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REVIEWS

Evolutionary genomics of dog domestication

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Abstract We review the underlying principles and tools used in genomic studies of domestic dogs aimed at understanding the genetic changes that have occurred during domestication. We show that there are two principle modes of evolution within dogs. One primary mode that accounts for much of the remarkable diversity of dog breeds is the fixation of discrete mutations of large effect in individual lineages that are then crossed to various breed groupings. This transfer of mutations across the dog evolutionary tree leads to the appearance of high phenotypic diversity that in actuality reflects a small number of major genes. A second mechanism causing diversification involves the selective breeding of dogs within distinct phenotypic or functional groups, which enhances specific group attributes such as heading or tracking. Such progressive selection leads to a distinct genetic structure in evolutionary trees such that functional and phenotypic groups cluster genetically. We trace the origin of the nuclear genome in dogs based on haplotype-sharing analyses between dogs and gray wolves and show that contrary to previous mtDNA analyses, the nuclear genome of dogs derives primarily from Middle Eastern or European wolves, a result more consistent with the archeological record. Sequencing analysis of the *IGF1* gene, which has been the target of size selection in small breeds, further supports this conclusion. Finally, we discuss how a black coat color mutation that evolved in dogs has transformed North American gray wolf populations, providing a first example of a mutation that appeared under domestication and selectively swept through a wild relative.

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Introduction

With regard to phenotypic diversity, the domestic dog is positioned as the most unique domesticated animal. Dogs range in size over two orders of magnitude from the diminutive 1-kg Chihuahua to the 100-kg Mastiff, with an equally impressive range apparent in breed conformation. Dogs far exceed the variation in skeletal and cranial proportion exhibited by the 35 species of wild canids and the entire carnivore order (Wayne 1986a, b; Drake and Klingenberg 2010). Similarly, behavioral and physiological attributes are far more extreme in dogs, ranging from sight and scent hounds to dogs with near pathologic tendencies for herding, swimming, running, attentiveness, hunting, lethargy, and aggression (American Kennel Club 1992; Wilcox and Walkowicz 1995). However, a less well-recognized distinction of the dog is that it is the only large carnivore ever to have been domesticated. Moreover, rather than being domesticated in association with agriculture beginning about 10,000 years ago, the archeological record suggests dogs first appeared 15,000–33,000 years ago in Europe and eastern Siberia, when humans were largely hunter-gathers (Sablin and Khlopachev 2002; Germonpré et al. 2009; Ovodov et al. 2011). Nuclear genetic evidence is consistent with European as well as Middle Eastern wolf populations contributing to the dog genome, whereas mtDNA evidence suggests an East Asian origin (Pang et al. 2009; vonHoldt et al. 2010). However, backcrossing to

various wolf populations complicates a simple scenario for dog origins (Vilà et al. 1997, 2005; Savolainen et al. 2002).

The early origin of dog domestication implies that both the initial conditions and the object of selection differed for the dog in comparison with other domesticated species. These conditions may have involved a loose association of humans and protodogs, perhaps initiated with specific wolf populations that followed humans and adapted to the human niche (Morey 2010; Ovodov et al. 2011). About 10,000 years ago, with the development of agrarian societies, there was likely more intense selection for dogs of smaller size and with behaviors, such as docility, that allowed for close contact with humans (Zeuner 1963; Epstein 1971; Davis and Valla 1978; Morey 2010). Finally, the third phase in the radiation of dogs was the most dramatic, having been initiated in the last 200 years with the advent of breed clubs and systematic breeding practices (Ash 1927; Dennis-Bryan and Clutton-Brock 1988). Historical evidence supports the view that many breeds were formed rapidly, sometimes taking advantage of novel mutations, recognized early on as "sports" by Darwin (Darwin 1859; Ash 1927; Epstein 1971; American Kennel Club 1992; Wilcox and Walkowicz 1995). Examples include body size, and skeletal mutations such as chondrodysplasia (foreshortened limbs), brachycephaly (pathologically short face), and coat color and texture mutations (reviewed in Shearin and Ostrander 2010a; Boyko 2011). Standard breeding techniques to preserve these phenotypes in breeds were relatively simple, generally involving crosses between pairs of individuals from different breeds followed by selection of specific traits in the F2 generation (e.g., Stockard 1941) or multigenerational selection for desirable traits (Hutt 1979).

These differing selective regimes are predicted to have led to distinct signatures in the genome of dogs. Indeed, the dog genome project found two population bottleneck signatures, one likely associated with first domestication and the other with the most recent formation of dog breeds (Lindblad-Toh et al. 2005). Although major histocompatibility complex (MHC) evidence suggests that the initial domestication event was not extreme and was augmented by backcrossing (Vilà et al. 2005), the recent and rapid genesis of breeds from a limited number of individuals with subsequent inbreeding has left a signature of autozygosity throughout the dog genome (Boyko et al. 2010). Moreover, selection practiced during this period suggests that in many cases, mutations in a small number of genes of large effect are responsible for many breed characteristics (Sutter et al. 2007; Cadieu et al. 2009; Parker et al. 2009; reviewed in Shearin and Ostrander 2010b; Boyko 2011).

In this review, we briefly summarize recent genome-wide studies of discrete dog breed phenotypes utilizing association or selective sweep mapping approaches. Our intent is to interpret these findings in a new evolutionary context made possible by analysis of SNP genotyping arrays. For more detailed discussion of phenotypic traits and disease loci in dogs, there are several excellent in-depth reviews (e.g., Sutter and Ostrander 2004; Parker and Ostrander 2005; Wayne and Ostrander 2007; Shearin and Ostrander 2010a, b; Boyko 2011). We begin by discussing the conceptual framework that allows for identification of genes responsible for breed phenotypes and the development of SNP genotyping arrays that have allowed for a recent proliferation of studies. We follow with a brief summary of the general nature of changes that give rise to breed-specific traits, and interpret these findings with regard to patterns of breed diversification. Finally, we discuss how evolution in dogs has contributed to genetic change of its closest living relative, the gray wolf (*Canis lupus*).

Selective sweep mapping

Many domestic dog breeds have been formed by intense artificial selection through the fixation of discrete mutations. Population genetic theory predicts that intense selection on a mutation should cause the haplotype on which the mutation is embedded to rise in frequency, thus altering the genomic landscape surrounding the target of selection (Fig. 1) (Smith and Haigh 1974; Kaplan et al. 1989; Stephan et al. 1992; Pollinger et al. 2005). Specifically, recent intense selection is predicted to result in reduced levels of heterozygosity in the region surrounding the target of selection (a "selective sweep") and increased levels of differentiation. This effect can be demonstrated by simulations of breed history that vary several critical parameters, such as the strength of artificial selection, and rates of local recombination and mutation (Fig. 1) (Pollinger et al. 2005). Specifically, in Fig. 1, 50 evenly spaces SNPs were assayed along a region with a population recombination rate of $4N_e r = 80$, where N_e is the effective population size and r is the recombination rate per generation. The strength of the sweep was varied from $s = 10\%$ to $s = 50\%$. The choice of marker density is varied from 1 per 0.08 cM to 1 per 3.2 cM for a region containing 50 markers for a population an effective size of 100. These results strongly suggest that a region of low diversity is detectable with even a modest number of markers (less than a few thousand SNPs) over a variety of selective sweep scenarios.

