Canine Genetics Facilitates Understanding of Human Biology

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Abstract In the past 15 years the field of canine genetics has advanced dramatically. Dense comparative maps, production of $\times 1.5$ and $\times 7.5$ genome sequences, SNP chips, and a growing sophistication regarding how to tackle problems in complex genetics have all propelled the canine system from a backwater to the forefront of the genomics landscape. In this chapter, we explore some of the critical advances in the field that have occurred in the past 5 years. We discuss the implications of each on disease gene mapping. Complex trait genetics and advances related to finding genes associated with morphology are also discussed. Finally, we speculate on what advances will likely define the field in the coming 5 years.

1 Introduction to Dogs and Breeds

The domestic dog is believed to be the most recently evolved species from the family Canidae. Within the Canidae there are three distinct phylogenetic groups (Wayne et al., 1997; 1987a, b). The domestic dog shares a clade with the wolf-like canids such as the gray wolf, coyote, and jackals. Dogs are thought to have arisen in quite recent time, perhaps as little as 40,000 years ago, with the initial domestication events occurring in eastern Asia (Savolainen et al., 2002; Vila et al., 1997).

Most dog breeds arose in the last 200–300 years and many of the most common modern breeds were developed in Europe in the 1800s. Currently, there are over 400 recognized and distinct dog breeds of which 155 are registered by the American Kennel Club (AKC) in the United States (American Kennel Club, 1998). While a breed of dog can be recognized by its physical attributes such as size, shape, coat color, head shape, leg length, etc., the concept of a breed has been formally defined by both dog fanciers and geneticists.

According to registering bodies like the AKC, becoming a registered member of a breed simply requires that both of a dog's parents are documented members of the same breed, and that a small fee be paid. As a result, dog breeds are essentially

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closed-breeding populations with little opportunity for introduction of new alleles. Dog breeds are characterized by a lower level of genetic heterogeneity than that seen in mixed breed dogs as a result of small numbers of founders, population bottlenecks, and the over representation of some males (popular sires) who perform well in dog shows (Parker et al., 2004; Parker and Ostrander, 2005). As a result, the current population of ∼10 million purebred dogs in the United States represents an ideal group in which to study the genetics of both simple and complex traits.

Recently, attempts have been made to define the concept of a breed at the genetic level (Koskinen, 2003; Koskinen and Bredbacka, 2000; Parker et al., 2004). For example, Parker et al. (2004) utilized data from 96 (CA)n repeat-based microsatellite markers spanning all dog autosomes on 414 dogs to determine the degree to which dogs could be assigned to their appropriate breed using a clustering algorithm. Only a small set of closely related breed pairs (i.e., Whippet and Greyhound; Alaskan Malamute and Siberian Husky) could not be reproducibly distinguished when compared to other breeds. Similarly, using the Doh assignment test, 99% of the dogs tested were correctly assigned to their distinct breed group using only the microsatellite data.

The above results are interesting in light of studies on genetic diversity in human populations. In the Parker et al. (2004) study, we showed that humans and dogs have similar levels of overall nucleotide diversity, 8×10^{-4}. Genetic variation between dog breeds, however, is much greater than the observed variation between human populations (27.5% versus 5.4% by AMOVA). The degree of genetic homogeneity, not unexpectedly, is much greater within the membership of any given individual dog breed than it is within distinct human populations. So the concept of a dog "breed" is much more definitive, at the genetic level, than is the concept of a human "population" or a human "race."

