Canine Molecular Genetic Diseases

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Focal Point

- The explosion in DNA-related technology offers a unique opportunity to greatly reduce the frequency of serious genetic diseases in dogs.

Key Facts

- The molecular genetics revolution makes detecting carriers of genetic diseases feasible.
- Genetic diseases are a major health problem in purebred dogs, but reducing the occurrence of these primarily recessive diseases is difficult.
- Once a DNA test to detect carriers of a particular disease gene is available, that disease can almost be eliminated through appropriate breeding.
- DNA tests are now available for approximately 15 canine disease genes.
- Genetic testing and counseling for genetic diseases are likely to become standard in veterinary medicine.

Abstract

The field of molecular genetics has generated substantial information about how genetic diseases are inherited. Discovery of the causative gene for a particular disease can allow a DNA test to be developed to identify carriers of that gene. Selective breeding can then be used to reduce the frequency of that disease in the general population. This article reviews basic genetic principles and discusses how DNA tests are developed. Information about DNA tests currently available to detect inherited disease in several canine breeds is also provided.

A molecular genetics revolution is being fueled by funding for the Human Genome Project and the hope that gene therapy can revolutionize the prevention and treatment of human diseases. *Molecular genetics* refers to the DNA- and RNA-based technologies undergoing explosive growth in such areas as disease gene discovery, genetic engineering, paternity testing, and other forensic uses.

The impact of molecular genetics may initially be more profound in the veterinary field than in human medicine. For example, discovery of the causative gene for a disease often leads to a DNA test to detect disease gene carriers. The frequency of the disease gene, and thus the frequency of the disease, can then be greatly reduced through selective breeding. However, when a DNA test to detect carriers of a human genetic disease becomes available, the disease gene frequency in the population is not reduced as rapidly because humans rarely practice selective breeding.

GENETICS PRIMER

Veterinarians do not need to be professional geneticists to develop a fundamental understanding of the effects of molecular genetics on veterinary medicine. However, knowledge of basic genetic principles is required; readers who are familiar with these principles may proceed to the section on Establishing a DNA Test for a Genetic Disease.

DOMINANT VERSUS RECESSIVE DISEASES

With the exception of genes on the X and Y chromosomes (i.e., the sex chromosomes), genes come in pairs. Non-sex chromosomes are called *autosomes*, and the paired genes on them are termed *autosomal genes*. Diseases caused by mutations in autosomal genes are classified

according to whether one or two copies of the mutant gene are needed to produce disease. If only one copy of a mutant gene is needed to produce the disease and the other copy of the gene is normal, the resultant disease is called *autosomal dominant*. If both copies of the gene must be mutant to cause disease, the term *autosomal recessive* is used.

Dominant diseases tend to be less troublesome to breeders than are recessive diseases: A dominant disease is often detected before an animal is bred, and thus that animal is not used for breeding. Dominant diseases can still be problematic, however, if they develop after breeding age is reached (late onset) or are incompletely penetrant. Examples of late-onset diseases in dogs include some forms of cataracts, epilepsy, and hip dysplasia, although whether these diseases are dominant is unknown. *Incomplete penetrance* refers to absence of disease despite presence of the dominant disease gene. For example, a dominant disease gene that causes disease 50% of the time is 50% penetrant. Thus absence of a disease in a dog's parents and grandparents does not indicate absence of an incompletely penetrant dominant disease gene; however, even an incompletely penetrant dominant disease gene should have caused the disease to surface somewhere in the animal's ancestry.

Autosomal recessive genes are entirely different. Identifying carrier animals usually is not possible until mating of two previously unknown carriers produces one or more affected offspring. By this time, the animal has already been bred. In addition, when undiagnosed carriers are mated to noncarriers, 50% of their offspring will carry the disease gene--and no one will know.