The first empirical demonstration of the selective sweep approach in dog breeds considered genomic patterns of variation and differentiation near *insulin growth factor 1* (*IGF1*), a candidate gene for body size in a panel of large and small dog breeds (Fig. 2a, b) (Sutter et al. 2007). A clear pattern of decreased relative homozygosity in 10-SNP windows in small breeds and increased differentiation

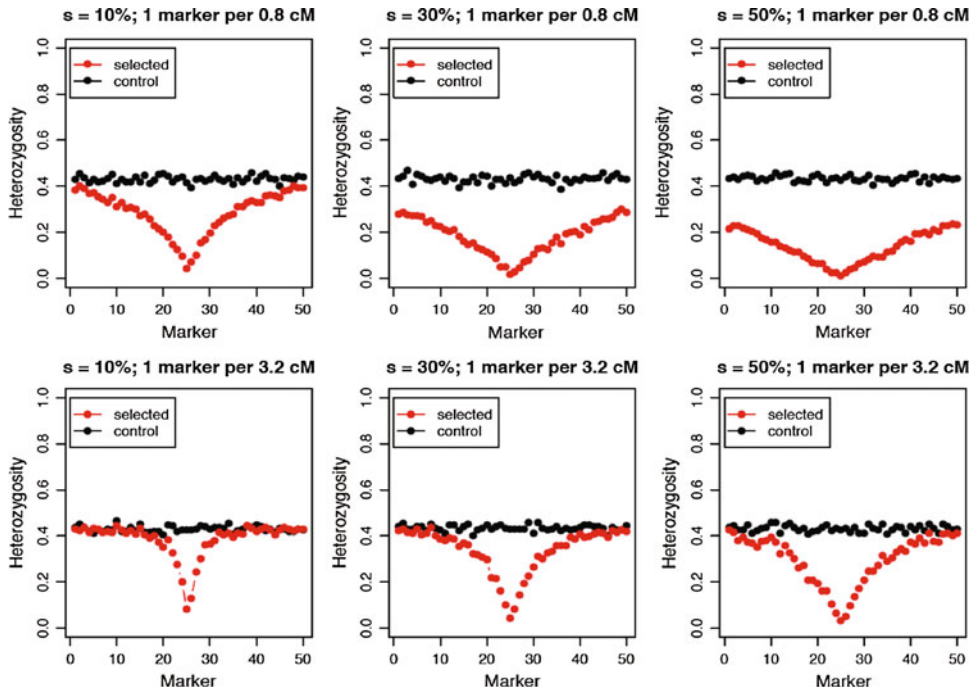

Fig. 1 Simulation summary results measuring the effect of various strengths of selection and marker density on average heterozygosity among 200 replicates (Pollinger et al. 2005)

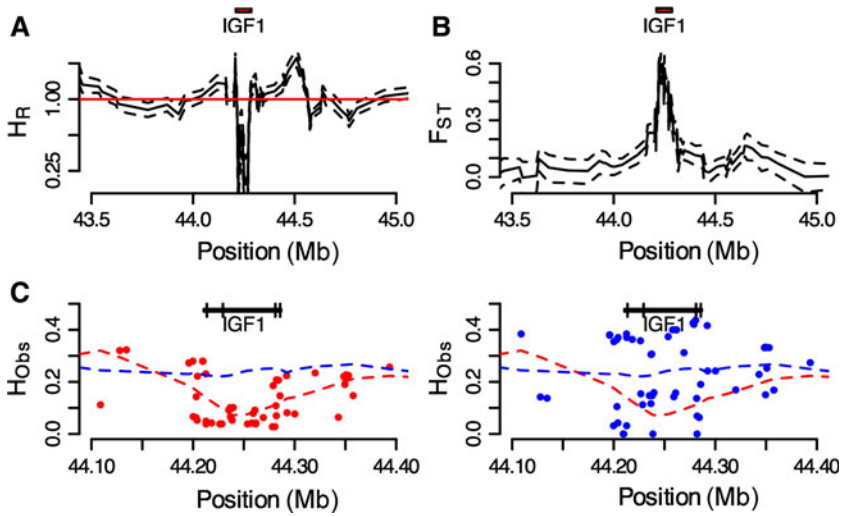

Fig. 2 Recent selective sweep on the *IGF1* locus across 22 small and giant dog breeds. **a** Heterozygosity ratio (HR; the ratio of heterozygosity in small vs. giant breeds). **b** Genetic differentiation (F_{ST}) using a 10-SNP sliding window across *IGF1*. The 95% confidence intervals are delimited by *dashed lines* and based on nonparametric bootstrap resampling. The *IGF1* gene is indicated as a box drawn to scale. **c** Observed heterozygosity (H_{Obs}) of SNPs near *IGF1* in small breeds (<9 kg; points in left panel) and giant breeds (>30 kg; points in right panel). Dashed lines represent the locally weighted scatterplot smoothing (LOWESS) that best fits the data, with the *bar* indicating the *IGF1* gene and exons as *vertical lines* (see Sutter et al. 2007)

between large and small breeds was evident. Even the traces of individual SNP heterozygosity values clearly showed a depression in the levels of variation of small breeds near *IGF1* (Fig. 2c, d). Finally, an analysis of haplotypes in small breeds revealed a recombination event between a small and large dog haplotype allowing the region containing the causative mutation to be narrowed to an 8.7-kb region. This region differs between small and large dogs by only two possible causative loci, one involving a transposable element insertion and the other a microsatellite repeat. This ambiguity provides an important caution in such selective sweep or association mapping studies (see below) as intense rapid selection can yield large regions in linkage disequilibrium and reduced heterozygosity.

Table 1 Traits and dog breed groups

Skeletal conformation traits		Hair pigmentation and texture	
Trait	Breeds	Type	Breeds
Limb achondroplasia (foreshortened limbs)	Dachshund (short, long, and wirehair)	Wire hair	Dachshund
	Corgis (Pembroke, Cardigan)		German wirehaired pointer
	Drever		Affenpinscher
	American and French basset hounds		Wire fox terrier
	Lancashire heeler		Miniature schnauzer
	Väsgötaspets		Scottish deerhound
Axial chondroplasy (foreshortened face)	Brussels Griffon	Curly hair	Curly coated retriever
	Braque de Bourbonnais		American water spaniel
	French bulldog		Bichon Frise
Brachycephalic (compact face and cranium)	Pug		Portuguese water dog
	Pit bull	Corded coat	Komondor
	Brussels griffon		Poodle
	Boston terrier		Puli
	Bulldog	Long coat	Flat
	Japanese Chin		Flat coated retriever
	Lhasa Apso		English cocker spaniel
	Pekingese		Rough
Doliocephalic (long narrow skull)	Greyhound		Rough collie
	Wolfhound		Otterhound
	Spanish greyhound		Wavy
	Borzoi		Borzoi
	Saluki		German longhaired pointer
Proportional dwarfism	Lhasa Apso	Hairless	American hairless terrier
	Pekingese		Chinese crested
	Pug		Inca hairless
	Poodles: standard, toy, Miniature-Toy, teacup		Mexican hairless
	Shih Tzu	Mask Color	Alaskan Malamute
			Malinois
			Jamthund
			Mastiff
			Pug

This table exemplifies the traits shared in common among breed groups. Many of the breed groups with these traits have already been subject to association studies (Table 2)

Consequently, a paucity of recombinants in these regions can provide only a course scale mapping of the potential causative mutations. Nonetheless, *IGF1* and the associated regions are clearly identified as a major contributing locus in size diversity in dogs, accounting for about 50% of the genetic variation in size (Sutter et al. 2007; Boyko 2011).