2 Mapping Disease Genes in Dogs

Because dog breeds represent closed-breeding populations, they offer unique opportunities for disease gene mapping (Ostrander and Kruglyak, 2000). Diseases that are problems for both human and companion animal health are excellent candidates for study, particularly those associated with complicated phenotypes. The mapping of complex traits in humans, such as cancer, diabetes, epilepsy, and heart disease, has been stymied by the lack of large pedigrees, limited statistical methods, and both locus and phenotypic heterogeneity. As a result, the ability to unambiguously identify critical susceptibility loci for diseases like cancer has been problematic (Ostrander et al., 2004). By working with canine families, researchers are able to overcome many of these disadvantages. Dog pedigrees are large, and often permit collection of several generations. For example, the pedigrees used to find the genes for a variety of forms of progressive retinal atrophy (PRA) (Acland et al., 1994, 1998, 1999; Kukekova et al., 2006; Moody et al., 2005; Sidjanin et al., 2002), copper toxicosis (Yuzbasiyan-Gurkan et al., 1997), renal

cancer (Jonasdottir et al., 2000), narcolepsy (Lin et al., 1999; Mignot et al., 1991), hyperuricosuria (Safra et al., 2006), pancreatic acinar atrophy (Clark et al., 2005), and epilepsy (Lohi et al., 2005) all involved large, multigenerational families of the sort unheard of in human genetics. In addition, the fact that all the dogs share a common, often inbred genetic background means that phenotypic expression among individuals with the disease is usually very similar. This latter point should prove particularly useful as the community moves from the mapping of single gene Mendelian disorders to identifying loci associated with complex traits such as behavior and morphology.

We have appreciated the importance of genetic predisposition in the occurrence of canine diseases for years (Patterson, 2000; Patterson et al., 1982). Indeed, the dog is second only to human in the attention to which clinicians offer their clients and the number of dollars spent on health care (American Veterinary Medical Association, 2002; Patterson, 2000). As a result, several hundred genetic diseases have been identified in the dog (Sargan, 2004), many of which share strong phenotypic similarities with human diseases. Many of these are collated in an online database called IDID (Inherited Disease in Dogs), which is similar to the Online Mendelian Inheritance of Man (OMIM) database (Sargan, 2004).

To date, dozens of loci have been identified for canine-inherited diseases and in many cases the causative genes have been identified (reviewed in Parker and Ostrander, 2005; Sutter et al., 2004; Switonski et al., 2004). Specific examples include metabolic disorders (van De Sluis et al., 2002; Yuzbasiyan-Gurkan et al., 1997), blindness (Acland et al., 1998, 1999; Aguirre et al., 1978; Aguirre and Acland, 1988, 1998; Kukekova et al., 2006; Moody et al., 2005), cancer (Jonasdottir et al., 2000; Lingaas et al., 2003), neurologic disorders (Lin et al., 1999; Lingaas et al., 1998), hip dysplasia (Chase et al., 2004), osteoarthritis (Chase et al., 2005b), hyperuricosuria (Safra et al., 2006), pancreatic acinar atrophy (Clark et al., 2005), Addison's disease (Chase et al., 2006), and epilepsy (Lohi et al., 2005).

The lessons learned have been plentiful. We have gleaned insight into new genetic mechanisms responsible for disease as well as learned something about the genes and pathways associated with many diseases. In some cases knowledge gained about the underlying disease genes have enlightened us about human conditions for which we had little prior knowledge, such as the inherited sleep disorder narcolepsy. In this case, the underlying mutation found in the genetically susceptible Doberman Pinscher was a splicing defect in the gene for the hypocretin 2 receptor (Lin et al., 1999).

In other cases we have learned about new types of genetic aberrations that can cause disease. Recalling again the example of narcolepsy, the disease has been shown to be caused at the molecular level by insertion of a canine-specific, short interspersed nuclear element (SINE; Bentolila et al., 1999; Minnick et al., 1992; Vassetzky and Kramerov, 2002). These retrotransposons are derived from a tRNA-Lys and occur frequently throughout the canine genome (Bentolila et al., 1999; Coltman and Wright, 1994; Kirkness et al., 2003). In addition to narcolepsy, aberrant insertion of SINEC_Cf elements are associated with centronuclear myopathy in the Labrador Retriever (Pele et al., 2005) as well as the gray merle coat coloring that appears in many breeds (Clark et al., 2006).

