

# Phylogenetic Relationships, Evolution, and Genetic Diversity of the Domestic Dog

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The spectacular diversity in size, conformation, and pelage that characterizes the domestic dog reflects not only the intensity of artificial selection but ultimately the genetic variability of founding populations. Here we review past molecular genetic data that are relevant to understanding the origin and phylogenetic relationships of the dog. DNA-DNA hybridization data show that the dog family Canidae diverged about 50 million years ago from other carnivore families. In contrast, the extant canids are very closely related and diverged from a common ancestor about 10 million years ago. The evidence supporting a close relationship of dogs with gray wolves is overwhelming. However, dogs are remarkably diverse in mitochondrial and nuclear genes. Mitochondrial DNA analysis suggests a more ancient origin of dogs than has been indicated by the fossil record. In addition, dogs have originated from or interbred with wolves throughout their history at different times and different places. We test the possibility of an independent domestication event in North America by analysis of mtDNA variation in the Xoloitzcuintli. This unusual breed is believed to have been kept isolated for thousands of years and may be one of the most ancient breeds in North America. Our results do not support a New World domestication of dogs nor a close association of the Xoloitzcuintli with other hairless breeds of dogs. Despite their phenotypic uniformity, the Xoloitzcuintli has a surprisingly high level of mtDNA sequence variation. Other breeds are also genetically diverse, suggesting that dog breeds were often founded with a large number of dogs from outbred populations.

The domestic dog (*Canis familiaris*) is morphologically the most variable mammal species. Dogs can differ in size by two orders of magnitude and have extremely varied conformation. The difference in size and conformation among dog breeds exceeds that among species in the dog family Canidae (Wayne 1986a,b). Differences in behavior and physiology also are substantial (Hart 1995). Why are dogs morphologically so diverse? Artificial selection seems to have been a powerful force in the rapid development of the spectrum of shape, color, and behavior of dogs (Clutton-Brock 1987; Epstein 1971; Zeuner 1963). However, the diversity under domestication must to a large degree be limited by the underlying genetic variation of loci affecting phenotypic traits.

