Domestic Dogs and Cancer Research: A Breed-Based Genomics Approach

Brian W. Davis and Elaine A. Ostrander

Abstract

Domestic dogs are unique from other animal models of cancer in that they generally experience spontaneous disease. In addition, most types of cancer observed in humans are found in dogs, suggesting that canines may be an informative system for the study of cancer genetics. Domestic dogs are divided into over 175 breeds, with members of each breed sharing significant phenotypes. The breed barrier enhances the utility of the model, especially for genetic studies where small numbers of genes are hypothesized to account for the breed cancer susceptibility. These facts, combined with recent advances in high-throughput sequencing technologies allows for an unrivaled ability to use pet dog populations to find often subtle mutations that promote cancer susceptibility and progression in dogs as a whole. The meticulous record keeping associated with dog breeding makes the model still more powerful, as it facilitates both association analysis and family-based linkage studies. Key to the success of these studies is their cooperative nature, with owners, scientists, veterinarians and breed clubs working together to avoid the cost and unpopularity of developing captive populations. In this article we explore these principals and advocate for colony-free, genetic studies that will enhance our ability to diagnose and treat cancer in dogs and humans alike.

Key Words: canine cancer; chip-seq, dog colony; exome; histiocytic sarcoma; osteosarcoma; RNA-seq; squamous cell carcinoma of the digit; transitional cell carcinoma; tumor sequencing; whole genome

Introduction

According to a 2009–2010 National Pet Owners Survey reported by the Pet Products Manufacturers Association, approximately 39% of American homes own at least one dog and 24% have two dogs (NumberofNet.com 2014). Thus, there are approximately 77.4 million pure-bred and mixed-breed dogs living in the United States (Texas Veterinary Cancer Registry 2012). Cancer is the leading cause of death in dogs over 10 years, with 50% of older dogs developing the disease and approximately one in four dogs eventually dying from it (Adams et al. 2010; Animal Cancer Foundation 2014; Bronson 1982; Dobson 2013; Vail and MacEwen 2000). Not surprisingly, dogs are diagnosed with many of the same cancers as humans (Khanna et al. 2006; Merlo et al. 2008), with an underlying presentation, clinical pathology, and treatment response mirroring that observed in humans (Cadieu and Ostrander 2007; Dorn 1976). This suggests that similar genetic mechanisms cause human and canine cancers and that genetic studies of canine disease may be a powerful way to advance our understanding of cancer in humans and companion animals alike (Cadieu and Ostrander 2007; Khanna et al. 2006; Ostrander 2012).

It is unclear whether cancer incidence in dogs is stabilized or increasing. Improved health care for pets now extends their lifespan, permitting the diagnosis of late-in-life diseases such as cancer. Also, as diagnostic tests improve in the veterinary community, dogs receive more accurate diagnoses than were available even a decade ago and, consequently, more effective therapy. In addition, owners are increasingly willing to pay for expensive diagnostic tests. Finally, as veterinary epidemiologists improve their ability to track canine cancer, scientists are increasingly able to predict which breeds are at an increased risk for each type of cancer. This allows diligent veterinarians to monitor individuals from at-risk breeds, leading to earlier diagnoses and more effective treatment.

In this article we explore our current understanding of canine cancer genetics. We argue that the days of maintaining dog colonies at veterinary schools, started with limited founders for the purpose of studying a single cancer type, are past. Rather, geneticists, veterinarians, and owners can work together to design highly accurate studies using pet dog populations (Karlsson and Lindblad-Toh 2008; Rowell et al. 2011; Shearin and Ostrander 2010). Typically, for any given cancer, the number of deleterious alleles segregating in a single dog breed is likely to be limited because dog fanciers use closed breeding programs to develop breeds with specific phenotypic traits (Karlsson and Lindblad-Toh 2008; Ostrander 2012; Ostrander and Kruglyak 2000; Parker et al. 2010). As a result, cancer genetic studies in pet dog

