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# Canine Cancer Genomics: Lessons for Canine and Human Health

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## Abstract

Dogs are second only to humans in medical surveillance and preventative health care, leading to a recent perception of increased cancer incidence. Scientific priorities in veterinary oncology have thus shifted, with a demand for cancer genetic screens, better diagnostics, and more effective therapies. Most dog breeds came into existence within the last 300 years, and many are derived from small numbers of founders. Each has undergone strong artificial selection, in which dog fanciers selected for many traits, including body size, fur type, color, skull shape, and behavior, to create novel breeds. The adoption of the breed barrier rule—no dog may become a registered member of a breed unless both its dam and its sire are registered members—ensures a relatively closed genetic pool within each breed. As a result, there is strong phenotypic homogeneity within breeds but extraordinary phenotypic variation between breeds. One consequence of this is the high level of breed-associated genetic disease. We and others have taken advantage of this to identify genes for a large number of canine maladies for which mouse models do not exist, particularly with regard to cancer.

## INTRODUCTION

Domestic dogs are remarkable members of our society. They serve as companions, guardians, herders, and hunters. Bred to specific standards, modern domestic breeds are the result of hundreds of years of strong selection for traits beneficial to human survival and aesthetic preferences as subtle as the shade and gradation of coat color for a given breed (1). Some physical and behavioral traits go naturally together; for example, a hunting dog must have a morphology that permits him to be active and athletic (2). Because there exist strict breeding programs to achieve true-breeding animals with high levels of specificity, domestic dogs experience a considerable amount of genetic disease as mutations become trapped within the closed gene pool (3, 4). Most canine diseases are reminiscent of human disorders, and studies of canine health inform human health (3).

The American Veterinary Medical Association reports that there are 70 million pet dogs at any time in the United States, distributed over 43 million homes with an average of 1.6 dogs per home (5). Because pets are viewed as bona fide family members in a majority of those homes, canine health is a booming business, with owners and breeders participating in more than 100 million veterinary visits each year (5). One of the most devastating diseases for dogs and humans is cancer (6–8). An estimated 4.2 million dogs will be diagnosed with cancer every year in the United States. Indeed, cancer occurs in dogs at essentially the same frequency as in humans.

Several scientists have argued that the dog is the heart of nonstandard model organism comparative genetics, particularly when it comes to cancer (3, 6, 9). Dogs are diagnosed with many of the same cancers as humans, with 17.5 million pet dogs in the United States predicted to get cancer at some point in their life (5, 10, 11), and with a similar underlying presentation, pathology, and treatment response (6, 9, 11–15). Unlike other cancer models, such as mice, canine cancers are generally spontaneous and do not need to be induced by exogenous means such as toxins or viruses (16). Cancer in dogs also follows the general epidemiology of human cancer occurrence. Although there are some early-age cancers that likely relate to genetic predisposition, most dogs develop cancer late in life, similar to humans (14). There are some exceptions in terms of frequency; e.g., prostate cancer is common in humans but rare in dogs, whereas sarcomas as a whole are proportionately more common in dogs than in humans (17). But the observed similarities in presentation, treatment, and outcomes make the dog an exceptional system in which to study a host of common human cancers, including invasive bladder cancer, leukemia, lymphoma, neural tumors, and melanoma (6, 14, 15).

To obtain a clear understanding of the unique canine population structure and how it contributes to the high incidence of cancer in dogs, we begin with an overview of canine history and domestication. This is followed by a dissection of breed structure and how that facilitates study of canine disease. We next review what is known about the canine genome and the features that make the dog an excellent genetic system for cancer studies and consider breed-specific disease risk. Finally, we discuss the specifics of several types of cancer and their relationship to human disease, concluding with a discussion of the curious case of transmissible tumors.

## CANINE DOMESTICATION

The dog (*Canis lupus familiaris*) was the first domesticated species, developed prior to the agricultural revolution (18). Although there is no firm consensus as to the location(s) and timing of key domestication events (reviewed in 19, 20), there is agreement that dog breeds share a common ancestor, the gray wolf (21), and no other canine has contributed to the genetic lineage of the modern dog (21–23). Importantly, the modern gray wolf is not closely related to the wolf populations that were originally domesticated, the latter of which are thought to be extinct (23).

Archeological remains from Israel and Germany suggest a domestication time frame of 12,000–15,000 years before present (24, 25), a result that was initially supported by mitochondrial DNA sequence variation studies (26) and subsequently by other methods, most recently including whole-genome sequence analysis (WGS) (23). Various studies suggest that key domestication events may have occurred in China (26), Siberia (27), Europe (28), Central Asia (29), and/or the Middle East (30), with indications that dogs were domesticated either once (31) or twice (32, 33), with the wolf–dog divergence taking place no longer than 40,000 years before present.

Although most studies, such as those referenced above, have focused on the impact of European and Asian dogs on modern breeds, very recent work has produced genetic evidence that early dogs from the Americas have also had a genetic impact on modern breeds (34). Analysis of 161 breeds with 170,000 single-nucleotide polymorphisms (SNPs) shows that breeds such as the Chihuahua, Mexican hairless, and Peruvian hairless form their own branches in a phylogenetic tree of dog breeds, distinct from the European and Asian breeds (**Figure 1**). The unique evolutionary history of these breeds has led to speculation that early dogs were brought to the Americas by humans across the Bering Land Bridge and dispersed to North America, South America, and Mexico. Over time these dogs mixed with European dogs brought by American colonists, producing modern dogs that retained the signature of the early American breeds. Parker et al. (34) show that the fingerprint of those early dogs persists in present-day breeds and has not been erased by introgression with dogs from modern colonists.

How does this affect canine cancer studies? Dogs have undergone thousands of years of human-directed breeding and selection, giving rise to hundreds of phenotypic variants (35–40), many of which define modern morphological or behavioral phenotypes. The history of humans and dogs is highly intertwined (18, 41), producing nearly 500 breeds/populations worldwide, most of which are fewer than 200 years old (30, 34, 42, 43). In aggregate, the evidence predicts that strong selection on small numbers of genes defines many modern phenotypes and suggests the hypothesis that selection for desired phenotypes may have led to piggybacking of deleterious alleles that contribute to cancer risk (14, 38, 39 and references therein).

## BREED STRUCTURE AND GENOMIC ANALYSIS

An understanding of modern breed structure is critical to finding cancer genes in dogs. Susceptibility to most human cancers, even so-called hereditary forms, is complex and characterized by both incomplete penetrance and genetic heterogeneity (44). It has been argued that many of these issues are circumvented in dog studies, as closely related breeds are likely to share common susceptibility genes (40, 45–47). Further, the closed breeding structure of purebred dogs means that fewer genes are likely to be critically responsible for susceptibility to any given complex disease, including cancer, compared with humans. Individual breeds, however, each possess a dense population structure with recognizable patterns of haplotype inheritance. These factors can both help and hinder attempts to map causal variants in dogs.