Genome-wide association mapping

Association (or linkage disequilibrium, LD) mapping takes advantage of the physical relationship between a causative locus and markers closely linked to it. Consequently, the approach is limited by the extent of LD in the genome. In species with large population sizes in which there is long history of recombination since the original mutation, a dense marker sampling is needed to resolve associations. Further, the use of common variants in SNP arrays limits the association to common variation and likely excludes the rare markers that may be more closely associated with causative loci (McCarthy et al. 2008). The unique inbreeding history within dog breeds often results in high LD; therefore, only a coarse association map is possible. However, the appearance of similar breed morphologies in several dog breeds (Table 1) allows for a replicated experimental design in which demographic history and the extent of LD differ among breeds. Because at least some of this variation is likely due to the same alleles or mutations in the same genes

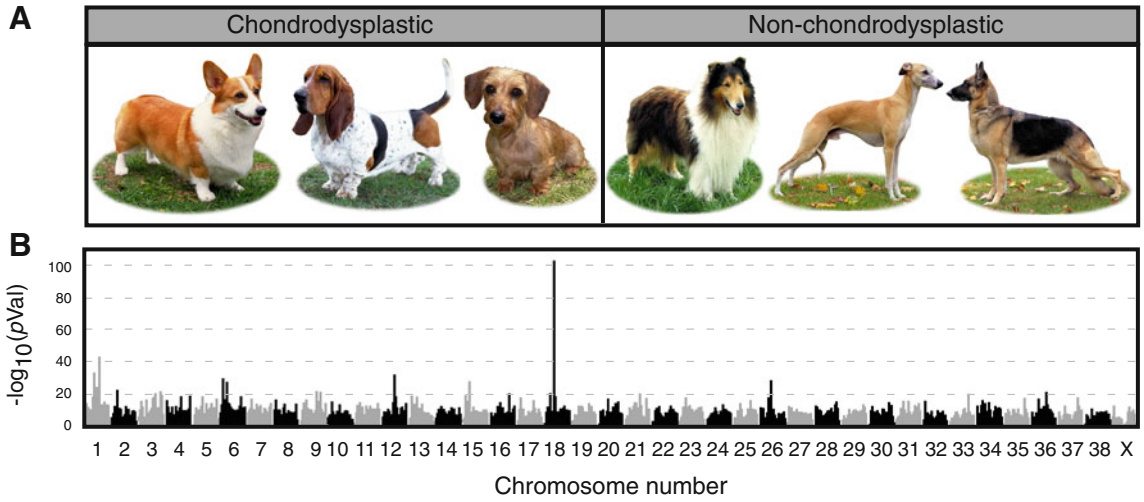

Fig. 3 A genome-wide case/control association study for chondrodysplasia across 72 breeds of dog. **a** Examples of dog breeds that were used as cases (Pembroke Welsh Corgi, Basset Hound, and Dachshund pictured) and controls (Collie, Whippet, and German Shepherd Dog) [Photos credit: Mary Bloom, AKC]. **b** Manhattan plot of the genome-wide association peaks, with the two highest peaks found on chromosome 18 at 23,298,242 and 23,729,786 bases and less than 0.5 Mb apart (CanFam2 assembly) (see Parker et al. 2009)

being shared across breeds (e.g., Sutter and Ostrander 2004; Ostrander and Wayne 2005; Parker and Ostrander 2005; Clark et al. 2006; Wayne and Ostrander 2007), comparative studies across breeds can lead to fine-scale mapping of mutations. For example, one of the most distinctive morphologies in domestic dogs is the foreshortened limb conformation characteristic of breeds such as dachshund, corgi, and basset hound. Such foreshortened limbs or chondrodystrophies are known in actually 19 distinct breeds; thus, if these phenotypes derive from the same mutations, then a case/control study may reveal the causative locus. In fact, Parker et al. (2009) showed by association analysis that the 19 breeds shared a unique transposed growth factor retrogene (Fig. 3) (Parker et al. 2009). This duplicated gene was expressed along with the normal gene in dogs with foreshortened limbs, and the double dose likely altered the pattern of limb growth causing the distinct morphology.

The genetic toolkit

Over 2.5 million SNPs were discovered as a result of the 7.5 × boxer genome sequencing project and were identified using three ascertainment schemes designed to maximize both the genome-wide marker distribution and SNP informativeness for mapping studies across multiple breeds (Lindblad-Toh et al. 2005). First, to capture the diversity of the dog population, the boxer chromosomes were compared to each other and to ~100,000 sequence reads from each of nine dog breeds (0.02×) selected to represent the seven American Kennel Club groups exhibiting a range of morphological characteristics, behavioral characteristics, and evolutionary history (900,000 sequence reads total). Second, ~22,000 sequence reads from each of four gray wolves and a coyote (~0.004×) were generated and compared to the boxer sequence. Third, the boxer sequence was compared to 1,321 Mb of sequence from the 1.5× poodle sequence assembly (Kirkness et al. 2003). The development of the SNP genotyping array was led by Dr. Kerstin Lindblad-Toh at the Broad Institute in collaboration with Affymetrix (Santa Clara, CA). An array with about 60,000 useful SNPs was developed with a density of approximately one SNP per 20–40 kb. This array has allowed numerous association studies of canine disease and phenotypes (see references in Table 2), demonstrating the power of genome-wide association studies in dogs, even with a limited array design. The Affymetrix array has been followed by a second-generation array from Illumina with about 170 k SNPs (http://www.illumina.com/products/caninehd_whole_genome_genotyping.ilmn), including most of the 60 k SNPs found to be informative on the Affymetrix array.

The dog as a model species

As discussed above, dogs demonstrate extreme phenotypic diversity that is partitioned into largely isolated breed gene pools (Parker et al. 2004; Parker and Ostrander 2005) and which have high levels of autozygosity (Boyko et al. 2010). Consequently, genome studies with even moderate densities of markers can identify regions containing genes linked to phenotypic traits and disease. However, a unique attribute of dogs, as mentioned above, is that similar traits are fixed in

Table 2 The genetic basis of breed-defining traits in domestic dogs based on genome-wide studies. Bold indicates the likely candidate gene(s) in an associated region

Phenotype category	Phenotype variant	Gene(s)	Variant mutation	CFA	References
Morphology	Body size	Haplotype association	Not fined-mapped	3	Boyko et al. (2010)
	Body size	SMAD2	Not fined-mapped	7	Jones et al. (2008)
	Body size	**HMGA2**, GNS, RASSF3	Not fined-mapped	10	Akey et al. (2010); Boyko et al. (2010)
	Brachycephaly	THBS2, SMOC-2	Homozygous haplotype	1	Bannasch et al. (2010)
	Chondrodysplasia	FGF4	Retrogene insertion	18	Parker et al. (2009)
	Ear type	MSRB3	Not fined-mapped	10	Boyko et al. (2010)
	Head size	IGFBP4	Not fined-mapped	9	Jones et al. (2008); Chase et al. (2009)
	Leg size	RNF4, MXD	Not fined-mapped	3	Jones et al. (2008); Chase et al. (2009)
	Limb/tail length	Haplotype association	Not fined-mapped	X	Boyko et al. (2010)
	Miniature size	IGF1	Synonymous SNP, exon 3	15	Chase et al. (2005); Sutter et al. (2007)
	Neck size	**STAT3**	Not fined-mapped	9	Jones et al. (2008); Chase et al. (2009)
	Skin wrinkling	HAS2	2-bp indel	13	Akey et al. (2010)
	Skull shape	Haplotype association	Not fined-mapped	X	Boyko et al. (2010)
	Snout length	Haplotype association	Not fined-mapped	1	Boyko et al. (2010)
	Tail curve	COL6A3	Not fined-mapped	25	Jones et al. (2008); Chase et al. (2009)
	Weight	**SMAD2, NPR2**	Not fined-mapped	7	Jones et al. (2008); Chase et al. (2009)
Hair type/pattern	Curly	KRT71	Arg151Trp	27	Cadieu et al. (2009)
	Furnishings and/or Wire	RSPO2	167-bp insertion 3′ UTR	13	Cadieu et al. (2009)
	Hair ridge	**FGF3, FGF4, FGF19**, CCND1, ORAOV1	133-kb duplication	18	Karlsson et al. (2007); Salmon Hillbertz et al. (2007)
	Long hair length	FGF5	Cys95Phe in exon 1	32	Housley and Venta (2006); Jones et al. (2008); Chase et al. (2009); Cadieu et al. (2009)
	White spotting	MITF	Promoter mutations	20	Karlsson et al. (2007)
Behavior	Boldness	DRD1	Not fined-mapped	4	Chase et al. (2009)
	Boldness	**IGF1**	Not fined-mapped	15	Chase et al. (2009)
	Boldness	**PCDH9**	Not fined-mapped	22	Chase et al. (2009)
	Compulsive disorder	CDH2	SNP allele association	7	Dodman et al. (2010)
	Herding	**MC2R**	Not fined-mapped	1	Chase et al. (2009)
	Pointing	CNIH	Not fined-mapped	8	Chase et al. (2009)
	Domesticated	ZNF407, **CNDP1, CNDP2**	Not fined-mapped	1	vonHoldt et al. (2010)
	Domesticated	NEDD4L	Not fined-mapped	1	vonHoldt et al. (2010)
	Domesticated	MEIS3, GPR77, C5AR1	Not fined-mapped	1	vonHoldt et al. (2010)
	Domesticated	SNP cluster association	Not fined-mapped	2	vonHoldt et al. (2010)
	Domesticated	OPRM1, hNT	Not fined-mapped	5	vonHoldt et al. (2010)
	Domesticated	**WBSCR17**	Not fined-mapped	6	vonHoldt et al. (2010)
	Domesticated	**SLC24A4**	Not fined-mapped	8	vonHoldt et al. (2010)
	Domesticated	SNP cluster association	Not fined-mapped	12	vonHoldt et al. (2010)
	Domesticated	**ADCY8**	Not fined-mapped	13	vonHoldt et al. (2010)

