

Deciphering the puzzles of dog domestication

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ABSTRACT

The domestic dog, as a highly successful domestication model, is well known as a favored human companion. Exploring its domestication history should provide great insight into our understanding of the prehistoric development of human culture and productivity. Furthermore, investigation on the mechanisms underpinning the morphological and behavioral traits associated with canid domestication syndrome is of significance not only for scientific study but also for human medical research. Current development of a multidisciplinary canine genome database, which includes enormous omics data, has substantially improved our understanding of the genetic makeup of dogs. Here, we reviewed recent advances associated with the original history and genetic basis underlying environmental adaptations and phenotypic diversities in domestic dogs, which should provide perspectives on improving the communicative relationship between dogs and humans.

Keywords: Dog; Domestication history; Adaptation; Phenotypic diversity, Domestic legacy

INTRODUCTION

Dogs, as the first domesticated mammal, have interacted with

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humans for thousands of years (Freedman & Wayne, 2017). This domestication occurred in two main phases: the initial domestication of the wild gray wolf to primary dog and the subsequent improvement of these indigenous dogs into various modern breeds. In the first phase, highly specific behaviors valued by nomadic hunter-gatherer societies, such as tracking and consuming prey, drove the initial evolution of primary dogs at the beginning of domestication (Ostrander et al., 2017). During this process, selection was not the only mechanism of evolution, as genetic drift likely also caused fit, unfit, or neutral alleles to become fixed due to bottleneck or founder effects (Doebley, 1989; Eyre-Walker et al., 1998). Moreover, features commonly associated with domestication were not selected directly but rather represented side effects of the relaxation of selection (Dobney & Larson, 2006). For example, domestication relaxed the selective pressure on male dogs to compete for mates. Thus, genes involved in producing traits relevant to this endeavor were no longer under selective pressure and thus became effectively neutral or even detrimental as they involved the diversion of resources from traits under selection such as tameness. With the advent of agricultural societies, dogs adapted to the introduction of starch within their diets, a crucial step in their evolution from the wolf (Arendt et al., 2016). Over the past few hundred years, phenotypic radiation among domesticated

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dogs accelerated the breeding process, resulting in the development of nearly 400 breeds to fulfill specialized functions in human society, with clear morphological and behavioral differences, such as big or small, lean or squat, and independent or loyal (Freedman & Wayne, 2017). This breeding improvement was largely shaped by the extreme influence of artificial selection, with a dramatic increase in deleterious alleles, i.e., “domestic cost” (Cruz et al., 2008). The tremendous diversity in the morphology and behavior of present-day breeds illuminates the power and appeal of artificial selection, which has been widely used over a long period and exhibits inestimable potential.

Domestic dogs have spread to every corner of the world following human migration and thus adapted to highly distinct environments. This long-term accompaniment has not only promoted a much closer relationship between humans and dogs than with any other domesticated animal, but also similar genetics underlying as many as 360 diseases suffered by both, especially mental diseases (e.g., canine compulsive disorder, Alzheimer’s disease, epilepsy) (De Risio et al., 2015; Dewey et al., 2019; Ostrander et al., 2017; Shearin & Ostrander, 2010b), which may partially result from the same natural environmental pressures and similar social exposure. Therefore, dogs are good models for both evolutionary and pathological research.

Integrating molecular phylogenetics, bioinformatics, and biotechnology has helped to decipher puzzles about dog domestication history. Here, we summarized the progress of dog domestication, including the timing and origin, adaptation to different local environments, and genetic basis underlying phenotypic diversity, to highlight our current understanding of dog domestication and provoke enthusiasm for further breeding according to genetic information.

ORIGIN OF DOGS

Archaeological evidence demonstrates that the dog has been a human companion since the Mesolithic Age. Genomic sequencing data also suggest that initial dog domestication predated the advent of agriculture, occurring instead alongside hunter-gatherers (Freedman et al., 2014). Both genetic and phenotypic research has clearly demonstrated that the dog originated from an extinct gray wolf population and was domesticated in the Old World (Fan et al., 2016). However, there is ongoing debate regarding the geographic origin of monophylogeny or polyphylogeny due to discrepancies in study ideas and methods. Fortunately, growing evidence is shedding light on the origin and evolutionary trajectories of dogs.