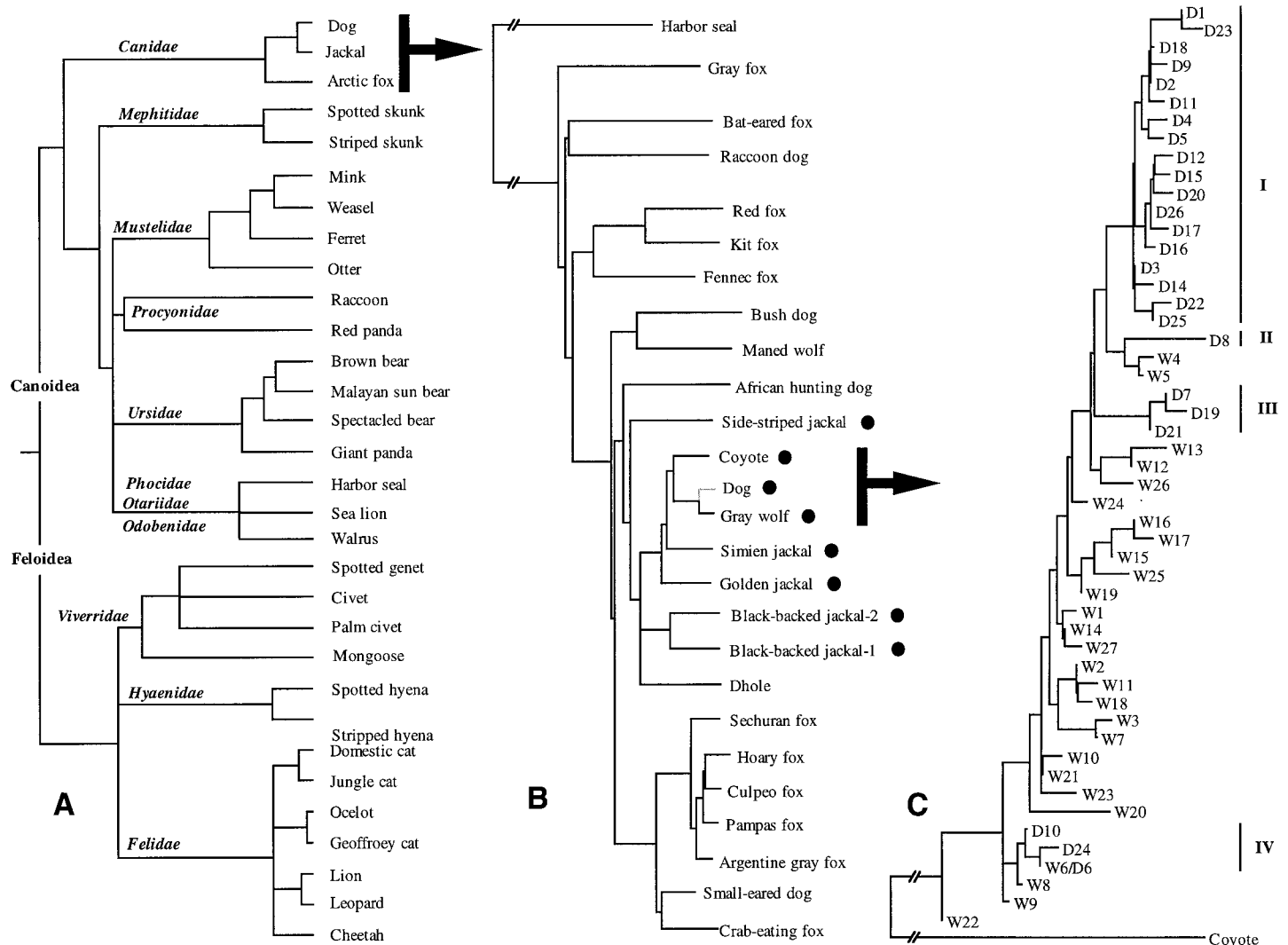
Critical to this issue is the genetic diversity of the founding population. If dogs were founded from only a few wild canids, much of the remarkable morphologic diversity of dogs must be due to mutations that occurred after the supposed origin 14,000 years ago as suggested by the fossil

record (Nobis 1979; Olsen 1985). In contrast, if dogs originated from a large population of wild canids and have interbred with them throughout their evolutionary history, then the influx of genetic variation from wild populations may be an important reason why domestic dogs are morphologically so diverse. The source of variation in domestic species, such as the domestic dog, is a fundamental issue in understanding constraints on evolutionary diversification (Wayne 1986a,b).

Here we review molecular studies concerned with the phylogenetic relationships and origin of domestic dogs. First, we review studies that have utilized DNA-DNA hybridization, allozyme electrophoresis, microsatellites, and mitochondrial DNA sequencing to reconstruct phylogenetic relationships and measure variability of dogs and wild canids. We then address the issue of the number and timing of origination events leading to the present-day genetic diversity of the domestic dog. We also discuss how this genetic diversity is distributed among dog breeds.

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**Figure 1.** (a) Relationship of carnivores based on DNA hybridization data (Wayne et al. 1989). Family and superfamily groupings are indicated. (b) Phylogenetic tree of canids based on 2,001 bp from the mitochondrial DNA (cytochrome *b*, cytochrome *c* oxidase I, and cytochrome *c* oxidase II genes) (Wayne et al. 1997). Neighbor-joining tree based on a Kimura two-parameter model of sequence divergence with a transition/transversion ratio of 6. Black circles indicate species of the genus *Canis*. The position of the dog in this tree was determined using 736 bp of cytochrome *b* sequence (Wayne 1993). (c) Neighbor-joining tree of wolf (W) and dog (D) haplotypes based on 261 bp of mitochondrial DNA control region I sequences (Vilà et al. 1997). Dog haplotypes are grouped in four clades, indicated I-IV.

Finally, we analyze genetic variation in an ancient North American breed, the Xol-oitzcuintli (Mexican hairless dog). This breed has a several thousand year history in the New World and can be used to test if a separate domestication from wolves occurred in the New World.