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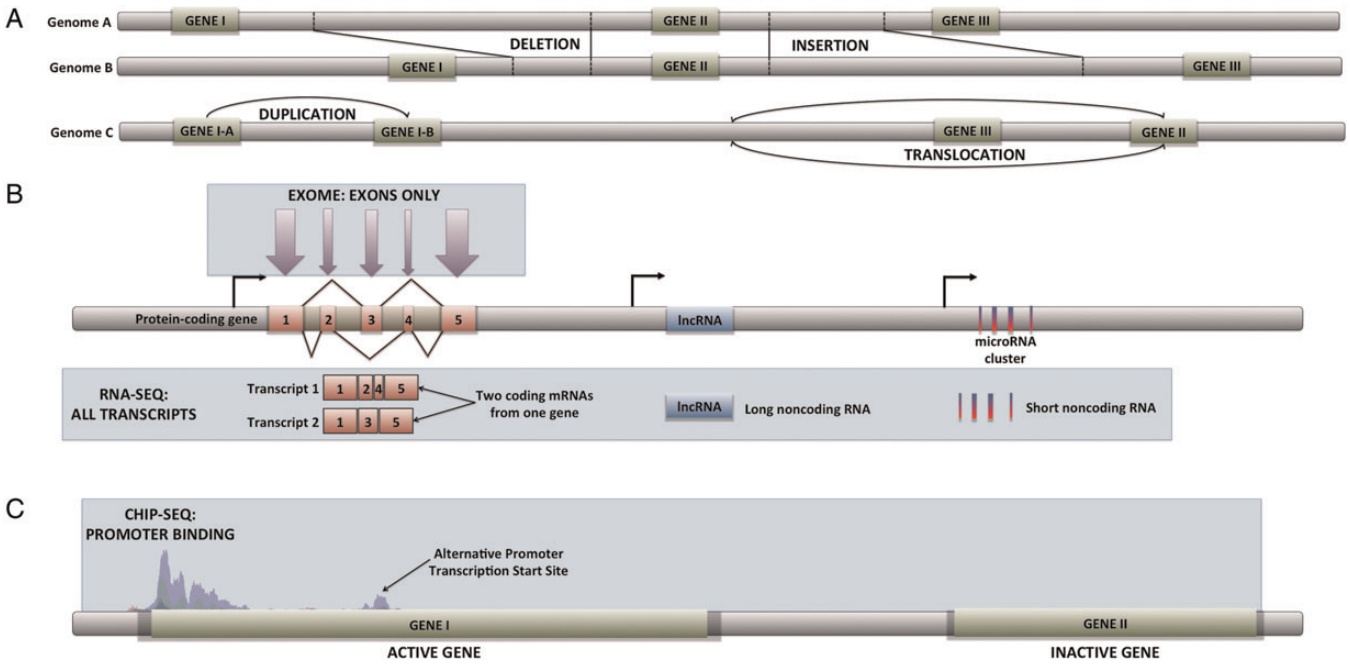

Figure 1 Graphic representation of the most commonly used HTS technologies. (A) Whole genome sequencing allows the detection of changes in genome structure such as insertion/deletion events, gene duplications, and translocations. (B) Whole exome sequencing produces only sequences within exons from genomic DNA. RNA-Seq generates the complete sequences of every RNA transcript, including alternative transcripts, and noncoding RNAs. (C) ChIP-Seq is able to identify the DNA-binding sites for specific transcription factors, as well as any other protein capable of binding to DNA.

populations presents a mechanism to circumvent the small families, outbred population structure, and locus heterogeneity that plague human cancer gene mapping (Karlsson and Lindblad-Toh 2008; Shearin and Ostrander 2010), while allowing scientists to avoid setting up breeding colonies at veterinary schools. These facts, combined with the ability to easily collect and sequence DNA and tissue-specific RNA from dogs underscores the notion that pet dogs are uniquely positioned to change our view of both human and canine cancer (Khanna et al. 2006; Ostrander 2012; Rowell et al. 2011).

At the heart of the proposition is the fact that by using multiple, recently developed genomic technologies, we can thoroughly scan any single dog's genome for variants as simple as a single nucleotide change or as complex as a gene family expansion. We can ascertain both allele-specific gene and noncoding RNA expression profiles. We can also develop somatic mutation profiles from individual tumors (Figure 1). Indeed, with the arrival of high-throughput sequencing (HTS), the first breed-specific whole genomes, together with catalogues of breed-specific variants, are now emerging in the scientific literature (Kim et al. 2012; Owczarek-Lipska et al. 2013), as is data from wild canids. These data will facilitate the detection of both rare and common disease alleles, and the resulting databases will aid clinical researchers in advancing their knowledge regarding cancer, as well as other complex genetic diseases.

Cancer Registries

The Surveillance, Epidemiology and End Results registry of the National Cancer Institute collects information on incidence, prevalence, and survival from a set of predetermined geographic regions of the United States, allowing researchers to assemble statistics regarding cancer mortality and trends for the entire country. Unfortunately, no such organization exists in veterinary science. However, individual registries have emerged in recent years, such as the National Veterinary Cancer Registry (http://nationalveterinarycancerregistry.org/about-nvcr/naturally-occuring-models), which, among other tasks, collects data for a national registry while developing a network of veterinary oncologists. The National Veterinary Cancer Registry is a strong advocate of pets as naturally occurring animal models for cancer studies. As such, they work to connect researchers with oncologists who share interests and to inform owners regarding ongoing clinical trials. Other similar organizations exist, including the Texas Veterinary Cancer Registry and the Veterinary Cancer Society. Although useful, such organizations provide little publically available data on cancer trends, breed-specific incidence of cancers, and treatment response. In addition, they often lack the resources to link breeders of at-risk populations with geneticists or epidemiologists studying a particular cancer type. Thus, a need for this type of research exists and cannot be done by colonies.