Vilà and colleagues investigated dog origin based on mtDNA control region sequences and were the first to suggest a polyphyly origin from multiple ancestral wolf populations with backcrossing events after initial domestication (Vilà et al., 1997). Alternatively, Savolainen et al. (2002) proposed East Asia as the single origin center some 15 000 years ago due to the presence of rich genetic and phylogeographic variations

and as the origin of the Australian Dingo (Savolainen et al., 2004). Furthermore, evidence also suggests that native American dogs originated from Old World dogs that crossed the Bering Strait following human activity during the late Pleistocene (Leonard et al., 2002). Although evidence that mtDNA haplotypes from African village dogs are as diverse as those from East Asia challenges the East Asian origin hypothesis (Boyko et al., 2009), this hypothesis is supported by previous diversity analyses on mitochondrial and Y chromosomes from an almost exhaustive sampling (Ding et al., 2012; Pang et al., 2009).

However, the East Asian origin hypothesis has been rebutted by nuclear genomic single nucleotide polymorphic (SNP) analysis, which supports a Mid-Asian origin (Vonholdt et al., 2010). The Mid-Asian origin hypothesis relies on two findings: (1) breeds of East Asian origin do not have the highest level of nuclear variability; and (2) most breeds share most haplotypes with Middle Eastern wolves. Nevertheless, this conclusion has been weakened by a lack of village dogs from the Yangtze River where the uniparentally inherited markers present the most genetic diversity (Ding et al., 2012; Pang et al., 2009) and by the significant bias of SNPs designed by array technology. Another study based on canid samples from Africa, Asia, Europe, the Middle East, and North America disproved the East Asian origin hypothesis through genomic resequencing analysis (Fan et al., 2016). However, subsequent genomic resequencing of canid samples across the Eurasian mainland elucidated an “Out of Southern East Asia” migration route, thus emphasizing an East Asian origin and predating the beginning of domestication by ~33 000 years ago (Wang et al., 2016). Research on ancient DNA has also suggested that the dog may have been domesticated independently in Eastern and Western Eurasia from distinct wolf populations. Western Eurasian dogs were then partially replaced by Eastern dogs following Near Eastern Neolithic farmer expansion into Europe (Frantz et al., 2016; Ollivier et al., 2018). American dogs likely originated in East Asia and dispersed into the Americas alongside people (Ni Leathlobhair et al., 2018), but they almost completely disappeared after the arrival of Europeans, leaving the closest detectable genetic legacy of canine transmissible venereal tumor to an individual 8 000 years ago.

Taken together, genetic material following different inheritance rules has been used to infer the origin of dogs. Genetic markers on mitochondrial DNA (mtDNA) and Y chromosomes are stably inherited from their maternal lineage and paternal lineage, respectively, which facilitates investigation of gene flow from maternal and paternal ancestors. However, the absence (or near absence) of recombination and the sensitivity of genetic drift make these markers defective at deciphering exact demographic history. Whole genomic SNP data have provided more information, especially on gene flow and incomplete lineage sorting (ILS), for phylogenetic reconstruction, resulting in inconsistent results to those obtained by mtDNA or Y chromosomes for dog domestication (Ding et al., 2012; Savolainen et al., 2002;

Vilà et al., 1997; Vonholdt et al., 2010). Fortunately, recent research incorporating different inherited markers has provided more convincing clues on the evolution of wild animals like mosquitoes and domestic animals like dogs and cattle (Frantz et al., 2016; Thawornwattana et al., 2018; Wu et al., 2018). Therefore, the incorporation of different genetic markers, in combination with large-scale samples across diverse geographic regions and time points, high-depth sequencing data, and the development of more advanced methodologies, will improve our understanding of the evolutionary origin and genetic makeup of dogs.