## Origin of the Dog

### Phylogenetic Relationships of the Domestic Dog

The modern carnivore families originated over 40–50 million years ago (Flynn and Galiano 1982). An appropriate metric to reconstruct relationships of families with such ancient divergence times is DNA-DNA hybridization (Sibley and Ahlquist 1983; Werman et al. 1996). DNA hybridization data confirm that Carnivora is divided into

two superfamilies, Canoidea and Feloidea (Figure 1a; Wayne et al. 1989). The former includes the dog (Canidae), skunk (Mephitidae; see Dragoo and Honeycutt 1997), weasel (Mustelidae), raccoon (Procyonidae), bear (Ursidae), and three marine mammal families (Phocidae, Otariidae, and Odobenidae). The Feloidea includes the cat (Felidae), civet (Viverridae), and hyena (Hyaenidae) families. Assuming a constant rate of sequence evolution, canids diverged from other carnivores more than 50 million years ago, at the beginning of the Eocene. This divergence is the earliest within the superfamily Canoidea (Figure 1a). However, the extant canids have radiated from a common ancestor more recently, about 10 million years ago. The early divergence of canids from other Canoidea families has been confirmed with mi-

tochondrial DNA sequence data (Dragoo and Honeycutt 1997).

The phylogeny of the family Canidae was reconstructed by comparing 2001 bp of DNA sequence of the mitochondrial protein coding genes cytochrome *b*, cytochrome *c* oxidase I, and cytochrome *c* oxidase II (Figure 1b; Wayne et al. 1997). All species from the genus *Canis* form a monophyletic group that also includes the dhole or Asian wild dog (*Cuon alpinus*). This result suggests that the dhole should be included in the genus *Canis*. The gray wolf (*Canis lupus*), coyote (*C. latrans*), and Ethiopian wolf (*C. simensis*) form a monophyletic group, with the golden jackal (*C. aureus*) as the most likely sister taxon. However, jackals do not have a single exclusive common ancestor. Basal to *Canis* and *Cuon* are the African wild dog (*Lycyaon*

*pictus*) and a clade consisting of two South American canids, the bush dog (*Speothos venaticus*) and the maned wolf (*Chrysocyon brachyurus*).

All *Canis* species, as well as the dhole and the African wild dog, have identical chromosome numbers ( $2n = 78$ ; Wayne et al. 1987a,b; Wurster-Hill and Centerwall 1982), and all species in the genus *Canis* are known to hybridize (Gray 1954). However, only gray wolves and golden jackals have been suggested to be the ancestor of domestic dogs, each wild species potentially giving rise to different breeds of dog (Coppinger and Schneider 1995; Darwin 1871; Lorenz 1954). A phylogenetic analysis of 736 bp of the cytochrome *b* gene shows that only gray wolves are directly ancestral to domestic dogs (Figure 1b; Wayne 1993). Coyotes and Ethiopian wolves are the next most closely related canids to dogs and wolves, but have sequence divergence values greater than about 4% as opposed to about 1.8% between dogs and gray wolves (Girman et al. 1993; Gottelli et al. 1994; Wayne and Jenks 1991).

The comparison of the mtDNA sequences among *Canis* species suggests that dogs originated from gray wolves. Do nuclear markers support the close relationship of dogs and wolves? Of importance, a mating between male golden jackals and female dogs would not be recorded in the mitochondrial haplotype of the offspring because the mitochondrial genome of mammals is maternally inherited. However, limited studies using nuclear markers (allozyme and microsatellite data) support the wolf ancestry of dogs. In an extensive study of 10 microsatellite loci in domestic dogs, gray wolves, red wolves, golden jackals, and coyotes, the genetic distance between dogs and gray wolves was always smaller than that between them and coyotes or golden jackals (Table 1; García-Moreno et al. 1996; Hedrick et al. 1997). Similarly, allozyme genetic distance between dogs and wolves was much smaller than that between them and any other canid (Table 1; Lorenzini and Fico 1995; Wayne and O'Brien 1987).

