

Origin, genetic diversity, and genome structure of the domestic dog

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Summary

Comparative analysis of mammalian genomes provides important insight into the structure and function of genes. However, the comparative analysis of gene sequences from individuals of the same and different species also provides insight into the evolution of genes, populations, and species. We exemplify these two uses of genomic information. First, we document the evolutionary relationships of the domestic dog to other carnivores by using a variety of DNA-based information. A phylogenetic comparison of mitochondrial DNA sequences in dogs and gray wolves shows that dogs may have originated from multiple wolf populations at a time much earlier than suggested by the archaeological record. We discuss previous theories about dog development and evolution in light of the new genetic data. Second, we review recent progress in dog genetic mapping due to the development of hypervariable markers and specific chromosome paints. Extensive genetic homology in gene order and function between humans and dogs has been discovered. The dog promises to be a valuable model for identifying genes that control morphologic differences between mammals as well as understanding genetically based disease. *BioEssays* 21:247–257, 1999. © 1999 John Wiley & Sons, Inc.

Introduction

We will review recent studies of genetic diversity and genome mapping of dogs to demonstrate the use of genome information in evolutionary and biomedical studies. Initially, we will discuss the evolutionary history of dogs and their relationship to other canines and carnivores as revealed by DNA-based research. These results show that canines belong to a very unique and long distinct genetic lineage of carnivores. Thereafter, we will describe new genetic studies suggesting that dogs were domesticated over 100,000 years ago. Although all dogs appear to have been derived from the gray wolf, origination or interbreeding events may have occurred sev-

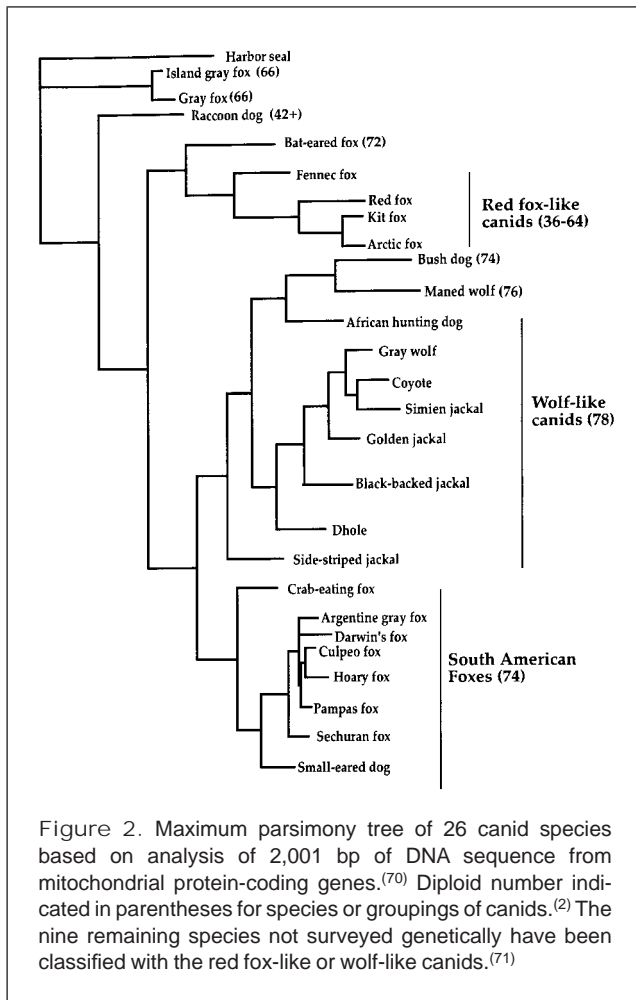
eral times over human history. Gray wolves may continue to influence the genetic diversity of dogs through the interbreeding of dog-wolf hybrids and domestic dogs. We will conclude with an overview of dog genome mapping studies and their relationship to similar studies in humans and other mammals. Progress in the physical map of genes has been slow because dogs have a high numbered karyotype ($2n = 78$) and the smallest chromosome elements are difficult to identify. However, recent advances in banding studies and the development of hypervariable markers and chromosome paints have resulted in more extensive syntenic and physical maps.

