THE CARDIOMYOPATHY CHRONICLES 1: THE SCIENCE NEWS AND GENETICS...

SCIENTISTS DETERMINE MODE OF INHERITANCE FOR DILATED CARDIOMYOPATHY IN DOBERMAN PINSCHERS

By Rod Humphries

While the hunt continues for the gene or genes which cause dilated cardiomyopathy (DCM) in Doberman Pinschers, a team of scientists led by one of America's leading geneticists, Dr. Kathryn Meurs, has determined the mode of inheritance which will dramatically impact the breed.

In a scientific study published in the September-October 2007 issue of the Journal of Veterinary Internal Medicine, Dr. Meurs announced that an eight year study involving 41 Dobermans in four generations of one extended family – a shocking 25 of 35 able to be fully diagnosed had DCM— proved that the mode of inheritance is **autosomal dominant**.

By definition, this mode expresses the disease in a dominant gene, not a recessive, and therefore has no classic "carrier" as in autosomal recessive mode. It needs only one affected parent to transmit the disease and without exception there are affected dogs of either sex in consecutive generations. Two affected parents can produce some unaffected offspring

The dramatic impact for Doberman breeders – many of whom believed DCM had "carriers" in the autosomal recessive mode — is that **a single animal affected with DCM will, regardless of the genetic status of its mate, transmit the disease to between 50 and 100 per cent of its offspring**.

As autosomal dominant needs only one dominant mutant gene to transmit a disease or trait, it is also expressed in the heterozygous state (Heterozygous means the gene pair for a disease or trait is not matching. In this case there is a mutant gene for DCM and a normal, clear gene). Therefore:

- **A heterozygous animal is affected with DCM and even when bred to an unaffected (clear) mate will transmit the disease to 50 percent of its offspring.**
- **An animal that is homozygous dominant (two matching mutant genes for DCM) will transmit the disease to 100 percent of its offspring regardless of the genetic status of its mate.**
- **If two heterozygous (affected) parents are mated, 75 per cent of the offspring will be affected and 25 per cent unaffected. (All the percentages are true over a large sample size. See the Punnett Squares and genetic breakdown later in the article).**

These high transmission rates clearly show why the Doberman has the highest incidence of DCM in the dog world. It has been estimated that Dobermans likely have more DCM than all other breeds combined.

Normally autosomal dominant traits are easy to eliminate because there is no "carrier" with a hidden recessive gene and the disease can be halted by simply not breeding affected animals. But adult late onset diseases such as DCM in Dobermans make control without a DNA test extremely difficult because almost all affected animals are not diagnosed until after the peak breeding years.

There are major complications because many affected dogs fail to be diagnosed at all when they die of some other cause, or sudden death at 10-plus years is misread as simply old age – factors which have hidden the true spread of the disease in Dobermans and have given a false sense of security for many breeders.

Over time there has evolved a dangerous level of acceptability – maybe even dodging responsibility –by some breeders who think it is alright if a dog dies of DCM at 10 or more years. But those which die at 10-plus years are producing more and more dogs which die at three, four and five years.

DCM deaths in Dobermans have been reported from 2.5 to 14.5 years with 70 percent in the range of 6 to 10 years. Dr. Meurs said the median age for diagnosis in her study was 7.5 years.

"An autosomal dominant mode of inheritance was defined by the appearance of the disease in multiple generations, equal gender representation, and evidence of male to male transmission. Finally, the mating of two affected animals produced unaffected dogs," the study reported as part of the evidence that nailed down the mode as autosomal dominant (see the published geneticist's pedigree chart from the study).

Meanwhile, Doberman breeders will still have to wait for discovery of the deadly gene or genes in the canine genome which would eventually lead to a DNA based screening test to help completely eradicate the disease. In concluding the study, Dr. Meurs

simply declared: "the causative gene(s) responsible for this condition remain unresolved."