### The Genetic Diversity and Origin of the Dog

The recent appearance of the domestic dog in the fossil record about 14,000 years ago (Nobis 1979; Olsen 1985) implies that its diversification should be studied with markers that have a high mutation rate. Consequently we selected region I of the mitochondrial control region because it is

**Table 1.**

	Golden jackal <sup>a</sup>	Coyote	Red wolf	Gray wolf	Dog
Golden jackal	<b>0.412 ± 0.055 (1)</b>	1.267 ± 0.255 (6)	1.459 (1)	1.093 ± 0.158 (7)	1.133 (1)
Coyote	0.240 (36)	<b>0.583 ± 0.061 (6)</b>	0.338 ± 0.052 (6)	0.515 ± 0.151 (42)	0.762 ± 0.153 (6)
Red wolf	Unavailable	Unavailable	<b>0.507 ± 0.082 (1)</b>	0.518 ± 0.161 (7)	0.874 (1)
Gray wolf	0.193 (36)	0.036 (44)	Unavailable	<b>0.528 ± 0.067 (4)</b>	0.672 ± 0.135 (7)
Dog	0.176 (36)	0.050 (43)	Unavailable	0.013 (44)	<b>0.401 ± 0.055 (1)</b>

<sup>a</sup> For the allozyme data, the values shown are for the Black-backed jackal (*Canis mesomelas*).

Above diagonal, mean (± SD) Nei's (1978) unbiased genetic distance for pairs of species based on analysis of 10 microsatellite loci (García-Moreno et al. 1996; Roy et al. 1996). On the diagonal (bold) the mean observed heterozygosity (± SD) is given for 10 microsatellite loci (García-Moreno et al. 1996). Number of pairwise population comparisons used to compute the mean genetic distance or mean observed heterozygosity is in parenthesis. The dog population consists of 42 dogs from different breeds (García-Moreno et al. 1996). Below diagonal is given Nei's (1978) unbiased genetic distance based on allozyme markers (Wayne and O'Brien 1987); in parenthesis, number of loci examined.

highly polymorphic and has a high mutation rate in mammals (Aquadro and Greenberg 1983). A comparison of 261 bp of mtDNA sequence from the control region of dogs, gray wolves, coyotes, Ethiopian wolves, and golden jackals supported the origin of dogs from gray wolves (Vilà et al. 1997). Dog and wolf sequences differed by 0–12 substitutions, and dogs always differed from coyotes, Ethiopian wolves, and jackals by at least 20 substitutions. Some of the sequences found in dogs were identical to those in wolves (D6 and W6, in Figure 1c). The sequence diversity within dogs was surprisingly large; the mean sequence divergence in dogs,  $2.06 \pm 0.07\%$ , was almost identical to the  $2.10 \pm 0.04\%$  found within wolves.

Phylogenetic trees of dog and wolf sequences (Figure 1c) show that dog sequences cluster into four clades (I–IV). This result suggests that either wolves were domesticated in several places and at different times or that there was one domestication event followed by several episodes of admixture between dogs and wolves. Whichever is the case, the results imply that dogs have a diverse origin involving more than one wolf population.

One group of dog sequences, clade I (Figure 1c), included 18 of the 26 haplotypes found in dogs. After confirming that there were no differences in the substitution rates of dogs and wolves, the time required to attain such diversity was estimated to be about 135,000 years. This estimate is based on an analysis of 1,030 bp of control region sequence in a subset of dog and gray wolf samples and assumes an evolutionary rate calibration based on a divergence time between wolves and coyotes of one million years (Vilà et al. 1997; Wayne et al. 1991). Therefore the molecular results suggest a much older divergence time than indicated by the fossil record.

Independent support of these findings comes from mitochondrial control region studies of Japanese dogs (Okumura et al. 1996; Tsuda et al. 1997). Okumura et al. found four distinct dog clades that shared a common ancestry approximately 76,000–121,000 years ago. However, in their study, no control region sequences from wild canids were included, so it is difficult to determine the influence of wild canids on the variability of Japanese dogs. The phylogenetic tree of Tsuda et al. is less well resolved but clearly indicates a diverse and ancient origin for the domestic dog.