Evolutionary relationships of the domestic dog
The domestic dog is a species in the family Canidae, order Carnivora, and superfamily Canioidea that includes seals, bears, weasel-, and raccoon-like carnivores (Fig. 1). The dog family is sometimes considered representative of the superfamily, but the Canidae is, in actuality, the most phylogenetically distinct family, diverging from other carnivores over 50 million years ago (Fig. 1). In fact, the canine karyotype holds

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of the several hundred extant dogs breeds have been developed in the last few hundred years, but even for these, the specific crosses that led to their establishment often have not been recorded.⁽⁸⁾ The genetic diversity of the founding populations is essential knowledge for understanding the immense phenotypic diversity of dogs. A diverse gene pool suggests that gene diversity is critical to phenotypic divergence, whereas a limited gene pool suggests development plasticity is more important in breed evolution. Moreover, an understanding of genetic diversity is needed in order that genome mapping studies can document and use efficiently the genetic diversity that exists in the dog.

All species in the dog genus *Canis* are phylogenetically closely related and can potentially interbreed. Charles Darwin felt that domestic dogs were phenotypically so diverse that they likely had originated from two or more wild canine species.⁽⁹⁾ Similarly, Konrad Lorenz initially suggested that traits from wolves and jackals could be observed in dogs.⁽¹⁰⁾ However, such polyphyletic theories of dog origin are uncommon, and most researchers maintain that dogs were derived

from one or more populations of gray wolves.^(6,7) Molecular genetic data clearly support the origin of dogs from wolves; dogs have protein alleles in common with wolves,^(11,12) share highly polymorphic microsatellites,⁽¹³⁾ and have mitochondrial DNA sequences similar or identical to those found in gray wolves.^(14,15) Recently, a comprehensive survey of several hundred gray wolves and dogs found that the two species had only slightly divergent mitochondrial DNA control region sequences.⁽¹⁶⁾ For example, the average divergence between dogs and wolves was about 1.5% in comparison to 7.5% between dogs and coyotes, their next closest relation.

More controversial is the specific number of domestication events and their timing and location. The archeologic record suggests that the first domestic dogs are found in the Middle East approximately 14,000 years ago.^(6,7) However, remains close to this age are known from Europe, and 8,000-year-old specimens are known from North America.^(6,7,17) Morphologic comparisons suggest that dogs are closest phenotypically to Chinese wolves.⁽¹⁸⁾ The phenotypic plasticity of dogs is a problem when attempting reconstructions of their origin. Some dogs approach closely the phenotype of wild wolves, whereas others do less so.⁽¹⁹⁾ Consequently, the first appearance in the fossil record of domestic dogs, as marked by their phenotypic divergence from wolves, may be misleading. Rather than the first domestication event, the appearance of the first differentiated dogs in the fossil record instead may have recorded a change in artificial selection associated with a cultural change in human societies.⁽¹⁶⁾

An independent assessment of dog domestication is provided by mitochondrial control region sequence data (Fig. 3).⁽¹⁶⁾ Phylogenetic analysis of control region sequences reveals four divergent sequence clades. The most diverse of these clades contain sequences that differ by at most 1% in DNA sequence (Fig. 3, clade 1). Therefore, because wolves and coyotes diverged about 1 million years ago and have control region sequences that are 7.5% different, dogs and gray wolves may have diverged 1/7.5 as long ago or about 135,000 years before present. Consequently, the molecular results suggest an ancient origin of domestic dogs from wolves. In fact, wolves and humans lived in the same habitats for as much as 500,000 years.⁽⁶⁾ Therefore, they may have been domesticated earlier and have only recently changed in conformation with changing conditions associated with the shift from hunter-gather cultures to more agrarian societies about 12,000 years ago.⁽⁶⁾ The role that dogs played in societies before this period may have been dramatically different, perhaps restricted more to protection and hunting and living less closely with humans. Alternatively, dogs may have had a more recent origin, but are descended from a now extinct species of canid whose closest living relative was the gray wolf.

At least four origination or interbreeding events are implied by the genetic results because dog sequences are imbedded

sequences identical to those found in other dogs breeds. Moreover, representatives of all four sequence clades were found in the Xolo (Fig. 3), indicating that the population of dogs that migrated with humans into the New World over 10,000 years ago was large and diverse and had a recent common ancestry with dogs of the Old World. None of the Xolo sequences were similar to New World wolves, suggesting that they were not independently domesticated from them.

