From caveman companion to medical innovator: genomic insights into the origin and evolution of domestic dogs

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Abstract: The phenotypic and behavioral diversity of the domestic dog has yet to be matched by any other mammalian species. In their current form, which comprises more than 350 populations known as breeds, there is a size range of two orders of magnitude and morphological features reminiscent of not only different species but also different phylogenetic families. The range of both appearance and behavior found in the dog is the product of millennia of human interference, and though humans created the diversity, it remains a point of fascination to both lay and scientific communities. In this review, we summarize the current understanding of the history of dog domestication based on molecular data. We examine the ways that canine genetic and genomic studies have evolved and look at examples of dog genetics in the light of human disease.

Keywords: dog, population, GWAS, mapping, comparative genetics

The origin of the domesticated dog

The origin and history of the domestic dog has been a topic of interest to humans for centuries. As the earliest domesticated animal, our association with the dog far predates our historical records; therefore, the circumstances surrounding our initial meeting and collaboration must be deduced from data that we can obtain through scientific means. The archeological record places the remains of dogs or proto-dogs in sites in Belgium and Siberia more than 30,000 years ago (ya).^{1,2} Evidence from mitochondrial DNA (mtDNA) sequences suggests that these findings represent domestic lines that died out and do not contribute to our modern dogs; however, analysis of the morphometrics of the skulls suggests that they are extinct wolf lineages rather than dogs.³⁻⁵ Fossils that are molecularly or phenotypically more similar to modern dogs have been found in the Middle East and Europe dating 14,000–17,000 ya.^{3,6} This creates a gap in the archeological record to time the first domestication event. The conditions may have been right for canine domestication as much as 30,000 ya, and it was achieved at least 15,000 ya. Experiments with selection on tameness in foxes have shown that under rigorous selective pressures, phenotypic changes can be accomplished within 20 generations.⁷ Phenotypic changes may have happened quickly in the dog if we assume that humans had an active role in the domestication process. However, if we assume the domestication of the dogs came from a more gradual move into the human niche, it may have taken much longer to significantly alter their appearance. Because it is possible that the process was repeated multiple times and in multiple locations, the exact temporal placement of the episode or episodes that created our modern dogs is most likely somewhere in between 15,000 ya and 30,000 ya.

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Molecular studies have attempted to date the divergence of dog from wolf using multiple data sets and methodologies. mtDNA analyses have timed the divergence of the dog from wolf between 5,400 ya and >100,000 ya.^{3,8–10} Two recent studies that examined whole-genome sequences of both dogs and wolves estimate the divergence time at 13,000–32,000 ya.^{11,12} The difficulty in establishing an exact time of domestication stems from multiple sources of conflict. First, the mutation rate of the dog genome is not known. The divergence times are often estimated based on assumed mutation rates, which vary with each study (ie, 1.4×10^{-8} vs 2.2×10^{-9} mutations per base pair per generation).^{11,12} Additionally, wolf–dog introgression must be factored into the calculations. During early domestication, dogs and wolves would have been in close contact and fully capable of interbreeding. Examination of mitochondrial haplotypes and nuclear microsatellite markers in a collection of dogs and wolves from the Caucasus in Georgia indicates that 13% of dogs and 10% of wolves show evidence of hybridization.¹³ Pervasive hybridization throughout the natural history of the domestic dog confounds attempts at precise estimates of divergence, making dogs and wolves appear more similar and therefore more recently diverged. Finally, the genome of the domestic dog, as a close companion of humans, has been consistently altered through intensive selective pressures to obtain specialized traits.^{14,15} Thus, while the molecular clock works well in determining species divergence in wild populations, assuming a steady rate of mutation could produce misleading results for a genome in which large regions are being driven to fixation and purifying selection is prevented.¹⁶ As we continue to gather more complete genomic information about the full range of dogs and their wild progenitors, we will be able to take all of these factors into account in our search for a precise answer to the time of first domestication.

In the mean time, there are other directions that can be explored to understand early domestication. The large influx of whole-genome sequence data that are currently being produced offers the opportunity to examine the functional genetic alterations that have developed between domesticates and their closest wild relatives. Recent studies have taken this route to identify the genes that were disrupted when dogs became domesticated from wolves.^{11,17–23} In a comparison of 60 domestic purebred dogs and 12 pooled wolf DNAs, 36 regions of the genome containing 122 genes were found to be under strong selection in the dogs. By mining the gene ontology database, three main gene groups were significantly highlighted: nervous system development, sperm competition, and metabolism/digestion.¹⁷ Specifically,

under the metabolism heading, three genes involved in starch metabolism stood out. One of these was a copy number increase in dogs (4–30 compared to two in wolves) that increased the expression of the *AMY2B* (alpha-2B-amylase) gene. The authors hypothesized that the change in diet from largely meat to more plant-based food sources was a primary contributor to domestication, supporting the idea that wolves were first domesticated by scavenging around human agricultural settlements.¹⁸ Further investigation of the *AMY2B* locus, however, shows that the copy number variant (CNV) is not increased in all dog breeds and is polymorphic in some wolves.¹¹ Rather than driving domestication, the *AMY2B* CNV may be a marker of more recent adaptation to a high-starch diet. A similar, though less dramatic, association has been identified in humans from high starch-consuming populations and the *AMY1* genes.¹⁹

A second study comprising whole-genome data from three wolves and ten dogs identified fixed clusters of single-nucleotide polymorphisms (SNPs) in each species. Using this method, the study found 204 genes with at least six fixed sequence changes and significantly reduced nucleotide diversity.²⁰ The gene ontology terms that were most significantly overrepresented in this set of genes were behavioral, including response to stress, fear, and defense. These findings were verified in a second set of three wolves and three indigenous dogs. The overrepresentation of behavioral genes in the fixed differences between dogs and wolves suggests that a reduced fear response may have been the driver of early domestication allowing the proto-dog to live comfortably in close contact with early humans.