The best resources for establishing breed-specific trends in cancer research are highly targeted academic studies, some of

which are discussed below, and selected veterinary school studies. The first such set of studies, done in the late 1960s, focused exclusively on Alameda and Contra Costa Counties in California (Dorn 1976; Dorn et al. 1968) and then on data from veterinary schools (Priester and Mantel 1971). Subsequent reviews were among the first to collate breed excesses of several of types of cancer (Madewell 1981), which had previously been reported as just single cancers or as case–case studies. These were also the first studies to suggest that spontaneous dog tumors could be informative for learning about human cancers (Schneider 1970; Schneider et al. 1968).

In recent years, American studies have been dwarfed by those from Europe, which often use registry data provided by pet insurance companies. For instance, the Animal Tumor Registry of Genoa, Italy, established in 1985, reported that cancer incidence is threefold higher in female dogs then male dogs (Merlo et al. 2008), 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. Operating since 1990, the Norwegian Cancer Registry also reports that mammary tumors are the most common (Arnesen et al. 1995). As expected, risk increased with age, with 10 years being the critical cut-off (Merlo et al. 2008). Breeds at highest risk include Leonbergers, Irish wolfhounds, Bernese mountain dogs, and great Danes, among others (Jitpean et al. 2012; Schneider 1970).

Although all studies seem to agree on at-risk breeds, there is a lack of agreement regarding specific rankings. The commonly cited study of UK Kennel Club–recognized breeds reports that overall cancer incidence is highest in the Irish water spaniel, followed by the flat-coated retriever, Hungarian wirehaired vizsla, Bernese mountain dog, Rottweiler, Italian spinone, Leonberger, Staffordshire bull terrier, Welsh terrier, and giant schnauzer (Adams et al. 2010). In Sweden, the list is slightly different, with the Bernese mountain dog topping the chart, followed by the Irish wolfhound, flat-coated retriever, boxer, and Saint Bernard (Bonnett et al. 1997).

Jane Dobson, 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 (Dobson 2013). This list obviously includes both malignant and benign tumors. A study from the Danish Veterinary Cancer Registry reported that the frequency of benign and malignant tumors is similar in their country, with the most commonly reported malignant neoplasms being adenocarcinomas (21%), followed by mast cell tumors (19%) and lymphomas (17%) (Brønden et al. 2010).

Breed-Specific Cancers

When multiple dog breeds are at an elevated risk for the same type of cancer, it is possible, even probable, that the breeds share an underlying genetic predisposition (e.g., all at-risk breeds segregate the cancer because they shared a common founder during breed development) (Goldstein et al. 2006; Karlsson et al. 2007; Ostrander 2012; Parker et al. 2007) (Figure 2). To investigate specific cancers, DNA from blood or cheek swab samples are collected from cases and aged-unaffected controls of one or more related at-risk breeds. The genomes of the two populations are then compared using arrays of single nucleotide polymorphisms (SNPs). The practice of comparing whole genomes of several dogs simultaneously as a predetermined set of SNPs is called a genome-wide association study (GWAS), and it remains a powerful tool for finding loci associated with any disease. The most commonly used commercially available SNP chips contain approximately 170,000 SNPs, allowing interrogation of every chromosome, and costing approximately $250 per individual to perform. A variety of statistical tools can be applied to find loci that distinguish cases from controls. This is followed by fine-mapping experiments that narrow the region of interest and DNA sequencing to identify the precise disease-associated mutation.

Increasingly, because of greater efficiency, scientists are circumventing GWASs and proceeding directly to whole-genome sequencing, which requires no fine-mapping or follow-up sequencing. This method produces the entire repertoire of variation within an individual's genome at once, including SNPs, structural variants such as insertion–deletion events, translocations, and copy number changes (Figure 1A). One Illumina HiSeq 2500 machine, which is typically used for such experiments, is able to generate 600 billion sites of genomic sequence in a matter of hours (Eisenstein 2012). The data produced is sufficient to scan the 2.5-billion base-pair genome of 10 dogs 10 times. Although the cost of DNA sequencing is about an order of magnitude more per individual than that of one SNP chip, the price of these methods continues to drop, with the expectation that sub-$1000 genomes will soon be within reach. These data are increasingly used also for the examination of a variety of morphologic, behavioral, or disease traits. In the interim, as scientists wait for the price to drop, some are focusing on studying only the 1% of the genome that codes for proteins and generating whole-exome sequences at a very low cost (Figure 1A). Our lab has tended to avoid such an approach because disease variants are not exclusive to coding genes and may reside within noncoding regulatory regions.

