsd.uchicago.edu). The sample set of 1040 individuals of recognized breed and 24 outbred cats was amplified in a multiplex of 11 STRs previously selected for their polymorphism in cat breeds [8]. The data set, with the exclusion of one locus (FCA736), which demonstrated a high incidence of "null alleles" [25] in some breeds (M. Menotti-Raymond, manuscript in preparation), was assessed under the assumption that there was an unknown number of genetically distinct clusters. Values of K from 2 to 32 were examined. STRUCTURE runs were performed using two to five repetitions of

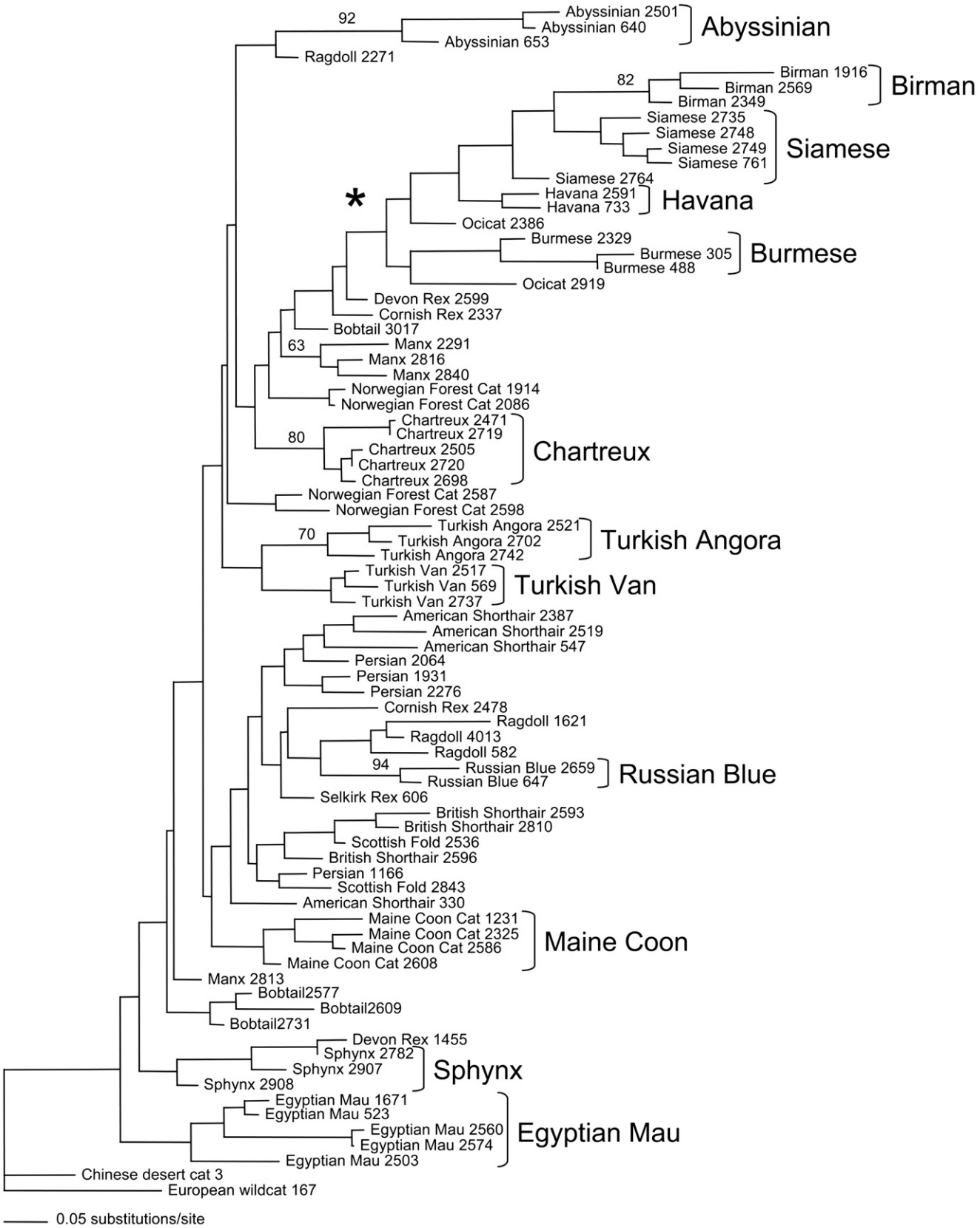

Fig. 4. Phylogenetic maximum-likelihood tree generated using PAUP [27] from a data set of 269 SNPs genotyped in 77 domestic cats representing 24 cat breeds. Bootstrap values for nodes greater than 60% are listed. A Chinese desert cat and a European wildcat are utilized as outgroups. Breeds that demonstrated monophyly are clustered in large print. Individuals are labeled by breed and an individual identifier. The asterisk identifies a group of breeds that was derived completely or in part from Southeast Asian ancestors.

100,000 iterations after a burn-in length of 50,000, using an admixed model with allele frequencies set at independent. Empirical observation has demonstrated that the allele frequencies are strikingly independent between breeds [8].

Pairwise genetic distances were estimated using the proportion of shared alleles (Dps) algorithm with a $(1 - M)$ correction as implemented in the program MICROSAT [10] (version 1.5). Phylogenetic trees of cat breeds, as well as of the individual cats, were constructed from the Dps distance matrices using the NEIGHBOR option of the program PHYLIP (version 3.572) and was drawn using the program TREEVIEW (version 1.5). Reliability of nodes defined by the phylogenetic trees was assessed using 100 bootstrap replications.

SNP population and phylogenetic analyses

SNP variation was assessed in 10 sequence blocks of approximately 600 kb selected from regions of heterozygosity identified in the whole genome sequencing of the domestic cat [12]. Thirty-five SNPs were selected across each of the sequence blocks and genotyped in 77 individuals from each of 24 cat breeds.

Sequences were built for each individual by compiling all SNPs, using ambiguous nucleotide codes when individuals were heterozygous for a specific SNP. Two measures of genetic variation within breeds, the number of variable sites and the mean percentage of pairwise differences, were estimated using MEGA [26].

Phylogenetic relationships among the individuals were estimated in PAUP [27] using a maximum-likelihood (ML) algorithm with a GTR+G model and a shape parameter (α) of 1.3796. The reliability of the nodes was assessed by 100 bootstrap iterations for the ML analyses and for minimum evolution analyses using maximum likelihood distances.

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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.2007.08.008.

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