The discovery last year of the gene mutation for dilated cardiomyopathy in Doberman Pinschers and the development of a genetic test were welcome breakthroughs. Breeders had hope that using the genetic test as a tool and practicing selective breeding would help reduce the incidence of this devastating disease. In the long term, fewer dogs would die from the complex heart disease that affects nearly 40 percent of Dobermans, more than any breed.

The complexity of dilated cardiomyopathy (DCM) is reflected in the uncertainty of the results of genetic testing. Dogs that test negative might later develop the disease. Likewise, those that test positive might never develop signs or only experience a mild form of the disease. The erratic clinical manifestation of the disease is rooted in its mode of inheritance: autosomal dominant with variable penetrance.

“Our laboratory identified a mutation on chromosome 14 that is responsible for the gene in some Dobermans,” explains Kathryn Meurs, D.V.M., Ph.D., associate dean of research and graduate studies at North Carolina State University College of Veterinary Medicine. “It is likely that at least two mutations are responsible for DCM in this breed. DCM is different in every breed. In Dobermans, we are not sure if DCM is two diseases or the same disease with two forms: the enlarged heart that causes congestive heart failure and the ventricular arrhythmia form that causes sudden death.”

In Europe, it is estimated that 58 percent of Dobermans carry DCM genes. The May 2011 issue of PLoS ONE, an online research journal, published the findings of European researchers indicating that half of DCM-affected Dobermans carry the risk allele on chromosome 5. Studying Dobermans from Germany, they conducted a genomewide association scan comparing the DNA of 71 DCM-affected dogs with 70 normal dogs. The results were validated in an independent study of Dobermans from the United Kingdom.

“We don’t yet know which gene is the DCM gene on chromosome 5,” says Tosso Leeb, a molecular geneticist and professor at the Institute of Genetics at the University of Berne in Switzerland. “Our findings that about half of Dobermans with DCM carry the risk allele on chromosome 5 are major, but this is not the only genetic risk factor for DCM in this breed. The unexplained 50 percent of DCM cases could be due to several genetic risk factors.”

The research was funded by LUPA, a European initiative that promotes collaboration among genetic experts at universities and private laboratories in several countries. Among the goals was to learn more about dilated cardiomyopathy in humans. The autosomal dominant inheritance pattern in Doberman Pinschers is similar to most forms of dilated cardiomyopathy in humans.

Founded about 150 years ago by a German breeder, Friedrich Louis Doberman, the Doberman Pinscher was developed from a limited number of dogs. The breed’s tight gene pool enabled the mapping of the risk loci by the European researchers. In the U.S., experts believe that DCM traces back to seven closely related Dobermans imported from Germany in 1941. All seven dogs died from cardiac disease.

DCM is the most common cause of heart failure in people. An enlarged and weakened heart muscle occurs due to conditions such as coronary heart disease, viral infections and genetic predisposition. Twenty-four genetic mutations have been found in humans, but in most cases, the causative mutation is a mystery.

Besides Dobermans, DCM affects other large breeds, including Afghan Hounds, Boxers, Dalmatians, Golden Retrievers, Irish Wolfhounds, Labrador Retrievers, Newfoundland, Old English Sheepdogs, Portuguese Water Dogs, Saint Bernards, and Scottish Deerhounds. Breeds and individual dogs vary in the age of onset, rate of disease progression, and frequency of sudden death versus congestive heart failure.

Meurs, who has studied DCM in dogs for 13 years, discovered the mutation in Dobermans on chromosome 14 while working at Washington State University College of Veterinary Medicine. Her research involved looking at the 24 gene mutations in humans and comparing them to dogs.

“We looked at the chromosomes of 48 affected and normal dogs from three generations of unrelated dog families,” Meurs says. “Using a SNP (single nucleotide polymorphism) array, we looked for genetic differences. Fine mapping allowed us to identify markers tightly linked to the targeted gene regions identified in the SNP array. “We pinpointed a genetic deletion — 16 base pairs on chromosome 14 — that is missing in Dobermans affected by DCM. The missing DNA should encode for a mitochondrial protein responsible for moving energy into the heart and helping it work efficiently. Dobermans with DCM do not produce enough mitochondrial protein, which affects the structure and energy of cardiac cells and results in a dilated dysfunctional heart muscle.”

An Irreversible Heart Disease
Fifty percent of Doberman Pinschers with DCM die from sudden death due to ventricular arrhythmia (erratic heartbeats). Thirty-three percent of these dogs have no prior sign of disease until their sudden deaths. Ventricular arrhythmia and sudden death are common in dogs 3 to 4 years of age.

“Normal heartbeats are interrupted by rapid beats that fire too closely together, subsequently shorting out the heart, and the dog faints,” Meurs explains. “Some of these dogs recover, yet others die suddenly.”

“We used to call it sudden death but now recognize it was DCM,” says Marjorie Brooks, chairwoman of the

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Doberman Pinscher Club of America (DPCA) Breeder Education Committee.

“An owner may be watching his dog play, and the dog simply drops dead in front of his eyes.”

An inherited, irreversible heart muscle disorder, DCM is most commonly diagnosed in dogs around 7½ years of age. Males and females are affected equally, and dogs may have been bred when the disease is discovered. Affected dogs generally appear normal until they are 5 to 7 years of age, and their heart muscles are no longer able to mask the disease.

