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Evolutionary History, Selective Sweeps, and Deleterious Variation in the Dog

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Abstract

The dog is our oldest domesticate and has experienced a wide variety of demographic histories, including a bottleneck associated with domestication and individual bottlenecks associated with the formation of modern breeds. Admixture with gray wolves, and among dog breeds and populations, has also occurred throughout its history. Likewise, the intensity and focus of selection have varied, from an initial focus on traits enhancing cohabitation with humans, to more directed selection on specific phenotypic characteristics and behaviors. In this review, we summarize and synthesize genetic findings from genome-wide and complete genome studies that document the genomic consequences of demography and selection, including the effects on adaptive and deleterious variation. Consistent with the evolutionary history of the dog, signals of natural and artificial selection are evident in the dog genome. However, conclusions from studies of positive selection are fraught with the problem of false positives given that demographic history is often not taken into account.

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1. INTRODUCTION

1.1. The Focus and Organization of This Review

The phenotypic diversity of the dog is unmatched by any wild or domestic vertebrate species. Dogs vary in two orders of magnitude in size from 1-lb teacup poodles to giant mastiffs weighing over 200 pounds. Scaling relationships vary as well, with breeds having different limb, body, and skull proportions. Quantitative comparisons with other carnivore groups suggest dogs contain more phenotypic diversity than is found in the entire carnivore order (Drake et al. 2010; Wayne 1986a,b). Similarly, functional and behavioral diversity is striking among dogs, with certain breeds excelling in traits such as herding, retrieving, scent detection, and guarding (American Kennel Club 1992). The genetic mechanisms that have led to this diversity are now becoming more clear with the development of genomics techniques and tools following the publication of the first high-resolution dog genome in 2005 (Lindblad-Toh et al. 2005). Along a different evolutionary axis, dogs represent a dramatic behavioral divergence from their wolf ancestors, showing decreased aggression, increased tameness, and the capacity to learn tasks through interactions with humans (Hare & Tomasello 2005, Miklósi 2009). Whereas modern breeds vary in their morphological divergence from wolves, breeds such as malamutes and Siberian huskies are clearly more wolf-like but, like early protodogs, are nonetheless morphologically distinct (Germonpré et al. 2009, 2012; Ovodov et al. 2011; Pionnier-Capitan et al. 2011). In this review, we summarize findings concerning the genetics of phenotypic traits in dogs in light of the historical framework of domestication. We discuss how dog diversity was augmented during the long history of domestication, beginning with the loose association with hunter-gatherers more than 25 thousand years ago (kya) (Skoglund et al. 2015, Thalmann et al. 2013) and most recently continuing with the explosion of phenotypic diversity associated with selective breeding in the Victorian era and the formation of modern breeds through strong artificial selection within closed breeding pools.

The evolutionary history of the dog is controversial, but there is general agreement that it occurred over a longer timescale than occurred for any other domestic species and involved unparalleled levels of admixture among distinct lineages of domestic dog and between dogs and wolves (Fan et al. 2016, Freedman et al. 2014, Larson et al. 2012, Skoglund et al. 2015, vonHoldt et al. 2011). First, we first examine genome-wide selection scan (GWSS) studies that contrast dog and wolf diversity to identify the genetic basis of dog-specific traits that arose early in dog history. These studies identify putative genomic regions that underwent positive selection in dogs by searching for signals of selective sweeps manifest as reduced diversity in dogs relative to wolves and elevated dog–wolf divergence. Second, we review the genetic basis of variation in traits that vary in their prevalence among breeds. These studies generally take two complementary approaches: (*a*) genome-wide association studies (GWAS) that define genomic intervals harboring causative variants associated with breed-specific phenotypes and (*b*) selective sweep mapping that defines candidate genes as contained within genomic intervals bearing signals of positive selection. We discuss the problems with these approaches and suggest avenues to gain power and precision for inferring the genetic basis of phenotypes in dogs and other domesticated species. Third, after reviewing evidence for positive selection on candidate genes, we approach a poorly researched but critical consequence of domestication, which is the increase in deleterious variation associated with drift in isolated breed gene pools. The inefficiency of selection in small populations has general evolutionary implications and is a concern in declining populations worldwide. We show that the dog is a useful and unique system for addressing and testing population genetic theory and understanding how phenotypic diversity is generated under domestication and in nature.

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1.2. Evolutionary History of the Dog, from Fossils to Complete Genomes

The domestic dog belongs to the family Canidae, a group of 35 extant species that share a very recent common ancestry approximately 10 Mya (**Supplemental Figure 1; follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org**). The domestic dog is assigned to a group of wolf-like canids that are members of the genus *Canis*. As confirmed by numerous independent genetic studies, the closest living relative of dogs are wolves, with no evidence of other canid species having contributed to the genetic legacy of the domestic dog (Fan et al. 2016, Thalmann et al. 2013, Vilà et al. 1997, vonHoldt et al. 2010). However, despite decades of phenotypic and genetic studies, the specific centers of origin are controversial. Complete genome sequence data, genome-wide single nucleotide polymorphism (SNP) studies, and mitochondrial genome sequence data from recent and ancient dogs and wolves, have suggested domestication in geographically disparate areas, ranging from east or central Asia, Siberia, the Middle East, and Europe (Shannon et al. 2015, Skoglund et al. 2015, Thalmann et al. 2013, vonHoldt et al. 2010, Wang et al. 2016).

Nonetheless, certain generalizations have emerged from these studies. First, dogs define a monophyletic group sister to the Old World wolves, and together the clade comprised of these dogs and wolves are sister to gray wolves in the New World (**Supplemental Figure 2**). This finding suggests that no living wolf population is directly ancestral to modern dogs, and it implies that dogs are conspecific with wolves, as designating them a separate species would result in a paraphyletic group. Second, dogs are clearly the first domesticated species, having an origin more than 15 kya, with most studies now suggesting closer to 27 kya (Fan et al. 2016, Frantz et al. 2016, Freedman et al. 2014, Skoglund et al. 2015, Thalmann et al. 2013). This divergence time far predates the origin of other domestic species, which all began no earlier than approximately 10 kya, and suggests dogs were domesticated by hunter-gatherers rather than the first agriculturists. Consequently, the nature of selection and demographic contractions associated with domestication are distinct from other domestic species. Further, these studies support a two-bottleneck model of domestication, one associated with first domestication and the other with breed formation, each with distinct population changes and selective pressures (**Figure 1**). Third, ancient and modern lineages are apparent within dogs. Ancient lineages are more prevalent in Asia, whereas the European population appears to be populated by dogs derived from the Victorian age explosion of modern dogs breeds, which sampled a smaller subset of the ancient gene pool (Frantz et al. 2016, Shannon et al. 2015, vonHoldt et al. 2010). Virtually all living dog populations, including breed dogs and village and semiferal dog populations, show some evidence of admixture between modern and ancient dogs, with some ancient populations, such as those that formerly occupied Europe and the New World, having completely disappeared (Frantz et al. 2016, Larson & Fuller 2014, Larson et al. 2012, Leonard et al. 2002, Thalmann et al. 2013). These results imply dynamic turnover of dog populations and imply that some ancient populations were entirely replaced, whereas others were admixed to various degrees across the long history of dog domestication. Fourth, admixture between geographically proximate wolf and dog populations has taken place for nearly all lineages, with the possible exception of wolves in the New World and those on the Tibetan plateau (Fan et al. 2016, Freedman et al. 2014). Dog–wolf admixture likely occurred throughout this history of domestication, and the traces of admixture moved across the landscape, much as the evidence of Neanderthal ancestry is shared by humans across the Old World, although the actual admixture events were likely regionally localized (Meyer et al. 2012, Wall et al. 2013). Moreover, some dog populations may show evidence of very recent admixture with local wolves (Fan et al. 2016). Consequently, statistical analysis of domestication and selection can be confounded by differences