Regardless of how the data is collected, such experiments require a number of a priori considerations (Karlsson and Lindblad-Toh 2008; Karlsson et al. 2007; Shearin and Ostrander 2010). For instance, the number of cases and controls to be collected should be carefully considered. Ideally, the more cases assayed for a GWAS, the better. Obtaining unrelated samples from at least the grandparent level for both cases and controls is important to minimize false positives (Shearin and Ostrander 2010). Data from breeders can be extremely useful at this point. Controls are preferentially dogs from the same or a closely related breed that have passed the median age at which the disease usually presents (Shearin

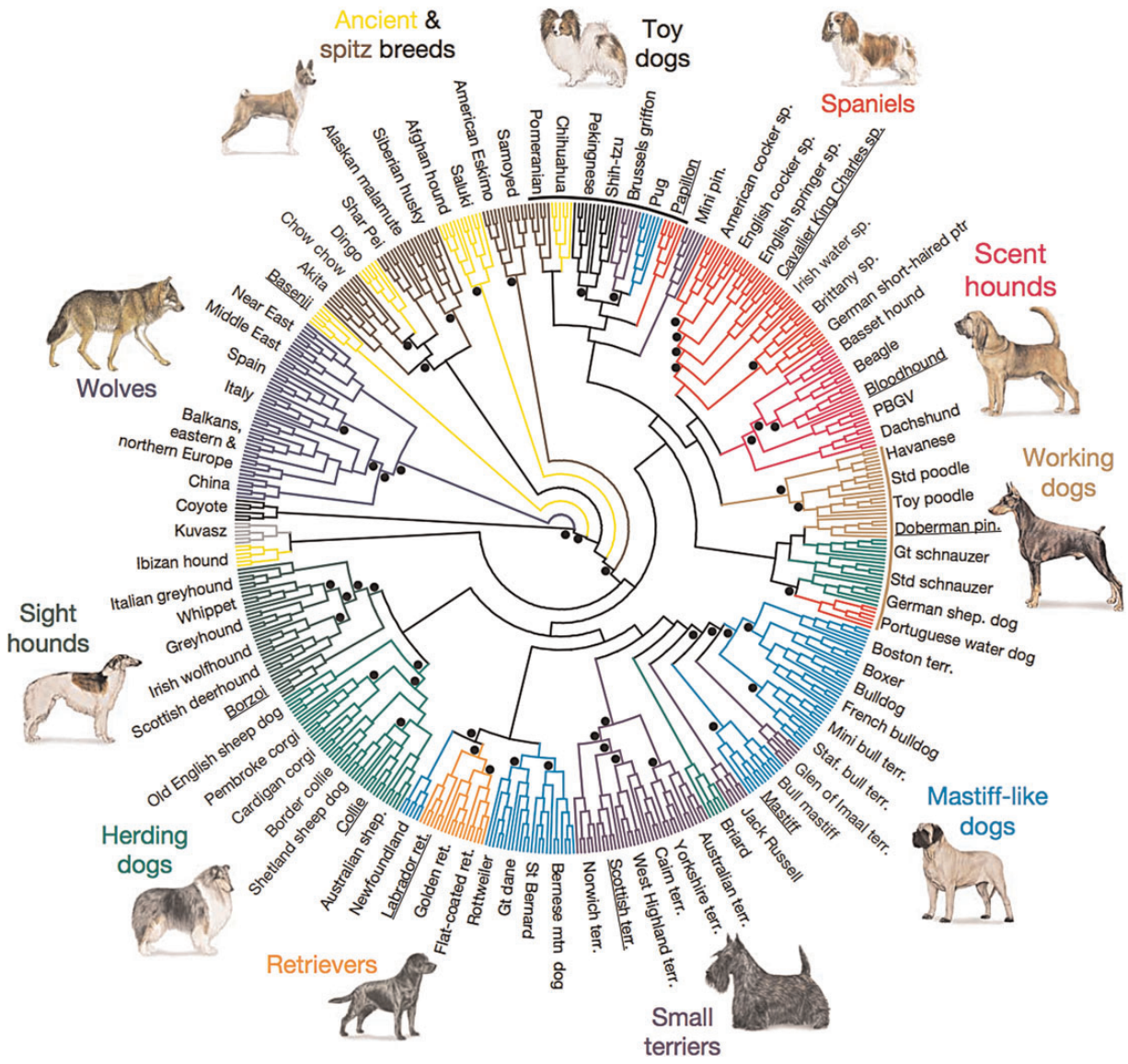

Figure 2 Cladogram from (vonHoldt et al. 2010) depicting the structure of domestic dog breeds as ascertained from 48,036 autosomal SNP loci. Relationship between breeds was determined by haplotype-sharing for 10-SNP windows with at least 6 members representing each breed.

and Ostrander 2010). However, the older the control, the better the choice. Although it is likely that any set of controls will contain at least a few individuals with the risk allele, that number will be dwarfed by the number who lack it. Data are readily available regarding how breeds relate one to another and should be used in experimental design (vonHoldt et al. 2010).