Another interesting example is found in a form of epilepsy similar to human Lafora disease. The canine disease affects several breeds including the miniature wirehaired dachshund. Lohi and collaborators have shown that the disease is caused by expansion of an unstable dodecamer repeat in the Epm2b (Nhlrc1) gene (Lohi et al., 2005). While trinucleotide repeat expansion has been reported in association with several human neurologic disorders, this is the first report of a dodecamer repeat expansion causing a disease in any species.

By far, the most interesting advances have been those that highlighted not only new mechanisms of disease, but new genes as well. For instance, extensive progress has been made in understanding the genetic basis of PRA in the dog (Acland et al., 1994, 1998, 1999; Aguirre et al., 1978, 1998; Aguirre and Acland, 1988; Kukekova et al., 2006; Lowe et al., 2003; Moody et al., 2005; Sidjanin et al., 2002). PRA refers to a collection of ocular disorders reminiscent of the constellation of human diseases known as retinitis pigmentosa (reviewed by Petersen-Jones (2005)). Recently, a gene for progressive rod cone degeneration (prcd) was identified in the Poodle, Labrador, and several other breeds (Goldstein et al., 2006; Zangerl et al., 2006). This disease had previously been mapped to a gene-rich region of canine chromosome 9 (CFA9) (Acland et al., 1998). As the disease is present in several related breeds, the authors used linkage disequilibrium (LD) data from a combination of 14 breeds to reduce the disease-associated interval from several megabases (Mb) to just 106 Kb (Goldstein et al., 2006) (Fig. 1). They then identified a single missense mutation that accounted for both the canine disease and the autosomal recessive retinitis pigmentosa in a patient from Bangladesh (Zangerl et al., 2006).

In many cases, disease genes have been found in dogs after identification in humans, or simultaneous with the disease gene in humans. For example, the gene for canine renal cancer in the German Shepherd Dog, although linkage mapped first

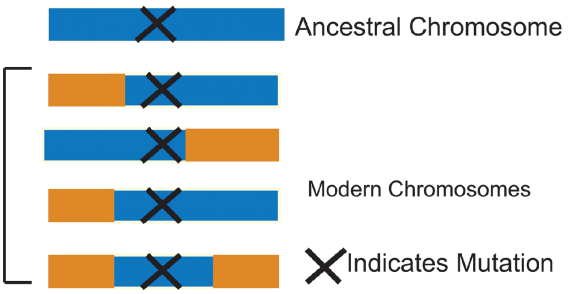

Fig. 1 Linkage disequilibrium. The *top* chromosome represents an ancient chromosome with an initial ancestral mutation as marked by the X. Meiotic recombination whittles away the shared haplotype around the chromosome. Modern day chromosomes will share only a small region of commonality around the mutation. Identification of this shared haplotype by SNP genotyping facilitates fine mapping studies

in the dog (Jonasdottir et al., 2000), was actually found (Lingaas et al., 2003) after the orthologous human gene, which causes a similar disease called Birt-Hogg-Dube Syndrome, was identified (Nickerson et al., 2002). The example of identifying the gene for prcd remains one of the few, together with the identification of the gene for copper toxicosis in the Bedlington Terrier, where the canine community has led the human genetics community in the hunt for truly novel susceptibility genes (van De Sluis et al., 2002).

3 Canine Breed Relationships

The above study by Goldstein et al. provides a nice example of how data can be combined across breeds to identify disease loci of interest (Goldstein et al., 2006). To generalize this concept, Parker et al. have studied over 85 breeds using a clustering algorithm to understand the relatedness of one breed to another (Parker et al., 2004). In their initial analysis, 85 breeds were ordered into four clusters, generating what is now considered to be a new canine classification system for dog breeds (Ostrander and Wayne, 2005) based on similar patterns of alleles, presumably from a shared ancestral pool (Fig. 2). Cluster 1 comprised dogs of Asian and African origin as