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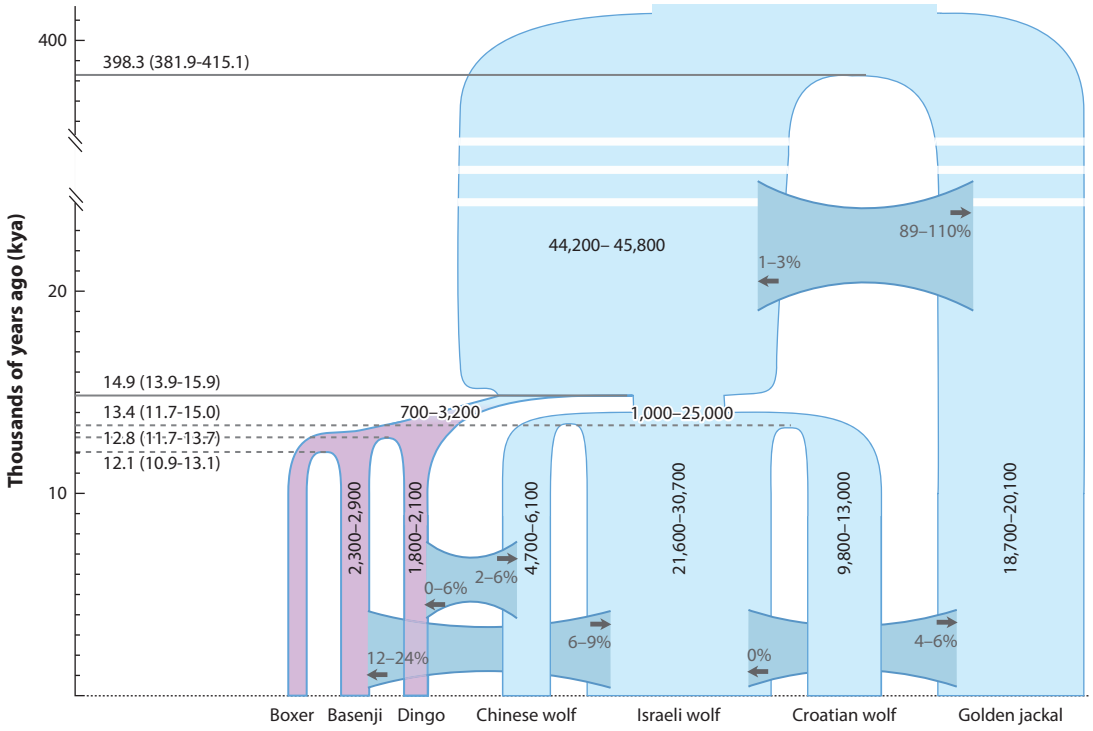

Figure 1

Demographic model for dog domestication inferred using the Generalized Phylogenetic Coalescent Sampler (G-PhoCS) on genome sequence data. The bar widths correspond to effective population sizes, and horizontal bars indicate admixture. Parameter ranges denote 95% credible intervals. Estimates were calibrated assuming 3 years per generation and an average mutation rate of 1 × 10–8 per site. Adapted from figure 5 of Freedman et al. (2014) with permission from *PLOS Genet*.

in demography and admixture history. Signals of domestication from specific wolf populations may actually represent admixture (e.g., vonHoldt et al. 2010), as suggested by Freedman et al. (2014).

1.3. Problems That Remain and Possible Solutions

The complex history of dog domestication suggests the need for joint consideration of demography, divergence time, and admixture with wolves and among various ancient and modern populations of dogs. Initial attempts to include specific models of admixture, divergence time, and population size suggested that admixture between dogs and wolves was a general phenomenon and that bottlenecks associated with domestication had been greatly underestimated by comparisons with modern gray wolves, as they experienced a worldwide bottleneck subsequent to the domestication of dogs (**Figure 1**) (Freedman et al. 2014, Lindblad-Toh et al. 2005). As a result, naive comparison of dog and wolf diversity would underestimate the strength of the domestication bottleneck. A more extensive analysis of complete genome sequence data from wolves and dogs worldwide further confirmed these findings and demonstrated the near universal patterns of wolf–dog admixture (Fan et al. 2016). Finally, the use of explicit demographic models based

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on these findings showed that scans for positive selection on the dog lineage that fail to explicitly incorporate demography will be enriched for false-positive signals (see Section 2.1) (Freedman et al. 2016). As a consequence of these concerns, an effort to completely characterize patterns of ancient and modern variation in dogs and wolves was initiated to directly study the temporal genetic changes over time using ancient DNA. These data will enable the construction of a more accurate demographic model of domestication (Grimm 2015), which will then allow a more precise quantification of neutral expectations for the diverse metrics employed in selection scans, improving our ability to distinguish genomic regions behaving in a non-neutral fashion. Initial efforts to analyze mitochondrial DNA sequences in ancient dog and wolf DNA have suggested a surprising origin of dogs in Europe from a now-extinct population of wolves (Thalmann et al. 2013), although recent genetic evidence suggests a dual origin in Europe and Asia is also feasible (Frantz et al. 2016).

1.4. Dog Domestication in the Context of Human Evolution

Both demographic history and the intensity and focus of selection are strongly influenced by the interactions of dogs and wolves with humans. In dogs, two phases of interaction can be inferred from demographic modeling (Fan et al. 2016, Freedman et al. 2014) (**Figure 1**). The first phase is defined by the early association of protodogs and humans and likely involved multiple sampling from diverse populations as suggested by high diversity in the major histocompatibility complex, mitochondrial DNA, and genome data (Fan et al. 2016, Freedman et al. 2014, Parker et al. 2004, Vilà et al. 2005, vonHoldt et al. 2011). One possible scenario is that some wolves began following hunter-gatherers to scavenge kills and take advantage of protein sources discarded in temporary camps. New evidence suggests that substantial mammoth remains beginning up to 45 kya were available to large carnivore scavengers as humans could transport only a limited portion of large prey (Pitulko et al. 2016; Shipman 2015a,b). In fact, village and semiferal dogs (the vast majority of dogs today) exist in such loose associations with humans and scavenge on refuse and even human feces. As humans became more sedentary with the advent of agriculture approximately 10 kya, dogs had to adjust to more confined conditions with livestock, resulting in more intense selection for smaller dogs and selection for a greater variety of functions appropriate for work and livestock management.

A second, more dramatic, demographic change occurred with the advent of modern breeding practices and strong trait-based selection during the Victorian era. Selection for dogs with specific, often pathologic phenotypes, followed by line breeding, sequestered genetic variation into discrete breeds. Subsequently, breeding was tightly controlled through focus on pedigree dogs adhering to breed standards. In modern breeds, champions that best approach breed standards are favored by breeders, resulting in a popular sire effect whereby the effective population size of breeds is greatly reduced by the limited pool of popular breeding males. The focus on discrete mutants of large effect in the formation of modern breeds (Darwin called them "sports") is predicted to lead to a simpler genetic basis of breed-defining traits and more intense signals of selection at the molecular level. Likewise, given the small effective population size of many modern dogs breeds, selection should be less efficient and deleterious variation should accumulate. In fact, inbreeding and small effective population sizes have been suggested as major causes of the breed-specific patterns of genetic disease in dogs (Karlsson & Lindblad-Toh 2008). These considerations suggest dogs are a model for understanding the genomic effects of intense selection in small populations. In the following sections, we characterize the effects of selection and drift on the dog genome in light of the inferred evolutionary framework for domestic dogs.