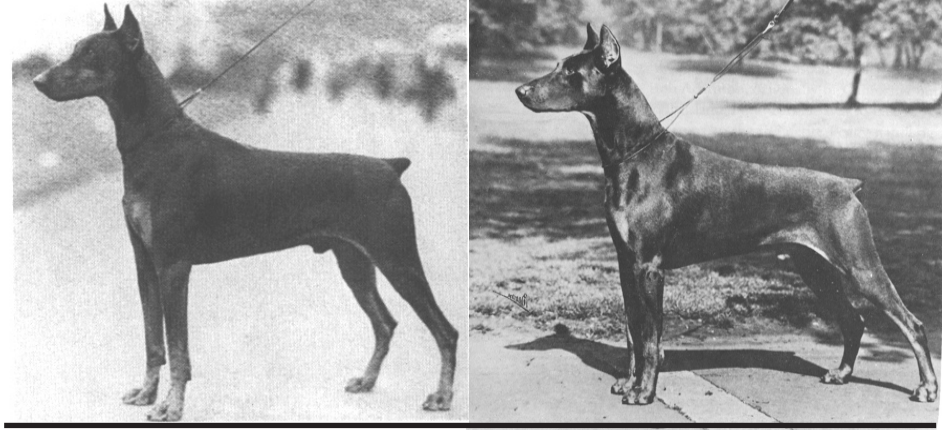
Dr. Meurs, who has a PhD in genetics and heads the Department of Veterinary Clinical Sciences at Washington State University, told me in an interview that she believed the eventual discovery would likely be a single primary gene with an unknown number of "modifiers." Modifiers are also genes which can change the expressivity of the disease and cause variable manifestations in affected dogs.

The study also noted that the "penetrance of DCM in the Doberman Pinscher is unknown, but it is incomplete in human beings." Incomplete penetrance means that a dog with the mutant gene (who would be classified as "affected") would not contract the disease. Because it does not conform to normal theory it can prove tricky for those trying to track a disease in a family of dogs.

So the undiscovered primary gene, undiscovered modifiers and the possibility of incomplete penetrance, underscores the daunting task in the search in the canine genome. (See genome sequencing later in this article).

From my telephone interview and an exchange of emails, it was obvious that the discovery of the gene(s) is unlikely in the foreseeable future. Obviously other scientific teams around the world are working on gene discovery, but when I asked Dr. Meurs about a timetable on finding the gene(s) responsible for dilated cardiomyopathy in Dobermans and Boxers, she was quite adamant that she could not, and would not, put a timetable on it.

"...I could make a breakthrough on any of these diseases tomorrow (hope so) or it could be a decade away (hope not)," she wrote. "This is the type of thing where we work on it every single day and it could be tomorrow that we find a mutation or it could be much longer…it is not the type of thing that you can see in the distance and say 'oh, we are really close, we need a few more months.' I know that it is very dangerous to tell people an estimated time since it is never correct and leads to disappointment," she added.



Ch. Emperor of Marienland and Ch. Dictator von Glenugel, two of the Seven Sires. According to the study, three of the Seven Sires are reported to have died of cardiac disease.

I reminded Dr. Meurs of one announcement in the scientific community in the late 1990s in which it was declared that the discovery of the DCM gene in Dobermans was less than two years away. "You noted a perfect example of why I do not tell people a date. I remember that as well in the 1990s and actually had been at some meeting in 1997 or 1998 when they said it would be two months! The fact that we both remember this so well is exactly why I NEVER give time frames until I find something," she wrote.

Dr. Meurs said that in a genetic search nothing is "black and white." In the study report she pointed out that it may be possible for different families of Dobermans to demonstrate a different mode of inheritance which is the case in humans. Obviously that statement was meant to leave the door cracked open in case of an obscure incidence somewhere in the breed.

But after speaking to Dr. Meurs and reading her study it is obvious that she and her team of six other experts have absolutely no doubt that the Doberman Pinscher has DCM inherited by an autosomal dominant mode of inheritance. She wrote in the study that an alternate mode "would seem unlikely given that the Doberman Pinscher is a pure bred dog with a closed gene pool at least in registered dogs. Therefore it is more reasonable to assume that most of the affected dogs in this breed would share a pattern of inheritance."

The study pointed out that the Doberman Pinscher is a relatively new breed established in the late 1890s in Germany and that the gene pool of the American breed mostly emanated from seven closely related sires in the 1940s (Ilena and the Seven Sires, author Peggy Adamson) which were immediate descendents of German stock prior to the Second World War. "Three of these dogs are reported to have died of cardiac disease," the study said.

I have written extensively in the past about Ilena and the Seven Sires and their dramatic effect on DCM in the breed (also see accompanying "Rod Humphries Writes" article) and it is understood that a fourth sire died of a heart attack at 10 years of age and that at least one other may have had the disease.

"The proband (the primary affected female studied) in the family presented here is a direct descendent of one of these dogs," the study said.