Lindblad-Toh has done an elegant series of calculations to aid scientists in optimizing the number of samples needed for their GWASs (Lindblad-Toh et al. 2005). Because the linkage disequilibrium observed in dog breeds can be extensive, the number of SNPs needed for a canine GWAS is much smaller than that required for a comparable human study (Karlsson and Lindblad-Toh 2008; Lindblad-Toh et al. 2005; Sutter et al. 2004). By taking advantage of breed structure and selecting maximally unrelated dogs, the required number of samples can also be minimized. Thus, for a hypothetic trait with dominant inheritance, high penetrance, and no phenocopies, less then 20,000 SNPs would be needed to reach a confidence level of greater than 99% using data from 100 cases and 100 controls. Of course, no such ideal trait exists, and as genetic complexity increases, the number of samples must increase as well (Lindblad-Toh et al. 2005). Still, many complex disorders in dogs have been mapped using modest numbers of samples (e.g., Ahonen et al. 2013; Forman et al. 2013; Frischknecht et al. 2013; Pfahler and Distl 2012; Yokoyama et al. 2012), including cancer (Karyadi et al. 2013; Shearin et al. 2012).

For many of the above principles, squamous cell carcinoma of the digit is a particularly demonstrative case (Karyadi et al. 2013). Squamous cell carcinoma of the digit, the most frequent cutaneous squamous cell carcinoma in dogs, is

found in giant schnauzers (odds ratio [OR] = 22.7), Gordon setters (OR = 11.1), Briards (OR = 10.4), the Kerry blue terrier (OR = 7.7), and black standard poodles (OR = 5.9; 95% CI = 4.8–7.2) (Goldschmidt and Shoufer 1998). Our GWAS, initially based on 31 standard poodle cases and 34 controls, identified a locus on canine chromosome 15 with a high level of significance that spanned a little more than 1 million base pairs. Additional mapping using 85 standard poodle cases as well as a small number of Gordon setters and Briards resolved the region to 24 kilobases. Sequencing revealed that all affected dogs, regardless of breed, carry the same founder mutation, a copy number variant that likely affects expression of *KITL* (Karyadi et al. 2013). This is an example of a regulatory mutation playing a role in disease susceptibility and highlights how data from a small number of dogs can contribute to our understanding of a disease that is important in canine and human health (Chung and Chanock 2011).

Breed-Specific Cancer Susceptibility

There are many other examples of breeds with either a predisposition for, or apparent protection from particular cancers. For instance, when considering brain and central nervous system cancers, a 2013 study showed that the boxer, golden retriever, French bulldog, and Boston and rat terriers were at a significantly increased risk, whereas the cocker spaniel and Doberman pinscher were at a low risk (Song et al. 2013). Interestingly, meningiomas were seen more frequently in dolichocephalic breeds (those with elongated muzzles), whereas glial tumors were observed more in brachycephalic breeds (short, upturned muzzles).

One frequently discussed breed-enriched cancer is osteosarcoma, which predominates in the long-limbed breeds such as the Irish wolfhound (Urfer et al. 2007), Scottish deerhound (Phillips et al. 2007) and great Dane, as well as other large breeds (Dobson 2013; Phillips et al. 2010). It has a standardized incidence rate of about 52 per 100,000. The dog is generally considered a good model for human osteosarcoma (Angstadt et al. 2011; Mueller et al. 2007; Rankin et al. 2012; Rowell et al. 2011; Withrow and Wilkins 2010). Particularly compelling are reports that *IL-8* and *SLC1A3*, which are frequently overexpressed in canine osteosarcoma, are associated with poor outcome in human osteosarcoma (Paoloni et al. 2009). This knowledge will expand in the near future because researchers have used an HTS technique called RNA-Seq to detect the misexpression of these and many other genes between human osteosarcoma tumors and normal bone tissue (Märtson et al. 2013).