Wolf-dog hybridization

Wolves continue to influence the genetic diversity of dogs. In the United States, over 100,000 wolf-dog hybrids exist. Wolf-dog hybrids are frequently interbred with dogs, and the progeny of hybrids, by having a lower proportion of wolf genes, may be more docile. Consequently, wolf genes will diffuse into the dog population at large. Dog genes may also be influencing the genetic composition of wild wolves. In Italy and Spain, gray wolves interact and may interbreed with semi-feral populations of domestic dogs.⁽²⁰⁾ Such hybridization can threaten the genetic integrity of wild wolf populations, although the frequency of occurrence may not be as high as previously thought.⁽²⁰⁾

Implications for genome mapping

The implication of these results for genetic studies of dogs is that despite intense selection for phenotypic uniformity within breeds, the genetic diversity within many dog breeds is similar to that in wild gray wolf populations. Consequently, breeds without a closely controlled history of inbreeding should not be considered genetically uniform, except as regarding specific genes affecting conformation and breed defining traits. Additionally, these results suggest that the diversity of functional genes in dogs should be systematically explored to complement efforts in genome mapping. A genome map based on studies from a limited sample of dogs will not adequately represent the genetic diversity of dogs. However, crosses between distinct dog breeds to create highly heterozygous individuals for mapping studies may not be very useful because of the low level of divergence among breeds. Crosses between dogs and coyotes may be more informative in this regard (Fig. 2).

Developmental and genetic diversity

An intriguing question concerns the origin of phenotypic diversity in domestic dogs. Dogs are clearly the most diverse domestic species. The range in size and conformation is exemplified by the petite Chihuahua (0.5 kg) and the massive Great Dane (80 kg). This two orders of magnitude difference in size has no parallel in other domesticated animals. Past theories to explain the origin of phenotypic diversity in dogs have hypothesized that it is related to the profound developmental alterations that occur from neonate to adult.⁽¹⁹⁾ Neona-

tal dogs have an extremely broad and foreshortened cranium, whereas an adult German Shepard has a long tapered face and cranium (Fig. 4). Developmental alterations that truncate, accelerate, or retard aspects of this ontogenetic transformation create dramatically divergence skull morphologies that can readily be selected by breeders. Puppy-like features in adult animals are often cultivated by humans.⁽²⁶⁾ In contrast, neonatal and adult domestic cats vary little in proportion and, thus, changes in growth rate or timing will not cause such a dramatic change in conformation (Fig. 4). Breed diversity is reflected by ontogenetic diversity in other domestic mammals as well.⁽¹⁹⁾ This finding suggests that the difference in diversity between dogs and other domestic animals reflects the degree to which neonates and adults differ in conformation. The action of only a few development genes on growth will cause more dramatic change in dogs than in other domestic animals. However, this conclusion was based on the assumption that dogs and other domestic species had similar initial levels of genetic variation. The finding that dogs have had a diverse and ancient origin suggests that genetic variation may be an important prerequisite for phenotypic variation in dogs and other domestic species.

The canine genome: Genome organization and cytogenetics

Among the many methods for studying genetic variation are those based on cytogenetic analyses, comparative studies of gene families, and molecular genetic analyses. The first of these, cytogenetic analysis, has been extremely difficult to perform in the dog due to the large number of small acrocentric chromosomes ($2n = 78$). Based on high-resolution banding of metaphase chromosomes from dog fibroblasts, an ideogram of 460 numbered bands and landmarks has only recently been proposed.⁽²⁷⁾ But standards for chromosome identification by G-banding have been established for only the largest 22 canine autosomes by the Committee for the Standardized Karyotype of the Dog.^(27,28) Thus, efforts to reproducibly distinguish canine chromosomes have had to rely largely on newer molecular approaches, such as chromosome painting after isolation of flow-sorted single canine chromosomes.⁽²⁹⁾ This particular approach has worked well; application of dual-laser flow cytometry has allowed high-resolution sorting of canine chromosomes in 32 distinct peaks. This flow sorted material can be amplified by using the polymerase chain reaction (PCR) and then used as a probe in cytogenetic analyses on metaphase spreads of dog chromosomes. Twenty-two of the canine chromosome paints allow the identification of a single canine chromosome; the remainder identify two chromosomes that are similar in size. Reagents such as canine chromosome paints are expected to play a key role in unraveling the organization of the canine genome and determining the relationship between closely related mammalian genomes.