### Distribution of the Genetic Variability Among and Within Breeds

Well-sampled breeds generally contain more than one control region haplotype (Table 2). In 17 breeds represented by three or more individuals, 15 had at least two different sequences (Vilà et al. 1997). These sequences often were classified in divergent sequence clades (see Figure 1c). For example, five different haplotypes were found in eight German shepherds, and three haplotypes were found in three Siberian huskies. Since many breeds are thought to be inbred and to have originated from only a few founders, high levels of mtDNA variability were unexpected. In addition, because the time to fixation of mtDNA sequences is one-quarter the time required for fixation of nuclear markers, loss of mitochondrial variation should be rapid if breeds were significantly inbred.

There are at least two reasons for the high variability of dog breeds. First, most breeds have a recent origin (Dennis-Bryan and Clutton-Brock 1988). The founding stock of recent breeds was likely drawn from a previously well mixed and outbred pool of dogs. For thousands of years, dogs

**Table 2. Phylogenetic distribution of haplotypes found in 17 breeds of dogs<sup>a</sup>, including the Xoloitzcuintlis, and their distribution in the four groups of dog haplotypes**

	I	II	III	IV
Chow chow ( <i>n</i> = 3)	D1, D2, D3			
Border collie ( <i>n</i> = 3)	D1, D5			
Wirehaired dachshund ( <i>n</i> = 3)	D5			D10
Australian dingo ( <i>n</i> = 4)	D18			
Norwegian elkhound ( <i>n</i> = 9)	D3	D8		
German shepherd ( <i>n</i> = 8)	D4, D5		D7, D19	D6
Afghanistan hound ( <i>n</i> = 3)	D6			
Siberian husky ( <i>n</i> = 3)	D3, D18		D7	
Jämthund ( <i>n</i> = 3)		D8	D7	
Flat-coated retriever ( <i>n</i> = 3)	D4			D10
Golden retriever ( <i>n</i> = 6)	D4, D15			D6, D24
Labrador retriever ( <i>n</i> = 6)	D4, D12			
Samoyed ( <i>n</i> = 3)	D1, D4, D5			
Giant schnauzer ( <i>n</i> = 3)	D4		D7	
English setter ( <i>n</i> = 4)	D3, D5			
Irish setter ( <i>n</i> = 3)	D1, D9			
Xoloitzcuintli ( <i>n</i> = 19)	D1, D3, D4, D26		D7, D21	D6

<sup>a</sup> At least three individuals were sequenced in Vilà et al. (1997).

may have been transported with the movement of humans as companions or for trade, and thus the area over which gene flow occurred was substantial (e.g., Schwartz 1997). It was not until the advent of modern breeding practices that many breeds became closed gene pools and obtained a high degree of phenotypic uniformity. Second, breeders occasionally outcross their pure breed dogs to avoid deleterious effects associated with high levels of inbreeding or to eliminate specific genetic defects (e.g., Ubbink et al. 1992). Hybrid individuals and their progeny may have increased vigor and may have been selected by breeders, hence foreign haplotypes derived from such crosses may initially increase in frequency.

Microsatellite and allozyme data support the conclusion that breeds were founded from a large genetically diverse population and were not highly inbred. Surveys of microsatellite loci in a few dog breeds have shown them to have moderate to high levels of heterozygosity relative to wild canids (Table 1, diagonal; García-Moreno et al. 1996; Gottelli et al. 1994; Lingaas et al. 1996; Wilkie et al. 1997; Zajc et al. 1997; Zajc and Sampson 1997). This implies little or only moderate inbreeding within breeds as is also suggested by the mitochondrial control region analysis. High levels of variation were also found in extensive allozyme survey of 25 loci in 2,959 dogs from 40 breeds (Tanabe et al. 1991). Both the microsatellite and allozyme data imply that the founding population size of common breeds was large and genetically diverse.