Finally, an analysis of the sequence of four purebred dogs, four wolves, and four indigenous dogs identified 311 genes under positive selection in the dogs.¹² These genes largely represent three gene ontology groups that are identical or nearly identical to those identified in the first study: reproductive, neurological processes, and metabolism/digestion. The authors compared these genes to those under selection in humans and found 32 in common, including genes involved in neurological processes, metabolism, and cancer. The common sites of selection across the genomes of both species indicate similar selective pressures, which is likely the result of our shared environments and constant close interaction. This parallel selection can be seen in the sequence comparison of dogs from high, mid, and low altitudes in the People's Republic of China.²¹ The dogs that come from the highest altitudes differed from those of low-altitude regions over the *EPAS1* gene and a beta-hemoglobin cluster. *EPAS1* is a transcription factor that activates in response to hypoxic

conditions or oxygen deprivation and has been identified as a target of selection in the Tibetan highlanders.^{22,23}

Selection on both the *AMY2B* polymorphism and the *EPAS1* gene highlights the convergent selective pressures found in dogs and humans and encourages the further use of dog genetics to inform human evolutionary history. The finding that disease-associated genes, such as those that lead to cancer development, are under selection in both species further strengthens the commonly held hypothesis that disease mutations mapped in dogs will be directly applicable to human-disease studies.²⁴

Techniques used in the study of canine genetics and genomics

The techniques researchers have used to study canine genomics have evolved with the field. Early insights into canine genetics came from pedigree analysis and trait observation. These methods were used to determine the inheritance pattern of physical traits. Physical characteristics of dogs such as blood pressure, pupil diameter, and rectal temperature were attributed to heredity through studies of different breeds of purebred dogs. In a pioneering study, such methods were used to demonstrate that genetic factors, and not just environment, are main contributors to diversity across dog breeds.²⁵

Karyotyping and cytological methods became popular in the 1960s and were used to study a number of aspects about the dog including, but not limited to, sexual abnormalities,²⁶ reproduction,²⁷ and disease.²⁸ Cytogenetics found a resurgence in molecular biology with the advent of more specific probes that allow for chromosome painting and fluorescence in situ hybridization. These methods were used to compare the arrangement of the dog's small, acrocentric chromosomes to the human genome and showed that gene order is highly conserved between the two.^{29,30} Further refining the probes has also allowed for more precise identification of chromosome abnormalities and genomic rearrangements.³¹

Proteins were the focus of canine studies during the 1970s. Many investigations focused on blood diseases or traits such as the clotting disorder von Willebrand disease. Further information on canine biology and its similarities to human was gained through comparison of protein functions across species such as the catalytic properties of enolase,³² retinol transport in plasma,³³ and pituitary dosage curves of prolactin,³⁴ which implied a similar structure and function between the dog and human proteins.

New molecular techniques in the 1980s allowed for direct assays of the DNA sequences improving the ability to make comparisons between dogs and humans. Southern

blot analysis using cDNA from human leukocyte antigen genes as a probe was able to detect dog leukocyte antigen gene regions, indicating a high level of similarity in the gene sequences of both species' major histocompatibility complex³⁵ and highlighted the importance of the canine in modeling human diseases. The similarity in dog and canine immune systems was irreplaceable in developing strategies to overcome graft-versus-host disease in bone marrow transplantation and will likely play a future role in disease therapeutics.^{36–38} It was not until sequencing methods became more automated, however, that large-scale homology studies between dog and human became feasible.

Genetic maps of the dog were created once marker genotyping and analysis methodologies improved in the 1990s.³⁹ Microsatellites, or short tandem repeats, are sequences of DNA that can be identified through restriction enzyme assays or polymerase chain reactions and are the backbone of linkage maps.^{40–42} The identification of a large number of highly polymorphic microsatellites enabled the construction of the first genetic maps of the dog genome.^{43,44} These genetic maps made possible the discovery of many genes involved in disease and phenotype determination (reviewed in Parker et al²⁴) and produced the scaffold for assembly of the first complete genome sequence of the dog. The most recent comprehensive linkage map was developed based on the completed sequence specifically to determine recombination rates, given the small size of the dog chromosomes.⁴⁵

The release of the 7.5× whole-genome sequence of the dog in 2005 represented the culmination of the preceding work on characterizing the dog genome.³⁹ The assembled reference sequence was that of a Boxer and was done through a whole-genome shotgun approach, in which the DNA was fragmented into smaller, clonable segments that allowed for Sanger sequencing. With the assembly of a dog genome sequence, over two million SNPs were identified enabling genome-wide association studies (GWASs). These became a high-powered tool to study dog disease and morphology.

GWASs compare a large number of SNPs across the entire genome of two disparate groups, usually affected cases and unaffected controls for categorical traits, or a range of phenotype values for quantitative traits. Statistical methods are used to identify differences between the groups that associate with the affected status. Such studies have been successful in identifying variants in a number of genes as well as in suggesting candidate regions for specific traits (reviewed in Parker et al²⁴ and Karlsson and Lindblad-Toh⁴⁶).