Histiocytic Sarcoma

Not every case in which multiple cancers are found in the same breed is there is a common founder. Rather, in some cases, the same rare cancer is seems to have arisen independently in distinct breeds. Histiocytic cancer covers a broad range of clinical presentations, from benign cutaneous histiocytoma to highly aggressive histiocytic sarcoma (HS) (Affolter and Moore 2000, 2002), which is an aggressive and lethal disorder of dendritic cell origin. Localized HS most commonly develops in the skin or subcutis of an extremity, although it can be found in other organs. Disseminated HS is a multisystem disease with tumors appearing in numerous organs simultaneously.

Both flat-coated retrievers (FCR) and Bernese mountain dogs (BMDs) are at high risk for HS, which affects approximately 20% of FCRs and 25% of BMDs (Abadie et al. 2009; Affolter and Moore 2002; Moore et al. 2006; Proschowsky et al. 2003). BMDs tend to present with a disseminated or visceral form of the disease, generally around age 6 to 7 years, with tumors appearing in the spleen, liver, and lungs (Abadie et al. 2009; Affolter and Moore 2002; Moore et al. 2006; Proschowsky et al. 2003). By comparison, approximately two-thirds of FCRs present with a mass in a joint and/or the surrounding muscle. Earlier literature referred to these as localized and disseminated malignant histiocytosis, respectively (Affolter and Moore 2002). However, they are now more correctly referred to as periarticular and visceral forms (Boerkamp et al. 2013).

In 2012, we reported the first GWAS results in the BMD, showing an association between the *MTAP-CDNK2A* locus and increased susceptibility to HS (Figure 3). This is one of what is likely to be a growing number of cases where canine studies have preceded human studies. Interestingly, genetic studies done using both microsatellites and SNPs suggest no recent common ancestor to the FCR and BMD (Parker et al. 2004; vonHoldt et al. 2010). Thus, it is not surprising that their clinical presentation is different and that studies of copy number variation in BMD and FCR tumors highlights differences between breeds as well (Hedan et al. 2011). Ongoing studies include both GWASs as well as direct sequencing of affected and unaffected dogs from at-risk breeds.

Nearly all human cancer studies are being expanded using HTS in lieu of GWAS-based SNP arrays. HTS provides the ability to detect all variants within the genome rather than focusing on predetermined loci and, as described, obviates the need for later fine-mapping studies. Also, as the importance of rare variation becomes increasingly evident, it can be expected that more and more studies will use HTS rather then GWAS to find the mutation of origin (Cirulli and Goldstein 2010). Finally, the ability to characterize both common and rare structural variation is essential for the study of a complex disease such as cancer, where a considerable component of susceptibility may result from insertion–deletion events, copy number variation (Demichelis et al. 2012) and retrotransposion events (Lee et al. 2012).

Gene expression studies have also been illuminating in the case of HS, where fresh-frozen tissues from FCRs with either periarticular or visceral disease reveal changes in genes from 24 distinct pathways that the authors argue are involved in tumor development. Interestingly, most of the implicated pathways were important in either DNA repair or replication. Nine genes in particular, not previously implicated in HS,