Rarely are haplotypes unique to a breed. Only the genotype D8 is unique but not fixed in two Scandinavian breeds, the

Norwegian elkhound and Jämthund (Vilà et al. 1997). Similarly, microsatellite and allozyme surveys have shown that breeds rarely contain unique alleles, although they may be differentiated with respect to allele frequency (Lingaas et al. 1996; Wilkie et al. 1997; Zajc et al. 1997; Zajc and Sampson 1997). However, Wilton et al. (1999) have found a diagnostic 1 bp difference between dingo and other breeds in a dinucleotide microsatellite locus. Dingoes have been isolated from domestic dogs for about 5,000 years (Corbet 1995). The scarcity of breed-specific markers suggests that genetic exchange between breeds has stymied the accumulation of unique alleles or haplotypes. However, the genetic divergence in allele frequency suggests founder effects or partial isolation has been important in the evolution of some dog breeds.

#### **The Xoloitzcuintli (Mexican Hairless Dog): A Possible New World Domestication?**

Although most breeds appear to be genetically diverse, a small number may have originated from a restricted pool of founders and subsequently been closely inbred. For example, most of the pure bred Tibetan spaniels from the United Kingdom derive from the three Tibetan spaniels that survived after World War II (Binns M, personal communication). The Xoloitzcuintli or Mexican hairless dog also has gone through a population contraction followed, presumably, by close inbreeding for several hundred generations. Thus it is likely to have reduced genetic variation. Moreover, the ancient North American origin of this breed suggests it may possibly

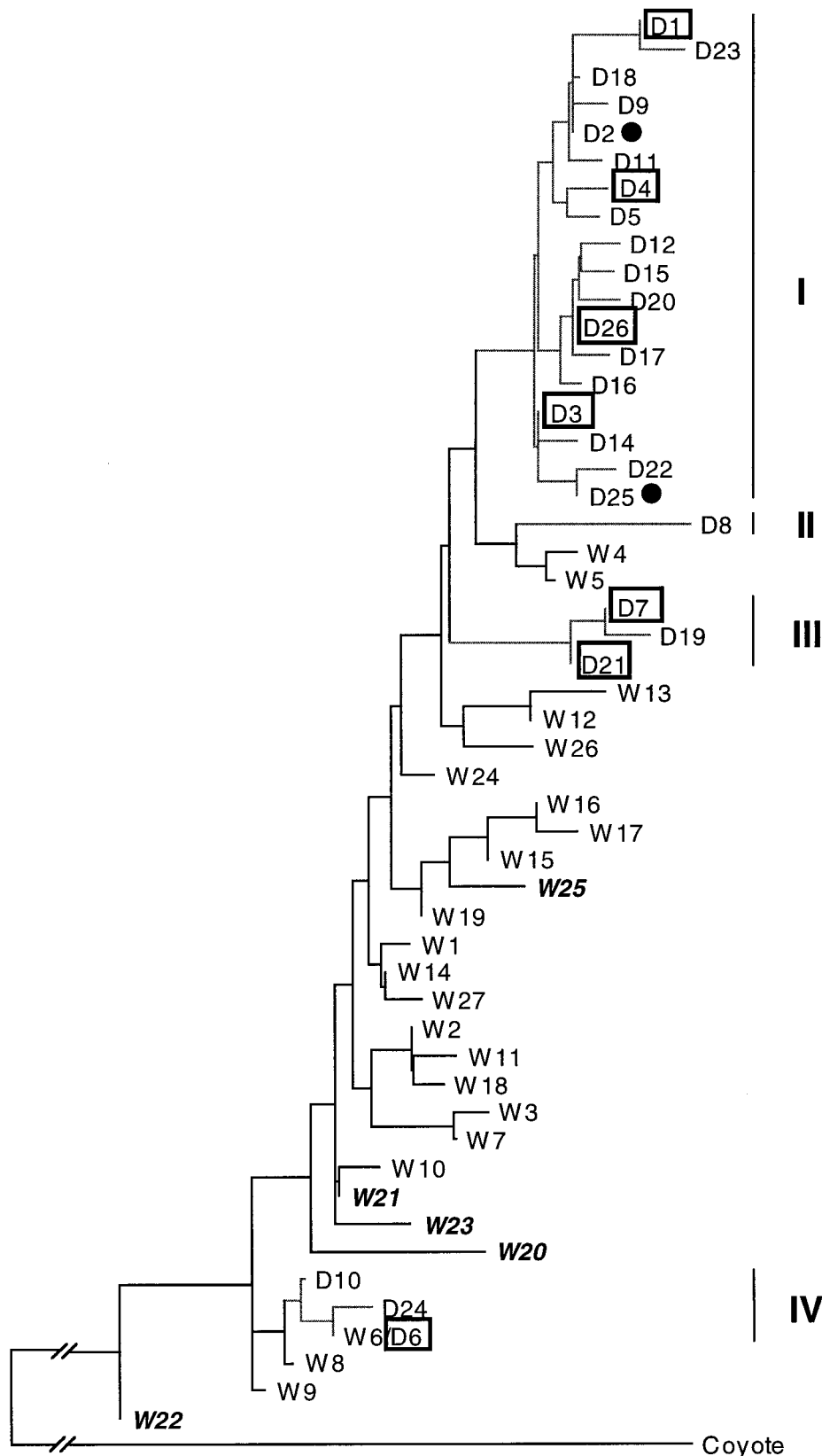
have had a separate derivation from New World wolves.