During breed development, individual dogs were selectively bred to propagate desirable traits, resulting in a population bottleneck, with large chromosomal regions concentrated within smaller populations. The practical result of this is that linkage disequilibrium (LD) may extend for lengths up to fifty-fold longer than that observed in human populations (48, 49). The increased LD permits the use of fewer markers to capture patterns of selection and divergence than would be possible in species with smaller average LD. Thus, whereas 300,000 SNPs might be required for a successful genome-wide association study (GWAS) in humans, Lindblad-Toh et al. (49) predicted that 10,000 SNPs would be sufficient for an equivalent association study in dogs, assuming the

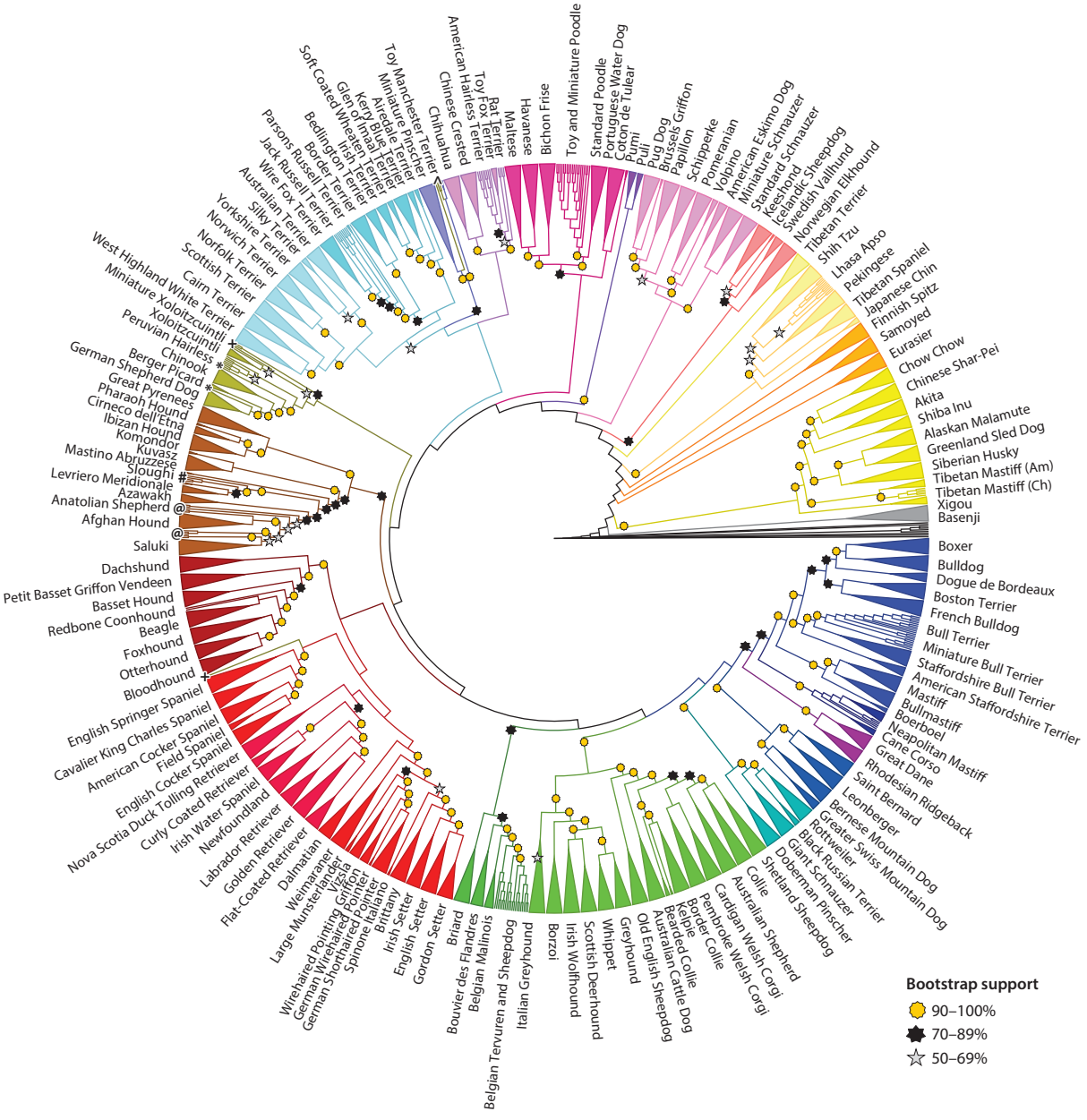


**Figure 1**

Cladogram of 161 domestic dog breeds. Single-nucleotide polymorphism genotypes for 1,359 canids were analyzed in 100 randomly sampled marker sets (bootstraps) to compare breed relatedness. Dog breeds that form unique groups, or clades, supported by 100% of bootstraps are combined into triangles. For all other branches, a gold star indicates 90% or better bootstrap support, meaning that at least 90 out of 100 replications resulted in this grouping; black and silver stars reflect 70–89% and 50–69% support, respectively. Breeds are listed on the perimeter of the circle. Related breeds sharing a common ancestor cluster together to form 23 multibreed clades (color-coded), branching out from the gray wolf (*black*). A small number of dogs do not cluster with the rest of their breed, indicated as follows: *Cane Paratore, +Peruvian Hairless, #Sloughi, @country-of-origin Saluki, and ^Miniature Xoloitzcuintli. Figure adapted from Parker et al. (34) under a Creative Commons Open Access license.

allele in question was highly penetrant and dominant. This was validated by simulations using 15,000 SNPs, 100 each of cases and controls, and genomic parameters replicating those of the dog genome. Test studies were able to identify causal loci for 99% of Mendelian dominant test traits and 50–97% of tested multigenic traits (49).

Several traits have been mapped using the above parameters, including those associated with both disease and morphology (35–37, 50; reviewed in 39). Recently, the ability to detect signals of genome-wide significance using a semicustom SNP array of 180,000 markers was tested for qualitative traits, within or across breeds, and using variable cohort sizes (37). The within-breed association identified genes for seven traits, all associated with complex canine disease, using very small sample sizes. For instance, a haplotype for idiopathic epilepsy was found using just 34 cases and 168 controls. Across-breed association analyses yielded fewer results, with significant loci found in just two instances.

Although causal variants through within-breed SNP profiling using 170,000 markers have been successfully identified with modest sample sizes for Mendelian diseases (e.g., 51–54), the overall approach of a modest number of SNPs and samples in association studies has limitations. Many loci identified through GWAS extend for megabases, and genes and causal variants will not easily be found. Further, this approach, with few exceptions (50, 55), does not readily identify recessively acting alleles of modest to low penetrance, gene–gene interactions, and copy number variants (CNVs) (56, 57). Also, single-breed analysis can lead to false-positive signals owing to breed-specific population structure.

Employing multiple breeds in a well-balanced association study can negate many of the issues of single-breed studies, including population substructure and long stretches of LD, and allow for greater cohort sizes to improve statistical power (4, 34, 49). However, this approach can also inadvertently skew results owing to inherent phenotypic or phylogenetic imbalances between cases and controls. One approach to address this problem is the application of patterns of homozygosity for individual dogs in GWAS (58). To test this idea, values of single-dog homozygosity, shared homozygosity over 10 same-breed dogs, and the rate at which any one dog will reduce the calculated shared homozygosity for its breed were determined for 80 breeds using a panel of 170,000 SNPs (58). Shared homozygosity over 10 dogs of the same breed differed greatly among the 80 breeds tested, ranging from 48.09 to 769.78 Mb (**Figure 2**). However, the most important value is the breed-specific rate of homozygosity decay. This value, ranging from 0.1996 to 0.6065 across 80 breeds, reflects the percentage of the shared homozygosity by which every additional dog of the same breed will reduce the calculated shared homozygosity for that breed. It is therefore possible to estimate the number of dogs for a given breed that would be required to theoretically represent the entire amount of expected variation within that breed (58). Multibreed GWAS could be adjusted accordingly to ensure that a given breed is not overrepresented among the case or control group.

Recently a new strategy has been proposed for canine GWAS, using variants derived from whole-exome sequencing (WES) instead of simply SNPs (59, 60). Broeckx et al. (60) used WES and genome-wide SNP profiles for a small number of dogs and then estimated the power of exome sequence variants to identify genes controlling fixed traits. Using simulated phenotypes, they showed that exome sequence–based GWAS has a higher power to detect associations within coding regions compared with moderately dense (170K) SNP chips. Forman et al. (59) applied a similar approach, leading to identification of a glaucoma-associated inversion that disrupts the *ADAMTS17* gene. However, this approach is less useful for finding high-impact variants in regulatory regions where we expect many cancer mutations lie.