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2. THE GENETICS OF PHENOTYPIC DIVERSIFICATION IN THE DOG

2.1. Positive Selection Early in Dog History

Two primary molecular approaches have been used to identify genes under selection, namely, SNP genotyping arrays (mentioned above) and low or moderate coverage of complete genome sequences (Axelsson et al. 2013; Freedman et al. 2016; vonHoldt et al. 2010; Wang et al. 2013, 2016). The underlying principle for these efforts is that intense selection for a phenotypic trait causes a selective sweep at the locus underlying the trait, which decreases heterozygosity near the selected locus and increases the divergence between populations for variants causing or associated with the selected locus (e.g., **Figure 2**). A general criticism of GWSS studies is that the identification of regions under selection is sensitive to the lineages assayed and the methods employed, such that there is little overlap between studies (Schlamp et al. 2016, Teshima et al. 2006). Consistent with this criticism, a meta-analysis of four studies suggests only approximately 10–20% of the candidate genes are common to studies comparing dogs and gray wolves (**Figure 3**) (Freedman et al. 2016). Even so, it is notable that many of these genes concern lipid or starch metabolism, immunity, behavior, brain function, and pigmentation. These findings are consistent with what is known about the history of humans and domestic dogs. For example, with the development of agriculture, metabolic mechanisms to digest increasing proportions of starch from crops were under selection. As a result, in both dogs and humans amylase copy number increased, presumably to assist in the breakdown of starch, which takes place in saliva for humans (Meisler & Ting 1993) and in the pancreas for dogs (Simpson et al. 1984). In dogs, the copy number varies from 2 to 23, and in only the few breeds with a predominantly meat diet (dingo, Huskies) do low copy numbers persist (Axelsson et al. 2013, Freedman et al. 2014). However, as the origin of dogs predated

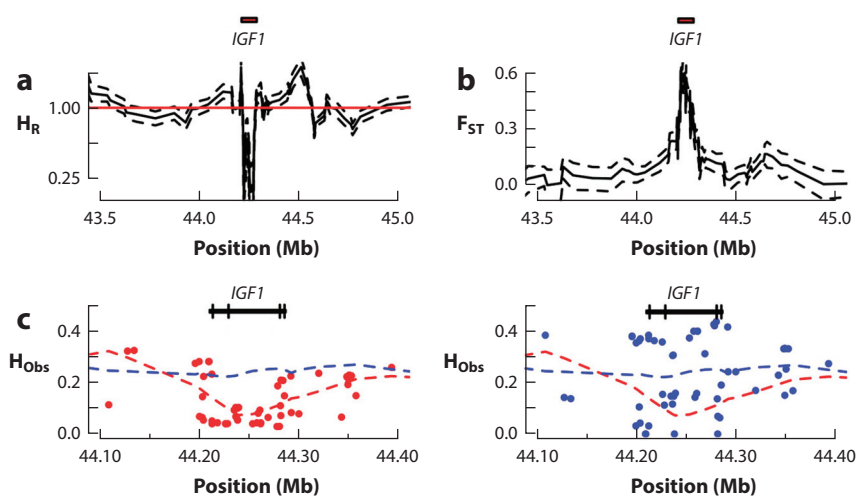

Figure 2

Signatures of selective sweeps surrounding the interleukin growth factor 1 (*IGF1*) gene in dogs. (*a*) Ratio of heterozygosity (H_R) in small dogs relative to giant dogs. Note that this ratio drops surrounding *IGF1*. (*b*) Allele frequency differentiation (F_{ST}) between small and giant dogs. (*c*) Observed heterozygosity (H_{Obs}) in small breeds (*red*) and giant breeds (*blue*). Dashed lines denote the lowess fit to the data. Data have been displayed in two panels to better visualize the differences in distribution for the small and giant breeds. Note the reduction in heterozygosity surrounding *IGF1* in small dogs but not large dogs. Adapted from figure 2 of Sutter et al. (2007) with permission from *Science*.

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Region	This study				CanMap Data			Other studies				Genes
	Δπ	F_{ST}	ΔTD	CMS	Δπ	F_{ST}	Joint	1	2	3	4	
18:15.49–15.78	4.03	0.63	1.74	0.97	0.76	0.7	99.25	94.8				*LHFPL3*
18:0.57–1.02	4.36	0.67	1.62	0.97							28	
19:3.55–3.72	3.16	0.51	2.09	0.93	0.58	0.83	99.22	93.1				*CCRN4L*
31:1.95–2.14	2.9	0.65	2.17	0.92	0.54	0.4	94.22					*CADM2*
12:59.02–59.17	3.93	0.64	1.32	0.92	−1.06	0.01	0.57					*RPL3*, *ACA64*
10:4.04–4.22	2.42	0.53	2.21	0.9	0.3	0.61	96.02				18	*SNORA31*
11:37.55–37.76	3.18	0.69	1.62	0.89	0.03	0.47	79.33					*SH3GL2*
24:4.37–4.59	2.17	0.59	1.91	0.89	0.12	0.12	48.36					*DTD1*
24:23.25–23.48	8.91	0.69	1.4	0.89					0.7	0.64		*ASIP*, *AHCY*, unknown
2:21.9–22.16	1.87	0.93	2.14	0.88	0.18	0.19	68.71					*FAM107B*
32:0.64–0.78	4.09	0.43	2.66	0.88								*ART3*, *NUP54*, unknown, *SCARB2*
13:46.85–47.02	3.54	0.42	2	0.87	0.19	0.54	92.4	92.5				
13:53.99–54.13	3.71	0.43	1.65	0.87	0.05	0.3	75.43					Unknown
1:2.93–3.19	2.75	0.75	2.13	0.86	−0.04	0.13	40.36				1	*MBP*, *ZNF236*
1:28.36–28.52	2.83	0.6	1.52	0.85	0.1	0.51	87.23	93.3				*PDE7B*
2:46.35–46.53	3.19	0.43	2.4	0.85	−1.39	0.34	3.67					
6:28.39–28.49	2.1	0.45	1.79	0.83	0.24	0.52	93.8					Unknown, *PDXDC1*, *NTAN1*, *RRN3*
4:57.36–57.48	2.49	0.45	1.87	0.82	0.16	0.62	91.71					*GLRA1*
37:16.14–16.27	1.9	0.46	2.5	0.82	0.47	0.67	98.18	91.5				*PLEKHM3*
4:60.02–60.27	3.71	0.6	1.01	0.81	−0.14	0.52	54.44					
15:9.83–9.93	3.48	0.47	1.12	0.81	−0.36	0.4	31.01					*EPS15*, *TTC39A*
8:71.21–71.31	3.11	0.4	1.79	0.8								*MARK3*, *U2*, *CKB*, *TRMT61A*, *BAG5*, *APOPT1*
4:61.87–62.1	4.16	0.43	1.89	0.8	0.04	0.21	64.58					Unknown
16:39.84–39.99	3.44	0.39	2.15	0.8	−0.11	0.07	19.51					
4:4.17–4.34	2.54	0.42	2.04	0.8	−1.29	0.06	1.34					*LYST*, unknown, *GNG4*

Figure 3

Meta-analysis of dog selection scans. The 25 most extreme outlier regions were identified in a recent study using a demographic model to simulate neutral expectations for selection scan statistics and control for the false discovery rate (FDR) (Freedman et al. 2016). Overlaps with outlier regions detected in previous studies were also identified (1, vonHoldt et al. 2010; 2, Vaysse et al. 2011; 3, Boyko et al. 2010; and 4, Axelsson et al. 2013). Δπ is the ratio of wolf-to-dog nucleotide diversity, and ΔTD is the difference in Tajima's D between wolves and dogs. The composite of multiple signals FDR (CMS_{1-FDR}, labeled CMS in figure), is the product of 1-FDR for each of the three statistics used to analyze 100-kb sliding windows across the genome. CanMap data are from single nucleotide polymorphism array data for ancient breeds (see vonHoldt et al. 2010). Joint is the joint empirical percentile of allele frequency differentiation (F_{ST}) and Δπ. Warmer heat map colors indicate regions with stronger evidence for selection.