SNP genotyping has also been a key in allowing for other genome-wide analyses such as homozygosity mapping and

identity-by-descent mapping, in which areas of the genome are compared across multiple individuals to identify common regions of shared alleles.^{15,47} Both methods can be successfully used to identify genomic regions that are under selection for specific traits or to identify recessive disease traits. For example, homozygosity mapping of six Spinone Italiano with spinocerebellar ataxia and six healthy controls of the same breed identified a disease locus on chromosome 20 that was further narrowed to a repeat expansion in *ITPR1*.⁴⁸ This gene has also been associated with ataxias in humans (Table 1).

Haplotype mapping is another powerful tool that employs SNPs to establish a pattern of variants that are commonly inherited. A combination of homozygosity mapping and haplotype comparisons was used to fine map the region associated with chondrodysplasia in a multi-breed GWAS.⁴⁹ A 24 kb region on canine chromosome 18 (CFA18) was found to be homozygous in 26 dogs from eight chondrodysplastic breeds. All breeds carried an identical haplotype indicating a common ancestral source of the mutation, an *fgf4* retrogene inserted in the homozygous region. This technique has been used successfully multiple times in both disease and morphology mapping (Figure 1).

There are now many canine sequences available due to the advent of next-generation sequencing technologies. The new sequences have been used to identify additional SNPs such as the 4.6 million found by comparing the Korean Jindo sequence to the publically available Boxer and the 1.5× Poodle sequences,⁵⁰ and to identify insertion/deletions and structural variants.⁵¹ The relative low cost and general availability of next-generation sequencing allow for large-scale sequencing to supplement GWASs and linkage studies when searching for disease-associated variants. For instance, a GWAS of patellar luxation in Flat-Coated Retrievers identified four distinct regions of association.⁵² Instead of fine mapping each of the loci or picking candidate genes, custom genomic hybridization arrays were used to enhance the coding regions in all loci for targeted resequencing in 15 cases and 15 controls. SNPs with the largest difference in frequency between cases and controls were genotyped on a larger panel revealing eight genes that appear associated with the disorder.

Similarly, targeted next-generation sequencing was used to investigate a region on CFA4 that was associated with ataxia in both GWASs and linkage analyses of Old English Sheepdogs.⁵³ The sequencing combined with genotyping and haplotype comparisons in additional affected breeds identified a missense mutation in the *RAB24* gene. In contrast, whole-genome sequence of a single Chinese Crested dog with

neuronal ceroid lipofuscinosis was compared to the sequence of 101 unaffected dogs of other breeds to identify what was predicted to be a rare disease-causing variant. A deletion was identified in the *MFSD8* gene that was homozygous in the diseased dog, absent from the other 101 dogs, and predicted to alter protein structure.⁵⁴

Next-generation sequencing can enhance the ability to identify variants that are resistant to traditional sequencing or genotyping methods. Targeted next-generation sequencing of a locus from a GWAS in Tibetan Spaniels with late-onset progressive retinal atrophy identified a short interspersed nuclear element (SINE) insertion in an intron of the *FAM161A* gene that creates a reading frame shift and exon skipping.⁵⁵ SINE insertions are not annotated in the public sequence databases and can only be identified through exploratory sequencing. Targeted sequencing of the entire associated region proved instrumental in finding this causative mutation.

As it stands today, the dog reference genome is on its third and most updated derivation, CanFam3.1, which includes approximately 2.41 billion base pairs across the 38 autosomal chromosome pairs, the X chromosome, and the mtDNA. The available data have led to the development of highly informative tools for genome analysis in the dog including a high-density SNP chip, expression chips, and a whole-exome enrichment array, which offers a less-expensive alternative to whole-genome sequencing.^{47,56} The addition of RNAseq data from ten canine tissues has improved the annotation of the canine genome with the current version displaying 20,700 protein-coding genes, 4,600 antisense transcripts, and 7,200 noncoding RNA transcripts positioned confidently and available for mutation analysis.⁵⁷ Some of the most common resources discussed above can be found in Table 2. The next step in genome annotation will be to identify the regulatory regions, as there is likely to be a subset unique to the dog that will be invaluable for disease studies.

Phenotypic diversity among breeds

By far, the most intriguing aspect of canine genetics is the chance it offers to understand the source of extreme phenotypic diversity (Figure 2). The dog, as we know it today, is the result of centuries of controlled breeding to obtain specialized traits and behaviors. The physical differences between the breeds have long been recognized, but it is through genomic analysis that we have been able to understand the differences at a genetic level. Shortly after the first microsatellites were discovered in the dog, they were being used to assess differences between the breeds. These early studies, often analyzing

Table 1 A summary of naturally occurring diseases in dogs and humans that are caused by or associated with mutations in orthologous genes and gene family members