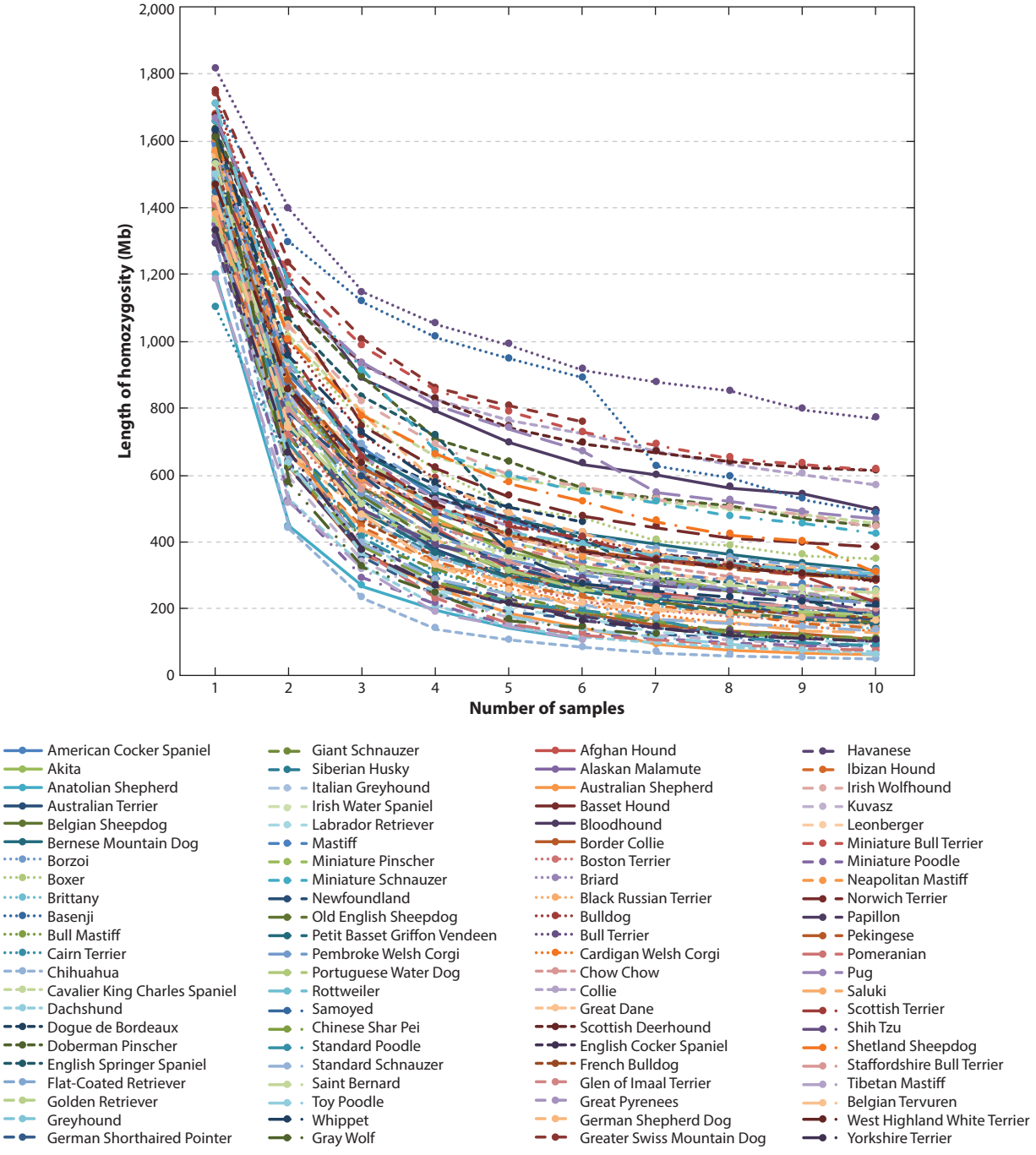


**Figure 2**

Length of homozygosity from single-nucleotide polymorphism chip genotypes, recalculated with sequential addition of single same-breed dogs. The overall pattern of loss of private homozygosity with the inclusion of additional dogs, up to 10 per breed, is shown for 80 breeds. Figure adapted from Dreger et al. (58) under a Creative Commons Open Access license.

## CANINE PHYLOGENY

Determining the relationships between dog breeds, as well as the traits they likely share, is critical for informing the study design of any canine GWAS. Related breeds are much more likely to share a trait caused by a common variant, inherited from a recent ancestor that gave rise to multiple breeds. However, until recently, no published studies of breed structure (61–63) or relatedness (30, 63, 64) have explained the mechanisms through which distinct breeds have developed, such as geographic separation and immigration, the role of hybridization, or the timeline of breed formation.

Toward that end, we recently assembled a cladogram using a neighbor-joining tree algorithm defining 23 multibreed clades reflecting shared physical traits, behaviors, and/or geographic origin. Haplotypes (combinations of alleles) within 100-SNP sections were determined from 150,000 SNP genotypes for 1,359 dogs. The total length of haplotype sharing was summed for all pairs of dogs to assess admixture during breed development (34) (**Figure 3**). We found that there was four times more haplotype sharing within breed clades than across clades. Individual instances of enhanced haplotype sharing between breeds with diverse phylogenetic backgrounds suggest that interclade crosses were done thoughtfully and for the introduction of a desired new trait into an existing population. For example, we observe haplotype sharing between the unrelated terrier (**Figure 3**, *teal group*) and bully-type/mastiff clades (**Figure 3**, *dark blue group*), illustrated by blue ribbons connecting the clades, that coincides with historical crosses of bully and terrier dogs in Ireland in the late 1800s to create dogs who excelled at dog fighting when it was a popular sport. By establishing a linear relationship between the total length of haplotype sharing and the age of known introgression events, it is possible to estimate critical breed formation events that occurred within the last 200 years. These data can be used to increase the power of GWAS by improving the way in which breeds are combined for analysis. No longer are investigators limited to a single breed or dogs within a single clade, but the history of the breed, and likely migration of disease alleles, can be incorporated into analysis as well; i.e., using breeds with a shared genetic background increases the likelihood of identifying identical mutations underlying the trait or disease of interest present in those breeds.

## BREED-SPECIFIC CANCER RISK

Cancer is the leading cause of disease-associated death in dogs, affecting one in four individuals, with 50% of dogs >10 years old developing the disease (65–67). Studies indicate that the genes and pathways involved in canine cancer development are similar to those found in humans (68, 69). The compressed life span of dogs means that cancers that take 15–20 years to mature in humans can be studied in the dog in 2–3 years (7, 70). Perhaps most importantly, canine cancers are spontaneous, distinguishing the dog from other mammalian cancer models such as the mouse, in which many cancers must be induced (reviewed in 3, 11, 13–15). Overall, this rationale argues that genetic studies of canine disease are a powerful way to advance our understanding of cancer in humans and companion animals alike (3, 11, 13, 71).