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agriculture by at least 10,000 years, selection on starch metabolism must have occurred subsequent to the initial divergence between dogs and wolves. In contrast, in a recent study, one of the strongest signals of selection between dogs and wolves is centered on *CCRN4L* (i.e., nocturnin), a gene that mediates lipid metabolism through its interaction with PPAR-ϒ (Freedman et al. 2016). Selection on this candidate gene is consistent with shifting lipid content in the diet as protodogs increasingly fed at hunter-gatherer kill sites.

Similarly, the behavior of dogs has been highly modified from gray wolves and has affected docility and the canine comprehension of human facial expressions and actions (Müller et al. 2015). Thus and perhaps unsurprisingly, all selection scans to date that have contrasted wolves and dogs have found evidence for selection on neurobehavioral candidate genes (Axelsson et al. 2013; Freedman et al. 2016; vonHoldt et al. 2010; Wang et al. 2013, 2016). For example, *MBP*, a gene linked to schizophrenia and responsible for myelin sheath formation, and *SH3GL2*, a gene involved in synaptic vesicle formation, were found in regions experiencing positive selection in dogs (Axelsson et al. 2013, Freedman et al. 2016).

Despite the intriguing findings from GWSS studies of dogs, the approach is fraught with uncertainty. First, the statistical methods used to identify sweeps must assume certain evolutionary model. Specifically, these methods often assume the hard sweep model in which changes in diversity have resulted from new, adaptive mutations that occur on one haplotype (Smith & Haigh 1974). Although debate continues, a number of recent theoretical and empirical investigations suggest that selection on standing variation, in which a selected allele is present on multiple haplotypes, is more prevalent in natural populations than previously supposed (Messer & Petrov 2013a). The more haplotypes an adaptive allele is found on, the lower the power of methods designed to detect hard sweeps. Although dogs are often regarded as ancient because their origins predate agriculture, in reality the effective number of dog generations since domestication is relatively small, meaning that dog–wolf phenotypic divergence may not be dominated by new mutations resulting in hard sweeps. To the extent that this is true, previous studies may have missed regions containing functionally important variants simply because they occurred across a diversity of haplotypes.

A second problem is that demographic fluctuations, particularly bottlenecks such as those experienced by dogs during domestication, can skew the site-frequency spectrum and the distribution of haplotype lengths in ways that mimic positive selection (Barton 1998, 2000; Crisci et al. 2013). Similarly, population subdivision can also produce signals that are hard to distinguish from selection (Santiago & Caballero 2005, Slatkin & Wiehe 1998). As a result, studies that fail to explicitly incorporate demography in generating neutral expectations are prone to false-positive signals (Crisci et al. 2013, Jensen et al. 2005, Thornton & Jensen 2007). To date, all but one of the GWSS studies on dogs have not incorporated a demographic model and instead have used an empirical outlier approach, whereby some arbitrary percentile cutoff for the regions containing the strongest signals is used to classify regions as putatively experiencing positive selection. In contrast, Freedman et al. (2016) used a previously inferred, robust demographic model (**Figure 1**) (Freedman et al. 2014). This model was used to perform coalescent simulations that generated distributions of selection scan statistics under neutrality, from which false discovery rates could be calculated for individual windows of the genome. These rates were then combined across statistics to rank genomic regions. This study compared the regions identified using the demographic model with those identified using an empirical outlier approach and found limited overlap at the level of both candidate regions and genes. The top regions in the demography-grounded analysis produced a gene list containing previously unreported candidate genes in dogs related to brain function and behavior, as well as lipid metabolism. The latter might be predicted as necessary early in dog domestication before the advent of agriculture when dogs were likely

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scavenging on the carcasses of ungulates killed by humans, who stripped the most protein-rich portions and left behind those more rich in lipids.

A third concern is that the tangible results of previous GWSS efforts are long lists of candidate genes. These lists include plausible genes presumably related to the phenotype of interest (from which authors attempt to weave just-so stories about function) and genes of unknown function or a function that is not directly linked to the phenotype. The latter may include a diversity of potentially critical genes such as transcription factors that actually contain the causal variants that influence gene expression underlying the phenotypes. A solution to these difficulties is functional confirmation. In one such study, researchers demonstrated that an increased copy number of the amylase gene resulted in higher levels of expression and greater efficiency in starch digestion (Axelsson et al. 2013). However, such functional studies are expensive and time consuming and may be difficult or impossible to perform for other genes that have multiple functions across many organs and for which gene expression differences are not evident. For such genes, function can potentially be explored in cell lines through genetic manipulations such as CRISPR/Cas9. An alternative first step toward functional confirmation may involve resequencing of candidate genes in a larger sample to determine if there are coding or regulatory variants that differ between dogs and wolves, or among dog breeds, within these genes. For example, Schweizer et al. (2016) used a capture array approach containing baits for >1,000 candidate genes to assess the proportion that contained potentially functional variants that were divergent in allele frequencies among gray wolf populations or correlated with environmental gradients. These researchers found that approximately 30–50% of genes contained potentially functional variants significantly divergent among wolf populations and found underlying changes in coding or regulatory regions at an approximately equal frequency. These results support the candidate gene approach that identifies genetically swept regions by genome-wide SNP surveys if further supported by resequencing of specific candidate genes.

2.2. Phenotype Mapping in Breeds: Genome-Wide Association Studies, Linkage, and Selective Sweep Mapping

Understanding the genetic underpinning of phenotypic traits has long been a primary goal for understanding adaptation and the action of natural selection. Classical genetic analyses in dogs, using pedigrees in which specific traits are segregating, have succeeded in identifying some genes that cause genetic disease and discrete phenotypic traits, such as coat color variation (Ostrander & Kruglyak 2000). However, the genetic architecture of complex traits such as body size and conformation had been elusive until the development of SNP genotyping arrays that allowed genome-wide surveys and the association of SNPs with discrete and quantitative traits (Davis & Ostrander 2014, Rimbault & Ostrander 2012). Uncovering the underlying genetics of such traits is essential for understanding how dogs have diversified so rapidly into a varied array of phenotypes. The first SNP genotype arrays sampled approximately 60,000 informative polymorphisms across the genome and were used to detect genes for body size, skull shape, leg length, fur type, and coloration and the genes influencing specific disease disorders (e.g., Schoenebeck & Ostrander 2014). A conclusion emerging from these studies is that much of the phenotypic diversity in dogs owes its origin to dog-specific variants not found in wolves (e.g., Gray et al. 2009, Ramirez et al. 2014) and that often much of the variation in a specific trait is due to variation in a few genes (Boyko et al. 2010, Hayward et al. 2016). For example, with regard to body size, >70% of variation across breeds in morphological traits can be explained by fewer than 10 quantitative trait loci (Boyko et al. 2010, Hayward et al. 2016, Rimbault & Ostrander 2012). In contrast, in humans,

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697 variants in 432 loci explain only approximately 20% of variation in human height (Wood et al. 2014). Other classic examples of the simplified architecture of breed traits include a variant in the 3′UTR of *RSPO2*, an amino acid–changing mutation in *FGF5*, and an amino acid–changing mutation in *KRT71* responsible for variation among breeds in furnishings (elongated eyebrows and moustaches), hair length, and coat curling, respectively (Cadieu et al. 2009). Similarly, this architecture contrasts with most studies in other species in which quantitative traits have been found to be generally influenced by many genes of minor effect with few explaining more than a few percent of the genetic variance in the trait. Dogs are unique in this regard, which likely reflects the unique mode of historical selection that was aimed at fixing discrete variants that appeared in a litter through line breeding, often involving breeding a specific variant with littermates. Such line breeding programs may be augmented by progressive selection that enhances the variant through the accumulation of modifier genes. An example is the evolution of the bulldog's abbreviated rostrum, which became increasing foreshortened after the founding of the breed beginning in the early twentieth century (Thomson 1996).