A classic example of the problems associated with recessive diseases is canine copper toxicosis (CT) in Bedlington terriers.(1) CT is an autosomal recessive disease that causes copper accumulation and resultant liver failure; affected animals become ill and, if untreated, die of liver disease at 2 to 5 years of age.(1) Because disease onset is at a relatively late age, affected animals are often bred before being diagnosed. Affected animals can be diagnosed at 1 year of age by measuring copper in a liver biopsy, but no test for carriers (other than test-mating) existed before the advent of DNA technology.(2) Because of the high disease gene frequency, CT has been a substantial problem for the breed: 25% of Bedlington terriers are affected, 50% are carriers, and only 25% are clear of the disease gene.

TEST-MATING

One historic method to detect carriers is test-mating. The animal being assessed is bred to a known affected animal, and the progeny are evaluated for the presence of disease. If affected puppies are produced, the animal under evaluation is a carrier. If exactly five puppies are produced and none is affected, the odds are 31 of 32 (about 97%) that the dog in question is not a carrier. These odds are derived as follows: If the dog being tested is a carrier, each puppy has a 1 of 2 (50%) chance of being affected. If all five puppies are free of disease, the probability that the dog being tested is affected is (1 of 2)(5) (i.e., one half raised to the fifth power) or 1 of 32.

This approach has several disadvantages. If the animal being tested is a carrier, test-mating will produce affected animals, which must then be euthanized or placed with owners willing to treat them. With late-onset disease, such as CT, the progeny should be maintained by the breeder (or at least be under the breeder's control) until a liver biopsy can be performed to determine whether the puppies are affected. In breeds that tend to have small litters, more than one test-mating may be needed to attain five progeny. As a result of all these disadvantages, only a handful of Bedlington terriers have been cleared of CT through progeny testing during the several decades that breeders have dealt with the disease. An excellent and complete discussion of the advantages and disadvantages of test-mating has recently been published.(3)

X-LINKED DISEASES

Females have two X chromosomes, whereas males have only one. Most X-linked disease genes are recessive; thus carrier females, which have one disease gene and one normal gene, do not have the disease. However, males that have the disease gene do exhibit the disease because a normal gene is not present. Hemophilia is an X-linked recessive disease that occurs in both humans and dogs. As with autosomal dominant genes, X-linked genes are less of a problem for breeders than are recessive genes because the male ancestry of potential breeding stock is

likely to have exhibited the disease. (The Y chromosome is so small that Y-linked diseases are very rare.)

ESTABLISHING A DNA TEST FOR A GENETIC DISEASE

Developing a DNA test for a genetic disease is always complex, but the process is simplest when a disease has the same genetic cause in more than one species and the disease gene has been cloned in one species (in this context, *cloned* means that the causative gene has been identified and its DNA isolated). For example, von Willebrand's disease (vWD) is a bleeding disorder that affects humans and dogs. The human disease gene had already been cloned and the DNA sequence established. To develop the test for a canine breed (e.g., Scottish terrier), the gene was sequenced in an affected Scottie and compared with the normal sequence, the causative mutation found, and a DNA test developed to differentiate between normal and mutant DNA.(4) A different causative mutation was identified in Shetland sheepdogs(5) and another in Doberman pinschers.(6) The Doberman mutation is shared by Manchester terriers, poodles, and Pembroke Welsh corgis.

Although this is the most straightforward approach, it is not always simple. Sequencing the canine vWD gene was difficult and time-consuming. The vWD gene is very long and has many introns (noncoding regions interspersed among coding regions). Using messenger RNA material (i.e., material from which the introns have already been removed) to sequence a gene is therefore desirable. However, because messenger RNA for canine vWD is produced only in blood vessels, vWD messenger RNA material had to be isolated from tissue samples containing blood vessels.

Unlike the situation with vWD, the causative gene is unknown in most genetic diseases. However, geneticists can usually identify a number of potential causative genes (referred to as *candidate genes*). For example, a fairly large number of genes possess mutations that have produced cataracts in humans and mice; each of these genes is a candidate for causing cataracts in a canine breed. A candidate gene may prove to be causative for cataracts in one or a few breeds but not in others, in which case the remaining candidate genes must be evaluated.