Cancer incidence is threefold higher in female dogs than male dogs (10), with mammary cancer the most frequently diagnosed malignancy [incidence rate (IR) = 191.8; 95% confidence interval (CI) = 182.2–201.4], followed closely by non-Hodgkin's lymphoma (IR = 22.9; 95% CI = 19.7–26.5) in bitches and non-Hodgkin's lymphoma (IR = 19.9; 95% CI = 17.4–22.7) and skin cancer (IR = 19.1; 95% CI = 16.6–21.8) in male dogs. Which breeds are most cancer prone remains a topic of debate. The UK Kennel Club contends that the Irish water spaniel, flat-coated retriever (FCR), Hungarian vizsla, and Bernese mountain dog (BMD) are at particularly high risk (67), and

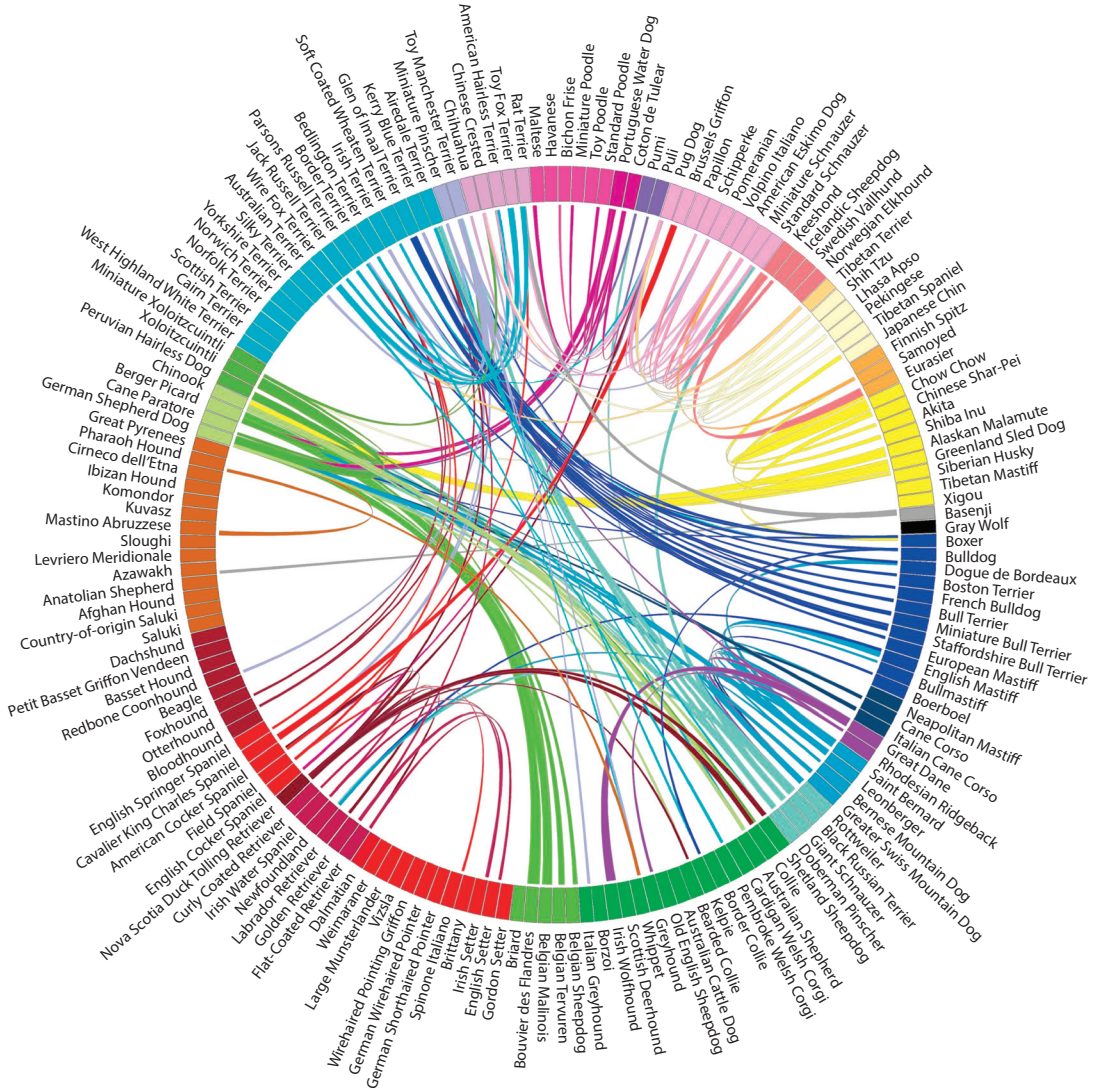


**Figure 3**

Haplotype sharing between breeds from different phylogenetic clades. The circos plot is ordered and colored to correspond with the tree in **Figure 1**. Ribbons connecting breeds indicate a median haplotype sharing between all dogs of each breed in excess of 95% of all haplotype sharing across clades. Figure adapted from Parker et al. (34) under a Creative Commons Open Access license.

other European lists include the boxer, St. Bernard, and Irish wolfhound (72). Jane Dobson (65), a longtime expert in the field, reports that cutaneous histiocytoma is the most common canine tumor type reported overall in the United Kingdom, followed by lipoma, adenoma, soft tissue sarcomas, mast cell tumor, and lymphomas.

Many tumor types are comparatively more common in subsets of breeds owing to population structure and breed formation, the same characteristics that make them mappable (3, 4, 64, 74). For instance, tumors of the central nervous system are diagnosed most frequently in the boxer, golden retriever, French bulldog, and Boston terrier (75). Meningiomas are observed more frequently

in the dolichocephalic breeds (which have elongated muzzles), and, coincidentally, glial tumors are diagnosed more often in brachycephalic breeds (which have shortened, upturned muzzles). Osteosarcoma occurs with high frequency in long-limbed breeds like the Scottish deerhound and Great Dane (65, 76–78). Histiocytic sarcoma (HS), although rare in dogs, is prevalent in FCR and BMD (79–81), although in this case the disease origins may be different for each breed. Finally, invasive transitional cell carcinoma (InvTCC) of the bladder is observed with highest frequency in Scottish terriers. InvTCC also occurs with modest frequency in West Highland white terriers and Shetland sheepdogs (7 and references therein). Studies of these breeds and their associated cancers provide opportunities for dogs to reveal new genetic susceptibility information regarding tumors of interest to human and animal health.

Among the first type of informative cancer studies done in dogs were those associated with cytogenetics. The development of a canine cancer gene microarray for comparative genome hybridization of tumors (82–84) was a critical first step in understanding the genomic rearrangements associated with various tumor types, for instance, lymphoma (83). Later versions of the array yielded a resolution of one megabase (84) and provided insight into early events in the development of common canine cancers, including mast cell tumor, leukemia, and lymphoma (85). Perhaps most importantly, comparative genome hybridization arrays have the potential to yield information regarding ancestral mechanisms of cancer development by identifying common rearrangements in comparable human cancers. Examples include formation of the BCR-ABL fusion (Philadelphia chromosome) in canine chronic myelogenous leukemia in dogs, the translocation of the *MYC* gene to the immunoglobulin heavy-chain enhancer region in canine lymphoma, and deletion of the *RB-1* locus in chronic lymphocytic leukemia (85). These early findings provided the impetus for researchers to assert that knowledge gleaned from canine cancer studies would almost certainly be of value for studies of comparable human cancers. Thus far, that has proven to be correct.



## HUMAN AND CANINE CANCERS

In many countries, humans spend an extraordinary amount of money caring for their dogs, often keeping them alive for months, if not years, beyond the end of their expected life span. This, coupled with rapid advances in veterinary science, means that canine cancer researchers have at their disposal an extraordinary amount of epidemiologic and histopathologic data for studies of canine cancer susceptibility. There are particular cancers for which significant progress has been made in understanding the genetics of susceptibility, whereas other cancer advances have focused on identifying factors that contribute to tumor growth and development. We review three specific tumor types: bladder cancer, HS, and squamous cell carcinoma. We then comment on transmissible tumors, the dog being one of only two nonlaboratory mammalian models for this rare but concerning cancer oddity.