In contrast to the simplified architecture found in traits that were under strong artificial selection during breed formation, such mutations of large effect are unlikely to have been preserved in the wild, given probable detrimental effects. Some phenotypes found in dogs are observed in wild canine populations, such as foreshortened chondrodysplastic limbs similar to those of dachshunds; however, this phenotype is unlikely to increase in the wild given its extreme effect on locomotion. Consequently, the genetic changes defining breed phenotypes are not good models for those under selection in nature and include a wide variety of mutations, from retrotransposed growth factors in breeds with foreshortened limbs, to coding and promoter changes, to short interspersed nuclear elements (SINE) insertions (reviewed in Wayne & vonHoldt 2012). Finally, in many cases, because linkage disequilibrium is so substantial in dog breeds (average of 100–200 kb in dog breeds; e.g., Sutter et al. 2004), association studies often can only narrow the region associated with a trait to a large genomic span, and without studies of pedigrees in which the trait is segregating, specific variants or genes cannot be directly connected to traits (e.g., Sutter et al. 2007). In this regard, studies that use both across-breed GWAS and selection mapping may have more power. For example, Sutter et al. (2007) used GWAS of both small and large breeds as well as selection and recombination mapping to narrow the genomic interval associated with small body size. Similarly, Boyko et al. (2010) identified a simple genetic basis for skeletal differences, body size, and tail curl among breeds using both approaches (also see Hayward et al. 2016). Finally, Vaysse et al. (2011) examined both morphological and behavioral traits and found that eight of nine regions with more than three high-F_{ST} (allele frequency differentiation) SNPs also overlapped with GWAS hits.

This more complex, and polygenic, genetic architecture of dog–wolf phenotypic divergence relative to breed diversification raises intriguing questions concerning the underlying evolutionary process. Whereas coding mutations are frequently responsible for breed traits, the only GWSS study controlling for demographic effects found few dog-fixed mutations (relative to the wolf ancestral state) in coding regions and found them only in regions ranked lower in the list of selection signals (Freedman et al. 2016). This finding suggests that regulatory mutations may have played a crucial role in the evolution of dog-specific traits, consistent with the hypothesis of King & Wilson (1975) that such regulatory tinkering can generate substantial phenotypic divergence among natural populations with minimal neutral genetic divergence.

2.3. Evolutionary Mechanisms of Phenotypic Diversification of the Dog

Analysis of microsatellite loci (Parker et al. 2004) and 42,000 SNPs on the canine genotype array suggests a distinct hierarchy of association of dog breeds into six to nine distinct groups

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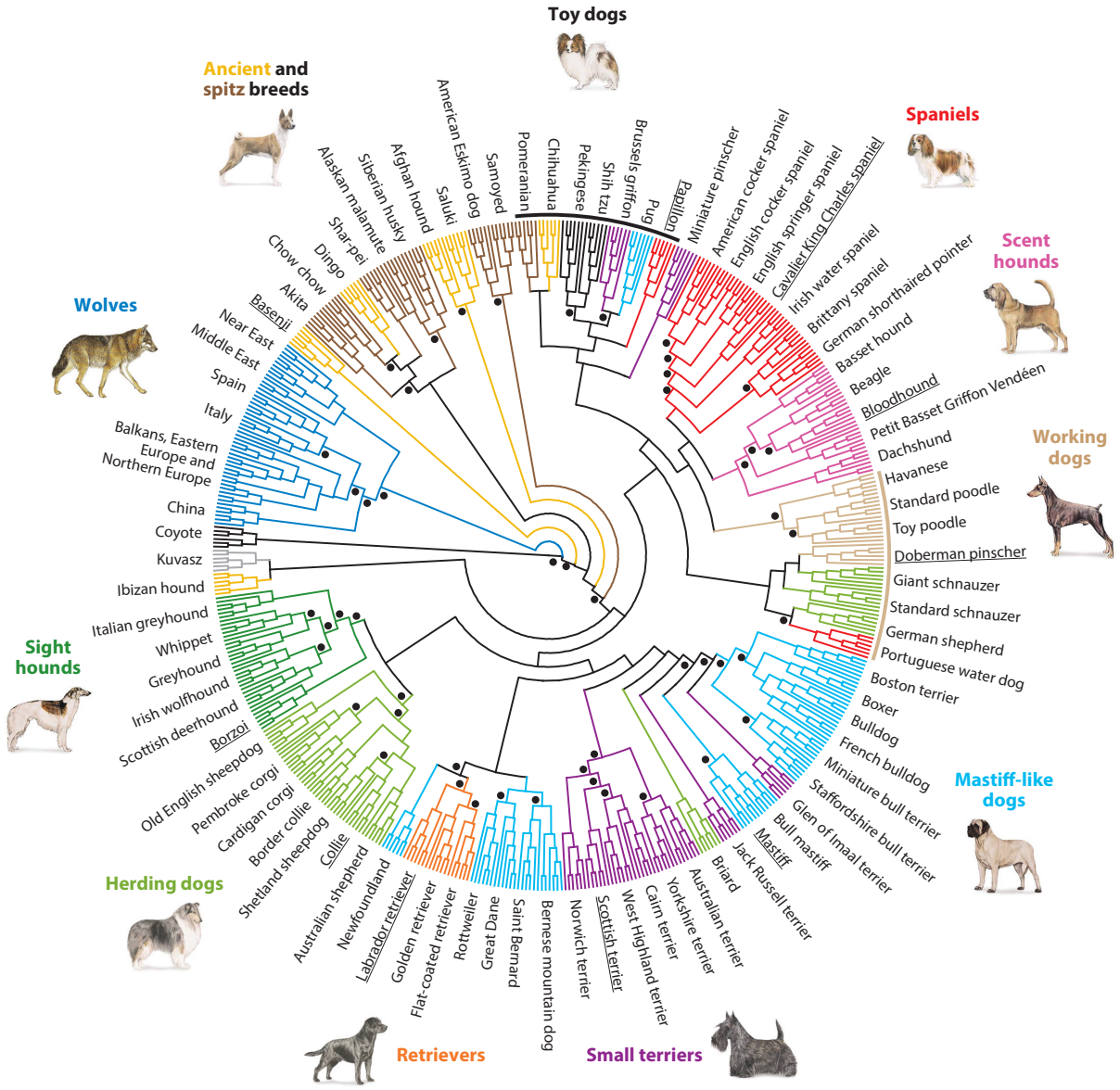

Figure 4

Haplotype-sharing cladogram of dogs and the breeds they belong to on the basis of 42,000 single nucleotide polymorphisms from vonHoldt et al. (2010). Images of the underlined breeds are shown, and the colors correspond to the different phenotypic/functional breed groupings. Figure adapted from vonHoldt et al. (2010), with permission from *Nature*.

(**Figure 4**). The most divergent group comprises ancient and spitz breeds and includes some Far North, Chinese, and Middle Eastern breeds. An unexpected result of this study was that the remaining breeds are grouped according to functional or phenotypic classifications, such as scent and sight hounds or working breeds. There is no a priori reason to believe that functional classification by breeders should correspond to genetic similarity, as traits defining these groups

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(such as retrieving or olfactory acuity) would be expected to occur independently on a wide variety of genetic backgrounds in different areas of the world. In contrast, toy breeds do fulfill this expectation, as each toy breed derives from a different breed lineage. We suggest that these patterns reflect two distinction evolutionary mechanisms for phenotype change in the domestic dog. First, for the majority of recent breed groupings, selection for new breeds of a given functional or phenotypic type utilizes preexisting breeds with that classification in the founding of a new breed. Hence, genetic similarity and function and phenotypic classification are conserved. Second, toy breeds derive from dwarfing mutations that likely appeared in discrete lines and were transferred across breed groupings by interbreeding. Consequently, a single dwarfing mutation can be placed on distinct phenotypic and genetic backgrounds by admixture, providing the appearance of a novel phenotype. In reality, the underlying mutation may be the same. An example is the foreshortened limbs (chondrodysplasia) of many breeds (e.g., dachshund, basset hound, corgi). Association studies showed that all 19 breeds with this phenotype share the same underlying expressed retrotransposed growth factor (Parker et al. 2009). Many such discrete mutations, for coat color, pattern and texture, skull shape, and behavior, may have been moved into a variety of discrete breed grouping through such a process (vonHoldt et al. 2010). Genetic studies suggest that a small number of discrete mutations, transferred to a wide diversity of breed groups, may explain the dramatic diversity in the domestic dog (Boyko et al. 2010, Hayward et al. 2016, vonHoldt et al. 2010). The genetic toolkit of diversification in the dog may be very small relative to other domestic species, but it has been effectively exploited to create a wealth of phenotypic diversity though divergence and admixture.