ADAPTATION TO DIFFERENT ENVIRONMENTS

The dog, which shares a closer relationship to humans than any other domestic animal, dispersed across the entire world following man and adapted to diverse local environments over a relatively short time period. The genetic mechanisms underlying adaptation have been widely considered by biologists. Here, we summarize the two main drivers: i.e., dietary change and environmental adaptation.

In the process of wolf to dog transformation, diet is thought to have played a crucial role. Unlike wolves, dogs can thrive on a diet rich in starch. Ten genes involved in digestion and fatty acid metabolism evolved rapidly during the domestication of dogs (Axelsson et al., 2013), providing evidence for domestication-induced changes in diet. Three genes (*AMY2B*, *MGAM*, *SGLT1*) have been identified as selective candidates that play key roles in the breakdown of starch. Different dog breeds possess a varying ability to process starch, which may be associated with copy number variations of the *AMY2B* gene influencing amylase activity (Arendt et al., 2014). The changes in *AMY2B* copy number in native dogs, modern breeds, and wolves across the world illustrate that a diet change involved a secondary shift, consistent with the development and spread of prehistoric agriculture in most parts of the world, rather than a single occurrence during initial domestication (Arendt et al., 2016).

In addition, environmental adaptation has also attracted the attention of biologists. The Tibetan Mastiff, which is a local breed native to the Tibetan plateau, has evolved special phenotypic traits adapted to high-altitude environments. Analysis of SNP array data has revealed several genes with selective signatures in the Tibetan Mastiff, especially the *EPAS1* gene, which is reported to influence environmental adaptation in Tibetan residents (Li et al., 2014b). Genomic resequencing of dogs from different altitudes has indicated that a G305S variant and non-synonymous mutations in *EPAS1* may decrease vascular resistance and thus promote oxygen transport (Gou et al., 2014). *EPAS1* and *HBB* have further been identified as candidates for convergent hemoglobin adaptations to hypoxia between Tibetan people and the Tibetan dog (Wang et al., 2014). From the perspective of the X chromosome, which has been neglected in previous studies, the haplotype frequency of the *AMOT* gene is significantly correlated with altitude (Wu et al., 2016).

Moreover, genome-wide scanning of the Tibetan Mastiff and Tibetan wolf indicate genetic introgression on *EPAS1* and *HBB* loci, implying the possibility that the Tibetan Mastiff acquired local adaptation quickly by secondary contact with its wild relative, the Tibetan wolf, although no such evidence has been found on the *AMOT* locus (Miao et al., 2017).

Another classic adaptation to the environment is the African dog's adaptation to malaria, which is pervasive on the African continent. Dogs migrated into Africa about 14 000 years ago. Liu et al. (2018) explored the genetic basis of adaptation to the tropical African environment through whole genome analyses of African indigenous dogs from Nigeria. Among the positively selected genes associated with immunity, angiogenesis, ultraviolet protection, as well as insulin secretion and sensitivity, the gene *ADGRE1* was found to confer African dogs with defense against *Plasmodium* infection (Liu et al., 2018). This gene is also associated with human immune response to malaria (Kariuki et al., 2013). Therefore, these results provide new clues on the convergent adaptation and evolution between humans and dogs.

PHENOTYPIC DIVERSITY AND DOMESTIC LEGACY OF MODERN BREEDS

With the development of human society and advancement of the industrial revolution, the demands of people became increasingly diverse, with dog breeding positively selected for two primary functions. First, certain dogs were bred to perform specific tasks to assist their human companions based on their distinct behaviors and functions. Second, other dogs were bred as ornamental pets to be integrated into human families. Presently, there are more than 400 dog breeds, which possess different morphological and behavioral characteristics. Here, we review their phenotypic diversity by examining behavioral and morphological phenotypes separately.