Dog disease	Dog gene	Breed	Human disease	Human gene	Reference
Orthologous genes					
Alport syndrome	COL4A5	SAMO	Alport syndrome	COL4A5	107
C3 deficiency	C3	BRIT	C3 deficiency	C3	108,109
Centronuclear myopathy	BINI and PTPLA	BORD	Centronuclear myopathy	BINI and PTPLA	110–112
Cleft lip and palate	ADAMTS20	NSDT	Cleft lip and palate	ADAMTS20	113
Cone degeneration	CNGB3	AMAL, GSHF	Achromatopsia	CNGB3	114,115
Cystinuria	SLC3A1	NEWF	Type 1 cystinuria	SLC3A1	116,117
Degenerative myelopathy	SOD1	BOX, PEMB	Amiotrophic lateral sclerosis	SOD1	118,119
Duchenne muscular dystrophy	DMD (dystrophin)	GOLD	Duchenne muscular dystrophy	DMD (dystrophin)	120
Dystrophic epidermolysis bullosa	COL7A1	GSHF	Dystrophic epidermolysis bullosa	COL7A1	121,122
Erythrocyte pyruvate kinase deficiency	PK	BSJI, WHWT	Erythrocyte pyruvate kinase deficiency	PK	123,124
Fucosidosis	FUCA1	ESSP	Fucosidosis	FUCA1	125,126
Glycogen storage disease type Ia	G6PT	MALT	Glycogen storage disease type Ia	G6PT	127,128
Hemophilia A	Factor VIII	IRSE	Hemophilia A	Factor VIII	129,130
Hemophilia B	Factor IX	BEAG, LHSA	Hemophilia B	Factor IX	131,132
Hereditary cataracts	HSF4	Multiple	Congenital cataracts	HSF4	133,134
Hereditary multifocal renal cystadenocarcinoma and nodular dermatofibrosis	FLCN	GSD	Birt–Hogg–Dubé syndrome	FLCN	135,136
Hypohidrotic ectodermal dysplasia	EDA	GSD	Hypohidrotic ectodermal dysplasia	EDA	137,138
Imerslund–Gräsbeck syndrome	CUBN or AMN	Multiple	Imerslund–Gräsbeck syndrome	CUBN or AMN	139,140
Insulin-dependent diabetes	DIA-DRB and DIA-DQA	SAMO, CAIR, TIBT	Type-1 diabetes	HIA-DRB and HIA-DQA	141,142
Lafora disease	NHLRC1 and EPM2A	Multiple	Lafora disease	NHLRC1 and EPM2A	88,143
Narcolepsy	HCRTR2	LAB, DOBP, DACH	Narcolepsy	HCRTR2	86,87,144
Neuronal ceroid lipofuscinosis	PTT1, TPP1, CTSD, ATP13A2	DACH, ABUL, TIBT	Neuronal ceroid lipofuscinosis	PTT1, TPP1, CTSD, ATP13A2	90,145
Neuronal ceroid lipofuscinosis	CLN family	DACH, ESET, BORD	Neuronal ceroid lipofuscinosis	CLN family	90,146
Junctional epidermolysis bullosa	LAMA3	GSHF	Junctional epidermolysis bullosa	LAMA3	147,148
Krabbe disease	GALC	WHWT, CAIR	Krabbe disease	GALC	149,150
Lamellar ichthyosis	PNPLA1	GOLD	Autosomal recessive congenital ichthyoses	PNPLA1	51
Leukocyte adhesion deficiency	CD18	IRSE	Leukocyte adhesion deficiency	CD18	151,152
Myotonia congenital	CLCN1	MSNZ	Myotonia congenita	CLCN1	153,154
Night blindness	RPE65	BRIA	Leber congenital amaurosis	RPE65	155,156
Progressive retinal atrophy	PDE6A	Multiple	Retinitis pigmentosa	PDE6A	157,158
Progressive rod-cone degeneration	PRCD	Multiple	Retinitis pigmentosa	PRCD	84,85
Retinal degeneration	RHO	MAST	Retinitis pigmentosa	RHO	159,160
Rod-cone dysplasia type 2	RD3	COLL	Leber congenital amaurosis type 12	RD3	161,162
Severe combined immunodeficiency	IL-2R (gamma)	BASS, CARD	Severe combined immunodeficiency	IL-2R (gamma)	163,164
Spinocerebellar ataxia	ITPR1	SPIN	Spinocerebellar ataxia type 15	ITPR1	48,165
Thrombasthenic thrombopathia	ITGA2B	OTTR	Glanzmann thrombasthenia	ITGA2B	166,167
von Willebrand disease	vWF	Multiple	von Willebrand disease	vWF	168

(Continued)

Table 1 (Continued)

Dog disease	Dog gene	Breed	Human disease	Human gene	Reference
Gene families and pathways					
Chondrodysplasia	<i>fgf4</i> retrogene	Multiple	Achondroplasia	FGFR3 ^a	49,169
Copper toxicosis	<i>COMMD1</i>	BEDT	Wilson disease	ATP7B ^b	170,171
Cyclic hematopoiesis	AP3	COLL	Cyclic hematopoiesis	ELA2 ^c	172
Neonatal encephalopathy with seizures	ATF2	SPOO	Neonatal encephalopathy	AP-1 ^d	173,174
Primary epilepsy	LGI2	LARO	Autosomal dominant lateral temporal epilepsy	LGI1 ^e	175,176
Somatic mutations					
Burkitt lymphoma	MYC-IGH translocation	GOLD	Burkitt lymphoma	MYC-IGH translocation	103,177
Chronic myelogenous leukemia	BCR-ABL translocation	GOLD	Chronic myelogenous leukemia	BCR-ABL translocation	103,178
Transitional cell carcinoma of the bladder	BRAF ^{V600E}	Multiple	Urothelial bladder cancer and other cancers	BRAF ^{V600E}	105,179
Behavioral disorders					
Canine compulsive disorder	CDH2	DOB	Obsessive-compulsive disorder	CDH2	180,181
Impulsivity and inattention; novelty seeking	DRD4	GSD, HUSK, SHIB	Activity-impulsivity-related traits (ADHD)	DRD4	182,183

Notes: ^aFGFR3 and ^bATP7B are both in the fibroblast growth factor family, one as ligand and one as receptor; ^cOMMD1 interacts directly with ATP7B; ^dAP3B1 and ELA2 act in the same pathway regulating intracellular trafficking of neutrophil elastase; ^eAP-1 is a member of the ATF family; ^fLGI1 and LGI2 are highly conserved members of the LGI gene subfamily.