2.4. Domestic Dog Coat Color Genes Transform North American Wolf Populations

In mammals, pigment variation is most often controlled by the *Agouti/Melanocortin 1 receptor* (*Mc1r*) pathway (Barsh 1996, Hoekstra et al. 2006, Protas & Patel 2008, Steiner et al. 2007), a ligand-receptor pair that modulates the amount and type of pigment produced. However, melanism in many dog breeds is caused by a mutation in a β-defensin gene, *CBD103* (the *K* locus), which encodes an alternative ligand for *Mc1r* (Anderson et al. 2009, Candille et al. 2007). The *CBD103* ΔG (K^B) allele contains a 3-bp deletion that confers a dominantly inherited black coat color phenotype, as opposed to the wild-type *CBD103*$^+$ (K^Y) allele that confers a gray color in homozygotes. Unique to North American gray wolves is a black coat color cline in the K^B allele from southern forest populations with equal proportions of black and gray wolves to northern, more open taiga/tundra populations in which black wolves are rare (Anderson et al. 2009).

Genetic characterization of black wolves in North America demonstrated that they generally carry the K^B allele, and analysis of the genetic history of the allele and flanking regions supports the hypothesis that it derives from historic breeding between dogs (when it originated) and gray wolves. Flanking regions clearly show evidence of positive selection in black wolves (Anderson et al. 2009). The interbreeding event likely occurred between Native American dogs and gray wolves after humans arrived to the New World approximately 13 kya (Anderson et al. 2009, Leonard et al. 2002). Surprising, observational studies show that individuals heterozygous for the black allele have higher survivorship during their lifetime and enhanced resistance against disease. In contrast, homozygote black wolves are extremely rare and likely have vastly reduced fitness. Consequently, a single copy of the K^B allele seems advantageous, whereas two copies are detrimental. Evidence from the Yellowstone population further suggests disassortative mating (Hedrick et al. 2014, 2016), which may reflect the higher survivorship of black heterozygotes (Coulson et al. 2011). One possibility is that, as a β-defensin gene, the K^B allele improves disease resistance of heterozygotes where domestic dogs act as a reservoir of these diseases. In this sense,

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the presence of dogs may be a prerequisite for maintenance of the polymorphism and black coat color. Supporting this speculation is the finding that wolf populations lacking the dog reservoir of disease in the High Arctic consist of nearly all gray wolves without the K^B allele (Anderson et al. 2009, Schweizer et al. 2016).

The unique transfer by admixture and rapid spread throughout the North American continent of the K^B allele provides a first example of a genetic variant that appeared under domestication that has then transformed the genetic legacy of a progenitor. Remarkably, the transfer of the black mutation from dogs occurs elsewhere, even between dogs and coyotes, and in Italy between domestic dogs and wolves (Anderson et al. 2009, Caniglia et al. 2013). This recent transfer of the black gene from dogs to wolves there has led for a movement to control black wolves as non-native hybrids. However, some gray wolves may be equally admixed with dogs but just missing the black mutation. This situation begs the question of what to do about foreign genes in protected species caused by admixture that may, nonetheless, enhance fitness (see discussion in Wayne & Shaffer 2016).

3. DELETERIOUS VARIATION

3.1. The Nature of Deleterious Variation

Evidence for the widespread nature of deleterious mutations comes from mutation accumulation experiments (Halligan & Keightley 2009), experimental evolution studies (Hietpas et al. 2011), and analyses of genetic variation in natural populations (Boyko et al. 2008, Eyre-Walker et al. 2006). Population surveys of genetic variation have shown a decrease in nonsynonymous polymorphism relative to synonymous polymorphism, as well as a skew toward rare variants at nonsynonymous SNPs (Boyko et al. 2008, Eyre-Walker et al. 2006, Keightley & Eyre-Walker 2007, Nelson et al. 2012, Tennessen et al. 2012), suggesting that purifying selection has kept nonsynonymous mutations at low frequency. Model-based approaches leverage the distribution of allele frequencies and allow quantification of selection coefficients for new deleterious mutations. Studies in humans (Boyko et al. 2008, Eyre-Walker et al. 2006), mice (Halligan et al. 2013), *Drosophila* (Keightley & Eyre-Walker 2007), gorilla (McManus et al. 2015), and orangutans (Ma et al. 2013) suggest that nonsynonymous mutations can have a distribution of effects on fitness. For example, in humans, 27–29% of nonsynonymous mutations are nearly neutral, each decreasing fitness <0.01% (Boyko et al. 2008). However, humans also have a large proportion (35%) of strongly deleterious mutations [selection coefficient (s) > 1%], with the remainder of mutations inferred to be moderately deleterious ($0.01\% < s < 1\%$).

The large proportion of mutations that have only weakly or moderately deleterious effects on fitness suggests that many deleterious mutations may not be quickly eliminated from the population by natural selection. Rather, the nearly neutral theory of molecular evolution predicts that mutations having a selection coefficient $<1/2N$, where N is the effective population size, will behave as though they were neutral and consequently accumulate in small populations owing to genetic drift (Akashi et al. 2012, Ohta 1976). That is, the extent to which populations accumulate deleterious mutations could depend, in part, on the demographic history of the populations. Domesticated species offer a unique opportunity to study how demography and selection affect patterns of deleterious variation.

3.2. Domestication and Deleterious Variation

The domestication process can affect deleterious variation in at least four ways. First, population bottlenecks associated with domestication can potentially allow deleterious variants to increase

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in frequency by genetic drift (**Supplemental Figure 3*a***). Second, domestication is often accompanied by inbreeding, which increases the frequency at which deleterious alleles are found in the homozygous genotype suspected to be linked to inbreeding depression (Charlesworth & Charlesworth 1987). Third, domesticated species experience a shift in the environment owing to living concomitantly with humans. This environmental shift could result in a change to the selection coefficient (s), which could allow nonsynonymous mutations to increase in frequency as they are less deleterious in the new environment (**Supplemental Figure 3*b***) (Björnerfeldt et al. 2006, Cruz et al. 2008). Fourth, domestication is often accompanied by strong artificial selection for desirable traits, perhaps traits previously deleterious in the ancestral environment. This selection can result in the hitchhiking of nearby deleterious variants with the positively selected allele (Lu et al. 2006). Below, we discuss recent work on several of these processes as they relate to domestic dogs.