The first step in evaluating whether a candidate gene is the actual causative gene is to establish genetic variation in a piece of DNA close to the candidate gene; these genetically varying pieces of DNA are usually microsatellites. DNA comprises a sequence of four nucleotide bases--adenine, guanine, cytosine, and thymine, which are identified using the first letter of each (A, G, C, and T, respectively). Approximately 1% of DNA is coding DNA (i.e., codes for a gene product); the remaining 99% is noncoding, and its purpose remains unclear. Perhaps it provides spacing for the genes themselves (the coding DNA). In noncoding regions, DNA may repeat itself 20 or so times. Repeats (or runs) composed of two nucleotide bases are termed *dinucleotide repeats*; repeats of three and four nucleotide bases are called *trinucleotide* and *tetranucleotide repeats*, respectively. These types of repeats in the DNA are also collectively referred to as *microsatellites*. (The term *satellite* DNA was previously used for much larger runs of repeat DNA.)

Microsatellites are useful because they show a large amount of genetic variation in the population. This variation is because chromosomes pair up at meiosis and mispairing can occur in an area of a repeat (**Figure 1**). If recombination occurs while the repeats are mispaired, two additional repeats of differing sizes are generated. In Figure 1, two $[CA]_{10}$ repeats mispaired and recombination generated $[CA]_{11}$ and $[CA]_{9}$. Through this process and over evolutionary time, microsatellites tend to accumulate size variants in the population.

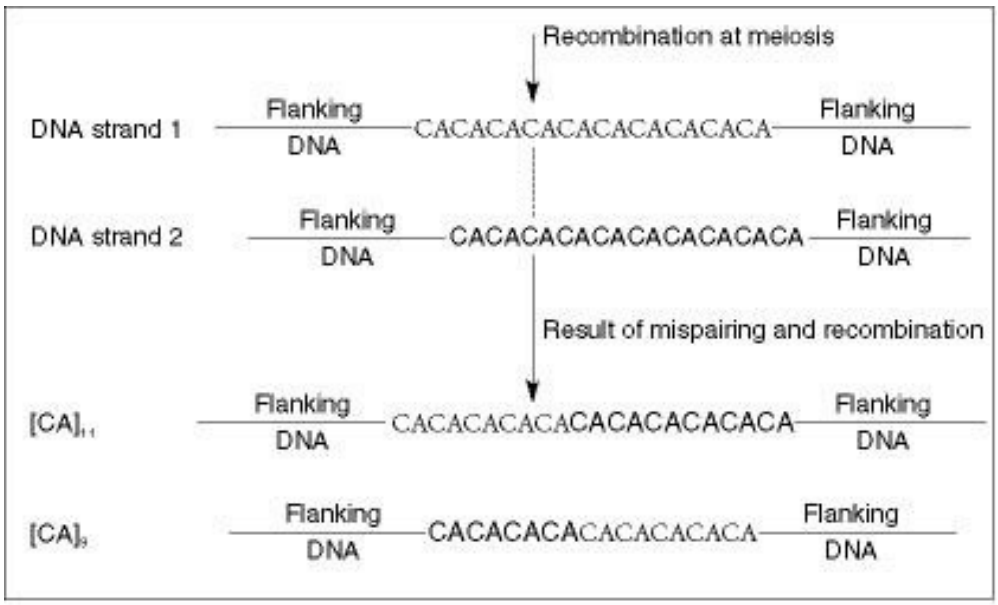

Figure 1—Illustration of microsatellite mispairing at meiosis, which generated a $[CA]_{11}$ and a $[CA]_9$ from two original $[CA]_{10}$.

Mammalian genomes, including that of dogs, have tens of thousands of microsatellites that can be used as a ready source of genetic variation. The size of microsatellite genetic markers can be detected by gel electrophoresis (**Figure 2**); the larger the DNA is, the slower it migrates in the gel. Each marker (or allele) is inherited like any other DNA. In Figure 2, dog 1 has alleles 24 and 22, dog 2 has alleles 24 and 20, and dog 3 has alleles 22 and 20.