Abbreviations: ABUL, American Bulldog; ADHD, attention-deficit/hyperactivity disorder; AMAL, Alaskan Malamute; BASS, Bassett Hound; BEAG, Beagle; BEDT, Bedlington Terrier; BORD, Border Collie; BOX, Boxer; BRIA, Briard; BRIT, Brittany; BSJL, Basenji; CAIR, Cairn Terrier; CARD, Cardigan Welsh Corgi; COLL, Collie; DACH, Dachshund; DOBP, Doberman Pinscher; ESET, English Setter; ESSP, English Springer Spaniel; GOLD, Golden Retriever; GSD, German Shepherd; GSH-P, German Shorthaired Pointer; HUSK, Siberian Husky; IRSE, Irish Setter; LAB, Labrador Retriever; LARS, Lagotto Romagnolo; LHSA, Lhasa Apso; MALT, Maltese; MAST, Mastiff; MSNZ, Miniature Schnauzer; NEWF, Newfoundland; NSDT, Nova Scotia Duck Tolling Retriever; OTTR, Otterhound; PEMB, Pembroke Welsh Corgi; SAMO, Samoyed; SHIB, Shiba Inu; SPIN, Spinone Italiano; SPOO, Standard Poodle; TIBT, Tibetan Terrier; WHWT, West Highland White Terrier.

small numbers of markers and dogs, revealed differences that appeared breed related.^{58–60} In 2004, a study was released that examined nearly 400 dogs from 85 breeds at 96 microsatellite markers. This study showed definitively that the breeds, with the exception of a single pair, were genetically distinguishable.⁶¹ In addition, the study showed that there were four primary clusters of breeds that shared genetic similarity with one another. The first was a group of breeds that were developed in Asia and Africa, the second consisted of mastiff-type breeds, the third cluster combined sighthounds with herding breeds, and the fourth (and the largest) was that of sporting/hunting and companion dogs. These breed clusters grouped on similar physical traits, behavioral traits, or geographic origin. When the study was expanded to over 100 breeds, a fifth breed cluster of large mountain dogs was identified.⁶²

With the development of large-scale SNP genotyping technologies came a large multi-breed study that examined breed relationships and phenotype diversity.^{63,64} Nearly 50,000 SNPs were genotyped on 912 dogs and 225 wolves collected worldwide. Using a phylogenetic analysis of the SNP genotypes and haplotypes built from the SNPs, the authors confirm that the breeds cluster by phenotype or functional ability (Figure 3). They further refine the breed relationships by defining additional clusters within the established groupings such as scent hounds and spaniels within the fourth cluster, and sighthounds separate from herding dogs in the third cluster. This same data set was instrumental in mapping phenotypes that are specific to breed development. Recently, another study examining 1,375 dogs and 19 wolves at the same loci confirmed the separation of the Asian/African breeds from the modern breeds. The authors postulate that this division is likely the result of isolation of these breeds during the explosion of breed creation in Europe preventing hybridization between the breed types.⁶⁵

Some of the earliest phenotype mapping in dogs was done through candidate gene studies of coat color, primarily in the *MC1R/ASIP* pathway (reviewed in Schmutz and Berryere⁶⁶). These studies showed that most mutations affecting canine phenotypes were shared across breeds indicating that they arose once and were then maintained in the breeds where the result was desirable. However, in a minority of cases, multiple mutations could be found in the same gene with no breed specificity.⁶⁷ For example, three mutations were identified in the *TYRP1* gene that creates brown coat color. Combinations of these mutations were identified within the same breed and even within the same dog that suggest that the phenotype has arisen multiple times independently in the history of the dog, likely before the advent of the breeds.

Figure 1 Examples of homozygosity and haplotype mapping from studies of morphology and disease phenotypes.

Notes: (A) Complete loss of heterozygosity in nine chondrodysplastic breeds (red) is observed across 50 SNPs in a 24 kb region. Observed heterozygosity remains unchanged throughout the region in the eleven control breeds (black). The x-axis shows the position on chromosome 18 (canfam2), and the y-axis shows observed heterozygosity. Copyright © 2015. Courtesy of JSTOR. Reproduced from Parker HG, VonHoldt BM, Quignon P, et al. An expressed *Fgf4* retrogene is associated with breed-defining chondrodysplasia in domestic dogs. *Science*. 2009;325(5943):995–998.⁴⁹ (B) Comparison of haplotypes found in 84 Standard Poodles with squamous cell carcinoma of the digit identifies a 28 kb haplotype shared by all, in which a CNV was identified that segregates perfectly with the disease. The red blocks on top indicate LD blocks, and the blue lines show the four haplotypes observed in the data set. The repeat elements that make up the disease associated CNV are outlined in red on the UCSC genome plot of the associated region on chromosome 15. Two copies are found in the reference. Affected individuals carry four to five copies. Reproduced from Karyadi DM, Karlins E, Decker B, et al. A copy number variant at the KITLG locus likely confers risk for canine squamous cell carcinoma of the digit. *PLoS Genet*. 2013;9(3):e1003409.³⁴

Abbreviations: SNP, single-nucleotide polymorphism; CNV, copy number variant; UCSC, University of California, Santa Cruz; LD, linkage disequilibrium.