Table 2 continued

Phenotype category	Phenotype variant	Gene(s)	Variant mutation	CFA	References
	Domesticated	TNRFSF11B	Not fined-mapped	13	vonHoldt et al. (2010)
	Domesticated	CADPS2	Not fined-mapped	14	vonHoldt et al. (2010)
	Domesticated	SNP cluster association	Not fined-mapped	16	vonHoldt et al. (2010)
	Domesticated	IL1F5, IL1F8, IF1F10, IL1RN, PSD4, Pax8	Not fined-mapped	17	vonHoldt et al. (2010)
	Domesticated	PRND, PRNP, SMOX, SAMD12	Not fined-mapped	24	vonHoldt et al. (2010)
	Domesticated	CHRM5, AVEN, **RYR3**	Not fined-mapped	30	vonHoldt et al. (2010)
	Domesticated	MRK	Not fined-mapped	36	vonHoldt et al. (2010)

multiple breeds (e.g., Fig. 3) and thus offer replicated cases to investigate the genetic basis of phenotypes. For example, in Table 1 we list numerous trait groups common to more than one breed that can potentially be mapped using a genome-wide approach. Many of these traits have been investigated (see below; Table 2). However, disease and behavioral traits are likely to prove more problematic because they do not uniquely segregate among breeds. Some breeds may have a higher incidence of specific diseases, which may facilitate disease mapping (e.g., Ostrander and Kruglyak 2000; Sutter and Ostrander 2004; Parker and Ostrander 2005; Shearin and Ostrander 2010b). However, statistical power is often lost because many disorders are not fixed within breeds, have variable penetrance, and can by influenced by environmental factors. Additionally, behavioral traits are often difficult to score objectively, although recently a rationalized scheme for scoring behavioral traits has been developed for the silver fox project (Kukekova et al. 2010). Extreme behaviors that appear pathologic and therefore likely have a simple genetic basis have been mapped in the domestic dog (e.g., Dodman et al. 2010).

Beginning with coat color mutations, genome-wide studies have revealed the genetic basis of coat color and texture, body size and leg length, ear floppiness, skin wrinkling, and a variety of cranial and external dimensions (Table 2; Fig. 4) (Boyko et al. 2010; Boyko 2011). Additionally, a large number of genes appear associated with the early phase of domestication (Table 2). A fundamental conclusion from these studies is that much of the distinct morphologic diversity of dogs reflects variation in a relatively small number of genes (Boyko et al. 2010). This finding is in striking contrast to studies in humans or domesticated species where quantitative traits often are influenced by a large number of major and minor genes that in aggregate explain only a small fraction of the phenotypic variation in a trait. For example, in humans, the top 40 genes associated with body height explain less than 10% of the genetic variation (Yang et al. 2010), whereas *IGF1* in dogs explains approximately 50% of the variation among breeds (Boyko et al. 2010; Boyko 2011; Gray et al. 2010). As discussed above, this difference likely reflects the unique history of selection in dogs which involved the appearance of discrete mutations followed by fixation through intense inbreeding. The whole process was accelerated by systematic breeding practices of the Victorian era beginning early in the 19th century when dogs of novel and even bizarre conformation became the object of selection (Ash 1927; Stockard 1941; Dennis-Bryan and Clutton-Brock 1988; Shearin and Ostrander 2010a; Galibert et al. 2011). Such breeds were desired by the nobility, which led to their general popularity in European society (Ash 1927). This desire for novelty continues to the present day.

The evolutionary framework

Dog origins

MtDNA sequence data suggest that East Asia was a center for dog domestication because sequence and haplotype variability is highest there (Savolainen et al. 2002; Pang et al. 2009). To test this model of dog domestication, vonHoldt et al. (2010) typed >48 k SNPs genome-wide in 155 gray wolves representing populations from Europe, the Middle East, North America, and Asia, and 912 unrelated dogs representing over 80 breeds registered with the AKC. These authors computed SNP heterozygosity based on different SNP ascertainment panels, and in contrast to Savolainen et al. (2002), only the small sample of African breeds in this study had substantially lower single SNP heterozygosity (Fig. 5a–c). This may reflect the use of purebred breeds because African village dogs have high mtDNA sequence and microsatellite variability (Boyko et al. 2009). Several aboriginal populations such as Dingo, New Guinea singing dogs, and ancient breeds such as Basenji and Canaan dog have low heterozygosity and polymorphism (Fig. 5a, b). The former are island populations and likely lost variation because of restricted founding events and subsequent small effective population sizes. Analysis of haplotype diversity showed the same basic