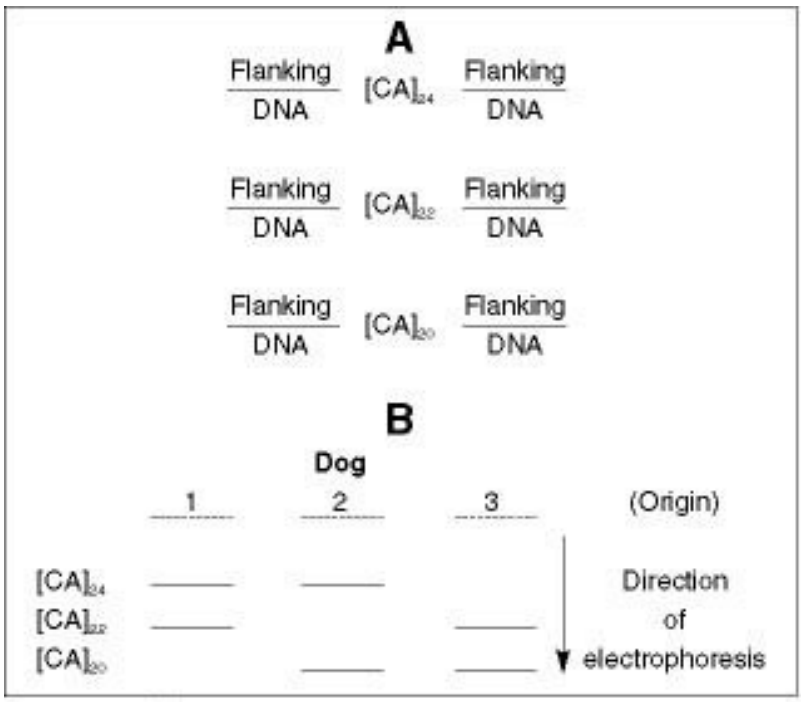

Figure 2—*(A)* The canine population being studied has three size variants (24, 22, and 20) of a particular CA repeat. *(B)* Results of a gel electrophoresis test to detect size variants. Each column represents a canine DNA sample placed at the *origin*; the DNA then undergoes electrophoresis. The different-sized CA repeats migrate different distances.

This article describes two uses of microsatellite markers. In the first use, a specific marker closely linked to a candidate gene is selected. A microsatellite marker provides the genetic variation needed to determine whether the candidate gene is being inherited concomitantly with the disease gene--a necessary event if the candidate gene is actually the disease gene. Alternatively, microsatellites can be used for a genome-wide scan.

Linkage studies are used to evaluate whether a candidate gene is actually the disease gene (because of the difficulties in sequencing studies, the linkage approach is more efficient than is wholesale gene sequencing to detect causative mutations). To perform a linkage study, 10 to 20 pedigrees (each containing a minimum of two affected dogs) are collected from the breed to be studied, and a microsatellite associated with the first candidate gene is established. It is necessary to have a detectable genetic variation associated with the candidate gene to test whether that particular genetic variation is co-inherited with the disease gene in the pedigree.

Figure 3 illustrates this method. For this example, it is assumed that the microsatellite used is closely associated with the candidate gene and that either allele (1 or 2) can be inherited in the breed being studied. The pedigrees are tested to determine whether alleles at the disease gene and candidate gene are inherited together (a process referred to as *co-segregation*). If the candidate gene does not co-segregate with the disease gene (i.e., if it is not genetically linked), that candidate gene is excluded as a disease gene and subsequent candidate genes are then similarly tested until one is found to be closely linked to the disease gene. When one is found, DNA in the vicinity is sequenced to search for a causative mutation, which, in turn, leads to a DNA test.