Behavioral phenotypes

Dog breeds are classified into seven groups according to their guarding, herding, obedience, and hunting abilities: i.e., gundogs, working dogs, herding dogs, hounds, terriers, and companion dogs. These behavioral traits have become fixed within breeds due to intensive artificial selection and are considered inheritable, as cross-bred dogs exhibit intermediate behavior from their purebred parents. A survey of over 10 000 German shepherd and Rottweiler individuals revealed a genetic contribution to 16 assessed behavioral traits (Saetre et al., 2006). Further genomic analysis also found the dopamine receptor to be associated with aggressive behavior among canine breeds (Ito et al., 2004). Canine compulsive disorder (CCD) is common in many breeds and exhibits a mechanism like that of human obsessive-compulsive disorder (OCD). The cadherin 2 (*CDH2*) gene is a crucial factor associated with CCD in Doberman pinschers (Dodman et al., 2010; Tang et al., 2014). Interestingly, variants in the *CDH2* gene may also contribute to OCD and Tourette disorder in humans (Moya et al., 2013). Moreover,

population genetic analysis has suggested that *CDH2* influences circling behavior in Belgian Malinois (Cao et al., 2014).

In addition to the breed traits mentioned above, the behavioral transformation from fear-aggressiveness to tameness is believed to have been a prerequisite to initial dog domestication. An experiment on silver foxes reconstructed this behavioral transformation in a domestication model (Lindberg et al., 2005; Saetre et al., 2004) and several genetic loci were found to be associated with this change (Kukekova et al., 2011; Spady & Ostrander, 2007). However, intensive breeding and selection only occurred very recently in dogs, resulting in an extremely small gene pool, which may have led to misconception about the genetic changes associated with behavioral transformation. Several studies have focused on the Chinese indigenous dog, an outbred dog living in the original center of Asia that shows the most robust genetic diversity and is assumed to be closest to the primary dog. Genomic analysis on this outbred dog revealed the genetic basis for the rewiring of dog brains and convergent evolution between dogs and humans (Li et al., 2013, 2014a; Lindberg et al., 2005; Saetre et al., 2004; Wang et al., 2013).

Morphological diversity

The genetic mechanisms underlying the morphological differences among dogs have been deeply researched as morphological traits are easily observed and estimated. Parallel studies on morphological characters from model animals such as mice and humans have also revealed the genetic underpinnings of morphological diversity in dogs.

Body size, one of the most important quantitative traits under evolutionary scrutiny, varies more in dogs than in any other terrestrial mammal. For example, the Cane Corso and Yorkshire demonstrate a 30-fold difference in body size (Shearin & Ostrander, 2010a). Research on the Portuguese water dog identified insulin-like growth factor 1 (*IGF1*) as the gene that controls body size (Sutter et al., 2007), as also reported in mice and humans (Baker et al., 1993; Woods et al., 1996, 1997). Variants of fibroblast growth factor 4 (*FGF4*) are the cause of short legs in many breeds and are correlated with chondrodysplasia (Parker et al., 2009). Unlike the results from association mapping of quantitative traits in humans and domesticated plants, a simple genetic architecture appears to underlie morphological variation in dogs (Boyko et al., 2010). For example, integrative research on multiple breeds found that six genes (*GHR*, *HMG2*, *SMAD2*, *STC2*, *IGF1*, and *IGF1R*) explain almost half of size variation in dog breeds with standard body weight (BSW) <41 kg (Rimbault et al., 2013). Moreover, a study of the X chromosome identified three genes (*IRS4*, *IGSF1*, and *ACSL4*) as responsible for body size variation in dogs with BSW >41 kg (Plassais et al., 2017).

Skull shape is another significant morphological trait found to be highly diversified among dog breeds. Analysis of skull shape among 374 dogs identified *SMOC2* as a crucial gene explaining approximately 36% of facial length variation (Marchant et al., 2017). Previous study on skull morphology

associations also identified *BMP3* as a causative gene affecting cranial development and linked with brachycephaly in some breeds such as the pug and bulldog (Schoenebeck et al., 2012).