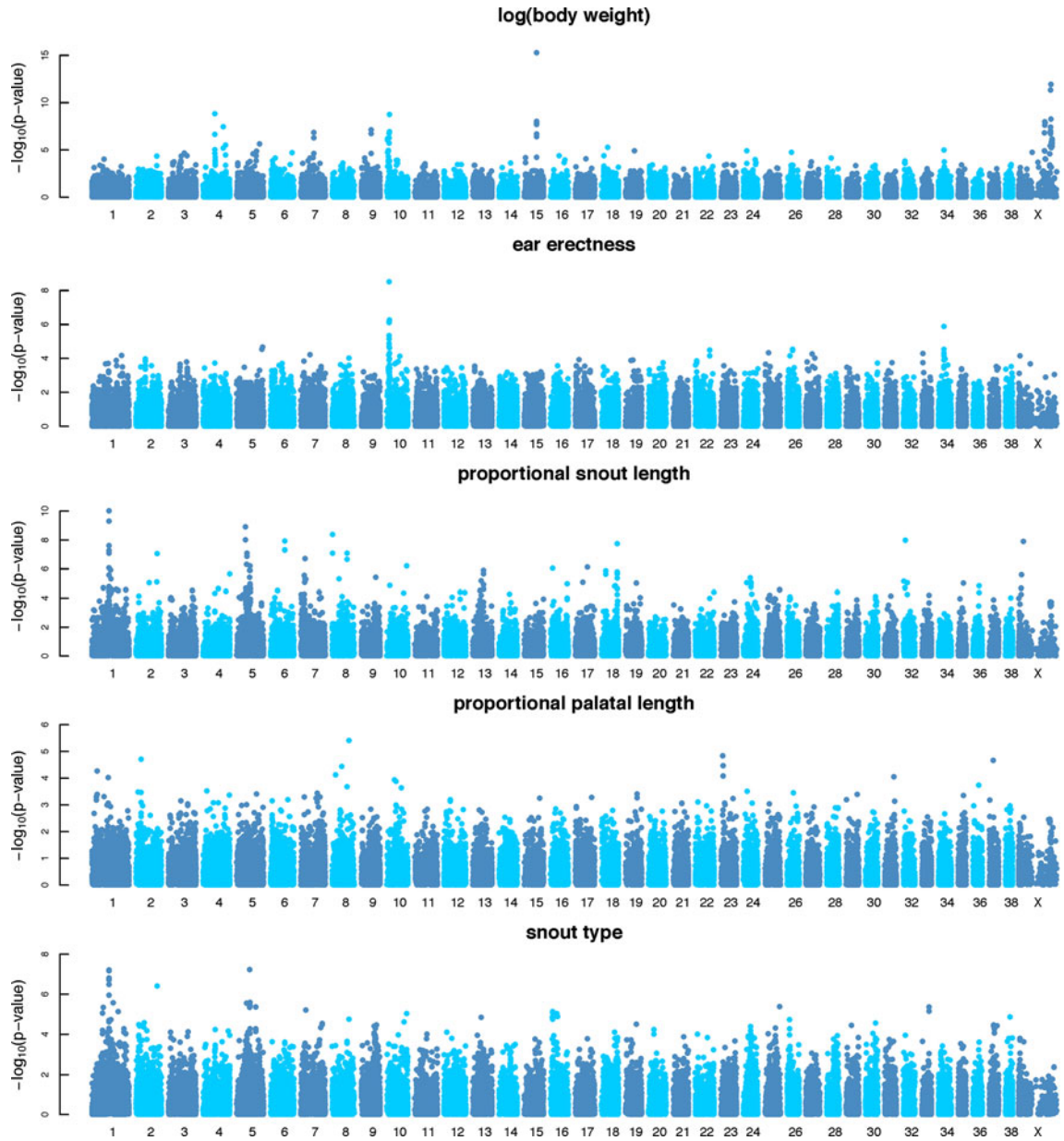

Fig. 4 Genome-wide association scans, uncorrected for breed relatedness. Traits are as follows: log(body weight); ear erectness (floppy vs. erect ears); proportional snout length; proportional palatal length; and snout type (brachycephalic vs. average) (see Boyko et al. 2010)

patterns except that wolves clearly have greater variation than domestic dogs (Fig. 5b). This reversal is likely due to the more limited effect of ascertainment bias on measures of haplotype diversity and implies that haplotype-based metrics may be a more accurate indication of variation in populations (e.g., Reich et al. 2001). Finally, these basic results are supported by previous microsatellite analysis where no specific geographic area has lower variation (Fig. 5c, Parker et al. 2004). These estimates of SNP heterozygosity and haplotype diversity, as well as previous microsatellite data, clearly do not support an East Asian origin for dogs but suggest multiple centers of origin or ancient backcrossing, or indicate a bias in mitochondrial DNA variation reflecting a higher rate of trade or female-biased dispersal (Sundqvist et al. 2006).

To better resolve which wolf population most likely contributed to the genome during the early phases of dog domestication, vonHoldt et al. (2010) assessed the level of haplotype sharing among dog breeds and wolf populations (East Asia, Europe, and Middle East). Archaeological data suggest domestication occurred in multiple locations (Europe, Middle East, and East Siberia), but the mtDNA sequence data imply an East Asian origin (Olsen and Olsen 1977; Dayan 1994; Morey 1994; Sablin and Khlopachev

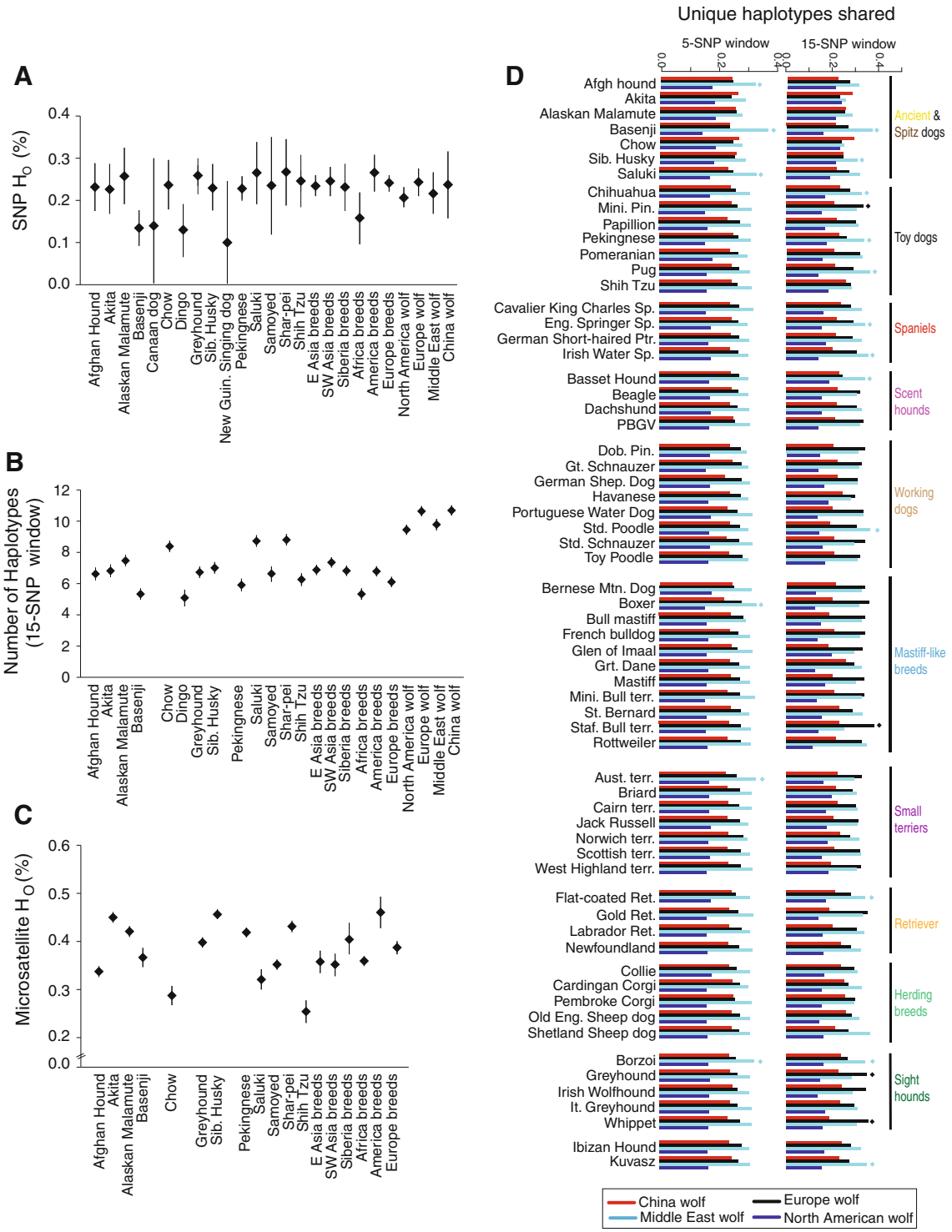

Fig. 5 Genetic diversity statistics for dog breeds and breed groups and private allele sharing with specific wolf populations. **a** Average observed heterozygosity (H_{obs}). **b** Number of haplotypes per breed or breed group for phased 15-SNP windows. **c** Average observed heterozygosity of microsatellite data. **d** The fraction of unique haplotypes shared between 64 dog breeds and wolf populations for 5- and 15-SNP windows (*left* and *right*, respectively). Diamonds indicate significant sharing ($P < 0.05$) from permutation testing. Six (**a**–**c**) or nine (**d**) individuals represent each breed and wolf population. *Error bars* indicate SEM. E, east; SW, southwest (see vonHoldt et al. 2010)

2002; Savolainen et al. 2002; Zeder et al. 2006; Germonpré et al. 2009; Morey 2010; Ovodov et al. 2011). A problem with archaeological inference is the paucity of fossils and the inability to distinguish early dogs from wolves (Germonpré et al. 2009). Phased chromosomes were partitioned into 2,634 windows, each spanning 500 kb and containing

minimally 5 or 15 SNPs (vonHoldt et al. 2010). From a total of 64 dog breeds and across the 5-SNP window analyses, Middle East wolves had highest sharing in all comparisons, with six breeds having significant sharing in at least one permutation test (Fig. 5d). Similarly, for the 15-SNP windows, 75% (48/64) had highest sharing with Middle East wolves, of which 38% (18/48) were significant for at least one test. The high degree of haplotype sharing among dog breeds and Middle Eastern wolves suggests an origin there or, as mentioned above, extensive backcrossing between Middle Eastern wolves and the ancestors of modern and ancient dog breeds. However, the similarity of some specific East Asian ancient breeds and Chinese wolves suggests that wolves from this area contributed to the dog genome as well (vonHoldt et al. 2010). Moreover, the significant component of haplotype sharing for 15-SNP windows implies both the Middle East and Europe may have contributed substantially to the genome of domestic dogs, a result that is consistent with the archeological record.