### Transitional Cell Carcinoma of the Bladder

Application of the canine system to InvTCC is particularly efficacious because multiple breeds are at high risk, suggesting a genetic predisposition. The disease is also important in humans and difficult to treat in both species, particularly in dogs, in part because owner finances may sometimes be limited (86–88). More than 16,000 people in the United States, and 160,000 worldwide, die from InvTCC each year (89). Approximately 20% of patients who present with InvTCC cancer already have metastatic disease (90). The initial course of treatment is bladder removal (cystectomy) (91). However, studies show that 50% of patients will go on to develop metastases even after

cystectomy for what was initially clinically localized disease (92). Among patients who opt for chemotherapy (usually cisplatin based), most will still experience drug resistance and metastases. Indeed, the median survival time for patients with metastatic disease is 14 months, and it is frequently reported that the number has not changed in >20 years (93). There is, therefore, a strong need for spontaneous animal models of InvTCC (7).

When considering InvTCC susceptibility, large human GWAS have identified several loci (94), and studies show that smoking increases risk (95). Indeed, human GWAS and WES have identified 17 loci on 13 chromosomes in populations from the United States, the Netherlands, Iceland, Japan, and China (95–101). Although some of these loci have been replicated, for the most part few causative mutations have been identified and validated.

In addition to germline susceptibility, previous human studies have identified genomic loci with CNVs (102), and sequencing tumor DNA has identified recurrent, potentially functional mutations (103). But most of these are not ubiquitous, and common variants that could serve as therapeutic targets remain to be found. The Cancer Genome Atlas recently documented WES of 131 muscle-invasive, high-grade human bladder tumors and matched normal samples, identifying 9 new and 23 previously reported mutations with potential therapeutic targets in the AKT/mTOR or RTK/MAPK pathways. However, most of these remain candidates, and therapies have not yet been developed, suggesting considerable work remains to be done to permit stratification of InvTCC tumors and/or drivers of metastasis for targeted therapies (104).

Increasingly, researchers are turning to animal models, including dogs, for genomic studies of InvTCC (105, 106). A total of 50,000 dogs will be diagnosed with bladder cancer each year, and distant metastases will be present in 15–20% at diagnosis, typically in the abdomen, bone, or lung (107, 108). Although there have been many suggestions of environmental risk factors, studies show that there is no increased risk associated with flea and tick products (109). However, cancer risk after exposure to lawns or gardens treated with both herbicides and insecticides [odds ratio (OR) = 7.19] or herbicides alone (OR = 3.62) was significant (110). There was no increased risk for dogs exposed to lawns treated only with insecticides in this study, but this result is controversial (110).

Canine InvTCCs are typically of intermediate to high grade, with the majority being high-grade papillary infiltrative tumors, and invasion into the lamina propria and muscle layers of the bladder wall is common (**Figure 4**). InvTCC is the most common cancer of the urinary bladder in dogs and is difficult to treat. The typical location makes surgical excision difficult, and complete cystectomy may result in incontinence, an understandably undesirable side effect for owners (71, 88). Finally, InvTCC is lethal in most dogs, making them an ideal system in which to develop nonsurgical treatment strategies that would improve both survival time and quality of life (105, 106).

To investigate the transcriptome of canine InvTCC, Decker et al. (111) conducted an RNA sequencing (RNA-Seq) analysis of canine tumors. Initial RNA-Seq results revealed that 4 of 4 InvTCC tumors carried a mutation in the canine *BRAF* gene, at position 595, which is identical to the *BRAF*(*V600E*) mutation reported with high frequency in human tumors (~8% of all human tumors). Testing of additional samples revealed that the mutation was present in 87.9% of canine InvTCC samples. The mutation was not found in any germline samples or in healthy bladder tissues. The study also demonstrated that the mutant allele was detectable in DNA shed in the urine for 100% of tumors that carried the *BRAF* mutation, with a limit of detection less than one mutant sequence read per 1,000 (111). In a paper published the same year, Mochizuki et al. (112) developed a digital droplet polymerase chain reaction (ddPCR) assay. With a sensitivity of 75–85%, they demonstrated its utility for the detection of *BRAF* DNA in urine, proving ddPCR was a viable diagnostic for not only InvTCC but also canine prostatic cancer (112).

To assess whether the canine *BRAF*(*V595E*) mutation recapitulates the downstream MAPK pathway dysregulation mechanism of its human homolog, MAPK/ERK kinase (MEK) and

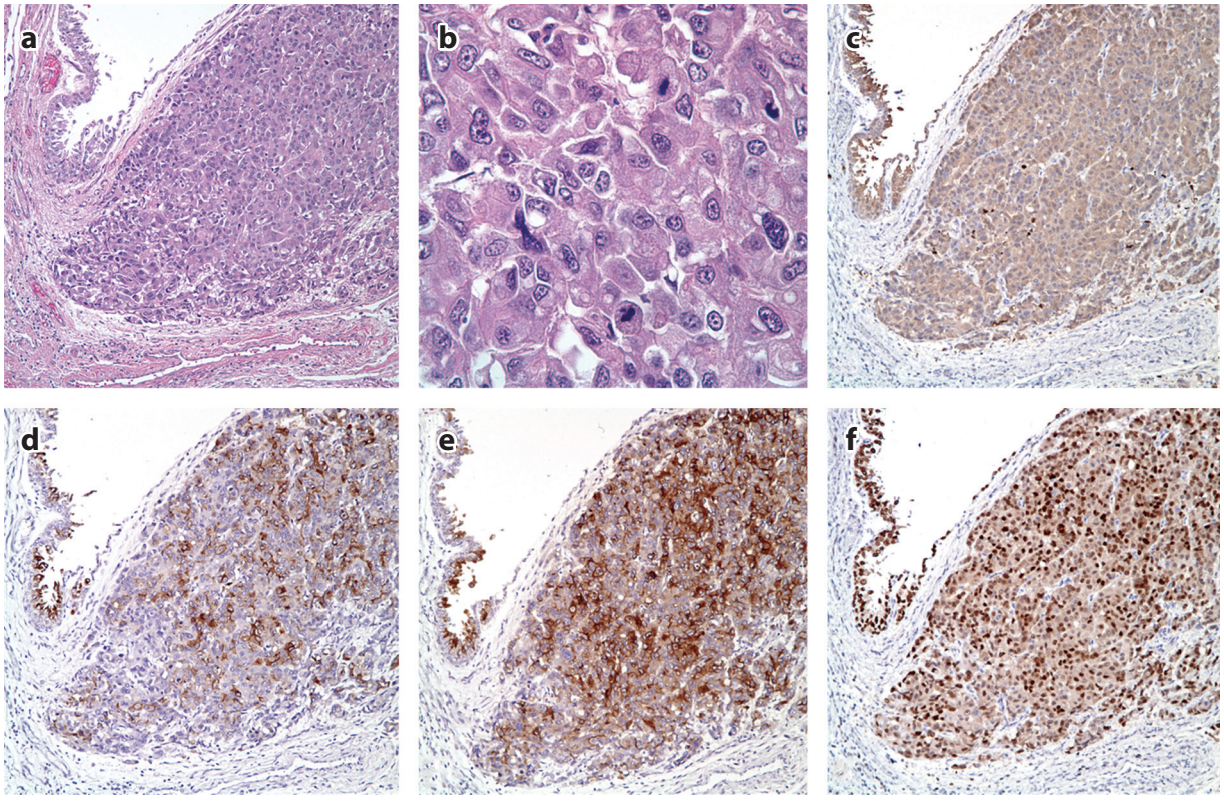


**Figure 4**

High-grade, invasive transitional cell carcinoma (TCC, urothelial carcinoma) in the urinary bladder of the dog. (*a*) Invasion of the lamina propria by a disorganized mass of atypical urothelial epithelium. The overlying urothelium is eroded. Hematoxylin and eosin (H&E) staining. (*b*) Detail of the neoplastic growth (H&E stain). Marked anisocytosis and anisokaryosis are observed. Note several mitotic figures. (*c–f*) Immunoperoxidase-3,3′-diaminobenzidine staining for four TCC markers: (*c*) placental S100, (*d*) uroplakin III, (*e*) uroplakin II, and (*f*) GATA-3. Figure adapted from Knapp et al. (107) with permission from *ILAR Journal*.