3.3. Demographic Effects of Dog Domestication on Deleterious Variation

The bottleneck that occurred during dog domestication is expected to shape patterns of deleterious variation across the dog genome. Weakly deleterious mutations that are efficiently selected in larger wolf populations could, in principle, drift up in frequency during the bottleneck as has been observed in bottlenecked human populations (Fu et al. 2014, Henn et al. 2016). The earliest study of deleterious variation across the dog genome documented an elevated nonsynonymous-to-synonymous polymorphism ratio in dogs relative to wolves using mitochondrial DNA (Björnerfeldt et al. 2006). The ratio of nonsynonymous-to-synonymous SNPs provides a benchmark as to the extent upon which nonsynonymous mutations are removed from the population by purifying selection population (Elyashiv et al. 2010, Fay et al. 2001, Lohmueller et al. 2008, Piganeau & Eyre-Walker 2009). A lower ratio indicates that more of the nonsynonymous mutations have been removed from the population by purifying selection. Thus, finding a higher nonsynonymous-to-synonymous ratio in dogs relative to wolves suggests that there are too many weakly deleterious mutations in dogs compared with the expected ratio, based on the reduction in neutral diversity in dogs relative to wolves. There are two mechanisms that could account for an elevated nonsynonymous-to-synonymous ratio in dogs compared with wolves (**Supplemental Figure 3**). Björnerfeldt et al. (2006) interpreted their findings to suggest a decrease in selective pressure (i.e., s became more neutral) in dogs relative to wolves as a result of the environmental shift. However, it is not clear whether bottlenecks could also generate this pattern or if this increase in nonsynonymous variation would hold across the autosomal genome. More recently, Cruz et al. (2008) extended this work through a comparative sequence analysis derived from wolves, dogs, and cats. They found that dog sequences had elevated nonsynonymous-to-synonymous ratios relative to that seen in wolves and cats. However, although this result shows an excess of nonsynonymous variants in dogs relative to the expected ratio based on the reduction in neutral diversity in dogs relative to wolves, it does not quantify, on an absolute scale, the change in the burden of deleterious variation associated with domestication.

Recently, Marsden et al. (2016) presented an analysis of deleterious variation using whole genome–sequencing data from purebred dogs, village dogs, and gray wolves. They confirmed the presence of an elevated proportion of nonsynonymous-to-synonymous variants in dogs compared with wolves (**Figure 5**). Importantly, Marsden et al. (2016) showed that this elevation was observed for dogs that originated from a variety of breeds, suggesting that this pattern is driven by evolutionary processes shared by all dogs, rather than those unique to certain breeds. As such, their results argue that an ancient domestication bottleneck, rather than recent bottlenecks that occurred during the formation of dog breeds, is driving this pattern. Their forward-in-time

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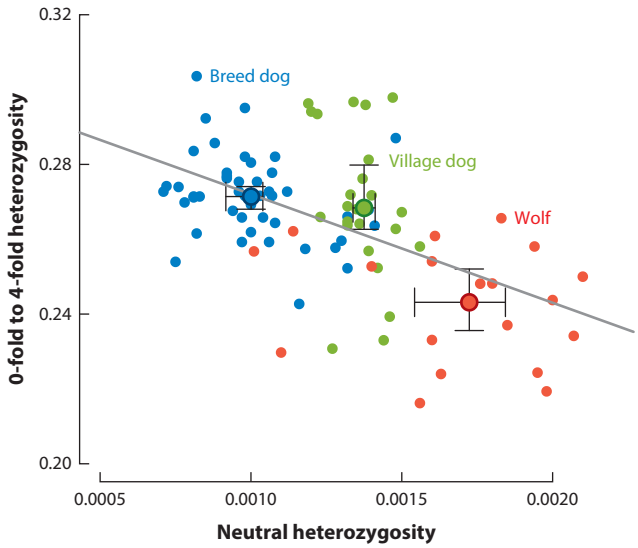

Figure 5

Ratio of 0-fold (amino acid–changing) to 4-fold (non-amino acid–changing) heterozygosity versus neutral heterozygosity in dogs and wolves. Each point represents a given genome. Breed dogs show lower neutral heterozygosity than wolves, consistent with their smaller population size. However, given this lower population size, they contain a disproportionate amount of 0-fold heterozygosity relative to wolves. The solid line denotes the best-fit linear regression. Large circles denote the trimmed medians, and error bars are the 95% confidence intervals. Adapted from figure 1 of Marsden et al. (2016) with permission from *PNAS*.

simulations showed that demographic models previously fit to genomic data accurately predict this proportional increase in nonsynonymous variation in dogs relative to wolves.

Marsden et al. (2016) also quantified the absolute numbers of putatively deleterious variants per individual. Unlike previous analyses, this type of comparison can provide an estimate of the genetic load of the population. The genetic load represents the reduction in fitness in a population due to deleterious variations compared with a hypothetical population at maximal mean fitness (Haldane 1937). Genetic load is a function of the strength of selection against deleterious mutations, the frequency of deleterious alleles, their dominance coefficients, and interactions among deleterious mutations; thus, it cannot be directly observed from genetic variation data. However, some useful approximate comparisons can be made, such as estimating the number of genotypes heterozygous or homozygous for deleterious alleles and the total number of derived deleterious alleles (Lohmueller 2014).

Marsden and colleagues used Genomic Evolutionary Rate Profiling (GERP) scores (Davydov et al. 2010) to identify deleterious variants within individual genomes. GERP scores provide a measure of evolutionary conservation across distantly related species. If a variant within a population occurs at a site that is conserved across distantly related species, it is inferred to be more deleterious than a variant occurring at a site that is less constrained across species. Thus, selection presumably frequently acts on this site to remove mutations from the population, as these mutations are likely to be deleterious. Using this approach, dogs have fewer heterozygous deleterious genotypes per individual but more homozygous deleterious genotypes relative to wolves (Marsden et al. 2016). If deleterious mutations are recessive, the increased count of homozygous deleterious genotypes in dogs compared with wolves would imply a greater genetic load in dogs, as the recessive deleterious genotypes will reduce fitness. Further, dogs have approximately 115

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more deleterious alleles per individual than wolves, corresponding to a 2.6% increase in additive genetic load. An alternate approach to quantify the additive genetic load involves summing the quantitative GERP scores for all sites within a genome carrying a deleterious allele (Schubert et al. 2014). Those mutations that are more likely to be strongly deleterious, as predicted by the extent of conservation across species, will contribute more to the load than those that have more neutral GERP scores. Using this approach to quantify genetic load, dogs have a 2.1% higher additive load than wolves (Marsden et al. 2016).

A final approach to quantify the burden of deleterious variants within a population is to use an explicit population genetic model. Here, researchers typically assume a particular demographic model for the species of interest as well as a distribution of selective and dominance effects (Fu et al. 2014; Gazave et al. 2013; Gravel 2016; Henn et al. 2015, 2016; Marsden et al. 2016). Forward-in-time simulations can provide the allele frequencies and selection and dominance coefficients of variants segregating in the simulated populations. From these metrics, researchers compute the genetic load from the precise population genetic definition (Kimura et al. 1963). However, this method is heavily dependent on the precise parameters of the population genetic models assumed. Marsden et al. (2016) applied this approach to quantify the genetic load in dogs and wolves. Forward-in-time simulations under the demographic and selective models described above indicate that these models of population history can lead to an elevation of the additive genetic load similar in magnitude to that seen empirically.

Interestingly, patterns of deleterious variation similar to those seen in dogs have been reported in other species, most notably humans. For example, non-African human populations show fewer heterozygous deleterious genotypes and more homozygous deleterious genotypes than African populations (Fu et al. 2014; Henn et al. 2015, 2016; Lohmueller 2014; Lohmueller et al. 2008), a pattern that becomes more apparent through surveys of populations that are increasingly distant from Africa. Estimates of the count of the number of derived deleterious alleles per genome, a proxy for additive genetic load, have been similar between African and non-African populations (Do et al. 2015, Simons et al. 2014) or slightly higher (1–2%) in non-African than African populations (Fu et al. 2014, Henn et al. 2016). The slight increase in the additive genetic load in both purebred dogs and bottlenecked human populations likely stems from the fact that both bottlenecks occurred relatively recently and were rather short, not allowing enough time for dramatic increases in the genetic load.

Longer periods of small population size, such as that estimated in Neanderthals (Castellano et al. 2014), led to a greater increase in the genetic load relative to human populations (Do et al. 2015). The increase in accumulation of deleterious mutations in the domestic dog also mirrors results from studies of other domesticated species. For example, domestic horses have a genetic load that is 1.5–11% higher than that seen in the ancient wild horse (Schubert et al. 2014).