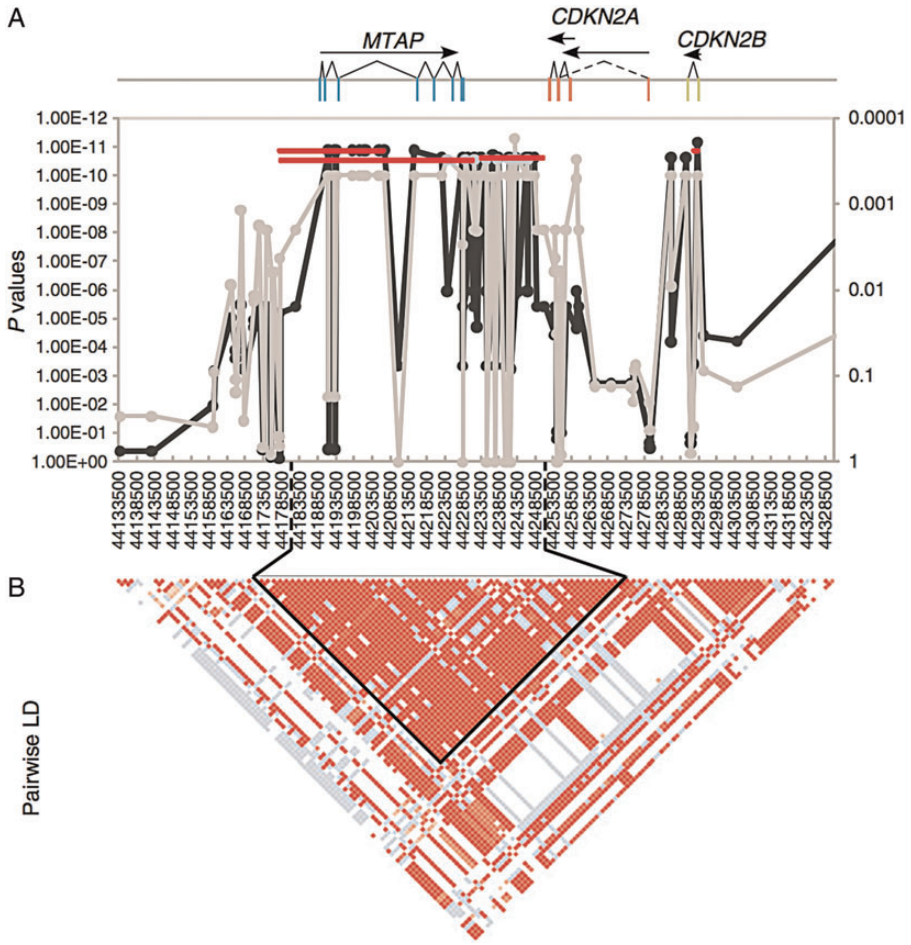

Figure 3 The region encompassing MTAP and CDK genes shown to be highly associated with histiocytic sarcoma from (Shearin et al. 2012). A 195-kb region on CFA11 is shown with X-axes for all plots listing SNPs in proximal-distal order. (A) 3 genes are shown with exons indicated as rectangles, introns as lines, and transcripts as arrows. Fisher exact association of HS with allele frequency is plotted along the Y-axis. The light gray line denotes association in a discovery cohort of 24 cases and 20 controls with *P* values on the right Y-axis. The black line indicates association in the complete cohort after imputation of genotypes (*P* values on left Y-axis). Horizontal lines depict haplotype association (*P* values on left Y-axis). (B) Pairwise LD plot with solid blocks indicating D′ = 1 and LOD score of 2. The black outline shows a haplotype block with 28 of 30 equally associated SNPs in this region.

including *ITGAD, SpiC, VCAM1, PPBP,* and *ENPEP*, were observed to be downregulated in tumors, whereas four others were upregulated (Boerkamp et al. 2013).

One problem with this type of data is that it is based on an analysis of known cancer genes and is inherently less comprehensive than the exhaustive technique of RNA-Seq, which requires no a priori information about the transcriptome, and thus data are acquired on every transcript that is produced within the sample (Wang et al. 2009). Because it is inherently unbiased, RNA-Seq also permits the discovery of new genes, changes in exon usage based on cell type (Trapnell 2010), noncoding transcripts including long noncoding RNAs (lincRNAs) (Pasquinelli 2012), and microRNAs (Figure 1B) (Ryan et al. 2010), and, of obvious interest to cancer, gene fusions (Maher et al. 2009). To date, no GWAS or RNA-Seq study of FCR HS has been published. But when they are, it will be interesting to see if the same loci or an overlapping set of loci contributes to at least the visceral form of the disease that is observed more commonly in the BMD.

Bladder Cancer

One final example of a cancer with extraordinary breed specificity is that of transitional carcinoma of the bladder (TCC), which accounts for 20,000 to 30,000 new cases of dog cancer each year (Knapp et al. 2000). TCC is an especially challenging cancer to treat (Boria et al. 2005; Knapp 2001; Mohammed et al. 2003; Mohammed et al. 2004) because the typical trigonal location precludes surgical excision and complete cystectomy is not a viable option in pet dogs. Tumor growth within the bladder, urethra, and ureters often leads to urinary obstruction, and there is typically spread to distant organs. Chemotherapy is only partially effective, and as a

result, most dogs with TCC ultimately die from the disease (Knapp et al. 2000; Mutsaers et al. 2003).

TCC occurs at the highest frequency in Scottish terriers, (18–20-fold relative risk compared with mixed breed dogs), followed by the West Highland white terrier (fivefold increase), and Shetland sheep dogs (4.5-fold increase) (Knapp 2001; Knapp 2007; Mutsaers et al. 2003). Other terrier breeds, collies, and beagles are also at an increased risk. TCC appears to arise from a combination of genetic and environmental factors, making it a particularly poor choice for colony-based studies (Glickman et al. 2004; Knapp 2001).

TCC is one cancer where the incorporation of HTS technologies is particularly advantageous. Using both whole-genome HTS and the lower-cost whole-exome sequencing, numerous high-frequency genome alterations have been identified in human TCC tumors (Guo et al. 2013). However, even at the whole-genome/exome level, this study was unable to detect gene fusion transcripts without additional RNA-Seq. Although not yet observed in human TCC studies, the potent combination of genome-level sequencing with RNA-Seq has been shown to yield unrivaled levels of information, including how tumor-dependent structural variation is linked to the allele-specific changes in expression (Tuch et al. 2010).