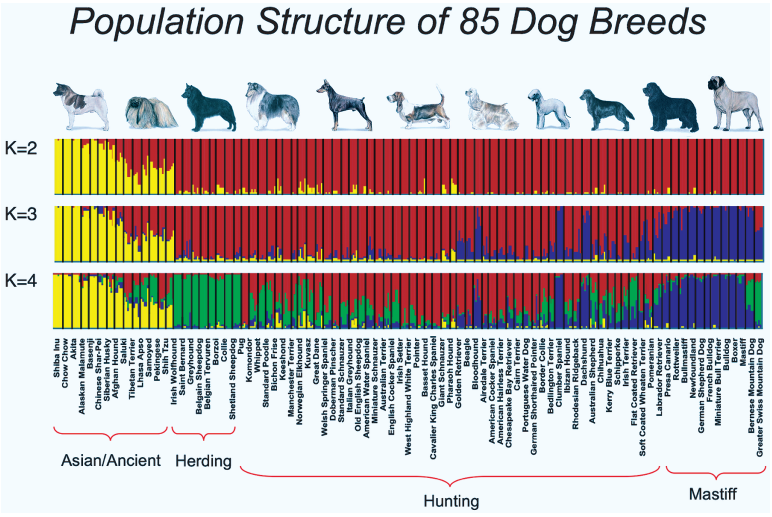

Fig. 2 Population structure of the domestic dog. Figure is derived from the work of Parker et al. (2004). Five dogs from each of 85 breeds were genotyped using 85 (CA)n repeat-based microsatellites. Markers spanned all autosomes at 30 Mb density. Analysis was performed using the computer program *structure*. Analysis at K = 2, 3, and 4 divided the population of 85 breeds into the most likely groups based on allele sharing. Group 1 is comprised largely of Asian breeds such as the Lhasa Apso, Shar Pei, and Akita. Group 2 is the mastiff group and includes, for example, the Boxer, Bull Dog, and Presa Canario. Group 4 includes a mixture of dogs including working breeds. Group 4 is enriched for sight and scent hounds and includes breeds such as the spaniels and retrievers

well as gray wolves. Cluster 2 is typified by mastiff-type dogs with big, boxy heads and strong, sturdy bodies such as the Boxer, Mastiff, and Bulldog. The third and fourth clusters split a group of herding dogs and sight hounds away from the general population of modern hunting dogs comprised of terriers, hounds, and gun dog breeds. Ongoing studies are underway to expand this work to include more breeds. It is expected that this should allow even higher resolution of the breed relationships picture, and a clearer understanding of how to best combine data across breeds for fine resolution mapping studies.

4 Advances in Canine Genomics

While canine genetics has demonstrated significant progress in the past few years, the rate at which we can expect new discoveries will accelerate dramatically in the coming months. This is due almost exclusively to two major advances. First, the publication of a gene dense canine radiation hybrid (RH) map allowed us, for the first time, to understand the evolutionary relationship between the canine and the human genomes (Hitte et al., 2005). In this study, a well-spaced set of 9850 sequence tagged sites (STS) corresponding to a set of evenly spaced human genes selected from the then available $\times 1.5$ poodle sequence (Kirkness et al., 2003) were localized on an RH map using a 9000 rad panel. Mutual-Blast alignments identified the best target (human) gene sequence using the dog sequence as a probe to ensure that we were, in fact, mapping the canine ortholog. A total of 9850 gene fragments were eventually mapped, which corresponds to approximately half of the genes in the dog genome, identifying some 264 conserved segments (CS) between dog and human.

Interestingly, most of these fragments (243) were later identified by the whole genome assembly (CanFam1.0) of the dog (Lindblad-Toh et al., 2005), generated from the $\times 7.5$ sequencing effort. This suggests that a dense RH map provides as much information for comparative genome mapping studies as a $\times 7$–10 whole genome shotgun sequence. In addition, detailed comparison of the canine $\times 7.5$ whole genome assembly (CanFam 1.0) to the 9000 rad RH map showed that 99.3% of the chromosomal assignments predicted by the RH map were in complete agreement with the sequence assembly. Those that were not were quickly resolved and found to represent issues such as the orientation of internal chromosomal fragments. This advance was critical in allowing scientists to move between the canine and the human maps, in assembling the canine genome sequence, and in finding the precise breakpoints between the canine and the human genomes (Murphy et al., 2005).