3.4. The Effect of Bottlenecks Versus Inbreeding

Breed dogs contain long runs of homozygous segments that are presumably caused by inbreeding within the previous few generations. Indeed, inbreeding has been a central component of dog breeding practices since the Victorian era (Boyko et al. 2010, vonHoldt et al. 2010). How has inbreeding affected patterns of deleterious variation? Marsden et al. (2016) showed that the proportional increase in amino acid–changing variation in dogs relative to wolves is likely not driven by the effects of recent inbreeding. First, they repeated the estimation of the ratio of nonsynonymous-to-synonymous heterozygosity, removing the effects of recent inbreeding. Briefly, recent inbreeding results in the two chromosomes within an individual being more likely to share a recent common ancestor with each other than with a chromosome from a different individual. Thus, considering

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chromosomes from different individuals, in a manner analogous to Wright's F_{IS} statistic (Wright 1951), should remove this inbreeding effect. The proportional increase in nonsynonymous variation that persisted in this analysis suggests that inbreeding cannot solely explain the patterns. Second, forward-in-time simulations that include recent inbreeding, but not bottlenecks associated with domestication, could not explain the increase in the proportion of nonsynonymous SNPs in dogs relative to wolves (Marsden et al. 2016). Third, the increase in the proportion of nonsynonymous SNPs in dogs relative to wolves persisted even after removing sites residing within long runs of homozygosity.

In summary, it appears that recent inbreeding has had little impact on patterns of nonsynonymous variation within individual dog genomes. Instead, ancient bottlenecks that are presumably associated with domestication have had a significant and detectable effect. Importantly, these results concern the majority of the nonsynonymous mutations carried within an individual's genome, and each mutation is expected to have only a slight effect on reproductive fitness. Mutations with severe impacts on fitness and disease may display different patterns compared with those included in the Marsden et al. (2016) study. For example, inbreeding could still impact fitness if strongly deleterious recessive mutations are found in homozygous genotypes.

3.5. Selective Sweeps and Linked Deleterious Variation

As discussed above, artificial selection has led to selective sweeps across the dog genome. Both simulations (Chun & Fay 2011) and theory (Hartfield & Otto 2011) predict that selective sweeps can increase the amount of linked deleterious variation within the sweep regions (**Supplemental Figure 4*a***). Consistent with this prediction, Marsden et al. (2016) found that the ratio of nonsynonymous-to-synonymous SNPs was significantly higher in regions of the genome near selective sweeps associated with domestication than other regions of the genome (**Supplemental Figure 4*b***). Further, the total number of derived nonsynonymous alleles per base pair was significantly (1.26-fold) higher surrounding the sweeps compared with the genomic background (**Supplemental Figure 4*c***). However, as only a small percentage of the total amount of coding sequence is found near a swept region, this mechanism is not the predominant factor increasing the amount of deleterious genetic variation across the dog genome.

Artificial selection may be associated with an increase in disease variants in dogs. Marsden et al. (2016) reported greater overlap between genes implicated in human Mendelian diseases and genes located within selective sweeps associated with dog breed formation than expected by chance (**Supplemental Figure 5**). One mechanism that could generate this enrichment is that Mendelian disease genes are a subset of genes that to lead to severe phenotypic effects when mutated. Consequently, dog breeders often unknowingly target mutations of large effect during selective breeding practices. Thus, this overlap between disease and sweep genes could imply that both artificial selection in dogs and Mendelian diseases target the same functional class of genes that yield large phenotypic effects when mutated.

4. CONCLUSIONS AND FUTURE DIRECTIONS

4.1. Identifying Loci Under Selection Early in Dog History

Just as the out-of-Africa human population bottleneck has affected genetic variation (Nielsen et al. 2009), the severe bottleneck associated with early dog domestication has left signatures in neutrally evolving regions of the dog genome that may resemble those generated by positive selection. Studies that do not take this demographic event into consideration will be enriched with

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false-positive signals for selection in the genome. Conversely, the well-documented historical and ongoing gene flow between dogs and wolves (Fan et al. 2016, Freedman et al. 2014) may have partly obscured signals of selective sweeps in both species. Thus, GWSS studies of selection need to explicitly incorporate a robust demographic model in generating neutral expectations for the statistics used to identify putatively swept genomic regions. However, this goal faces a number of challenges. First, applying such demographic models to hundreds (or even thousands) of genome sequences will push the limit of our current computational capacity, particularly when evaluating alternative models under diverse scenarios of admixture and effective population. Collaboration between statistical geneticists and computer scientists will be essential to engineer computationally tractable frameworks for demographic inference and hypothesis testing. Second, we continue to know little about the relative contributions of soft versus hard sweeps during domestication and the variation in the strength of selection across the dog genome. Accurate measurement of these factors should be an important goal, as should be quantifying the impact of other evolutionary processes that shape neutral variation and can impact GWSS studies, such as background selection (Charlesworth 2012, Messer & Petrov 2013b). Third, under neutrality the distribution of haplotype lengths are governed by both demography and recombination, and our maps of the latter in dogs remain coarse.

4.2. Functional Validation, Epigenetics, and Regulatory Variation

As sample sizes and marker densities increase for domestic dogs and wolves (see **http:www.dog10kgenomes.org**), both selection scans and association mapping studies will continue to discover novel candidate genes of potential importance to trait evolution. Consequently, it is imperative to winnow true from false-positive signals in the resulting gene lists. Although practical and ethical concerns constrain functional validation through *in vivo* experiments, a rapidly expanding set of methods for quantifying diverse genomic features will provide greater insight into the genetic architecture of phenotypic traits, especially with respect to candidate genes and regulatory elements. For example, Janowitz Koch and colleagues (2016) performed differential DNA methylation analysis between gray wolves and domestic dogs. They determined that, of the regions that were significantly differentially methylated, dogs were on average more methylated in transposons. Consequently, methylation may be linked to gene expression and phenotypic trait evolution. They also identified patterns of methylation that deviated from neutrality through a modified Tajima's D metric. Of the genomic regions that were found to be non-neutral in the dog, many overlapped with differentially methylated regions (e.g., neurotransmitters). Quantifying additional genomics features, such as gene expression variation (Roy et al. 2013, Wang et al. 2009), the genomic distribution of nucleosome-free chromatin [e.g., with formaldehyde-assisted isolation of regulatory elements (FAIRE)-seq (Giresi et al. 2007)], transcription factor binding via chromatin immunoprecipitation (CHIP)-seq (Johnson et al. 2007, Kharchenko et al. 2008), or copy number variation (Ramirez et al. 2014), has the potential to identify the mechanism on which selection acts and identify other potentially important interacting loci missed by association mapping and selection scans. A perspective on genome-level evolution is needed so as not to overlook functionally important processes that may be missed by solely focusing on candidate regions.

4.3. Is There an Evolutionary Solution to Deleterious Variation in the Dog?

Multiple processes have led to an accumulation of deleterious variation in dogs relative to wolves. The fact that the increase in deleterious variation associated with the ancient domestication

bottleneck is still present suggests it will be difficult to overcome this genetic legacy by altering modern breeding programs. Avoidance of inbreeding will still be important for preventing the accumulation and expression of large effect recessive deleterious mutations. However, modification of breeding programs may be more successful at reducing deleterious and disease mutations that accumulate as a result of artificial selection. The extreme selective pressure for mutations of large effect could lead to hitchhiking of deleterious mutations. Moreover, breeding to specific breed standards may fix genetically associated deleterious variations. Alternate breeding programs that focus on selecting for mutations of weaker effect or impose polygenic selection, in which many mutations experience only slight increases in allele frequency, should reduce the accumulation of deleterious variation in the flanking regions. Moreover, the practice of breeding to a standard could be relaxed such that variation within breeds could be tolerated. Just as variation is an essential component of adaptation and evolution in nature, so can it be a mechanism to improve the genetic health of dog breeds.

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