phosphorylated MEK (pMEK) levels were analyzed with Western blots of cell lysates treated with the BRAF(V600E)-specific inhibitor vemurafenib. Three canine InvTCC cell lines that express *BRAF*(*V595E*) showed high levels of pMEK with varying reactions to the vemurafenib treatment. In contrast, an InvTCC cell line that does not carry the mutation displayed low baseline levels of pMEK that, importantly, showed no change in response to the inhibitor. Because vemurafenib depressed MEK activation, researchers tested whether the drug inhibited proliferation of canine InvTCC cells. All cell lines with the *BRAF*(*V595E*) mutation were significantly more sensitive to vemurafenib than the wild-type cell line, suggesting relevance for clinical trials (111). Interestingly, human bladder tumors generally lack *BRAF* mutations. Hence, their commonality in dog tumors suggests an entirely new system for the study of the *BRAF* tumor suppressor gene.

Recently, a comprehensive RNA-Seq analysis has been published for InvTCC (113). Analyzing RNA from bladder tissues of 11 dogs with InvTCC and 5 healthy individuals, investigators found a large number of differentially expressed genes, of which 1,007 were upregulated and 1,524 were downregulated in tumors. The most activated upstream regulator was *PTGER2*, which shows

similar expression patterns in human disease. *TP53* was among the most downregulated. The study, overall, also identified potential therapeutic targets in *PTGER2*, *ERBB2*, *CCND1*, *Vegf*, and *EGFR*.

In dogs, InvTCC of the bladder shows dramatic breed specificity (106). Scottish terriers have a 20× increased risk compared with mixed-breed dogs (OR = 21.12, 95% CI = 16.23–27.49) (**http://www.vmdb.org**), followed by the closely related West Highland white terrier (OR = 5.84, 95% CI = 4.23–8.08) and Shetland sheepdog (OR = 6.05, 95% CI = 4.76–7.69) (71, 88, 114). Of the 20,000 dogs diagnosed with InvTCC each year, many will be Scottish terriers, with an extraordinary 33% of the breed developing InvTCC in their lifetime. This indicates that InvTCC has strong genetic underpinnings. But to date, no susceptibility genes have been found, likely for two reasons. First, the disease is almost certainly polygenic. Second, it may be that some mutations are approaching fixation, perhaps because they are adjacent to a gene that has been selected by breeders. As such, the corresponding locus would not show up in a GWAS; cases and controls would predominantly have the same haplotype. Whole-genome sequencing and searching for new mutations on old or existing haplotypes is the best way to reveal such mutations.

## Histiocytic Sarcoma

Histiocytic cancers are a group of related disorders with a broad range of clinical symptoms. HS, specifically, are characterized by unregulated proliferation of dendritic cells, which are themselves critical antigen-presenting cells of the immune system. In humans, the molecular etiology of the disease remains unclear, hampering the development of an effective therapy and resulting in no clear guidelines for treatment of human pediatric or adult cases, despite the disease's uniformly grave prognosis.

HS is generally rare in most dog breeds, but ∼15–25% of BMD and ∼20% of FCR will develop the disease (79, 81, 115–117). HS is fatal in both BMD and FCR, with a median survival of <100 days (118). The mean age at diagnosis is 7.7 years for BMD and slightly older, 8.6 years, for FCR. A histologically similar and overlapping group of histiocytic disorders can be found in humans, ranging from the fully treatable cutaneous Langerhans cell histiocytosis to terminal, disseminated HS (119–121). These disorders affect people of all ages (range 15–89 years), and there are no guidelines for standard of care, although recent treatments offer some encouragement (122, 123). In dogs, HS may present as localized, often to periarticular joint tissue, or disseminated, appearing in multiple organs. Approximately 85% of BMD present with the disseminated form of the disease, compared with 48% of FCR (79, 124). Indeed, localized HS is diagnosed sevenfold more frequently in FCR than BMD, whereas disseminated HS is diagnosed at a twofold higher incidence in the BMD (116, 124) (**Figure 5**).

Because the disease is late onset, it is essentially impossible to reduce its population frequency through selective breeding. Rather, genetic susceptibility studies must identify the locus, gene, and high-impact mutation, followed by implementation of individual testing. Using ∼450 DNA samples obtained from BMD cases and controls from North America and Europe, a GWAS identified two HS-associated loci, one each on CFA11 and CFA14 ($P_{\text{corrected}} = 1.76 \times 10^{-8}$ and $1.51 \times 10^{-7}$, respectively). Only the first locus is shared by the US and European populations (125). Fine mapping and sequencing narrowed the shared locus to a haplotype spanning *MTAP* and part of *CDKN2A*, a known tumor suppressor that codes for the protein $p16^{INK4a}$/$p14^{ARF}$ on CFA11. Quantitative PCR from the dendritic cells of healthy dogs revealed significantly increased expression of *CDKN2A/B* in dogs carrying the risk haplotype (125). The haplotype is present in 96% of affected BMD from both continents. This region is homologous to human 9p21, which

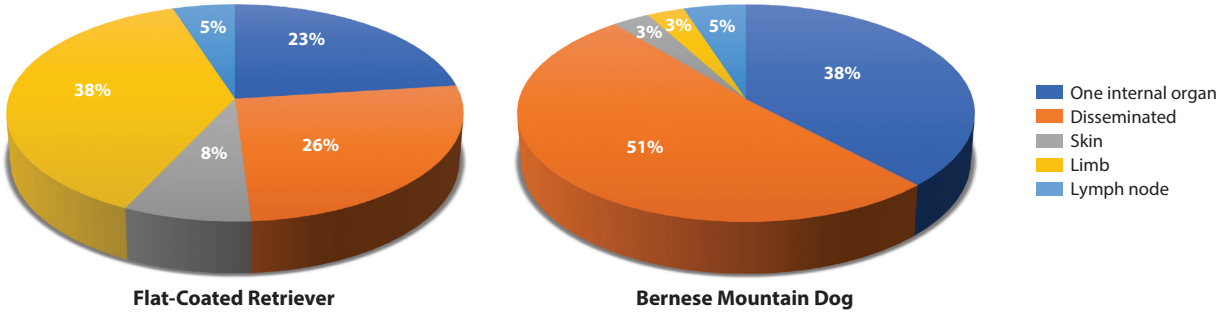


**Figure 5**

Anatomical distribution of histiocytic tumors in Flat-Coated Retrievers and Bernese Mountain Dogs. Tumor location is significantly different between the two breeds ($p$-value < 0.001, Fisher Exact test). Figure adapted from Hedan et al. (124) under a Creative Commons Open Access license.



has been implicated in several types of human cancer (126, 127). Interestingly, the same locus is also associated with canine osteosarcoma (56), raising the unanswered question as to whether it is a general susceptibility locus for canine sarcomas.

The above study provided ample evidence to support two hypotheses regarding canine cancer mapping. First, inherited forms of canine cancer will likely be controlled by a small number of genes within any single breed; just two HS loci appear to segregate in the BMD. Second, canine cancers are likely to inform human disease. Although little is known about the etiology of HS in humans, in dogs the disease is regulated, at least in part, by a well-known cancer locus. Thus, information we gain regarding dysregulation of this region of the genome in dog breeds will inform multiple human studies involving cancer and 9p21.