Dogs also exhibit tremendous coat diversity since their separation from their gray wolf ancestor. Whole-genome association analysis of 80 dog breeds identified three genes (*RSPO2*, *FGF5*, and *KRT71*) with an effect on coat growth, length, and curl (Cadiou et al., 2009). Furthermore, variants in the forkhead box transcription factor family (*FOX13*), which influence ectodermal development, are thought to be responsible for the hairless traits in Mexican and Peruvian hairless dogs and Chinese crested dogs (Drogemuller et al., 2008).

Three genes, namely agouti (*ASIP*), melanocortin 1 receptor (*MC1R*), and beta-defensin 103 (*CBD103*), are thought to encode the ligand-receptor system that controls pigment type-switching in dogs (Candille et al., 2007). The latter gene (*CBD103*), previously recognized as a component of innate immunity in most vertebrates, is predicted to play roles in functions associated with the melanocortin pathway in domestic dogs. More interestingly, North American wolves derived an allele in *CBD103*, resulting in a black coat color phenotype, through genetic introgression from dogs >500 years ago (Anderson et al., 2009). In addition, the *TYRP1*, *MITF*, and *SILV* genes are also thought to influence phenotypes like brown color, white spotting, and merle patterning (Clark et al., 2006; Karlsson et al., 2007; Schmutz et al., 2002). Detailed information about the allele patterns of genes involved in coat color and their associated phenotypes can be found in a previous review (Schmutz & Berryere, 2007).

Domestic legacy

During the progression of dog domestication, both the relaxation of selective pressure and accumulation of deleterious mutations from the hitchhiking-effect caused domestic legacy. On the one hand, breeders focused on the purification of varieties and ignored disease resistance in purebred dogs. Reduction in effective population size, mainly caused by breed purification, increased the fixation probability for many weakly deleterious mutations located close to functional loci under strong artificial selection (Cruz et al., 2008). On the other hand, selectively retained pleiotropic genes increased the risk of genetic diseases. For example, coat color-related sensorineural deafness has been widely described in numerous dog breeds (Webb & Cullen, 2010), and brachycephaly (flat-face) is commonly observed in breeds like the English bulldog, French bulldog, pug, Boston terrier, Pekingese, boxer, Shi Tzu and Cavalier King Charles spaniel (Dupre & Heidenreich, 2016). In addition, continuous circling, Alzheimer's disease, and epilepsy, which impact physical and mental wellbeing, are also commonly observed in dogs (De Risio et al., 2015; Dewey et al., 2019; Moon-Fanelli & Dodman, 1998). Therefore, a more detailed and robust understanding of the genomic make-up of dogs is required for

ongoing breeding strategies to satisfy both changing human demands and increased ethical concerns regarding dog welfare.

CONCLUSIONS

With the development of sequencing technologies and decrease in associated costs, high-quality sequencing data can now provide much deeper insights into the evolutionary history of dogs. In addition, improvements in data exchange within canine research communities have helped elucidate the genetic mechanisms underpinning heredity and variation. For example, the International Dog10K Genomes Project, which started in 2015, has produced enormous -omics data of dog breeds from around the world. The Dog Genome SNP Database (DoGSD) has also provide information on the differences between dog and wolf genomes (Bai et al., 2015). In addition to the genomic databases, international dog clubs have also provided phenotypic information on more than 400 dog breeds (Ostrander et al., 2017). The iDog integrated resource not only contains all the information mentioned above (Tang et al., 2019), which incorporates sequence alignment tools and genome browsers, but can also supply the global dog research community with genomic sequence assemblies, genomic variations, phenotypic/disease traits, gene expression profiles, gene ontology, and homolog gene information. These resources will promote our understanding of the evolutionary and genetic mechanisms of domestic dogs and help elucidate the genetic underpinnings of human genetic diseases. Finally, as man's best friend, dogs deserve more attention and responsibility to promote their welfare. Dog owners should acquire professional knowledge on the different physical states of their companion. Veterinary associations should also help with the introduction of new policies, edicts, regulations, and positive humane solutions to benefit dogs.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Y.L proposed the research ideas and revised the manuscript. Z.Z. and S.K. reviewed the literature and drafted the manuscript. All authors read and approved the final version of the manuscript.

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