In addition to the above, the availability of both a $\times 1.5$ poodle survey sequence and a whole genome assembly of a $\times 7.5$ boxer sequence is sure to impact canine genetics research at every level (Kirkness et al., 2003; Lindblad-Toh et al., 2005). We now know that the dog euchromatic genome is approximately 2.4 billion bases and is comprised of about 243 conserved segments when compared to the human

genome. The assembled sequence is estimated to cover 98–99% of the genome, with the majority of the sequence contained within two supercontigs per chromosome. That is, on average, two segments of continuous sequence cover each of the dogs' 38 autosomes. The gene count, at $\sim 19,000$, is less than what has been predicted for the human genome, perhaps due to complexities associated with splicing and gene families. There is a 1-1-1 correspondence between orthologs of human, mouse, and dog for 75% of the genes. The full genome sequence can be accessed through http://www.genome.ucsc.edu; http://www.ncbi.nih.gov, and http://www.ensembl.org. A discussion of mining the canine genome sequence is reviewed in O'Rourke (2005).

In addition to the Boxer sequence, a $\times 1.5$ partial sequence of the Standard Poodle is available (Kirkness et al., 2003). While in itself less complete than the Boxer sequence, together these two resources have enabled the identification of more than 2 million single nucleotide polymorphisms (SNPs). We now know that a SNP occurs about once in every 1000 bases in dogs (Lindblad-Toh et al., 2005) and a first generation canine SNP chip is now available from Affymetrix. The chip contains some 24,000 working SNPs that will change the landscape of whole genome association studies in the dog. While microsatellites have proven sufficient for mapping single gene traits, it has generally not been possible to analyze enough markers to fully interrogate the genome in a complex trait association study. With thousands of SNPs available on a single chip, we believe that it is now possible to identify subtle variants responsible for a host of phenotypic observations.

Key to the development of the canine SNP chip were studies by both Lindblad-Toh et al. (Lindblad-Toh et al., 2005) and Sutter et al. (Sutter et al., 2004) who addressed the issue of how many SNPs are "enough" for doing whole genome association studies in the dog. Sutter and colleagues examined the extent of LD in five breeds with distinct breed histories and reported that the average length of LD in these five breeds is approximately 2 Mb (Fig. 3). This is 40–100 times further

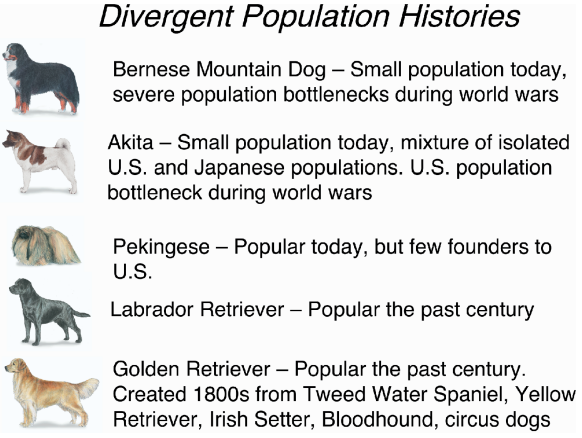

Fig. 3 Divergent population histories of dog breeds. Breeds were selected by Sutter et al. (2004) in their study of linkage disequilibrium in dogs. Breeds were chosen to represent a variety of morphologic types, levels of present-day and historical popularity, population structure, and history (Wilcox and Walkowicz, 1995)

than the LD that typically extends in the human genome (Fig. 4). Thus, while a typical whole genome association study in humans requires about 500,000 SNPs (Kruglyak, 1999), in dogs the same study would require only about 10,000–30,000 markers. For diseases of interest to both human and canine health such as cancer, heart disease, cataracts, etc., these LD findings argue that it will be far easier to do the initial mapping study in dogs than in humans. These investigators also found that the extent of LD varied over a near 10-fold range between breeds of dog (0.4–3.2 Mb) (Sutter et al., 2004), arguing that breed selection would be important for the initial mapping of any trait of interest.