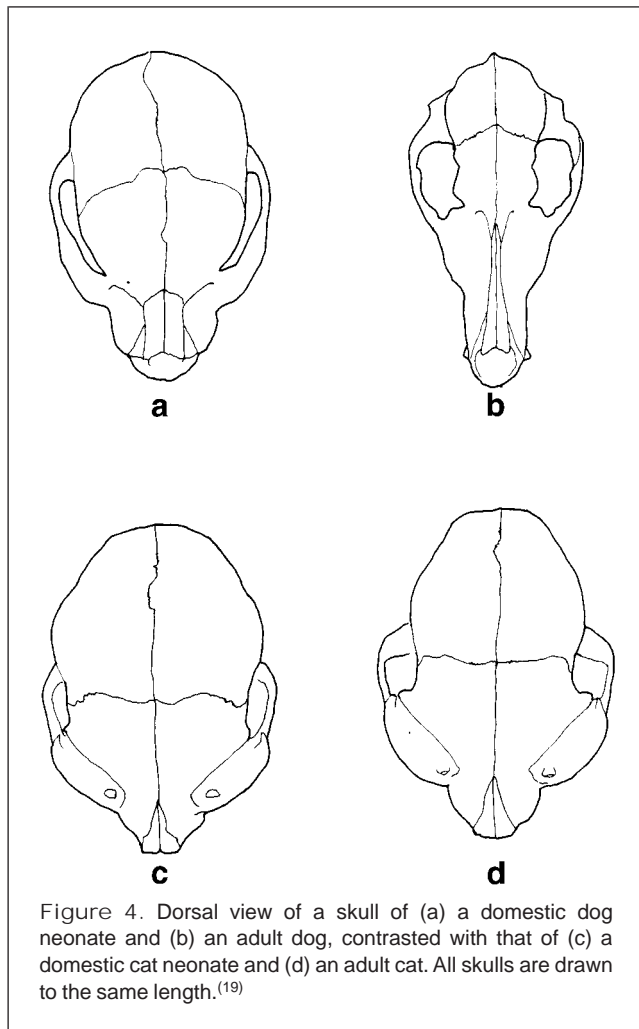


Figure 4. Dorsal view of a skull of (a) a domestic dog neonate and (b) an adult dog, contrasted with that of (c) a domestic cat neonate and (d) an adult cat. All skulls are drawn to the same length.⁽¹⁹⁾

Repeated elements in the canine genome

Like other mammalian genomes, the canine genome is characterized by several general classes of repetitive elements. The first of these, satellite DNA, exists as heterochromatin and is composed of long tandem repeats of closely related sequences that are not transcribed.⁽³⁰⁻³⁴⁾ One particularly interesting class, termed Bsp elements, appear to display genus and species specific patterns. In the fox, the organization of the Bsp repeat is two tandemly positioned units, each about 734-bp long, with 93% homology.⁽³⁰⁾ Southern blot analysis reveals species-specific patterns for the four major canids studied: red fox, dog, Arctic fox, and raccoon dog.⁽³⁴⁾ If this observation holds true for other species, Bsp repeats could prove to be extremely useful for studying canid evolution and relationships.

This result is in contrast to studies that use the minisatellite probes such as the “Jeffreys minisatellites” which give individual specific fingerprints in dogs. The “Jeffreys minisatellite” probes are DNA sequences isolated from the human

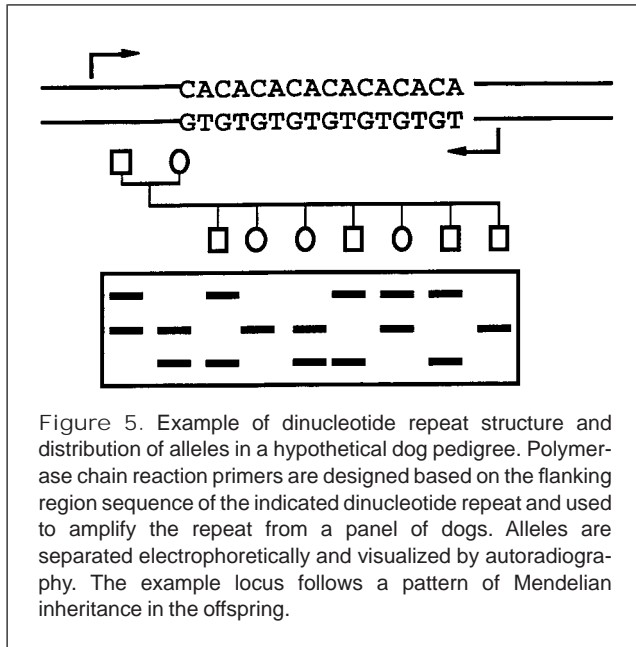
genome that have been shown to cross-hybridize to dog.^(35 and refs. therein) The probes consist of a reiterated short “core” sequence that hybridize to families of tandemly repeated DNA sequences that show multiallelic length variations. The typical assay involves hybridization of radiolabeled core elements to restriction enzyme cleaved DNA, thus producing a characteristic Southern blot fingerprint. With the exception of monozygotic twins and highly inbred populations,⁽³⁶⁾ DNA fingerprints are completely individual-specific. In one clear demonstration of this, fingerprints of any two purebred whippets were no more similar to each other than to fingerprints derived from dogs of completely unrelated breeds.⁽³⁵⁾ Although such probes have been useful for studies of small isolated populations,⁽³⁶⁾ or for cases of questionable parentage, they are relatively useless for comparisons of species or breeds over evolutionary time, because the DNA sequences mutate much too rapidly.

