Understanding hereditary diseases using the dog and human as companion model systems

Kate L. Tsai · Leigh Anne Clark · Keith E. Murphy

Abstract  Animal models are requisite for genetic dissection of, and improved treatment regimens for, human hereditary diseases. While several animals have been used in academic and industrial research, the primary model for dissection of hereditary diseases has been the many strains of the laboratory mouse. However, given its greater (than the mouse) genetic similarity to the human, high number of naturally occurring hereditary diseases, unique population structure, and the availability of the complete genome sequence, the purebred dog has emerged as a powerful model for study of diseases. The major advantage the dog provides is that it is afflicted with approximately 450 hereditary diseases, about half of which have remarkable clinical similarities to corresponding diseases of the human. In addition, humankind has a strong desire to cure diseases of the dog so these two facts make the dog an ideal clinical and genetic model. This review highlights several of these shared hereditary diseases. Specifically, the canine models discussed herein have played important roles in identification of causative genes and/or have been utilized in novel therapeutic approaches of interest to the dog and human.

Introduction

Model systems are vital for the study of disease and the development of new therapeutic approaches. The dog was not immediately recognized as a model for hereditary diseases and few genetic-oriented investigations were carried out until the mid-1990s. Since that time, the canine genetics research community has made significant strides, producing dense linkage and radiation hybrid maps, oligo-based microarrays, SNP arrays, and, most importantly, the sequence of the canine genome at 7.6X coverage (Breen et al. 2004; Clark et al. 2005; Guyon et al. 2003; Linblad-Toh 2006; Linblad-Toh et al. 2005).

The dog offers many of the same advantages of other small animal models. For example, homogeneous populations exist in each of the hundreds of pure breeds, and pedigrees can be easily established in rapid fashion. One advantage that other model systems do not have is that for the dog, pet populations can often be utilized, thereby often eliminating the need for establishment of colonies. Dogs possess other characteristics that are not found in traditional rodent models in that they (1) receive exceptional medical care, (2) have comparable organ sizes (to humans), and (3) generally cohabitate with their human owners, minimizing different environmental effects (Ostrander et al. 2000). The last issue is of particular interest. Specifically, because the dog does live with us, it is exposed to the same environment. Of course, the dog may react differently to such influences/stress than does the human, but living in the same environment is more advantageous when compared to environments in which classic laboratory research animals are maintained because those environments are far different from the ones inhabited by humans. Thus, when modeling the causes and pathogenesis of human hereditary diseases, any environment-gene interactions are likely better studied in an animal that lives in the same environment.

Perhaps the most exciting feature of the canine model is that 220 naturally occurring disease phenotypes are potential models for various human hereditary diseases.
While the mouse is indisputably a fundamental resource for the study of human hereditary diseases, the canine model offers the opportunity to gain knowledge in areas for which the mouse is deficient. For example, genetically altered mice are not available for every disease of interest and alternative models must be identified in these instances. There are more than 450 canine hereditary diseases that provide naturally occurring models in which to study diseases (Ostrander and Giniger 1997). Among these are diseases transmitted in X-linked, autosomal recessive, and autosomal dominant fashions. Also, there are diseases for which canine models were identified before the development of murine models and were used to investigate pathogenesis and treatment regimens. An example of this is hereditary nephropathy (Kashtan 2002).

Research pertaining to spontaneous phenotypes of the dog has revealed genes and pathways novel to diseases. A prime example of this is the work on narcolepsy. In the 1990s, identification of the genetic basis of narcolepsy in the dog led investigators to a pathway not previously known to be involved in the disorder (Lin et al. 1999). Another example is the recent identification of a novel gene that causes retinal degeneration in the dog. It was subsequently determined that an identical mutation in the homologous gene was also responsible for a similar phenotype in a human patient (Zangerl et al. 2006b). While these are hallmark examples of the utility of the canine system, its full potential has yet to be realized because, to date, only a fraction of all hereditary traits have been characterized at the molecular level (http://www.omia.angis.org.au).

Phenotypes resulting from induced models of disease are not always clinically equivalent to those observed in humans. For example, a dystrophin knockout mouse with muscular dystrophy shows muscular weakness but not the continued wasting that is found in human patients (Tanabe et al. 1986). Such incongruities may diminish the usefulness of the model, specifically with regard to testing of possible treatments. In the last decade spontaneous canine models have been instrumental in the development of molecular therapies for human disease; e.g., data obtained from a canine model of hemophilia B led to clinical trials in humans (High 2004). Presented here is a review of the aforementioned diseases for which examination of canine models has revealed previously unknown genetic bases and/or facilitated development of novel treatment options.