As part of the canine genome sequencing effort, Lindblad-Toh and colleagues undertook more extensive studies on canine LD, looking at more loci and more SNPs. They concluded that perhaps as few as 10,000 SNPs would be needed to fully cover the genome. They also found that the level of LD between breeds was different, but argued that the levels across the genome will likely vary more than the levels associated, on average, with any one dog breed versus another. Finally, both studies looked at the issue of haplotype sharing and demonstrated that there was low haplotype diversity and high haplotype sharing. Importantly, this means that a single set of SNPs, or a single SNP chip, is likely sufficient for mapping studies in any dog breed.

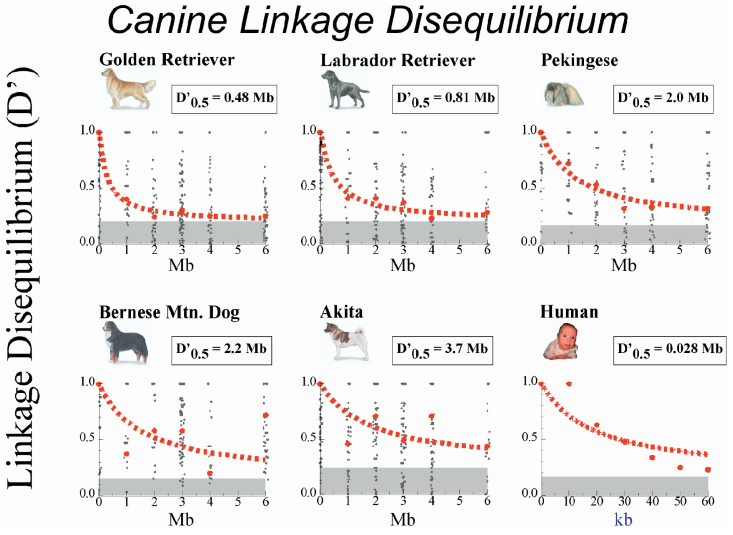

Fig. 4 Canine linkage disequilibrium. Summarized previously in Sutter et al. (2004) and Sutter and Ostrander (2004). Five breeds were analyzed and five loci each and the results averaged for each breed. D' statistic is shown for each breed and for human. Gray shading indicates background level. LD decay at the 50% level is indicated in upper right of each panel. LD extends the farthest for the Akita, at 3.7 Mb, and the shortest for the Golden Retriever, at 0.48 Mb. For human the comparable number is about 0.028 Mb. LD in dogs is about 50 times greater than that observed in most human populations

5 Mapping Genes for Morphology in the Dog

Breeds of dog differ by over 40-fold in size and display an amazing level of morphologic variation. Indeed, Wayne et al. (1986a, b) have argued that the diversity in skeletal size and proportion of dogs is greater than that observed in any other terrestrial mammal. Studies to map quantitative trait loci (QTLs) in the dog associated with body conformation have been led by Gordon Lark, Kevin Chase and collaborators and are based upon their work with the Portuguese Water Dog (PWD) (Chase et al., 1999, 2002). They chose the PWD because the breed offers several advantages for complex trait mapping. There are only about 10,000 living AKC registered PWD, and they derive historically largely from just two kennels (Chase et al., 1999). The breed standard allows for significant variation, offering a greater opportunity for mapping traits associated with morphology than would studies of other breeds.

To initiate their studies these researchers collected DNA samples, health information, pedigree data, and five standard X-rays of over 500 dogs (Chase et al., 1999). They undertook a genome wide scan using over 500 microsatellite markers. Analysis of the data suggested four sets of correlated traits or principal components (PC) (Fig. 5). Each PC described a set of correlated phenotypic features for which QTLs could be identified. PC1 regulates overall body size; PC2 describes the relationship between pelvis, head, and neck; PC3 is shown in the inverse relationship between the cranial volume and the length of skull and limbs; PC4 is the length versus width of the skull and axial skeletons, representing a tradeoff between speed and strength as illustrated by the hound-type dogs on the left and the mastiff-type dogs on the right of Fig. 5.