**Historical background.** It is thought that humans reached the New World 20,000–25,000 years ago (Foster et al. 1996), and as suggested by dog remains from Danger Cave, Utah, humans had domestic dogs by 7000–8000 B.C. (Schwartz 1997). These dogs could have arrived with the Paleo-Indians that immigrated across the Bering Strait (if dogs were domesticated much earlier than 14,000 years ago, as the mitochondrial DNA data suggest), or they could have been domesticated independently from North American gray wolves. Until recently, gray wolves were abundant in North America and had a geographic distribution stretching from Mexico to the Arctic Circle (Nowak 1991). The possibility of independent origination has been suggested by several authors (e.g., Dennis-Bryan and Clutton-Brock 1988; Pford 1987). If native American dogs have sequences very similar or nearly identical to North American wolves, then this suggests a New World domestication. In contrast, if North American dogs have sequences similar to those found in Old World dog breeds, then this suggests they have an ancient origination in common with Old World breeds.

In the 16th century, Francisco Hernández, a Spanish naturalist, described several fantastic native dogs that Spanish conquistadors found in Mexico (Valadez 1995). Among them was the Xoloitzcuintli, a medium-sized hairless dog that was used for food, companionship, and also to relieve the pain associated with rheumatism (Cordy-Collins 1994). More recently, archeologists have found pottery from the Colima culture (250 B.C.–450 A.D.), in western Mexico, depicting several Xoloitzcuintlis (Cordy-Collins 1994). The modern dogs of this breed are usually missing several teeth, and old burials in western Mexico (700–1000 A.D.) show the presence of dog remains with incomplete dentitions that have been assumed to be from Xoloitzcuintlis.

When the Spanish conquistadors arrived in Mexico they brought with them their own dog breeds. Dogs of the Native Americans crossed with these new arrivals and the native breeds were blended into nonexistence or were systematically eliminated as part of a program to replace the Native traditions with Hispanic culture (Valadez 1995). Native tribes made special efforts to save the Xoloitzcuintli because of its religious value and hid them in mountain villages in the western Mexican





**Figure 2.** Neighbor-joining tree of wolf (W) and dog (D) haplotypes based on 261 bp of control region I (from Vilà et al. 1997). Roman numbers indicate the groups of dog haplotypes. Boxes indicate haplotypes found in the 19 Xoloitzcuintlis included in this study. Haplotypes found in two Chinese crested dogs are indicated with a solid black circle. Bold italicized labels indicate haplotypes found in New World wolves (W20–W25).

states of Guerrero, Michoacán, Colima, and Jalisco (Valadez 1995). In these retreats, their breeding was carefully managed and the Xoloitzcuintli was not interbred with other dogs. Moreover, the Xoloitzcuintlis were unlikely to have escaped the confines of these villages; because of their hairlessness they are very sensitive to extreme temperatures and excessive UV radiation and are unlikely to survive in the wild.