The diversification of domestic dogs

To determine the genetic relationship among dog breeds, vonHoldt et al. (2010) used genetic similarity based on single-locus SNP data. The consensus tree clearly supported the basic divisions between wolves and domestic dogs (Fig. 6). In addition, genetic subdivisions that correspond to functional and phenotypic groups commonly defined by dog breeders were revealed (i.e., sight, scent, herding breeds, spaniels, small terriers). Moreover, there was a remarkable genealogical clustering of individuals within breeds. With one exception, all individuals in the tree cluster to their breed of origin, suggesting that breeds are highly differentiated units (e.g., Parker et al. 2004). However, the classification of breeds into functional and phenotypic groups is not true of all breed groupings. For example, toy breeds are completely heterogeneous, implying that they have originated independently by the interbreeding of different stocks. Similarly, more limited heterogeneity is apparent in working dogs and retrievers (Fig. 6). These two distinct patterns of relationships among dog breeds suggest that distinct mechanisms underlie domestic dog diversity. Specifically, the appearance and fixation of discrete mutations lead to novel breed phenotypes that are subsequently crossbred to other breed groups. This process transfers these mutations to a unique genetic and phenotypic background and results in the appearance of high phenotypic diversity without new mutations, rapidly adding to the spectrum of morphologies in dogs. To test this idea with regard to toy breeds, vonHoldt et al. (2010) examined historical records of breed origin and found that most toy breeds used in this study were founded by crosses with established toy breeds, supporting a model whereby discrete mutations are crossed to breeds representing the diversity of different breeding groupings (Table 3). In contrast, breed groupings that are not heterogeneous in origin probably reflect the more systematic selection for function or behavior such as in herding breeds and in scent and sight hounds. Essentially, when breeders of such dogs want to improve their stock and establish a new breed, they utilize existing breeds with similar traits. Consequently, over time, this will lead to genetic clustering as observed by vonHoldt et al. (2010). As a result, the immense diversity of domestic dogs distills to a small number of genes, and through crossbreeding among distinct dog lineages, it has led to the appearance of remarkable diversity that, in reality, has a limited genetic basis.

Ancient origin of mutations

The presence of the same mutation in many breeds implies a single ancient origin for many of the breed phenotypes in dogs. A prime example is *IGF1*, where small dogs share three closely related haplotypes, implying a single ancient origin (Sutter et al. 2007). To test this origin idea directly, Gray et al. (2009) explored the evolutionary history of the *IGF1* gene further by resequencing and genotyping key markers in the intron 2 region of *IGF1* across a global sampling of gray wolf populations. Neighbor-joining trees were constructed from 4,811 and 6,331 bp of sequence from 14 gray wolf populations ($N = 20$) and 8 small and large dog breeds ($N = 10$), respectively. Gray et al. (2009) observed that small dog breed sequences clustered with those from wolves in Israel, Iran, and India, with 68% bootstrap support out of 1,000–10,000 replicates (Fig. 7). Large domestic dog breed sequences clustered with those of all other gray wolves and had a bootstrap support of 75 and 94% (4,811 and 6,331 bp, respectively). To verify the tree topology, they constructed constraint trees in which the "small dog" haplotype was constrained to clusters containing the "large dog" haplotypes. Maximum likelihood analysis of the constraint trees confirmed that the likelihoods of the unconstrained trees were significantly better ($P < 0.001$ in all cases). Thus, these results demonstrate that all small dogs have *IGF1* sequences that cluster with wolves from the Middle East, suggesting an early evolution of small size in dogs there.

Mutations of dog origin transform wild gray wolf populations

In the history of domesticated species, mutations that have appeared under domestication, even in genetically engineered forms, do not succeed substantially in the wild. However, uniquely in North American wolves, gray and black coat-colored wolves exist in nearly equal proportions

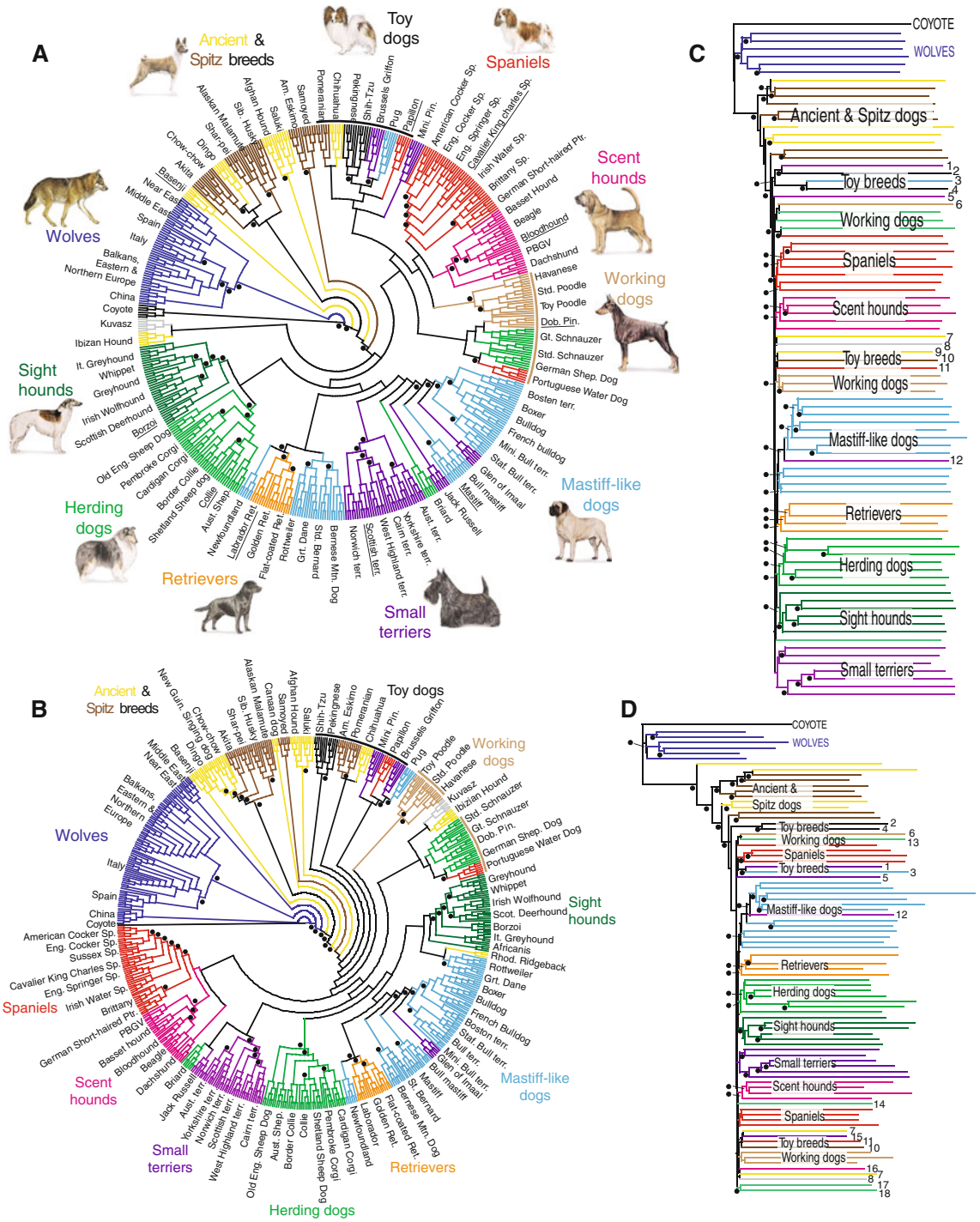

Fig. 6 Genetic similarity tree for dogs and wolves based on SNP genotyping data. Clades are labeled based on phenotypic/functional designations used by dog breeders. *Dots* indicate ≥95% bootstrap support from 1,000 replicates. **a** Haplotype-sharing cladogram for 10-SNP windows ($n = 6$ for each branch). **b** Allele-sharing cladogram of individuals based on individual SNP loci. **c** Haplotype-sharing phylogram based on 10-SNP windows of breeds and wolf populations. **d** Allele-sharing phylogram of individual SNPs for breeds and wolf populations. Wolf image adapted from Macdonald and Barrett (1993); dog images from the American Kennel Club (http://www.akc.org) (see vonHoldt et al. 2010)