The development of linkage and radiation hybrid maps of the dog genome allowed researchers to begin looking for novel gene variants that lead to major phenotypes. Using a linkage strategy in a crossbred pedigree of dogs, a new locus was identified that associated with solid black and brindle coat colors.⁶⁸ Sequencing and haplotype analysis across multiple breeds found that the beta-defensin gene (*CBD103*), a gene usually associated

with the immune system, was responsible for dominant black coat.⁶⁹

The first GWAS performed in the dog analyzed very small numbers to identify trait-associated loci of large effect.⁷⁰ Less than ten cases and ten controls were chosen to represent segregating coat types in Boxers and Rhodesian Ridgebacks and were genotyped at 27,000 SNPs. Complete sequencing of the associated haplotypes identified a 100 kb

Table 2 A list of common internet resources available for accessing canine genome information and tools

Resource	Source	Reference
Canine genome browsers	UCSC	185
	Ensembl	186
	NCBI	187
Transcript annotations	Broad Institute	188
	Ensembl	189
Canine BAC libraries	CHORI (Boxer)	190
	CHORI (Doberman)	191
Canine SNP genotyping	Illumina, Inc.	192
	Affymetrix	193
	Broad	194
Canine expression array	Agilent	195
Canine CGH array	NCSU	196
	Agilent	197
Canine linkage maps	NHGRI	198
	UCDavis	199
Canine RH maps	NHGRI	200
Comparative genome maps	Rennes	201

Abbreviations: BAC, bacterial artificial chromosome; CGH, comparative genomic hybridization; CHORI, Children's Hospital Oakland Research Institute; NCBI, National Center for Biotechnology Information; NCSU, North Carolina State University; NHGRI, National Human Genome Research Institute; Rennes, University of Rennes; RH, radiation hybrid; SNP, single-nucleotide polymorphism; UCDavis, University of California, Davis; UCSC, University of California, Santa Cruz.

region around *MITF* as the source of white spotting in Boxer and Boxer-related breeds. A follow-up analysis found that a large CNV on CFA18 was responsible for the hair ridge in the Rhodesian Ridgebacks.⁷¹ The success of these association studies confirmed the power of the canine GWASs to uncover simple genetic traits.

Many of the most interesting traits found in dogs are those that define the breeds. These cannot be traced through pedigrees because they do not segregate within breeds (Figure 2). In order to identify these genes, large multi-breed mapping sets were developed. Brachycephaly, the foreshortened skull and snout, is a complex trait found in many breeds such as Bulldogs, Pugs, and Pekingese. Multi-breed GWASs have identified up to eight loci significantly associated with the skull phenotype.^{64,72,73} Homozygosity mapping and haplotype comparisons at one of these loci identified a missense mutation in *BMP3* that was shown to have biological relevance through zebrafish knock-down and rescue assays.⁷³ The combination of multi-breed GWAS and homozygosity/haplotype analysis has been used successfully to identify mutations responsible for traits such as leg length, coat type and color, skull shape, and body size.^{47,49,64,74–76}

A comprehensive study of canine skeletal traits came from the collection of a large cohort of Portuguese Water Dogs (PWDs) with extensive morphologic data.⁷⁷ Based on radiographic measurements, genome regions were

associated with skeletal traits such as skull length, pelvic width, bone width, and overall body size. Body size was associated with two markers on chromosome 15, one of which was near the insulin-like growth factor 1 (*IGF1*). This finding was extended using a multi-breed approach to identify the causative alleles. The initial 4 Mb associated region was fine mapped by SNP genotyping both large and small PWDs as well as dogs from small (<9 kg) and large (>30 kg) breeds. A single haplotype was identified in all 14 small breeds that included the *IGF1* gene. This same haplotype was present in the small PWDs clearly displaying that studies carried out in a single breed could be significant in other breeds, especially in the case of highly selected morphologic traits.

Variation in canine body size is a particularly popular subject in mapping studies.^{64,78,79} From the smallest breeds like the Chihuahua to the giant English Mastiff, there can be a tenfold increase in height and a 50-fold increase in weight.⁸⁰ This variation is almost entirely inherited as it is maintained within breed structures where variation in size and weight is extremely low (Figure 4). A recent study shows that seven variants in six genes can explain 50% of size reduction in dogs.⁷⁶ The smallest breeds carry all seven of the mutations, while breeds averaging 41 kg (90 lbs) or more rarely carry any of the mutations (Figure 5). In comparison, the mapping of height in humans has identified 180 loci and yet explains approximately 10% of observed variation.⁸¹ This is an excellent example of how canine population structure can help simplify the genetics of a complex phenotype. The constant selective pressure on desirable traits while maintaining current standards can fix the most effective mutations while eliminating the steady build of lesser deleterious mutations. If this axiom holds true across phenotypes, it will prove especially important when applied to disease mapping.

The dog as a model to study human genetic disease

Dogs share more genetic similarity with humans than do traditional model organisms such as the mouse³⁹ and an estimated 360 naturally occurring analogous diseases.⁸² Further, many of the traditional gene discovery methods discussed above (linkage analysis, GWAS) can be difficult and costly in humans due to the need for large numbers of samples to make up for short stretches of linkage disequilibrium and extensive disease heterogeneity. These same studies can be enhanced in dogs due to the predisposition to certain diseases within breeds where the unique population structure limits heterogeneity and increases linkage

Figure 2 Domestic dogs display a range of morphologies some of which are represented here.