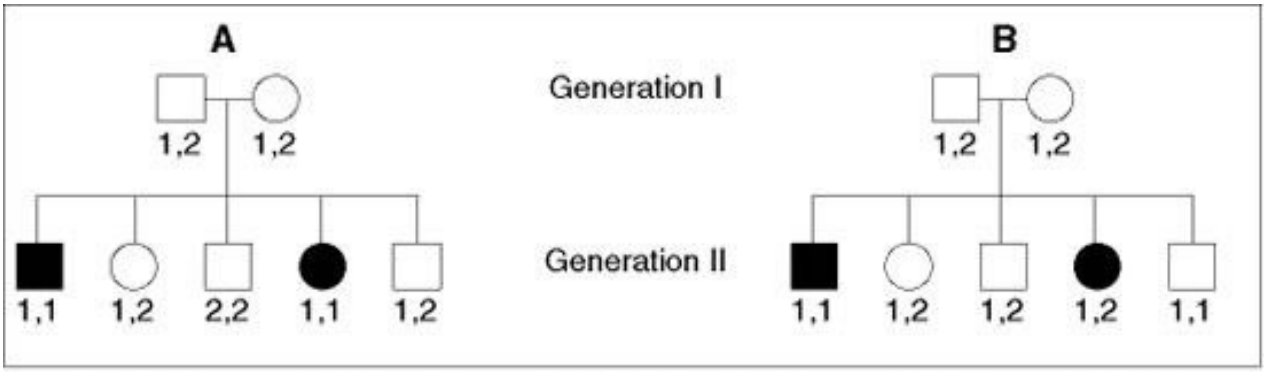

Figure 3—An example of *(A)* co-segregation and *(B)* lack of co-segregation of a candidate gene–associated microsatellite with a disease gene. The numbers below each symbol indicate the microsatellite typing for that animal. In both *A* and *B*, the parents *(Generation I)* are heterozygous for the two alleles (i.e., they each have alleles 1 and 2). *(A)* Both affected offspring *(Generation II)* have the same type (1,1), and none of the unaffected progeny has that type. These data are consistent with co-segregation of the disease gene and candidate gene, suggesting that the disease gene is linked to marker type 1 in both parents. However, this pedigree could behave in this manner through chance, even if the genes are unlinked; thus to establish linkage, another 10 to 20 pedigrees would need to be similarly studied to show a statistically high probability of linkage. *(B)* Close linkage is excluded because the affected siblings have different allele types (called *genotypes*), and unaffected siblings share the genotypes of affected siblings. (□ = males; ○ = females; ■ = affected male offspring; ● = affected female offspring)

Although it was successfully used to identify the causative gene for progressive retinal atrophy (PRA) in Irish setters,(7,8) the candidate gene approach is not always productive. If the causative gene has not been discovered in any species, it cannot be included on the candidate gene list. If a candidate gene search is unsuccessful, a genome-wide scan (i.e., the second use of microsatellite markers) is performed.

A large number of DNA markers (microsatellites) have been established for dogs. These microsatellites are not known to be associated with any particular genes but are merely distributed, more or less randomly, across the canine genome. Sufficient DNA markers have been developed to saturate the canine genome--regardless of where a disease gene is located on a chromosome, one or more established DNA microsatellite markers are nearby.

The same type of pedigrees used to screen candidate genes are used to perform a genome-wide scan. The DNA microsatellite markers are individually examined to detect co-segregation with the disease gene. Linkage is usually found by the time 200 markers have been examined, although scrutiny of 400 to 500 markers may be needed to find a close linkage.

Once a linkage between a microsatellite marker and a disease gene is found, it can be used to develop a pedigree linkage test (**Figure 4**). The test can then be used to counsel breeders about likely disease genotypes in some of their dogs. Because a DNA marker of this type is always somewhat distant from the disease gene, a small chance of error is possible because of genetic recombination (a DNA event that can separate the two alleles). Thus counseling is done in terms of probabilities (e.g., a 95% probability that a given dog is clear, a 95% probability that the dog is a carrier). Another disadvantage of this approach is that the pedigree used to establish a linkage phase must include an affected dog; thus testing of individual dogs is impossible. Consequently, dogs in many pedigrees cannot be evaluated because their pedigree does not include an affected animal. Because multiple dogs must be tested, this approach is more expensive.