**Hereditary nephropathy and Alport syndrome**

Hereditary nephropathy (HN) is a broad term for certain fatal inherited diseases that result in renal failure. Alport syndrome (AS) is a form of HN in humans caused by defects in the glomerular basement membrane (GBM) (Kashtan 1998; Tryggvason and Martin 2001). The only treatments currently available for AS are dialysis and renal transplant. Mutations in the type IV collagen genes cause AS, which is primarily inherited in X-linked (XLAS) and autosomal recessive (ARAS) fashions. There is also a rare autosomal dominant (ADAS) form (Hudson et al. 2003). XLAS results from mutations in COL4A5 and accounts for 85% of cases, while ARAS and ADAS are caused by mutations in COL4A3 or COL4A4 (Jais et al. 2000; Knebelmann et al. 1995; Lemmink et al. 1994; Martin et al. 1998; Mochizuki et al. 1994). Mutations in any of these genes alter the triple helix formed by the COL4A3, COL4A4, and COL4A5 proteins that are necessary for proper GBM formation in the kidney.

Murine models for AS did not exist until 1996 when two transgenic models for ARAS were developed and characterized (Cosgrove et al. 1996; Miner and Sanes 1996). A murine model for XLAS was not described until 2004, despite it being the most common genetic form of AS (Rheault et al. 2004). To date, a murine model for ADAS has not been developed. Naturally occurring HN has been identified in several canine families. The progression of the disease is very similar to AS in humans with the exception of auditory and ophthalmologic abnormalities, which have not been described in the dog. X-linked HN (XLHN) in the dog was identified first in the Samoyed and later in a mixed-breed family (Fig. 1) (Jansen et al. 1986; Lees et al. 1999). A single-base substitution in exon 35 in the Samoyed and a 10-bp deletion in exon 9 in the mixed-breed dog result in premature stop codons and truncated COL4A5 proteins (Cox et al. 2003; Zheng et al. 1994). The English cocker spaniel presents with a renal disease (termed ARHN) similar to ARAS that is caused by a nonsense mutation in exon 3 of COL4A4 (Davidson et al. 2007). The bull terrier is affected by ADHN but the mutation has not been characterized (Hood et al. 1995).

Because dialysis and renal transplants are the only treatments available for AS, correction of the defective GBM via gene therapy as a possible remedy is being explored. In an initial experiment, an adenoviral vector containing a human cDNA construct of COL4A5 was successfully expressed in the kidney of normal pigs (Heikkilä et al. 2001). This study proved that the construct could produce a functional protein capable of trimerizing with COL4A3 and COL4A4 (Heikkilä et al. 2001). To assess the functionality of this in a diseased system, a canine cDNA construct was designed for use in a canine model of the disease (Harvey et al. 2003). Because vector delivery methods are complicated in the kidney, studies were carried out in the bladder. In the smooth muscle of the bladder, COL4A5 and COL4A6 form a trimer composed of...
two transcripts of COL4A5 and one transcript of COL4A6. In XLHN-affected animals, COL4A6 is not deposited into the basement membrane because COL4A5 is not available to form the trimer. Therefore, for gene therapy to be effective, not only must the construct be produced, but the other type IV collagens must also be able to properly trimerize with it. An adenoviral vector containing the canine cDNA of COL4A5 was injected into smooth muscle of the bladder in XLHN-affected Samoyed dogs. Five weeks after injection, expression of both COL4A5 and COL4A6 was found in the basement membranes surrounding the injection site, indicating that COL4A5 was expressed and functional and that COL4A6 was made and deposited (Harvey et al. 2006). These findings are promising for gene therapy of HN and AS.

Narcolepsy

Narcolepsy is a neurologic condition characterized by excessive daytime sleepiness and cataplexy, the sudden loss of muscle tone (Mignot 2004). This rare sleep disorder, which affects less than 0.1% of humans, is debilitating and difficult to diagnose (Dauvilliers et al. 2003). Most cases are sporadic, with familial causes representing fewer than 10% of cases, and twin studies indicate a strong influence of nongenetic factors (Mignot 1998).

In the 1980s, an association with narcolepsy and specific HLA genes and alleles was identified in several ethnic populations (Juji et al. 1984; Seignalet and Billiard 1984). Subsequent studies of these genes have shown that they do not harbor deleterious mutations but rather confer susceptibility to the disease (Maret and Tafti 2005). Based on this significant association with the major histocompatibility (MHC) system, it has been suggested that narcolepsy may result from an autoimmune reaction to environmental agents (Lin et al. 2001).