Notes: Profiles of an (A) Afghan Hound and (B) Pug display two of the most prominent skull morphologies – dolichocephalic and brachycephalic, respectively. (C) The Irish Wolfhound standing side by side with the Border Terrier are examples of the range in sizes found in full-grown dogs of different breeds. (D) The group of Bernese Mountain Dogs display the phenotypic homogeneity that is found within a breed.

disequilibrium.^{82,83} As such, the dog offers an alternative and parallel system in which human diseases can be studied, both for discovering information about susceptibility and disease development and for predicting the course of a disease and optimal treatments.

Simple, monogenetic diseases in dogs often have the same genetic causes in humans (Table 1). One such example of this is progressive rod–cone degeneration (*prcd*) in dogs and its analogous disease in humans, retinitis pigmentosa (RP).⁸⁴ In one of the first linkage-mapping studies, *prcd* was mapped to canine chromosome 9, orthologous to human chromosome 17q where a human RP locus was suggested to reside. Using haplotype analysis and a retinal cDNA library, a novel gene (*PRCD*) was identified that harbored a mutation segregating

perfectly with the canine disease. The identical mutation was found in a woman diagnosed with autosomal recessive RP.⁸⁵ This is a perfect example of how canine disease genetics mimics human and in this case allowed for the identification of a previously unknown gene and mutation. There are many other examples in which genetic mapping of diseases in dogs has led to the discovery of mutations in a homologous gene in humans, some of which can be found within the list of gene mutations in Table 1.

Single-gene disorders have played an important part in establishing the canine system as an exemplary counterpart to human studies; however, complex diseases are the area of greatest need. Because of the nature of the disorder, complex diseases are difficult to model in a laboratory as

Figure 3 Phylogenetic tree of 80 domestic dog breeds rooted with the coyote.

Notes: The neighbor-joining cladogram is based on consensus haplotype sharing of phased, ten-SNP windows spanning the genome. Each breed is represented by six dogs. Color coding of the branches is based on phenotypical or historical groups developed by dog fanciers.¹⁸⁴ Dots indicate >95% bootstrap support from 1,000 replications. Reproduced from Vonholdt BM, Pollinger JP, Lohmueller KE, et al. Genome-wide SNP and haplotype analyses reveal a rich history underlying dog domestication. *Nature*. 2010;464(7290):898–902.⁶³

Abbreviations: SNP, single-nucleotide polymorphism; PBGV, Petit Basset Griffon Vendéen.

they require interactions or correlated action from multiple genes as well as some degree of environmental interaction. As an intermediate, the dogs provide an intriguing option to traditional models or human studies. They develop disease naturally through inheritance and interactions with our environment, yet their breed structure creates independent and unique strains in which heterozygosity is reduced and mapping is less complex.

One of the best examples of the canine role in elucidating genetic contributors to a complex human disorder can be found in the sleeping disorder narcolepsy. Canine narcolepsy with cataplexy was one of the first diseases mapped in the dog using microsatellites in a colony of narcoleptic Doberman Pinschers and Labrador Retrievers where the disorder segregated as an autosomal recessive trait. Extensive fine mapping

and resequencing identified a SINE insertion in the *HCRT2* gene.⁸⁶ This finding revealed a family of neurotransmitters that had not been previously associated with sleep. Shortly following this discovery, a mutation was identified in a human early-onset narcolepsy case, and more importantly, a deficiency in the hypocretin system was identified in the majority of cases of narcolepsy with cataplexy showing the importance of the gene family in the human disease and altering the future of sleep studies.⁸⁷

Many of the most prevalent complex diseases in people are also very common in dogs such as diabetes, epilepsy, heart disease, and cancer. In 2005, a canine GWAS identified a repeat expansion in *NHLRC1* (previously known as *EPM2B*) as the cause of a canine version of epilepsy in Dachshunds that is similar to Lafora disease.⁸⁸ This finding

Figure 4 Average size range of domestic dog breeds.
Notes: Average size of the domestic dog can range from 12 to 92 centimeters in height and 2 to 70 kilograms in weight. This range is found across all breeds, while individual breeds will cover only a subset of that range. The measured height at the withers and weight of five dogs from 21 different breeds are graphed with weight on the x-axis and height on the y-axis. The full range of sizes is represented, but each breed comprises only a fraction of the variation. Breeds are indicated by different colors. The points representing the five individuals of each breed are circled with the same color line.

Figure 5 Alleles at six size loci combine to reduce size in dogs.
Notes: The frequency of each size-associated allele is indicated by the shade of red in a block with red =100% and yellow =0%. Five hundred dogs were genotyped at each locus and grouped by breed average weight divided into 5-pound increments. The frequency of the derived variant allele increases with a decrease in size at all loci. Copyright © 2013. Rimbault M, Beale HC, Schoenebeck JJ, et al. Derived variants at six genes explain nearly half of size reduction in dog breeds. *Genome Res.* 2013;23(12):1985–1995.⁷⁶

coincided almost exactly with the discovery of mutations in the same gene in the human disease.⁸⁹ Since then, mutations in ten different genes have been identified as causative for forms of epilepsy in ten different breeds of dog (reviewed in Ekenstedt and Oberbauer⁹⁰). The availability of many breeds, each with independent disease inheritance, allows for the discovery of complex disease pathways, one gene at a time.