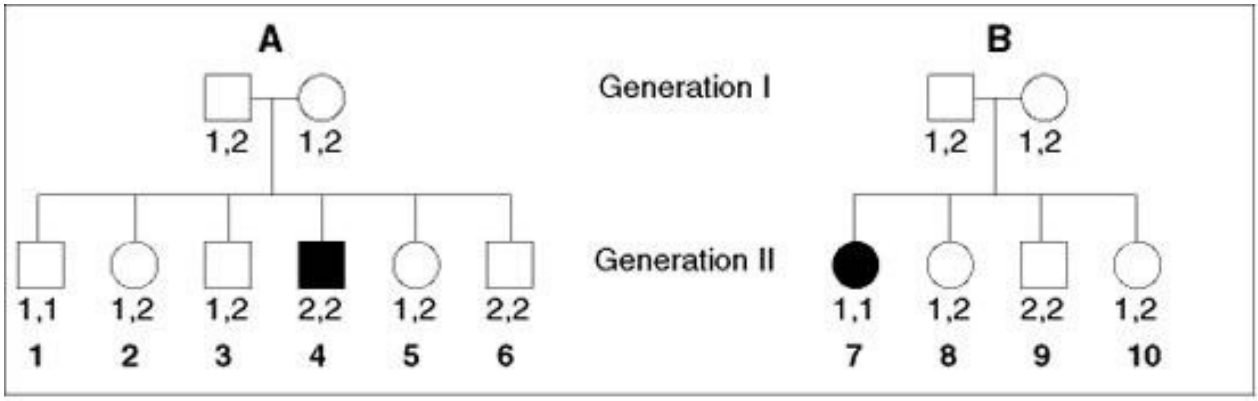

Figure 4—A pedigree linkage test. It is assumed that the microsatellite being studied, with alleles 1 and 2, has previously been shown via a genome-wide scan to be linked to the disease gene. The marker types are shown below each animal. In *Generation II*, the animals are numbered for easy reference. *(A)* Animal 4 establishes the linkage phase for the entire pedigree. It is affected and is type 2,2, which indicates that the disease allele is on the chromosome with marker 2 and was received from both parents. This allows the following conclusions to be made about the other siblings: 1 is clear; 2, 3, and 5 are carriers; and 6 can be expected to have the disease (such conclusions always have a slight potential to be erroneous because of occasional genetic recombination). *(B)* The same disease gene, breed, and marker are present, but the linkage phase is different. In this example, the disease alleles travel on chromosomes with marker 1. Animal 7 reveals this; it is affected and type 1,1. Furthermore, animal 9 is clear, whereas it would have been classified as affected in the pedigree in example *A*; this illustrates the need to have a typed, affected animal in the pedigree to establish linkage phase when using a pedigree linkage test. (□ = males; ○ = females; ■ = affected male offspring; ● = affected female offspring)

If the linked marker is sufficiently close to the disease gene, linkage disequilibrium may be present and can lead to a superior DNA test than can be created using the pedigree linkage test. Linkage disequilibrium occurs when a particular marker allele is associated with the disease allele in a disproportionately high frequency while another marker allele is highly associated with the normal gene (**Figure 5**). Linkage disequilibrium allows a pedigree linkage test to be converted to a linked marker test and permits testing of individual dogs rather than pedigrees. As with a pedigree linkage test, probabilities must be used when counseling breeders.

	Disease Phenotype	
Marker Genotype	*Affected*	*Unaffected*
2,2	25	4
1,2	2	151
1,1	1	240

Figure 5—Linkage disequilibrium. Dogs diagnosed as affected predominantly have a 2,2 marker genotype, even though the 1 marker allele is much more common in the population. Thus there is a strong disequilibrium: The 2 marker allele is predominantly on chromosomes linked to the disease allele, whereas the 1 marker allele is predominantly on chromosomes linked with the normal allele. The unaffected column includes both disease gene carriers (which are predominantly 1,2 genotype) and clear animals (which are predominantly 1,1 genotype). With these data, veterinarians can counsel breeders with better than 95% confidence that 1,1 animals are clear, 1,2 animals are carriers, and 2,2 animals are affected.