Naturally occurring narcolepsy was first described in the dog in the 1970s (Knecht et al. 1973). Narcoleptic dogs have clinical signs that parallel those observed in humans and were used as a model to elucidate the genetics underlying the disorder (Hungs et al. 2006). In the dog, narcolepsy is inherited in an autosomal recessive fashion and, unlike the human, is not associated with the dog leukocyte antigen (DLA) system (Foutz et al. 1979; Wagner 2000). In 1999, colonies of Doberman pinchers and Labrador retrievers with narcolepsy were used in positional cloning efforts that identified linkage with the hypocretin/orexin receptor 2 (Hcrtr-2) gene (Lin et al. 1999). Hypocretin proteins (orexins), discovered in 1998, are neurotransmitters processed from a common precursor, preprohypocretin (Hcrt) (de Lecea et al. 1998; Sakurai et al. 1998). Independent mutations in these canine families cause exon-skipping and result in altered proteins. In addition, Hungs et al. (2006) identified a single-base change resulting in an amino acid substitution in Hcrtr-2 that causes narcolepsy in a family of Dachshunds. Hcrtr-2 does not cause narcolepsy in a family of poodles or in 11 individual cases with no family history (Hungs et al. 2006).

The role of hypocretins in canine narcolepsy, and the simultaneous finding that orexin knockout mice have narcoleptic symptoms (Chemelli et al. 1999), led to the investigation of hypocretins in humans. Hcrt and its receptors encoded by Hcrtr-1 and Hcrtr-2 were sequenced in human patients with narcolepsy and a substitution mutation in Hcrt of a single patient was identified (Peyron et al. 2000). Although mutations in these genes may be a rare cause of human narcolepsy, expression studies show
Retinal degeneration

Retinitis pigmentosa (RP) is a group of hereditary disorders characterized by progressive retinal degeneration, eventual night blindness, loss of peripheral vision, and often complete blindness. RP affects 1 in 4000 people and may be inherited as an autosomal dominant, autosomal recessive, or X-linked trait (Hartong et al. 2006). More than 45 genes, accounting for 60% of all cases, have been implicated in RP (Hartong et al. 2006).

Progressive retinal atrophy (PRA) is a group of hereditary diseases of the dog that are phenotypically and molecularly similar to RP. Progressive rod-cone degeneration (prcd) is an autosomal recessive, late-onset form of PRA. In 1998, the prcd locus was mapped to the centromeric end of CFA9 using classical linkage analysis (Acland et al. 1998). Fortuitously, prcd in multiple breeds results from allelic or identical mutations in the PRCD gene. This allowed for multiple breeds to be used in a large-scale linkage disequilibrium (LD) approach, which further defined the interval that harbors the prcd locus (Goldstein et al. 2006). A retinal EST library was instrumental in the identification of novel candidate genes in this region (Zangerl et al. 2006a, b). A single G-to-A transition in a gene of unknown function, termed PRCD, was found to cause prcd in at least 18 breeds (Zangerl et al. 2006b).

Upon discovery of the canine mutation, human patients with inherited retinal disorders for which known causative mutations had been excluded were screened for mutations in the PRCD gene. A woman from Bangladesh having an autosomal recessive form of RP was found to harbor a homozygous mutation in the PRCD gene (Zangerl et al. 2006b). Interestingly, the mutation is identical at the genetic and protein level to the mutation causing prcd in the dog (Zangerl et al. 2006b).

Table 1 Mutations in canine hemophilia B

| Breed                              | Mutation          | Reference                        |
|------------------------------------|-------------------|----------------------------------|
| Not reported                        | Missense          | Evans et al. 1989b               |
| Lhaso Apso                          | 5-bp deletion     | Mauser et al. 1996               |
| Labrador Retriever                  | Complete gene deletion | Brooks et al. 1997          |
| American Pit Bull Terrier mix       | Partial gene deletion | Gu et al. 1999                 |
| Airedale Terrier                    | 5-kb insertion    | Gu et al. 1999                   |
| German Wirehair Pointer             | LINE1 insertion   | Brooks et al. 2003               |

Canine breed, mutation, and reference are shown for each of the six cases of hemophilia B in which the underlying genetics has been reported.

The similarities between humans and dogs can be exploited to develop treatments for retinal degenerative diseases, with significant strides in this field having already been made. In 2001, gene therapy restored vision to dogs with severe retinal degeneration caused by a homozygous, 4-bp deletion in RPE65 (Acland et al. 2001). The dose efficacy and safety data obtained from the successful use of the canine model have led to gene therapy studies in nonhuman primates and the consideration of human trials (Jacobson et al. 2006).