Congestive heart failure occurs when the diseased heart can no longer pump blood adequately to the body. The heart dilates to compensate for the weakened heart muscle, which causes it to hold a greater volume while the thinned walls continue to weaken. Fluid may back up in the dog’s abdomen or lungs. Signs of pulmonary edema include coughing, rapid breathing and lethargy.

By the time clinical signs appear, the disease may be advanced and the prognosis grim. The disease usually has been present six to 18 months before diagnosis. Drug therapy offers palliative care but does not alleviate the long-term effects of the disease. Research of stem cell therapy is under way, but no definitive treatment has been found. Sadly, 50 percent of dogs die within months of diagnosis.

DCM may seem to be a sudden death because without testing it goes undiagnosed. Due to the prevalence of the disease, the Doberman Pinscher Club of America recommends echocardiogram testing and Holter monitor examinations to help identify the disease sooner when treatment can help slow the disease progression, ease clinical signs and improve quality of life.

The tests are used together because while one may produce normal results, the other may pick up on an abnormality or vice versa. An echocardiogram detects heart structure and function abnormalities. If the testing occurs when the disease is in the subclinical or occult phase, a DCM-affected dog would appear to be asymptomatic. In contrast, the Holter monitor provides information about the heart over a 24-hour period. This test is useful in predicting dogs that might later experience sudden death or develop congestive heart failure.

The parent club recommends that Doberman Pinschers receive an echocardiogram when they are 1 to 2 years of age along with a baseline Holter monitor test. Dogs being used in breeding programs should be tested every six months.

“Health testing is the only way to begin to put an end to DCM,” Brooks says. “One of my Dobermans (CH Manorie Doves Five Star General, CD, RE, CSC, ROM) was diagnosed at age 7 with DCM after a Holter monitor test. It was a relief that he was diagnosed early enough to receive effective treatment.”

Practicing Selective Breeding
Since last November when the DCM genetic test first was offered, more than 2,000 Doberman Pinschers have been tested. Forty percent tested positive for the disease. Ninety-five percent of these dogs were heterozygous, and 5 percent were homozygous. Fifteen percent of dogs that tested negative had early signs of DCM.

“The mutant gene is probably not the only thing that could cause negative dogs to develop DCM,” Meurs says. “Environmental and lifestyle factors could play a role as well. Not all dogs that test positive for the mutation will show the same severity of the disease. Those testing positive homozygous are more likely to develop a severe condition and manifest signs of the disease early, yet some dogs may live long, unaffected lives.”

Testing for DCM results in one of three outcomes:
• Negative indicates a dog does not have the gene mutation.
• Positive heterozygous defines a dog with one copy of the gene mutation.
• Positive homozygous describes a dog with two copies of the gene mutation.

Due to the varied penetrance of the disease, the test results can be promising yet frustrating. A negative test does not mean a dog will never develop the disease. Rather, it means the dog does not have the only mutation known at this time to cause the disease.

A dog that tests positive heterozygous should be evaluated regularly using a Holter monitor test and echocardiogram. Dogs that do not show signs of disease and have positive attributes could be bred to negative dogs. Puppies produced from these breedings should be screened for the mutation. Over three generations, puppies that test negative for DCM should replace the mutation-positive sire or dam to help decrease the number of mutation-positive dogs in the gene pool.

Dogs that are positive homozygous should not be bred unless they represent the end of an established bloodline or have outstanding characteristics. These dogs appear to have more significant disease and will most certainly pass the mutation to their offspring.

“Breeders should avoid drastic decisions when using genetic screening in regard to their breeding programs,” says Meurs. “Removing all dogs that test positive could create a bottleneck effect and proliferate other disease traits. In fact, removing as little as 20 percent of the gene pool would change the profile of the Doberman breed. Using the genetic screening test, breeders should be able to reduce DCM in five to 10 years.”

While the genetic test for DCM does not provide definite answers whether a dog will have the disease or the potential severity of disease, it raises awareness about the incomplete penetrance of dilated cardiomyopathy. The parent club is working to educate owners and breeders about the disease and the availability of the genetic test, with an emphasis on reducing disease incidence through selective breeding.

“One of the pieces of the puzzle to help them make informed decisions. A positive test doesn’t mean that a dog shouldn’t be bred. It means that guidelines should be followed.”

Purina appreciates the support of the Doberman Pinscher Club of America and particularly Judith Brown, chairwoman of the DPCA Health Research Evaluation Committee, in helping to identify topics for the Purina Pro Club Doberman Pinscher Update newsletter.

Possible Test Results of DCM Genetic Test in Doberman Pinschers

Negative (N/N)
A dog does not carry the DCM mutation but could develop clinical signs later. Dogs should be evaluated regularly using echocardiogram and Holter monitor testing.

Positive Heterozygous (P/N)
A dog carries one copy of the gene mutation. Clinical signs vary, with some dogs never showing signs. Before breeding, breeders should consider whether the dog has a family history of DCM, has had questionable echocardiogram or Holter monitor findings, and is an excellent breed example. Half of puppies will be negative/heterozygous and half will be positive/heterozygous. Using selective breeding, breeders can replace positive heterozygous dams and sires with negative offspring in three generations.

Positive Homozygous (P/P)
A dog carries two copies of the gene mutation. These dogs will pass on a mutated copy of the gene to all their offspring. These dogs should not be bred except when they represent the end of an established bloodline. In such cases, positive/positive (homozygous) dogs only should be bred to negative/heterozygous dogs.