SOME CURRENTLY AVAILABLE CANINE DNA TESTS

COPPER TOXICOSIS IN BEDLINGTON TERRIERS

As discussed, CT has been a problem in Bedlington terriers. However, a linked microsatellite marker to the CT gene was found, and a pedigree linkage test was developed.(9) Strong linkage disequilibrium was later observed--the 2 marker allele was more than 95% associated with the disease allele, and the 1 marker allele was more than 95% associated with the normal allele--and led to the development of a linked marker test.(10) At least half the breeding population of Bedlington terriers has been tested,(10) and the disease frequency should be dropping rapidly. Because of the late onset of CT, this test is also useful to identify potentially affected animals, whether pets or breeding stock, so that they can be definitively diagnosed (via liver biopsy) and treated.

VON WILLEBRAND'S DISEASE

Scottish Terriers

von Willebrand's disease is severe in affected Scotties and usually fatal in puppyhood. The vWD gene was sequenced, the causative mutation discovered, and a DNA test developed.(2) Carrier frequency is about 10%.

SHETLAND SHEEP DOGS

Like in Scotties, von Willebrand's disease is severe in affected Shelties and usually fatal in puppyhood. The mutation differs from that in Scotties, and a different DNA test is required.(5) The carrier frequency in this breed is also about 10%.

DOBERMAN PINSCHERS, MANCHESTER TERRIERS, POODLES, AND PEMBROKE WELSH CORGIS

In Dobermans, vWD has been confusing. The disease is mild, and spontaneous bleeding is unusual; however, dogs undergoing surgery or suffering trauma are at risk for serious bleeding. Results of the vWD factor (protein) assay have also been very confusing. Low factor levels are very common in the Doberman population--up to 75% of animals have abnormal values(11)--but levels also vary widely over time. The mild nature of the disease made

identifying affected dogs truly difficult. Various genetic hypotheses, including dominant inheritance, abounded.

The disease gene was sequenced in an affected Doberman, the causative mutation discovered, and a DNA test developed.(6) This work immediately clarified much about vWD in Dobermans. In Dobermans, as in Scotties and Shelties, vWD is a simple autosomal recessive disease. Unlike the situation in Scotties and Shelties, in which the mutation completely disables the gene, the Doberman gene is only partially disabled. About 10% of the normal level of von Willebrand's factor is produced in affected animals, providing some protection against bleeding and making the disease much milder. Also, the disease gene frequency is very high in Dobermans: Approximately 30% of Dobermans are affected, and 50% are carriers, leaving only 20% of Dobermans completely clear of the disease gene.

Using only Dobermans that are clear of the disease gene for breeding is ill advised because it unnecessarily narrows the gene pool; it also places an undue hardship on breeders who have developed good lines of animals only to discover that all or most are affected with vWD or are carriers of the vWD gene. In addition to breeding clear animals to clear animals, a recommended breeding strategy is to breed carrier dogs to clear dogs. Litters produced by carrier-clear matings are half carriers and half clear animals; no affected animals are produced. This strategy further reduces the disease gene frequency and, in subsequent generations, eventually eliminates the gene. Even affected stud dogs with particularly favorable characteristics can be bred to clear bitches. (Affected bitches probably should not be bred because of the risk of bleeding during delivery or cesarean section.)

DNA testing for vWD is also useful in pets, especially Dobermans, to identify affected animals, which are at increased risk of bleeding during surgery. A forewarned veterinarian can take appropriate precautions.

The same disease-causing mutation that is present in the Doberman vWD gene is present in Manchester terriers, poodles, and Pembroke Welsh corgis, albeit at a lower frequency. As in Dobermans, vWD is mild in these breeds.

Renal Dysplasia in Shih Tzus, Lhasa Apsos, and Soft-Coated Wheaten Terriers

Renal dysplasia is a disease of inadequate kidney development that leads to kidney failure, which is common in these and other breeds. Although the genetic situation is not completely clear, a current favorite hypothesis is that defects in two different genes are required to produce the disease.

A linked marker to at least one of the genes has been found in these three breeds.(12) The marker is in linkage disequilibrium in all three breeds--one marker allele is associated with the disease allele approximately 80% of the time--a finding that led to the development of a linked marker test for these three breeds.

Pyruvic Kinase Deficiency in Basenjis

A defect in the gene coding for pyruvic kinase of erythrocytes causes an autosomal recessive hemolytic anemia in the Basenji breed.(13) The causative gene has been identified.