throughout the continent. The exception is in the high Arctic where light colored (gray or white) wolves have frequencies above 90%. In the Old World, black wolves are rare and are often associated with a high frequency of feral dogs and urbanization (Randi and Lucchini 2002). Genealogical studies of Yellowstone National Park wolves

Table 3 The origin of heterogeneous toy breeds (see Fig. 6 and vonHoldt et al. 2010)

Breed	Genetic cluster	Phenotypic/ functional group	Breed information	Concordance with historical evidence
Briard	Small terrier	Herding	Possible East Asian origin from crosses with local dogs to create a new breed used for flock guarding	No historical evidence for breed admixture between small terriers and herding dogs
Brussels Griffon	Toy	Terriers	European origins from crosses with Affenpinscher (terrier) and toy breeds (i.e., English Toy Spaniels, Yorkshire Terriers, Pekingese, or Pug) to miniaturize the breed	Evidence for breed admixture between toy and terrier breeds
Chihuahua	Toy	Ancient	Probable Chinese origins with introduction to Mexico from Spanish traders returning from East Asia	Evidence for breed admixture between East Asian Ancient and toy breeds
German Shepherd	Gun	Herding	European breed with recent origins	Inconclusive
Great Schnauzer	Gun	Herding	European origins likely from crosses with smooth-haired dogs and possibly Great Danes	Inconclusive
Glen of Imaal	Mastiff-like	Terriers	European origins from crosses of Bullterriers, Staffordshire terriers (Mastiff-like breeds), and other fighting dogs; Glen of Imaal is an aggressive hunter (e.g., badgers, rats)	Evidence for admixture between Mastiff-like and terrier breeds
Miniature Pinscher	Toy	Terriers	European origins from crosses of German Pinscher (terrier) and Dachshunds or Italian greyhounds	Evidence for admixture between toy and terrier breeds
Newfoundland	Retrievers	Mastiff-like	North American origins with possible crosses to Mastiff or Portuguese Water dog; considered an ancestor of the modern Labrador Retriever	Evidence for Retriever and Mastiff-like breed admixture
Papillon	Toy	Spaniels	European origins from crosses of spaniels and Bichon-type (toy) breeds	Evidence for admixture of toy and spaniel breeds
Pekingese	Toy	Herding	China origins; considered a dwarfed Tibetan terrier or Pug (toy)	Evidence of admixture of toy and other breeds
Pomeranian	Toy	Spitz	European origins from crossing European herding and spitz-type breeds	Inconclusive
Portuguese Water Dog	Gun	Spaniels	European origins; bred to be a water dog	Inconclusive
Pug	Toy	Mastiff-like	China origins; considered a "mini-mastiff," likely from miniaturizing the Affenpinscher (Terrier) or the English Bulldog and crossing with the Tibetan Mastiff (Mastiff-like breeds)	Evidence for breed admixture of Mastiff-like and toy breeds
Shih Tzu	Toy	Herding	Tibet/China origins; considered a dwarf of Tibetan terriers or Lhasa Apsos (herding breeds)	Evidence for admixture of toy and herding breeds
Standard Schnauzer	Gun	Herding	European origins from crossing the Standard Pinscher, Poodles, "Wolfspitzs," or Shepherds	Inconclusive

showed a pattern of simple Mendelian inheritance with black being dominant (vonHoldt et al. 2008; Anderson et al. 2009). Consequently, it was demonstrated that the black coat color gene derives from a novel mutation in the domestic dog that was transferred to gray wolves through interspecific hybridization. This mutation was then selectively swept to high frequency in gray wolf populations and shows signals of selection at the molecular level (Fig. 8). This finding remains a unique example of a mutation that appeared under domestication and was transferred to and subsequently transformed a wild progenitor. Recently, it was shown that the benefit of the mutation may not involve coat color alone but derives from other functions. Specifically, black wolves have higher survivorship (Coulson et al. 2011); on average they live 1.5 years longer, which is substantial for gray wolves as they live typically only 5–6 years. The reason for the increased survivorship is uncertain, but the class of genes represented by the black coat color gene, a canine β-defensin, also functions in cellular immunity and may provide black-colored individuals with an advantage against specific pathogens. The mutation likely appeared tens of thousands of years ago in dogs and was recently transferred in pre-Columbian times to gray wolves from Native American dogs. Thus, the long evolutionary history of the mutation in dogs may be due to novel properties that wolf-based