Hemophilia B

Hemophilia B is a recessive bleeding disorder that results from mutations in the Factor IX (FIX) gene on the X chromosome. FIX, synthesized by hepatocytes, is an essential part of the blood coagulation cascade. Clotting factor deficiencies result in bleeding into joints, soft tissue, and muscles. Such bleeding may occur spontaneously or be triggered by a minor injury. Hemophilia B is estimated to occur in 1 in 30,000 males and is both clinically and molecularly heterogeneous. Approximately 1000 unique mutations causing hemophilia B have been reported in humans (Green et al. 2004).

Canine hemophilia B is highly similar to the human disease and is well studied. In 1989, Evans et al. (1989a) published the coding sequence of canine FIX. The same group also identified the first known mutation to cause hemophilia B in the dog, a missense mutation resulting in the complete absence of detectable protein (Evans et al. 1989b). Since then, multiple cases have been described in different breeds and distinct mutations for five of these have been reported (Table 1) (Brooks et al. 1997, 2003; Gu et al. 1999; Mauser et al. 1996).

The standard treatment for hemophilia B is intravenous infusion of FIX concentrates to prevent or treat bleeding.
episodes. While treatment is effective and generally safe, it is expensive and inconvenient (Lillicrap et al. 2006). Molecular therapies for hemophilia B are being investigated not only to provide patients with treatment options but also to evaluate the overall efficacy of such approaches. The factors that make hemophilia a superior model for assessment of genetic intervention strategies are (1) tissue-specific gene expression is not necessary, (2) nominal increases in clotting factor levels will result in significant phenotypic improvements, (3) measurement of clotting factor levels can be achieved through simple blood tests, and (4) naturally occurring canine models are available (Lillicrap et al. 2006).

A colony of dogs with hemophilia B due to a missense mutation first characterized by Evans et al. (1989b), has been used in numerous pioneering gene therapy studies (Kay et al. 1993, 1994; Snyder et al. 1999; Wang et al. 2000). The first of these utilized a retroviral vector containing FIX cDNA and resulted in long-term expression of low levels of FIX (Kay et al. 1993). A subsequent study used a recombinant adenoviral vector and achieved short-term expression of therapeutic levels of FIX (Kay et al. 1994). To attain both long-term and therapeutic levels of FIX expression in these dogs, researchers found success by using adeno-associated viral (AAV) vectors (Herzog et al. 1999; Snyder et al. 1999; Wang et al. 2000). An AAV vector was also later used to correct a severe hemophilia B phenotype in dogs with a null mutation (Mount et al. 2002).

The data obtained using the AAV vector in these canine studies provided the proof of principle necessary to move forward with hemophilia B gene therapy trials in humans (High 2004). The dog has also been instrumental in advancing molecular therapy approaches for hemophilia A, which results from factor VIII deficiency (Lillicrap et al. 2006). Hemophilia A is significantly more common than hemophilia B, but gene therapy studies have been impeded by large size of the FVIII gene (Kay and High 1999).

Muscular dystrophy

The most common and severe muscular disorder in humans is Duchenne muscular dystrophy (DMD). DMD is an X-linked disorder that results in muscle degeneration and death around the age of 20. It affects approximately 1 in 3500 males and there are currently no effective treatments available. A naturally occurring form of DMD has been described in the golden retriever (Kornegay et al. 1988). Golden retriever muscular dystrophy (GRMD) is characterized by elevated serum creatinine kinase activity, progressive muscle atrophy and necrosis, and regeneration by fibrotic and adipose tissues. Affected dogs develop clinical signs in 8-10 weeks (Kornegay et al. 1988).

DMD is caused by a defective dystrophin gene, which codes for a cytoskeletal protein responsible for stabilizing the sarcolemma (Hoffman et al. 1987). Northern and Western blots using human probes failed to detect dystrophin transcripts or proteins in muscle tissue from GRMD-affected dogs (Cooper et al. 1988). Sequence analysis of the dystrophin gene revealed an A-to-G transition in the exon 7 splice acceptor of affected dogs (Sharp et al. 1992). This mutation causes either the deletion of exon 7 or the use of an alternative splice site 5 bp downstream; both result in a reading frame shift and a truncated transcript (Dell’Angola et al. 2004; Sharp et al. 1992).