Of particular interest to Chase and colleagues has been an understanding of the loci which control body size in males versus females (Chase et al., 2005a). In an analysis of 42 metrics derived from the five X-rays, they show that there are five QTLs controlling overall body size in the PWD. Differences in skeletal size between

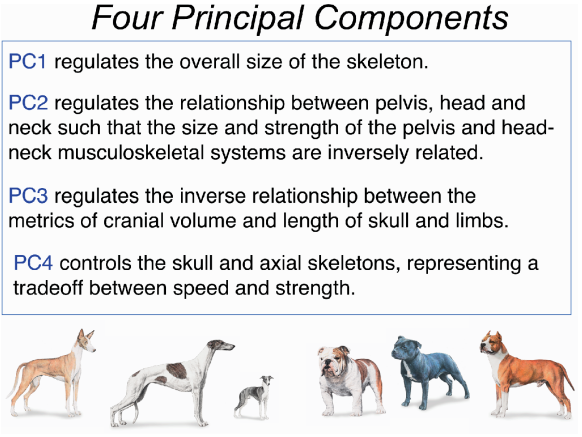

Fig. 5 Four principal components for morphology. Figure summarizes work of Chase and colleagues in their analysis of the Portuguese Water Dog (Chase et al., 2002). Data are based on analysis of 90 metrics derived for five X-rays taken from each of several hundred dogs. Analysis of each principal component allows identification of QTLs controlling each set of correlated traits

females and males are due to an interaction between a QTL on CFA15, adjacent to the insulin-like growth factor-1 (IGF-1) gene, and a locus on the X-chromosome defined by the CHM marker. The locus on CFA15 is defined by marker FH2017. Analysis of FH2017 genotypes suggests that in females the CFA15 allele controlling small size is dominant. However, in males the reverse is true and the genotype associated with large size appears dominant. The situation is partly explained by consideration of the QTL on the X-chromosome. Females that are homozygous at the CHM marker and homozygous for the large size CFA15 genotype are, on average, as large as the very largest males in the breed. However, any female that is heterozygous at the CHM locus will be small, regardless of her FH2017 genotype. Overall, this interaction explains about 50% of sexual dimorphism in the breed.

Why are these observations so important? First, they demonstrate that the canine system is amenable to mapping of complex traits that are of interest to all mammalian biologists. Second, these studies highlight the value of studying complex traits first in a single breed, especially one with small numbers of founders, but a large amount of phenotypic variation. Finally, the results demonstrate that the number of genes controlling complex traits is not so large as to be intractable. That is, body size is likely controlled by a small number of QTLs that are identifiable in the canine system. This has important implications for the mapping of complex diseases as well as truly complex phenotypes such as those associated with behavior.

6 Summary and Future Aims

Until recently, advancement in the study of companion animal health has relied on data from human and mouse studies. With the development of a $\times 7.5$ whole genome sequence assembly of the dog, a SNP chip, studies of canine breed relationships, and a growing understanding of the architecture of the canine genome we are, for the first time, mapping genetic traits of interest first in the dog. Our understanding of disease genes important for both simple and complex traits is advancing at a rapid rate, informing us about the underlying biology of diseases critical to both humans and companion animals.

In the coming decade, the dog is likely not only to lead man in the discovery of disease genes but to provide novel insights into our understanding of truly complex phenotypes. How many of those will be relevant to the human condition? Only time will tell, but we can rest assured that the dog, ever man's faithful companion, will be by our side as we unravel the mysteries of disease susceptibility, behavior, and morphology.

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During preparation of this chapter, the 12-year-old Border Collie of one of the authors died after a short and unexpected illness. We dedicate this chapter to the many pet owners who, in similar situations, have shown us how to deal with our loss with grace and dignity.

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