Cancers in dogs offer a unique opportunity to inform human disease. As a result of the founder effect, canine cancers are often breed specific or overrepresented in particular breeds. For instance, 25% of Bernese Mountain Dogs (BMDs) are estimated to develop histiocytic sarcoma, and 12.5% of Rottweilers develop osteosarcoma.⁹¹ That certain cancers tend to segregate within specific breeds reduces the genetic and environmental noise that is associated with those cancers, and allows for a genetic association to be made more readily than would be in human cases.

One example is histiocytic sarcoma, a rare, lethal cancer in humans that often strikes juveniles. It is also a rare tumor in dogs but is very common in BMDs allowing for mapping studies that can elucidate genetic factors that may be informative in both species. The first GWAS on histiocytic sarcoma was undertaken in BMD and revealed an association with the *MTAP-CDKN2A* locus on CFA11,⁹² a locus homologous to human 9p21 which is implicated in many human diseases including cancers.⁹³ Similarly, squamous cell carcinoma of the digit in Standard Poodles, Giant Schnauzers, and Briards is associated with a CNV on CFA15 near *KITLG*.⁹⁴ These studies capitalized on the minimal genetic heterozygosity of cancer inheritance in the dog. Lymphomas are common in both dogs and humans and represent an area of oncology study that would immediately benefit both species. A recent GWAS in Golden Retrievers has identified two loci on CFA5 that are associated with both lymphoma and hemangiosarcoma in the breed.⁹⁵ Different forms of cancers associated with the same locus suggest that there are mutations that affect tumor formation in general and comparing different tumor types with the same causative mutations may help to ferret out the genetics behind tissue specificity.

Conclusion and future prospects

The promise of dog genetic studies lies in translation of our findings to improved treatments in both dogs and people. For instance, Golden Retriever muscular dystrophy, a homologue of Duchenne muscular dystrophy (DMD), is caused by exon skipping followed by early truncation of the dystrophin (*dmd*) gene, the same gene that is mutated in two thirds of human beings with DMD.⁹⁶ Because *dmd* is one of the longest genes

in the genome, new genetic approaches to treat DMD have been to promote in-frame exon skipping of the mutated area of *dmd* to produce a more functional, partial protein leading to a less severe phenotype. To find a tolerable and long-lasting therapy, a small nuclear RNA delivered through a recombinant adenovirus was tested on Golden Retrievers with muscular dystrophy.^{97,98} The success of these trials has recently led to a delivery and safety trial specifically staged to prepare for human trials.⁹⁹

Muscular dystrophy is not the first area in which gene therapy has been used successfully in the dog leading to human trials. Multiple forms of canine progressive retinal atrophy have been successfully treated using gene supplementation (reviewed in Petersen-Jones¹⁰⁰). Clinical trials on RPE65-deficient RP, Leber congenital amaurosis type 2, treated with gene augmentation therapy, showed stable vision improvement and no adverse effect over 3 years.¹⁰¹ Recent success in treating X-linked RP in the dog shows similar promise for translation to human.¹⁰²

In addition to inherited mutations, studies are showing that canine diseases share many somatic alterations with human diseases. For example, the Philadelphia chromosome, a common translocation between human chromosomes 9 and 22 found in chronic myelogenous leukemia, is also found in dogs with the same disease (translocation between canine chromosomes 9 and 26).¹⁰³ A similar translocation has been found in human and canine Burkitt lymphoma (between human chromosomes 8 and 14 and between canine chromosomes 13 and 8), and the *RBI* gene locus is deleted in both human and canine chronic lymphocytic leukemia. These findings suggest that there are inherently fragile regions of the genome that support tumorigenesis and further comparison of human and canine tumor DNA may enable the discovery of novel cancer genes and mutations. Studies investigating osteosarcoma in dogs have suggested some candidate genes that may be important in the human disease. A comparison of the expression profiles of human and canine osteosarcoma found that overall, the expression profiles were indistinguishable, but a closer inspection of individual genes identified two genes that were expressed in all dogs but only a subset of humans. These genes, *IL-8* and *SLC1A3*, are associated with a more aggressive form of the cancer.¹⁰⁴

Highly similar mutation loads will allow for the testing of targeted treatments and therapies in dogs that have the potential to benefit humans as well. The goal of personalized medicine is to tailor treatment strategies to fit the individual patient. Sequencing of the transcriptome of canine invasive bladder cancers has recently identified the common human BRAF^{V600E}

mutations in >85% of tumors.¹⁰⁵ Because the BRAF^{V600E} mutations are present in 8% of all human cancers, they have been the focus of multiple clinical trials using targeted drug therapies.¹⁰⁶ Identification of identical mutations in a naturally occurring dog tumor puts the dog at the forefront of preclinical trial strategies for highly specific therapies enabling the determination of dosage amounts, testing combination therapies, and determining efficacy prior to costly human trials.

Tremendous advances have been made in canine genetic and genomic studies since the first backcrosses were performed and proteins isolated. As a system for scientific discovery, canine genomic researchers now have the necessary tools and the ability to answer questions of inheritance, association, and causality. Novel treatment strategies have been introduced based on canine genetic studies, and the population structure encourages the development of assays to interrogate the effects of environmental and genetic background on inherited mutations. With modern molecular techniques, canine genomic information is booming, adding to our knowledge of the dog, how we have shaped its history, and how it, in turn, is helping us to improve our future.

Disclosure

The authors report no conflicts of interest associated with this work.

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