In another study of interest, Hedan et al. (124) examined tumors from both high-risk breeds, BMD and FCR, for copy number alterations (CNAs). Studies in humans have shown that CNAs play major roles in tumor onset (128). Surprisingly, they found that the most recurrent (defined as occurring in >50% of tumors) CNAs were common to both breeds, suggesting that they may be early events in formation of HS. Hedan et al. did identify 13 loci with CNAs that were breed specific and speculated that these may account for the differing presentations observed in each breed (disseminated in BMD and localized in FCR). They also found a set of recurrent CNAs in known cancer genes, including *CDKN2A/B interacting protein* (*CDKN2AIP*) as well as *RB1* and *PTEN*. The *CDKN2AIP* finding is particularly interesting, as it was the most frequently detected CNA (86% of cases overall), and the *CDKN2A/B* locus was highlighted in the GWAS of Shearin and colleagues (125). Further, the same locus, or portions of it, is deleted in human dendritic sarcomas of the follicular cell type (129).

Other recent HS tumor studies in BMD have focused on known cancer genes, such as *TP53* (118), *HMGB1*, and *RAGE* (130), or genes identified in human HS, such as *PTPN11* (131). *TP53* tumor mutations are associated with poor outcomes and observed in many types of canine cancer (132–134); their association with HS has been described previously (124). In their study of HS in several breeds, Asada and colleagues (118) found that tumors from 12 of 26 (46%) affected dogs harbored variants in *TP53*. In 10 of the tumors with a *TP53* variant, the mutation was a two-base pair insertion that resulted in a premature stop in exon 5. Interestingly, the mutation did not predominate in any specific breed, sex, age at onset, or organ type. It was distributed equally

between disseminated and localized subtypes of disease. Although no formal studies have yet been done, the mutation is likely functional, as it removes several critical domains, including the nuclear localization signal. This interesting result warrants follow-up, particularly determination of whether it is an early or late event in tumor development.

Moving forward, HS research is going in several directions, but the most important are studies aimed at developing a clearer understanding of the associated phenotypes. Thus, Erich et al. (116) recently undertook a study aimed at developing a rigorous assessment in an effort to develop a definitive diagnosis protocol. In humans, HS refers specifically to the macrophage subtype, but in dogs there is considerable confusion and poor definition of disease types and subtypes. The differential diagnoses include many types of disease, ranging from hemolytic anemias to granulomatous inflammation (81, 124, 135). The most interesting findings of the study by Erich et al. (116) were the systematic morphological differences found in BMD versus FCR tumors. For instance, there were significant differences with regard to patterns of inflammatory cells between the breeds. Also, FCR tumors had a predominance of polygonal cells and spindle cells, which are reminiscent of human HS. Other features, such as the presence of invasive tumor cells in liver and lymph node, were found in the BMD, exclusively in disseminated cases, and absent from FCR. FCR tumors had more necrosis compared with BMD, indicating that it is likely a faster-growing tumor. This hallmark study identifies distinct subtypes of HS in dogs as measured by both cytology and histology. The key to disentangling the genetics likely lies in a more mature understanding of these subtypes.

## Squamous Cell Carcinoma

Squamous cell carcinoma of the digit (SCCD) is a locally aggressive canine cancer typified by lytic bone lesions, recurrence, and occasional death from metastasis (136, 137). Breeds at increased risk include standard poodles (OR = 5.9, 95% CI = 4.8–7.2), giant schnauzers (OR = 22.7, 95% CI = 16.0–32.3), and briards (OR = 10.4, 95% CI = 5.5–19.8) (55 and references therein). Interestingly, for standard poodles, only the dark-pigmented dogs are susceptible; cream and white dogs are unaffected (137, 138). A GWAS using 65 black standard poodle cases and controls demonstrated that the *Kit Ligand* (*KITLG*) locus is strongly associated with SCCD (55). After Sanger sequencing, Southern blot, and haplotype analysis, a 5.7-kb CNV with the signature of a transcriptional enhancer element was identified as the most likely causative mutation. Four *cis* copies of the CNV element represent the critical threshold for disease risk, suggesting a potential functional mechanism. Dogs without at least one allele with four copies in *cis* are not at increased risk for disease (55). This locus is under strong selective pressure in dogs (35, 36), likely in response to coat color preferences, as *KITLG* has been linked to pigmentation in humans, mice, and fish (139, 140).

Although it might be predicted that haplotypes harboring four copies of the CNV were lacking in light-colored standard poodles, this is not the case. Indeed, light-colored standard poodles carry the presumably causal variant at the same frequency as black standard poodles but do not develop the disease. A second GWAS comparing light and black standard poodles suggests that a compensatory nonsense mutation in the well-known coat color gene *MC1R* disables the necessary pathways for disease progression (55). This study provides an excellent example of an often postulated but rarely demonstrated dogma in canine genetics, hitchhiking mutations, in which a deleterious allele is carried along with an allele under selection for a given trait. In this case, the putative SCCD causing CNV abuts *KITLG*, which has likely been selected by breeders to enhance dark coat color.

## CANINE VENEREAL TRANSMISSIBLE TUMORS

No discussion of canine cancer is complete without mention of canine transmissible venereal tumor (CTVT). CTVT is a parasitic cancer clone (141, 142), akin to the well-known Tasmanian devil facial tumor, that has propagated for thousands of years via sexual transfer of malignant cells between dogs, generally evading the host immune system (143). Endemic in more than 90 countries (144–146), it is the world's oldest known continuously propagating somatic cell lineage (reviewed in 145, 147) and can affect any breed and both sexes of dog, with transfer in either direction (148; see 149 and references therein for review). This highly rearranged tumor harbors 7,338 deletions, duplications, inversions, and translocations comprising an aneuploid genome with 57–59 chromosomes versus 78 in healthy canids (**Figure 6**). The tumor is clonal in origin, suggesting a recent common ancestor (150, 151), which is believed to have existed several thousand years ago (151, 152). Diagnosis can be accomplished by detection of a LINE insertion near the *MYC* locus