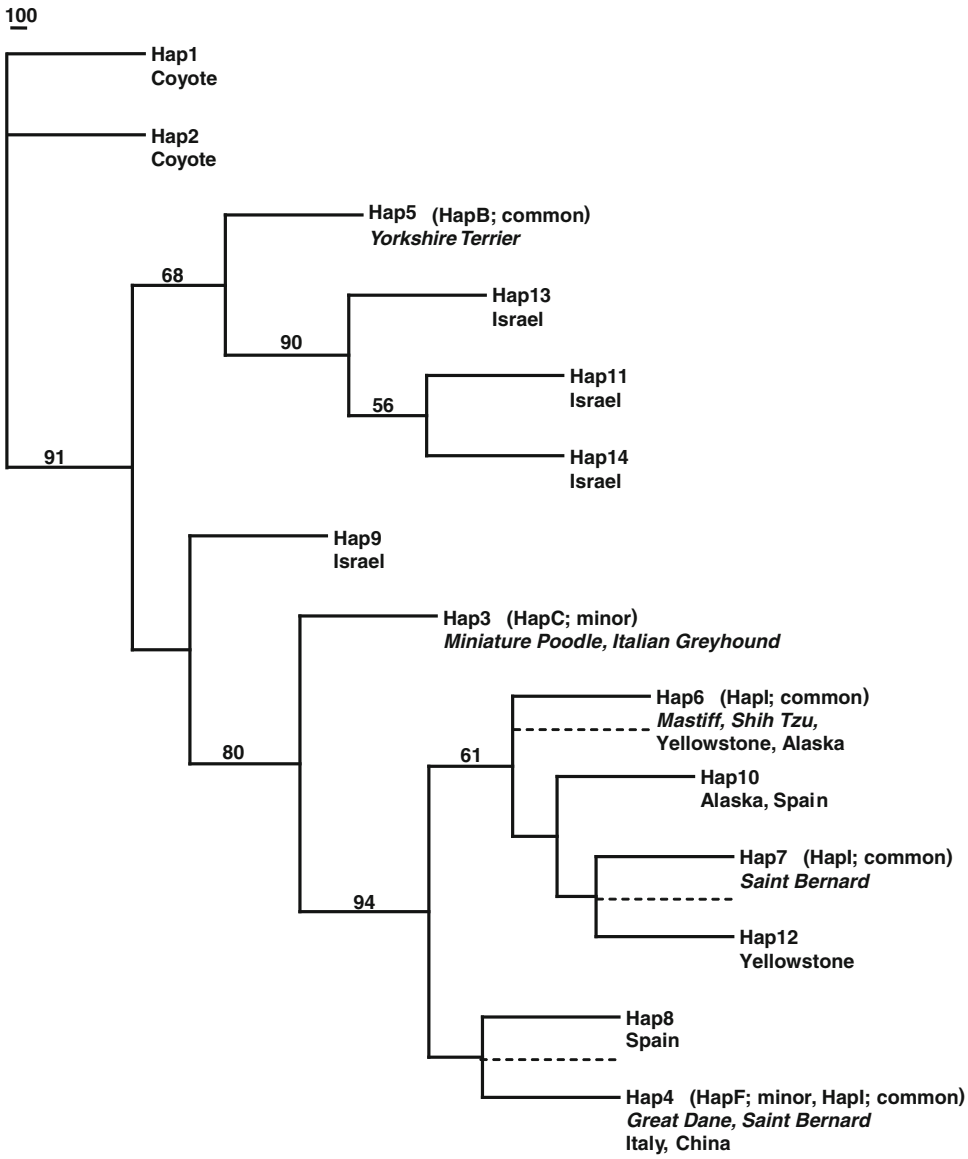

Fig. 7 Insulin-like growth factor 1 (*IGF1*) intron 2 neighbor-joining tree based on 6,331 bp of phased sequence. Proportional branch support (>50%) is based on 1,000 bootstrap replications. *Dashed lines* indicate the location that the small dog haplotype 5 was placed in the three constraint trees. Dog breeds are *italicized* while gray wolf populations are normal font and listed by geographic location (see Gray et al. 2010)

pathogens had not coevolved with, and consequently, conferred greater resistant in wolf populations.

The divergence between dog and wolf

The dog is commonly considered a subspecies of the gray wolf. However, it has been shown through recent genome-wide studies that dogs and gray wolves are genetically highly divergent (vonHoldt et al. 2010, 2011), and such divergence is evident even in resequencing studies where ascertainment is not an issue (Gray et al. 2009). In fact, wolves with dog ancestry are found in wild populations (vonHoldt et al. 2011) where feral dogs are common and wolves have recently recolonized (Kays et al. 2010). Dogs can readily be distinguished from all wild canids (vonHoldt et al. 2011) and rarely interbred except under exceptional conditions, suggesting that they should be considered separate species. Previously, the ability of genetic testing to resolve hybrids beyond the first or second generation has been limited (Pilgrim et al. 1998; Vilà and Wayne 1999; Andersone et al. 2002; Randi and Lucchini 2002; Adams et al. 2003; Vilà et al. 2003; Fredrickson and Hedrick 2006; Fain et al. 2010; Kays et al. 2010; Bohling and Waits 2011). The recent genome-wide study by vonHoldt et al. (2010) identified a number of SNPs that can readily distinguish dogs and gray wolves (see Supplementary Table 2 in vonHoldt et al. 2010). As laws governing wolves, dogs, and wolf–dog hybrids differ worldwide, such markers offer a means to assess legal compliance and forensically determine the genetic composition of dogs from trace remains.

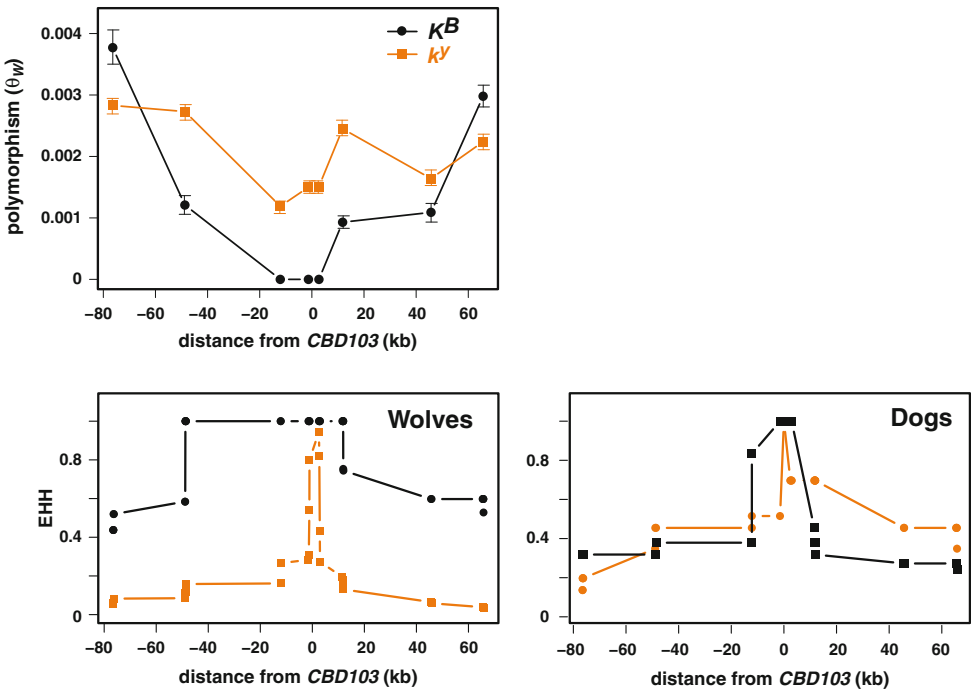

Fig. 8 Polymorphism and haplotype structure of the dominant black (k^y) and gray (K^B) coat color allele in dogs and North American gray wolves. *Top* Polymorphism (θ_W, ± SD) in dogs and wolves as a function of distance from the coat color locus (CBD103$^{\Delta G23}$). *Bottom* Extended haplotype homozygosity (EHH) for K^B- or k^y-bearing chromosomes in wolves (*left*) and dogs (*right*) as a function of distance from *the coat color locus* (see Anderson et al. 2009)

The future of dog evolutionary studies

Nearly all studies to date that have investigated canine traits and their evolution have excluded individuals of mixed breed ancestry (however, see Boyko et al. 2010; Boyko 2011). Human mapping studies have successfully applied admixture mapping which utilizes the mosaic structure of a genome within recently admixed populations to identify chromosomal fragments that have a specific ancestry and are associated with specific phenotypes (Patterson et al. 2004; Tang et al. 2006; Price et al. 2007; Buerkle and Lexer 2008; Cheng et al. 2009; Bryc et al. 2010a, b; Cheng et al. 2010a, b; Winkler et al. 2010; Seldin et al. 2011). This method can now be applied to mixed-breed dogs in which the breed composition has been resolved, as is the case for Alaskan sled dogs. For example, sled dogs have been bred for either short- or long-distance racing styles, with each racing style having a unique ancestry composition. Breeders will increase the spitz-derived ancestries (e.g., Siberian Husky or Alaskan Malamute) in their sled dog genomes if they breed for endurance, whereas Saluki and German Shorthaired Pointer ancestry is associated with increased work ethic (Huson et al. 2010). Admixture mapping is potentially one of the many novel methods that can untangle the polygenic nature of complex traits (e.g., physiology, temperament, and behavior). Gene mapping studies should no longer be limited to purebred dogs; rather, the breed composition can be determined via a simple genotyping assay using the CanMap reference population (Jones et al. 2008; Chase et al. 2009; Boyko et al. 2010) and ancestry analysis (e.g., Tang et al. 2006).

SNP genotyping arrays have proved their utility for genetic mapping of discrete traits of domestic dog breeds. With the advent of a second-generation array containing about 170 k SNPs, the power of such analyses is greatly enhanced and array-based studies will remain an important tool for many years. However, the advent of high-throughput next-generation sequencing platforms have allowed for inexpensive low-coverage (~6–8×) sequencing of large population samples such as in humans (e.g., 1000 Genomes Project Consortium 2010). Such studies have begun in dogs and promise to provide high resolution of genetic differences among dog breeds and associations with phenotypic traits, behavior, and disease. Importantly, the genome of the dog and wolf urgently need direct annotation through transcriptome-based studies, which will lead the way toward a better understanding of gene expression, function, and epigenetic regulation. It is truly an exciting time for canine evolutionary genomics.

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