Dr. Meurs also noted that the familial nature of the disease and the autosomal dominant form of inheritance "supports the observation that genetic disease may occur with high frequency in populations with closed gene pools and in which breeding of close relatives is used to propagate desired traits. Breeds established from a small number of founders and expanded rapidly are thought to be particularly susceptible."

Historians know that the Doberman breed was established on a handful of dogs in Germany and inbreeding was an important part of the explosion in Germany and later in the United States. Dogs from these countries were exported internationally and the disease has a high incidence throughout the Doberman population worldwide.

Dr. Meurs underscored the major problem facing Doberman breeders: the late onset of the disease. "The determination of the affected and unaffected phenotype in the present study was challenging due to the adult onset nature of DCM in this breed," the report said.

"All dogs in the present study were prospectively evaluated on an annual basis by both echocardiography and ambulatory electrocardiography (Holter monitor). Some dogs died before reaching the age of disease onset and were unavailable for post mortem evaluation. These dogs were classified as indeterminate.

"The number of dogs whose clinical status could not be definitely defined is a limitation of this study as well as others that study adult onset diseases in natural animal populations. Although careful attention was paid to reevaluation of all dogs on an annual basis, it is impossible to control premature loss of animals (from the study) as a result of death from other causes."

"Early identification of affected animals would allow for exclusion of these dogs from breeding programs and would allow early medical intervention, although it is not yet known if this would have a significant impact on survival. There is significant interest in the identification of the causative gene for Doberman Pinscher DCM and the development of a DNA-based screening test," she said in the report.

The study noted that the findings could aid in the search for the DCM gene. The study said that, "narrowing the list of candidate genes might be accomplished by determining the mode of inheritance."

"This would allow the exclusion of certain genes associated with specific modes of inheritance. In addition, the list could be more focused by performing linkage analysis to identify a statistical relationship between the disease and specific genetic regions of a gene. The objectives of this study were to prospectively evaluate an extended family of Doberman Pinschers with DCM to determine a pattern of inheritance and to perform genetic linkage analysis to identify a region of the canine genome that is linked to the disease. Ultimately, the region linked to the disease could contain important cardiac genes that could be evaluated as possible causes of DCM," the study added.

The study also noted that a similar form of cardiomyopathy exists in humans. "Familial DCM in human beings can be inherited in an autosomal dominant, X-linked, autosomal recessive or mitochondrial pattern, but the autosomal dominant form is reported more frequently," she wrote.

"...genetic disease may occur with high frequency in populations with closed gene pools and in which breeding of close relatives is used to propagate desired traits."

"Although in many of these cases the specific genetic mutation has not been identified, causative mutations have been identified in 24 genes, including actin, dystrophin and desmin among others.

"The majority of these genes encode for cytoskeletal proteins that have important structural functions in the cell including maintaining structural integrity, preserving cell shape, organizing the contractile apparatus, and enabling the cell to withstand mechanical stress.

"It has been suggested that an abnormality of a cytoskeletal protein may be a common factor in the development of DCM and that without the structural support provided by these proteins, a dilated, dysfunctional heart develops. Mutations within different genes, or within different areas of the gene, may result in different clinical manifestations and survival times," the study said.

The study reported that information about the human form of familial DCM can provide insight into the Doberman Pinscher disease. "A candidate gene approach can be pursued by evaluating the genes known to cause the disease in human beings as candidates for the Doberman Pinscher disease. However, because there are now 24 different genes known to cause familial DCM in human beings, the candidate gene approach would be quite time consuming. Narrowing down the list of candidate genes might be accomplished by determining the mode of inheritance," the study said.

A total of 41 dogs over four generations starting with an affected bitch were evaluated annually with a physical examination, 24-hour ambulatory electrocardiogram (holter), and an echocardiogram (ultrasound). Postmortem cardiovascular evaluation was also performed where possible. The team evaluated the pedigree and collected DNA samples from all dogs to perform simulated linkage analysis using special software.

Of the 41 dogs, 25 were classified as affected, 10 as unaffected and six were undetermined.

Of the 25 affected with DCM, 14 were males (three castrated) and 11 were females (four spayed). The unaffected group included 8 females (five spayed) and two intact males, while the undetermined group included 4 females (2 spayed) and two males, one intact and one castrated.

Also involved in the study with Dr. Meurs were Drs. Philip R. Fox (Animal