Cancer and Hormonal Pathways

When considering TCC, we made the point that environment can play a key role in the onset of some cancers, hence making it a poor cancer to study in a breeding colony. For other cancers, factors such as hormone levels are equally important and equally hard to study in the colony setting. Consider, for example, mammary cancer. It is well established that in addition to breed specificity, spaying and neutering, which is practiced on most American dogs, but only approximately 50% of European dogs (Trevejo et al. 2011), affects cancer risk. For instance, a study of golden retrievers done by University of California at Davis investigators revealed that nearly 10% of male dogs neutered before 1 year of age were eventually diagnosed with lymphosarcoma (Torres de la Riva et al. 2013). This is three times the rate observed by the same study for intact male dogs. Also significant was the fact that 8% of female dogs who were spayed after 1 year of age developed hemangiosarcoma (Torres de la Riva et al. 2013), four times the rate observed in intact female dogs and those spayed before age one.

This is true across breeds; other studies suggest an increase of approximately twofold to fivefold for spayed versus intact female dogs for hemangiosarcoma (Prymak et al. 1985). Even osteosarcoma rates increase with neutering (Cooley et al. 2002; Ru et al. 1998). Hormone-responsive cancers offer a unique avenue to leverage the combinatorial power of two comparative transcriptome-oriented techniques: RNA-Seq and chromatin immunoprecipitation sequencing (Figure 1C). Chromatin immunoprecipitation sequencing identifies modifications that modulate transcriptional activation given varying conditions, including presence and quantity of hormonal inducers. Coupling these methods has been used to great effect in identifying the activation of hormonal binding sites in responsive cancers and the resulting changes to the total transcriptional landscape (Prokesch and Lazar 2011; Ross-Innes et al. 2012).

Prostate Cancer and Dogs?

As a final consideration, it is important to keep in mind that for some rare cancers the dog is not the perfect genetic model but can nevertheless provide useful information. Prostate cancer is extremely rare in dogs, but curiously it occurs more frequently in neutered male dogs (Bryan et al. 2007). Neither GWASs nor family-based linkage studies are likely to be informative. However, aside from humans, the dog is the only animal to present with spontaneous prostate cancer, with clinical features, including late age at onset, and metastatic patterns similar to what is observed in humans (Cornell et al. 2000; Waters and Bostwick 1997a, 1997b).

Interestingly, polysomy of canine chromosome 13 has been observed in canine prostate tumors (Reimann-Berg et al. 2011; Winkler et al. 2006). This region is syntenic with human chromosomes 4q and 8q, the latter of which has been suggested as containing multiple prostate cancer loci (Barros-Silva et al. 2011; El Gammal et al. 2010). Recently, *PCAT-1,* a novel lincRNA believed to influence prostate cancer progression, was discovered on human chromosome 8q using RNA-Seq (Prensner et al. 2011). It will be interesting to see whether studies of canine tumors reveal similar or unique findings. In any case, the similarity in architecture and presentation makes the dog a unique model for studies of prostate tumor growth.

Summary

Technology moves rapidly and inexorably forward. Our need to improve our own health and the health of our family members, including our dogs, remains. For the past several years there has existed in public health the concept of One Health, which is a guiding principle acknowledging that the health of humans, animals, and the environment is highly intertwined (http://www.cdc.gov/onehealth/index.html). Although often focused on infections disease, the concept can be expanded to guide the way in which we conduct canine research in the future.

Gone are the days when captive colonies of dogs are easily justifiable for genetic studies. The rapid and striking advances in the quality, volume, and specificity of genomic information brought about by nascent technologies has ushered in an undeniable impetus for researchers to shift to other paradigms when tackling questions of animal health and their concomitant parallels to human health. Although we can debate the utility of such resources for other areas of study, for studies aimed at finding genetic loci that cause or protect from disease, the work can, as we have demonstrated here, be accomplished through collaboration and by embracing genomic technologies.

For humans, an era of personalized medicine, which uses genomic data to determine disease risk, select specific and effective treatment regimens, and predict relapse is rapidly becoming state of the art, particularly in the field of cancer (Chute and Kohane 2013). Although the scope and depth of available canine genomic data pale compared with what is currently collected on humans, we predict that directed or personalized treatments will soon become a reality for our pets (Khanna and Gordon 2009; Rankin et al. 2012; Rowell et al. 2011; Shearin and Ostrander 2010). Hence we seek to set forth principles that will guide researchers to responsibly work on improving the health and well-being of humans and animals, advocating that the complete compliment of modern genomic technologies be a part of every genetic researcher's tool kit.

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