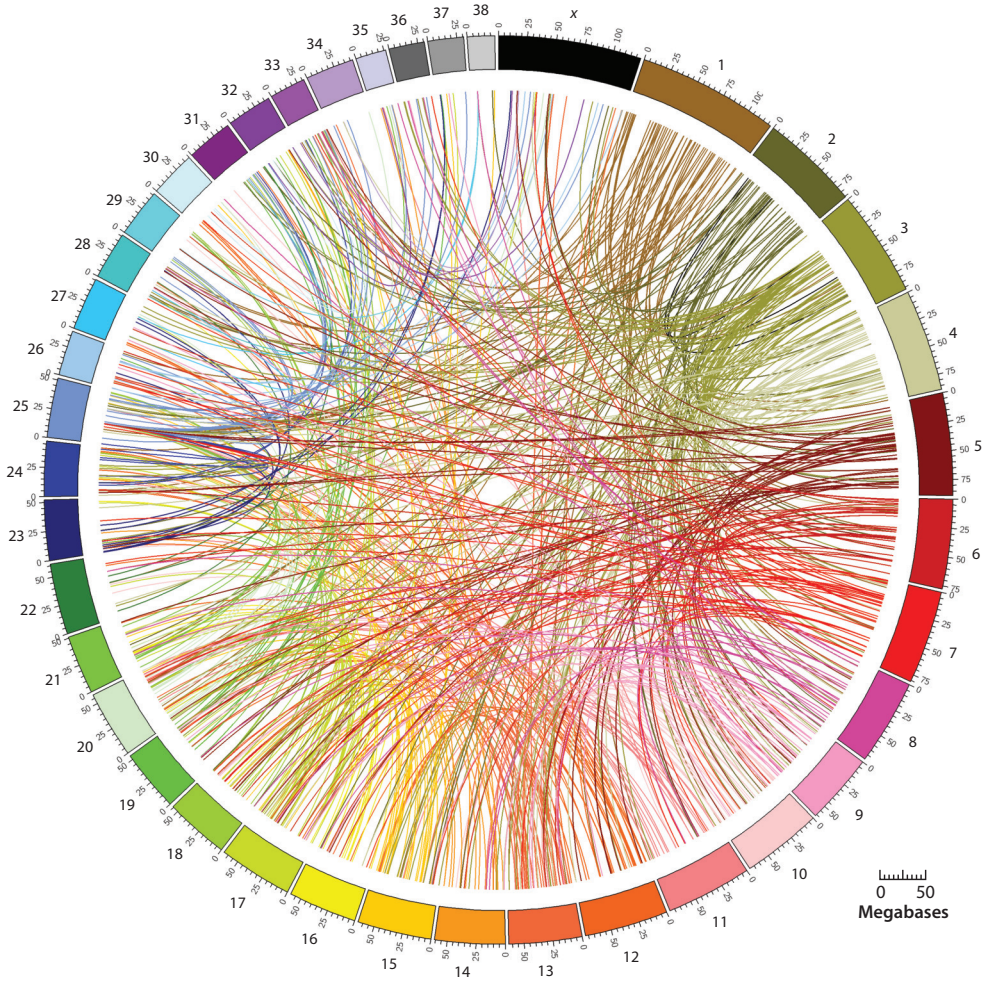


**Figure 6**

Somatic mutations shared by two canine transmissible venereal tumors. Circos plot illustrating 728 chromosome-to-chromosome translocations shared by the canine transmissible venereal tumors. Figure adapted from Decker et al. (152) under a CC-BY-NC license.

(153). An elegant series of studies by Murchison and colleagues (154, 155) and others (152, 156, 157; as reviewed in 144, 145, 147, 150, 158) has significantly advanced our understanding of this unusual tumor.

One of CTVT's most interesting features is that it can spontaneously disappear (144, 157, 159, 160). Karlson & Mann's (157) early study is particularly informative. Previously investigators had shown that the tumor was transferrable in controlled situations (142). Karlson & Mann (157) passed the tumor through 40 generations of dogs over a period of 7 years. The serial passage experiment was designed to test if the tumors increased their malignant properties during the 7 years and to test the infectious nature of the tumor. Of the 564 eligible dogs exposed to the tumor, 68% developed CTVT, and in 3 the tumor became metastatic. The number of dogs infected at each generation varied, but there was no evidence for tumor attenuation over time. Interestingly, there was a high rate of spontaneous regression, with tumor regression in more than half of dogs at 60 days and 87% of dogs at 80 days. In the wild, however, spontaneous regression is much less frequent and not well understood (see 149 and references therein for review).

The authors were especially curious about the 32% of animals that were resistant to implantation and speculate that the tumor is more widespread than thought, and that these animals were resistant because of previous exposure. There is some evidence to support this. Dogs that have undergone a spontaneous regression of their tumor cannot be reinfected (161), and puppies born to mothers exposed to the tumor are less susceptible to developing the tumor (162).

Two recent studies have addressed questions regarding the tumor's origins, as well as how it has avoided the host immune system so successfully (155, 152). The latter was addressed via a genomic approach: creation of a large catalog of canine genome-wide variation using WGS from 186 domestic dogs, most of which were purebred dogs of Western European origin. By comparing the WGS from only two CTVTs to each other (no germline DNA was available from the original founder dog) and then to the catalog, the authors separated alleles derived from the ancient founder's genome from somatic mutations that must drive clonal transmissibility. Both studies demonstrate that CTVT has undergone continuous adaptation to its transmissible allograft niche, with overlapping somatic mutations disrupting every step of the adaptive immune safeguards that typically detect and destroy allografted cells, particularly those related to self-antigen presentation and apoptosis (152, 155). Specifically, CTVT mutations block generation of antigenic peptides and prevent both their transfer into the endoplasmic reticulum and their ability to load onto antigen presenting machinery. CTVT also carries somatic mutations in both initiators and executors of apoptosis. Although all of these mechanisms are at play in most cancers, CTVT is unique in both the number of genes affected and the redundancy of mutations observed, with functionally redundant mutations reflecting thousands of years of evolutionary pressure (152, 155). Whereas MHC class I and class II cells seem to disappear during infection, they return in large numbers in regressing tumors (163).

Key to the success of the Decker et al. (152) study was the creation of a WGS variant catalog. This not only allowed the investigators to filter out millions of variants that were likely somatic versus of founder origin but also allowed them to construct a phylogenetic tree, place the tumor sequence in that tree, and determine the breed of origin (152). The results show clearly that the tumor originated in a Malamute/Husky-type dog (150) and not a wolf, as others have suggested (151).

The observations associated with CTVT and the Tasmanian devil tumor (164) beg the question of why these two mammals are susceptible. Although arguments exist that marine mammals also have transmissible clonal tumors, it is striking that only two types of land mammals do. Why dogs? The reasons are not obvious. Clearly the mechanics of canine reproduction, which require the dogs be "tied" together for several minutes, facilitate tumor transfer and implantation. But that fact alone cannot explain the observations above. What is clear, however, is that because the

tumor, at least in a laboratory setting, can recede, studies of this system are sure to inform studies of immune-mediated treatment of human cancers.

## CANINE GENOME RESOURCES FOR CANCER STUDIES

In 2015, in an effort led by the National Human Genome Research Institute, we revealed the first comprehensive analysis of dog genome sequences, releasing data on 186 canine WGS (152), a data set composed of 102 purebred dogs, 12 wild canids, and 72 semiferal village dogs. This initial analysis revealed 28.01 million single-nucleotide variants (SNVs), 12.62 million indels, and 31,613 structural variants (SVs) (**https://research.nhgri.nih.gov/dog_genome/**). Canine dbSNP contains only SNVs and includes less than one-third of the variants found in the average canid WGS, while we found that a mean of 99.55% of SNVs, 99.57% of indels, and 95.63% of SVs from any single canid were present in at least one other individual in our WGS catalog. All data are available through the National Center for Biotechnology Information Sequence Read Archive or database of structural variation.

On the horizon for sequencing resources is a collaborative initiative called DOG10K. This international group of collaborators has a goal of sequencing 10,000 canine genomes at 20× coverage within the next 5 years. The resulting catalog will contain comprehensive high-density genomic data, including SNVs, CNVs, SVs, and mobile elements. Recently, we and collaborators used these data to design an ultrahigh-density Affymetrix genotyping array (Affymetrix Axiom Canine HD Array). The array includes 710,000 variants and imputation panels that reflect WGS data for inference (165). With these tools in hand, the possibility finally exists to expand on initial studies of canine cancer in a meaningful way.

## CONCLUSIONS

The cancers discussed herein represent only a small portion of canine genetics research that can inform studies of human health and biology. Canine cancers mimic human disease in age at onset, disease presentation, treatment response, and outcomes. As human genetics turns increasingly to personalized medicine, in which the available treatments are restricted by the nuances of an individual's genome, the canine model becomes even more useful, as the breed barrier and vast number of breeds essentially recapitulate that scenario. Members of any breed share an extraordinary number of alleles as the result of the closed breeding program, providing an outstanding system in which to study the role of small numbers of changes on disease progression. The maturing canine genomics community adds an entirely new dimension to the study of canine cancer. With an ever-growing database of dogs that have undergone WGS, an increasingly effective tool is being developed to screen large numbers of potential mutations and determine their allele frequency in the general dog population, or specific breed population, and thus determine the likelihood that they are functionally relevant. The advent of the DOG10K project ensures that this approach will continue to expand in utility. Underlying genetics, therapeutic development, and quality-of-life issues are all things we wish to better understand about cancer. A partnership with veterinarians, owners, breeders, and dogs themselves offers a unique and unusually productive way to accomplish this.

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# Contents

**Errata**

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