The second major class of mammalian repetitive DNAs are the short- or long-interspersed nucleotide elements, known as SINES or LINES, which arise by retrotransposition. A canine specific 130-bp SINE has been cloned and sequenced from a domestic dog genomic library.⁽³⁷⁾ Dot blot analysis showed hybridization of the element to genomic DNA isolated from multiple canids, including the distantly related gray fox, yet no hybridization was observed to DNA from bear, raccoon, cat, mouse, rat, Chinese hamster, or human. Thus, this class of repeat appears to be largely canine-specific.

The third class of repetitive elements, which are common to all mammalian genomes are the microsatellites, which are small stretches of DNA, consisting of mono-, di-, tri-, or tetranucleotide motif sequences. These repetitive elements are of great general interest because of their utility in genetic mapping studies.^(38,39) Microsatellites are highly polymorphic, and there may be several thousand of the common repeat arrays (e.g., (CA)_n, (GATA)_n, or (CAG)_n) in the dog genome.^(38,39) Thus far, several hundred of these have been characterized.⁽⁴⁰⁻⁴⁴⁾ Individual alleles associated with each marker are tracked through the generations of a family by using PCR-based assays (Fig. 5).^(45,46) Any single marker is distinguished from the others by PCR primers generated from unique sequences of DNA that surround each repeat. Although there often appears to be a unique distribution of alleles within particular breeds, the primers that define each marker work well in all domestic breeds, and indeed, in other canids.^(22,23,40,47)

Mapping genetic diseases in dogs

Linkage analyses of large numbers of microsatellite markers on outbred reference families, composed of many distinct dog breeds, have led to the initial production of a 15 cM canine genetic map.⁽⁴⁸⁾ Recently, by building on the previously reported map, the development of a 10 cM map composed of



277 polymorphic microsatellite markers has been reported.⁽⁴⁹⁾ For the larger chromosomes, a high-density map appears well on its way to completion, with well-spaced, highly informative markers spanning entire chromosomes (Fig. 6). The map likely covers greater than 85% of the canine genome, although exact estimates are difficult to determine because the precise size of the canine genome is not known. Currently, the best estimates suggest that it is about 26.5 ± 1.1 Morgans (95% confidence interval = 24.3 M to 28.7 M).⁽⁴⁹⁾ Approximately 50% of markers currently assigned on the map are based on tetranucleotide repeat motifs, such as $(GAAA)_n$, which have been consistently shown to have high polymorphic information content, and hence, are suitable for mapping of traits in families of dogs that may be relatively inbred.⁽⁴⁴⁾ As the density and coverage of the map increases, the ability to identify loci through linkage analyses of families with traits of interest will increase proportionately.

The abundance of genetic disease in modern purebred dogs, coupled with the evolving canine genetic map, presents a rare opportunity to understand better the genetic basis for disease in all mammals.⁽⁵⁰⁾ The problem of disease heterogeneity, which often confounds human linkage studies, may be avoided in dogs, because breeding practices often ensure that a small number of genes, or even a single gene, will underlie a given disease in a specific breed. This presents a unique opportunity for studying heterogeneous diseases such as epilepsy, cancer, deafness, blindness, motor neuron disease, etc., where several genes are likely to cause diseases of similar phenotype. In addition, because canine families are much larger than human families, and because