The frequency and severity of DMD has fueled interest in the development of gene therapies for patients. Significant advancements have come from a murine model, but greater similarities in disease progression make the dog a more attractive model (Foster et al. 2006; Tanabe et al. 1986). Initial gene therapy studies in the dog focused on the dystrophin gene and were promising (Howell et al. 1997). An alternative approach involved upregulation of utrophin, a gene functionally and structurally similar to dystrophin, but not foreign to DMD patients (Cerletti et al. 2003). Delivery of mini-utrophin transcripts via an adenoviral vector mitigated the dystrophic phenotype in the muscles of GRMD dogs; however, slight immunologic reactions to the vector and transgene occurred (Cerletti et al. 2003). An additional method involved modified antisense oligonucleotides (AOs) that cause exon-skipping. By changing the splicing pattern, AOs can cause a mutated exon to be removed from the pre-mRNA, leading to a functional protein. McClorey et al. (2006) successfully used AOs to restore dystrophin expression in dogs.

Human gene therapy studies have been successful as well, with several types of vectors used to deliver dystrophin to dystrophic muscles. AAV vectors have been problematic because of their limited carrying capacity and the large size of the dystrophin gene. The use of microdystrophin (a truncated but functional version of the dystrophin gene) has shown promise and initial trials are underway (Foster et al. 2006). In addition, with the success of AO treatment in the dog, human phase 1 clinical trials have been initiated (Foster et al. 2006; http://www.muscular-dystrophy.org, http://www.ppuk.org).

In an effort to eliminate immune reactions against vectors and/or the dystrophin gene itself, researchers investigated the use of stem cells to treat GRMD. Hematopoietic stem cells have proven to be effective in muscle regeneration in the murine mdx model (Gussoni et al. 1999). Unfortunately, hematopoietic stem cells from normal littermates did not cause muscle regeneration in affected dogs (Dell’Angola et al. 2004). Vessel-associated stem cells,
called mesoangioblasts, were also studied. Mesoangioblasts were successfully transplanted and expressed dystrophin, allowing recovery of muscle use (Sampaolesi et al. 2006). Donor wild-type mesoangioblasts were found to be more effective than genetically corrected autologous mesoangioblast cells (Sampaolesi et al. 2006). All dogs treated with wild-type cells displayed initial mobility improvements and one dog was still walking five months after cessation of treatments (Sampaolesi et al. 2006).

Summary

Presented here are examples of studies that were critical to identification and treatment of genetically simple diseases that affect the human and dog. However, the genetics of complex diseases are more difficult to assess—in the dog and human. Nevertheless, with new genomic tools/resources now available for study of the dog, workers have now begun analyses of complex diseases such as cancers, cardiovascular diseases (e.g., cardiomyopathy), and neurologic diseases (e.g., epilepsy). In addition, the dog is being used to assess the genetics of morphologic development and behavior due to the unique physical and behavioral traits that characterize individual breeds. The hypothesis for such lines of investigation is simple: while there likely are additional factors that influence behavior, morphology, and progression of diseases in the dog and human, the major genes influencing these may very well be the same.

One complex disease for which data are available from the dog is canine hip dysplasia (CHD) or degenerative joint disease, the major orthopedic disease of the dog. This is a painful and crippling disease that has a counterpart in the human termed developmental dislocation of the hip. Researchers are exploiting the natural occurrence of CHD in both pet populations and designed outcrossed pedigrees in an attempt to delimit contributory genetic components to this disease (Chase et al. 2004; Todhunter et al. 1999; Tsai and Murphy 2006). To date, two QTLs have been identified in the Portuguese water dog (PWD) on CFA01 that are associated with joint laxity as measured by the Norberg angle. Interestingly, one of the QTLs is associated with joint laxity in the right hip while the other is associated with the left hip (Chase et al. 2004). The same PWD population was used recently to identify the insulin-like growth factor 1 gene (IGF1) as a determinant for skeletal size in dogs (Sutter et al. 2007). This is an important finding because understanding the genetics of growth and regulation may provide insight into complex diseases such as cancer and hip dysplasia.

The diseases discussed in this article highlight the importance of the dog to biomedical research, particularly the study of hereditary diseases. Perhaps most unique about the use of the dog as a model is this: study of those hereditary diseases common to the dog and human allows both to benefit as opposed to one serving merely as a model for the other. A paucity of genetic tools with which to study the canine genome previously prohibited researchers from exploiting the canine model. Thus, the majority of research in the dog was guided by our knowledge of the disease in the human. With the necessary resources now available, discoveries in the dog are being used to define causative genes and pathways and, importantly, develop new treatment regimens for the human.

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