Today the Xoloitzcuintli is very uncommon. There are only a few breeders, mostly in Mexico and the United States. The breed, previously accepted by the American Kennel Club, was excluded in 1959 due to lack of registrants and show entries (Wilcox and Walkowicz 1995). The purported ancient origin of this breed, together with its presumed isolation from other dogs, makes the Xoloitzcuintli a good candidate to test for an independent wolf domestication in North America. However, the American Kennel Club considers the Xoloitzcuintli to be derived from the Chinese crested dog, another hairless breed (American Kennel Club 1992). The reasons for this association seem based on a superficial similarity that may not reflect a recent common ancestry.

**Genetic analyses.** We obtained blood or hair samples from 19 individuals belonging to seven breeders from the United States and Mexico. Individuals obtained from the same breeder were of different varieties (i.e., standard, coated, toy) or of different matrilineal lines.

Hair or blood samples were digested with proteinase K and DNA was extracted with organic solvents and recovered by isopropanol precipitation (Sambrook et al. 1989). A total of 394 bp from control region I of the mitochondrial DNA was amplified by the polymerase chain reaction and sequenced using primers, protocols, and conditions described in Vilà et al. (1997). We compared the 261 bp sequence reported in Vilà et al. to the homologous sequences contained in the 394 bp fragment from the Xoloitzcuintli. The comparison sequences include those from 27 populations of wolves from throughout Europe, Asia, and North America and 67 dog breeds including the Chinese crested.

A total of seven different haplotypes were found in the 19 individuals studied: D1 ( $n = 3$ ), D3 ( $n = 1$ ), D4 ( $n = 3$ ), D6 ( $n = 5$ ), D7 ( $n = 2$ ), D21 ( $n = 3$ ), and D26 ( $n = 2$ ). These sequences were distributed among three of the four clades of dog haplotypes (Figure 2). Clade I included D1, D3, D4, and D26, clade III included D7 and D21,

and clade IV included D6. The only dog group for which no Xoloitzcuintli sequences were found was clade II, which includes dog haplotype D8 found only in two Scandinavian breeds (Norwegian elkhound and Jämthund). No unique Xoloitzcuintli haplotypes were found and none were identical or similar to any of the sequences found in New World wolves, including Mexican wolves. The most common haplotype (D6), found in five Xoloitzcuintlis, is the only one that was shared between dogs and wolves, but these wolves are presently found only in Romania and European Russia.

Our results do not support a New World domestication for the Xoloitzcuintli. Instead, the sequences found in the Xoloitzcuintlis are identical to sequences found in dog breeds originating in the Old World. In addition, we found that none of the Xoloitzcuintli shared any of the haplotypes present in the Chinese crested dog (D2 and D25; Figure 2). Consequently, our data does not support an origin from or a close relationship to the Chinese crested dog.

The Xoloitzcuintli sampled had a surprisingly high diversity of control region sequences. We found seven distinct sequences in the 19 sampled Xoloitzcuintli representing three distinct clades of dog control region sequences (Figure 1c). This result implies that the population of dogs that founded the Mexican hairless was large and genetically diverse. Minimally, seven females contributed to the founding population. However, the number of founding females was likely much larger, considering founding females may have had identical haplotypes and that many founder haplotypes were likely lost because of drift in small populations. The phenotypic uniformity of the Xoloitzcuintli is surprising given their diverse genetic heritage. The gene that determines hairlessness is dominant but lethal when homozygous (Cordy-Collins 1994).

In conclusion, the domestic dog is a genetically diverse species that likely originated from a large founding stock possibly derived from wolf populations existing in different places and at different times. Genetic diversity within breeds is often high and reflects an origin for a genetically diverse founding stock followed by occasional interbreeding among breeds and between dogs and wolves. However, genetic isolation between some breeds has been sufficient for them to have diverged in allele frequency. Although there may have been more than one domestication event from wolves in the Old World, an analysis

of the oldest New World dog breed suggests that it was not derived by an independent origination from North American wolves. The genetic diversity within the Xoloitzcuintli suggests a large and diverse population of dogs colonized North America.

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