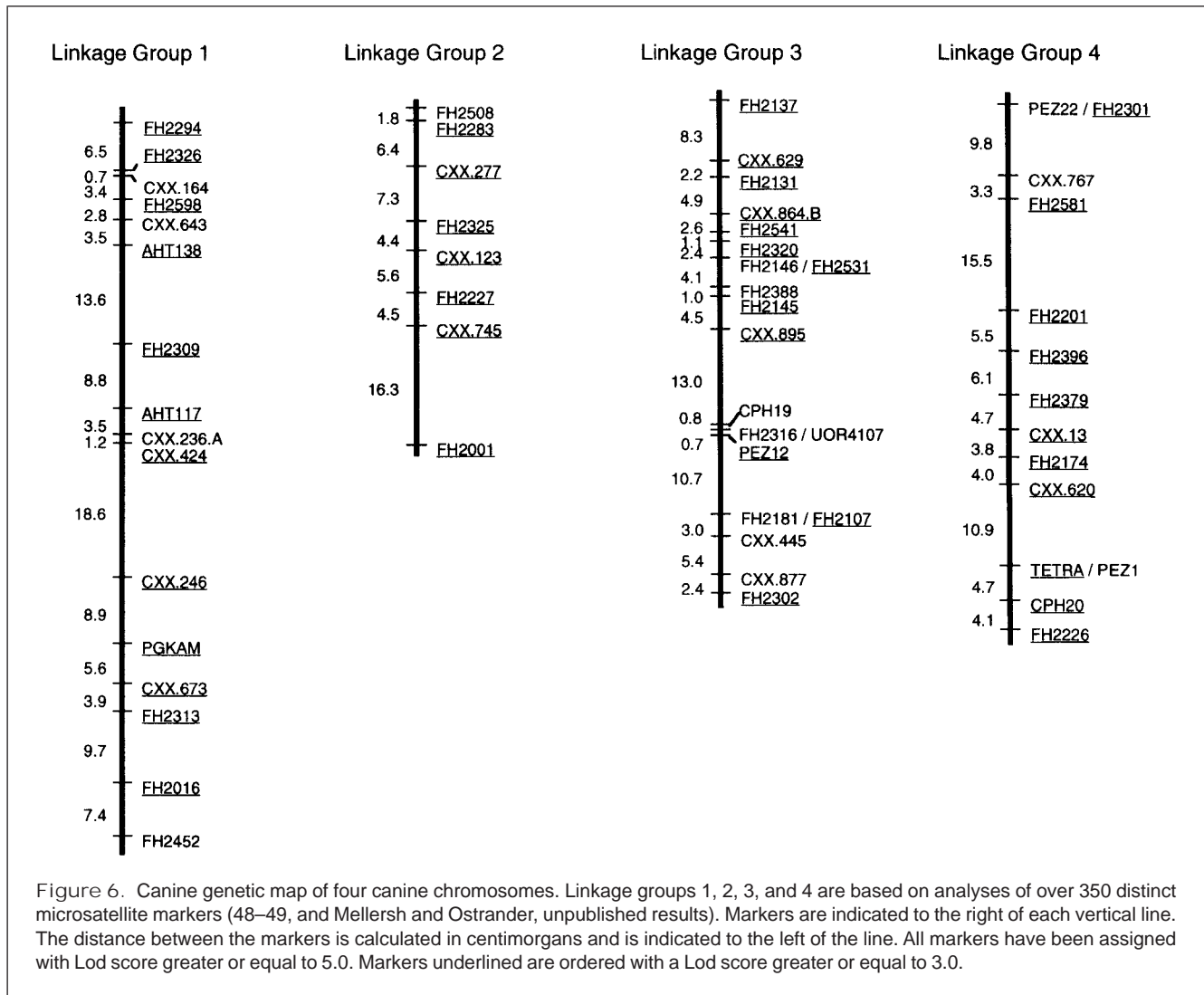
related individuals can be easily crossed to produce the most informative families for genetic mapping, levels of statistical power for canine linkage mapping are high. Hence, once the canine linkage map reaches sufficient density and coverage, it may be quicker to map mammalian disease genes in dogs than in humans.

Thus far, several canine diseases appear due to the same underlying genetic causes as phenotypically similar human diseases. For instance, von Willebrand's disease is a group of inherited bleeding disorders in mammals, including dogs, all of which are caused by a deficiency of the multimeric plasma glycoprotein, von Willebrand factor.⁽⁵¹⁾ Hematologic disorders in dogs, such as hemophilia A and B also share a similar genetic basis in dogs and humans, as do mucopolysaccharidosis type VII (MPS VII), X-linked severe combined immunodeficiency,^(52,53) and a host of others.

One arena in which there appears to be great promise that canine studies will unravel the underlying genetics of similar human disorders is in studies of hereditary blindness.⁽⁵⁴⁾ Progressive retinal atrophy (PRA) is the name given to a group of a heterogeneous diseases in dogs that are the counterpart of retinitis pigmentosa (RP) in humans. The gene for an early onset form of PRA in the Irish setter, classified as rod-cone dysplasia type 1, has recently been identified as the beta-subunit of cyclic guanosine monophosphate phosphodiesterase (GMP), which encodes a protein of the visual transduction cascade.⁽⁵⁵⁾ Mutations in GMP, however, only account for a portion of canine blindness, and studies in other dog breeds are under way to identify other relevant genes. Progressive rod-cone degeneration (*prcd*) is the most widespread retinal disease leading to blindness in dogs, and accounts for eye disease in several breeds including poodles, cocker spaniels, Portuguese water dogs, Labrador retrievers, and others. The *prcd* locus has recently been localized to a small region of canine chromosome 9, in a region that is partially syntenic with human chromosome 17q.⁽⁵⁶⁾ This established potential locus homogeneity with RP17, a human retinitis pigmentosa locus for which no gene has yet been identified due to the small number of relevant families. Cloning of the *prcd* gene, therefore, would likely identify the human RP17 gene as well. Several other breeds of dog, such as Norwegian elkhounds, miniature schnauzers, Tibetan terriers, and miniature longhaired dachshunds are characterized by similar, but apparently distinct, forms of hereditary blindness. The mapping of those disease genes, even if there is no comparable human disease, will likely provide insight into the cascade of interacting genes responsible for vision.