Phosphofructokinase Deficiency in English Springer Spaniels

A defect in the gene coding for phosphofructokinase leads to an autosomal recessive disease in this breed. The enzyme defect causes hemolytic anemia and muscular weakness. The causative mutation has been identified.(14)

Progressive Retinal Atrophy

Irish Setters

The gene causing the type of PRA leading to retinal disease and blindness in Irish setters has been identified.(7,8)

Cardigan Welsh Corgis

The gene causing PRA in Cardigan Welsh corgis has been identified.(15)

Portuguese Water Dogs, Chesapeake Bay Retrievers, and English Cocker Spaniels

A linked marker test for PRA has been developed for Portuguese water dogs, Chesapeake Bay retrievers, and English cocker spaniels.

Globoid Leukodystrophy in Cairn and West Highland White Terriers

The gene causing globoid leukodystrophy in Cairn and West Highland white terriers is the same as that causing a similar disease in humans. The disease is caused by a missing enzyme, galactocerebrosidase, which is required for production of stable and healthy myelin (the insulation around nerves in the central and peripheral nervous systems). No effective therapy is available for animals affected by this fatal neurologic disease. The mutation in these breeds has been identified.(16)

Congenital Stationary Night Blindness in Briards

Briards are affected with a recessively inherited retinal disorder characterized by congenital night blindness with various degrees of visual impairment under photopic illumination. Day vision in affected dogs ranges from normal to profound blindness.(17) The disease was initially described in Swedish dogs as a stationary disorder analogous to human congenital stationary night blindness. It is now believed to have a progressive component and has been termed *hereditary retinal dystrophy*.

Cystinuria

Cystinuria is an autosomal recessive disease caused by a defective kidney transporter of cystine and other amino acids. The cystine precipitates in acid urine and forms crystals and calculi (stones). The disease is characterized by difficulty in urination, blood-tinged urine, crystals and calculi in urine, or complete inability to urinate (especially in male dogs).

The Role of Veterinarians

It is appropriate for veterinarians to stay well-informed about DNA testing for genetic diseases and to advise breeders and pet owners about how such tests might be used. For example, breeders and owners of Dobermans should be made aware of the vWD problem in this breed and that a DNA test is available. Most breeders of breeds affected by vWD are confused about the differences between the new DNA testing and the old factor assay, which had notoriously variable results. Veterinarians can help educate breed fanciers about the differences between a DNA test (which provides life-long genotyping, even for carriers) and such phenotype assays as vWD factor assays.

Veterinarians should also offer breeding advice to help eliminate the causative gene(s) without unduly narrowing the gene pool. Doberman owners should be advised about the potential usefulness of DNA testing for vWD in case surgery is required later. Conversely, offering vWD testing to an owner of a Scottie who has no plans to breed the animal would be impractical--if the dog was affected, hemorrhagic disease would have been obvious. Knowing the carrier status of a dog that is not going to be bred is irrelevant.

Approximately 73% of canine patients seen in private veterinary practices in the United States are breed identifiable (purebred).(18) Veterinarians need to recognize the potential effect of genetic diseases on their practices. Many genetic diseases directly affect diagnosis, short-term treatment, and long-term care in addition to breeding practices.

The Future

Intensive research is underway on a number of canine genetic diseases, including hip dysplasia, progressive rod-cone degeneration (a type of PRA), cataracts, epilepsy, cardiomyopathy, and deafness. Simple DNA diagnostic tests will eventually be available to detect most canine genetic diseases. Economic incentives will spur progress toward common disorders affecting popular breeds. However, DNA tests for rarer diseases affecting breeds with fewer dogs will also be developed, fueled by the molecular genetics activity in human genetics.

Veterinarians must recognize that their practices are likely to change rather dramatically in terms of genetic diseases. The change will shift the focus from diagnosis and management to prevention using genetic testing. Veterinarians should keep abreast of advances in molecular genetics so that they can advise their clients about DNA testing for genetic diseases and

counsel them on breeding choices. The diseases for which DNA tests are currently available represent only the beginning.

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