Syntenicity between mammalian genomes

The ultimate identification of genes in the dog can be expedited by knowledge of the syntenic relationship between mammalian genomes for which extensive genome mapping information is available, such as the human or mouse. The



two best strategies for linking the evolving canine genetic map with those of the human and mouse is through identification of gene-containing cosmids that can then be used for fluorescence in situ hybridization (FISH) mapping and by the development of resources for physical mapping such as interspecies hybrid cell lines or radiation hybrid panels.

The first approach is best illustrated by the mapping of several loci from human chromosome 17q to the centromeric two-thirds of dog chromosome 9, where FISH has been used to localize cosmids containing genes from 17q.⁽⁵⁷⁾ Subsequent isolation of microsatellite-based markers from each cosmid followed by linkage analyses that use multiple large outbred families has allowed the placement of these “gene-linked markers” on the canine microsatellite map. Both FISH and linkage analysis now suggest that the gene order on canine chromosome 9 is similar to that of human 17q and mouse chromosome 11. All genes mapped between the

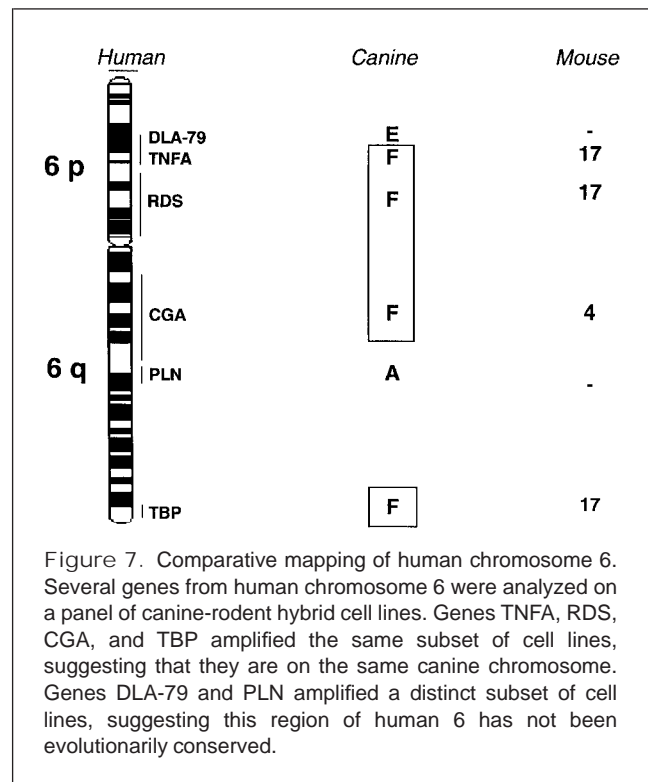
neurofibromatosis gene (NF1) and the thymidine kinase gene (TK1) appear to be present, although the gene order is inverted with respect to the centromere in the dog 9. In addition, two loci, GLUT4 and PMP22, which are located on human chromosome 17p, have been mapped by FISH analysis of gene containing cosmids to dog chromosome 5 in a region also identified by the whole human chromosome 17 paint, thus indicating a breakage of human chromosome 17 syntenic homology at the centromere. This finding is confirmed by the previous placement of the canine p53 gene on canine chromosome 5.⁽⁵⁸⁾ Consequently, other loci on human chromosome 17q may be localized to canine chromosome 9, whereas loci on 17p are likely localized to canine chromosome 5. Genes or expressed sequence tags (ESTs) mapped to human chromosome 17, therefore, serve as candidates for linkage to loci mapped to canine chromosome 9 and 1, respectively. This finding is likely to facilitate mapping of

canine *prcd* gene, which lies close to the *TK* gene on canine chromosome 9, and studies of a number of genes such as *BRCA1*, *her2*, and *RARA* which have a role in growth and regulation of malignant tumors.

In addition to studies of autosomes, a number of cosmids that hybridize to the canine X chromosome also have been localized.^(59,60) Together with data provided in an earlier study by Deschenes, these data suggest that the canine X chromosome has been evolutionarily maintained between humans and dogs.⁽⁶¹⁾ For instance, the genes for SCID, AR, PGK, and CHM are localized to the proximal region of Xq in the dog, in this case in Xq13-q21, as they are in the human.⁽⁶¹⁾ Similarly, factor VIII and IX are localized to Xq28 and Xq26.3, similar to their placement on the human map.⁽⁵⁹⁾ Karyotypic studies of the canine X predicted these results. Linkage mapping studies of additional X-linked disorders are likely to be one of the quickest ways in which the canine map will assist in studies of human disease, because a significant number of informative meioses can be more quickly collected in canine families than in human families.

A second approach for undertaking comparative studies of all mammalian genomes can be quickly undertaken if common sets of genes are placed on all mammalian genome maps. Toward this goal, a comprehensive panel of canine-rodent hybrid cell lines has been constructed and characterized.⁽⁶²⁾ Groups of microsatellite markers or cloned canine genes can now be assigned to putative syntenic groups by testing markers against this panel of cell lines in which each complete canine chromosome appears to be represented at least once (Fig. 7). In the example provided, several genes from human chromosome 6 were analyzed on 46 of the canine-rodent hybrid cell lines. PCR primers defining several genes from the central and telomeric regions of human chromosome 6 amplified the same subset of cell lines, suggesting these genes are likely on the same canine chromosome. Similar patterns of conservation are observed in mice. Until final nomenclature is established, this chromosome has tentatively been referred to as dog chromosome F. Genes *DLA-79* and *PLN* amplified a distinct subset of cell lines (dog chromosomes A and E), suggesting that this region of human 6 has not been evolutionarily conserved.

Due to the recent availability of a panel of 106 canine-hamster radiation hybrids containing the entire canine genome, this approach will be largely superseded by radiation hybrid mapping.⁽⁶³⁾ This panel has been used to construct a preliminary radiation hybrid map of the canine genome, which is composed of 182 microsatellite markers and 218 genes.⁽⁶⁴⁾ By integrating the resulting 56 RH groups with the 40 linkage groups that define the linkage map, it is expected that a high-density map of the canine genome, coordinated with the syntenic dog and human chromosomes, will be generated quickly. The more densely mapped mouse and human genomes, thus, will provide a resource of candidate



genes after a discovery of linkage between any microsatellite and a phenotype of interest.

Several sets of anchored reference loci have been developed to further facilitate these comparative mapping studies.^(58,65-67) The genes selected as anchor loci are evolutionarily conserved, are members of important gene families, and have been characterized in several mammalian species such as the cow, pig, and cat. Primer pairs that define each gene in the anchor set have been designed to span introns, thus maximizing the opportunity for development of polymorphic markers as well.⁽⁶⁷⁾ A concerted effort is under way for the developers of maps of all mammalian genomes to place the same set of 300-400 genes on their maps. In this way, analyses of a locus on any single mammalian chromosome will be enhanced by a wealth of data from the comparative chromosomes of other mammals.

Finally, a canine bacterial artificial chromosome (BAC) library of 8.2-fold density, averaging 145 KB inserts recently has been constructed.⁽⁶⁸⁾ In regions where linkage has been defined already, such as the localization of the *prcd* locus to canine chromosome 9,⁽⁵⁶⁾ BACs are being used to construct a physical map across the small chromosomal region defined by linkage analysis. Once a minimal "tiling path" of BACs is made that spans the region of interest, BACs will be individually studied for genes in the region by either screening cDNA libraries developed from canine-specific tissues, or by exon trapping methods. Once specific genes are identified in the

region of linkage, the sequence of affected and unaffected dogs can be compared to determine which gene is most likely disease-associated. Thus, BACs provide the bridge that moves the identification of disease genes from genetic to physical mapping. The entire process is aided by the fact that the human and canine genomes share synteny. For example, because canine chromosome 9 and human 17q share their chromosomal organization, information from human chromosome 17q can be used to target selected candidate genes from canine chromosome 9 for additional study.

One additional resource that is just emerging is the availability of databases of ESTs. Sequencing large numbers of cDNA clones to develop databases of partial genes of unknown function provides a resource of enormous potential. Examination of such databases after partial cloning of a gene can provide researchers with additional DNA sequence, as well as information about tissue-specific expression.

Summary remarks

The development of dogs as a model for analysis of inherited disorders and gene expression and regulation has been hampered by an inadequate genetic map. However, progress over the past few years in better defining the genetic map of dogs has been considerable. The high incidence of behavioral and physiologic disorders and genetic disease within specific dogs breeds as well as the available of multigeneration genealogies, now make the dog a tangible and attractive genetic model. Together will population level and evolutionary studies reveal that dog is swiftly becoming one of the genetically best-defined domestic species.

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