



PURINA Pro Club

Doberman Pinscher Update

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Researchers Continue to Learn More about Von Willebrand's Disease

Judith Steinberg realized that her Doberman Pinscher, "Greta," had clotting problems when the dog bled profusely during grooming.

"If I were to trim her nails and nick the quick, it took a minimum of 45 minutes to an hour to stop the bleeding," says Steinberg of Los Angeles. "If you knocked the clot off the end of her toenail, it would just keep bleeding."

That was before a genetic test was developed for Dobermans affected by a potentially fatal bleeding disorder known as von Willebrand's disease (vWD). Caused by an inability to form stable blood clots, vWD can put affected dogs at high risk for serious bleeding problems should they undergo surgery or experience trauma. Though Doberman Pinschers have a high rate of carriers and affected dogs, the breed fortunately has the milder type 1 vWD, compared to the more severe type 3 found in other breeds. In fact, type 1 vWD is the most prevalent form of the disease recognized in both humans and dogs.

Steinberg now knows that her bitch's bleeding episodes were warning signs that Greta was affected with vWD. "Hindsight is 20/20," she says. "If you haven't gone down that path, you don't know exactly what you're experiencing."

In contrast, Zuma Doberman Pinscher breeder Gwen Lucoff of Malibu, Calif., has a vWD-affected Doberman, "Lacy," who has never bled profusely. "Lacy has never had an incident where a wound would not stop bleeding," she says. "I have noticed, however, that her wounds take a bit longer to heal."

"Formation of a stable blood clot requires that von Willebrand's factor (vWF) be present at threshold concentrations, which may differ in individual Dobermans," says James Catalfamo, Ph.D., director of the Comparative Coagulation Laboratory at Cornell University College of Veterinary Medicine. "In addition to the requirement for vWF, more than 25 other blood proteins and several types of cells including blood platelets participate in a very complex and highly regulated process that leads to the formation of stable blood clots."

Besides the genetic test, two other types of tests provide veterinarians with diagnostic and disease management information about vWD. Available prior to the genetic test, an enzyme-linked immunosorbent assay (ELISA) is used to measure the level of vWF protein in a dog's plasma and estimate bleeding risk. A dog's risk for bleeding relates in part to the con-

centration of vWF in the plasma. The lower the level of vWF, the greater is the risk for bleeding complications following surgery or trauma.

"ELISA is still used today and remains a powerful tool when used in combination with the genetic test to diagnose and manage Dobermans with vWD," Catalfamo says. "The ELISA test also is used in dog breeds in which mutations have not been discovered. Results from the ELISA test, such as the vWF plasma protein level, are required for phenotype characterization and are used in subsequent development of genetic tests."

The second type of test for learning about canine vWD is a collagen binding assay (CBA) test that enables veterinarians to learn the function level and quantity of the clotting factor blood protein. Two CBA tests were recently developed independently by researchers at the University of Guelph in Ontario, Canada, and Cornell University in Ithaca, N.Y.

Reduced Concentration of vWF

Many breeds are affected with von Willebrand's disease. Depending on the type of mutation that causes the disorder, the condition ranges from mild to severe. Direct DNA tests

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Applying Good Breeding Practices

To help reduce the occurrence of von Willebrand's disease, a potentially fatal bleeding disorder, in Doberman Pinschers, breeders are encouraged to follow the guidelines in the table below. The disease has an autosomal recessive mode of inheritance, which means affected dogs inherit a copy of the gene mutation from both parents. The best breeding is breeding a clear male to a clear female. Dobermans identified as carriers can be bred to normal dogs that do not carry the gene mutation, thereby not spreading the disease while also maintaining genetic diversity.

	Clear Male	Carrier Male	Affected Male
Clear Female	100% Clear	50/50% Carrier/Clear	100% Carrier
Carrier Female	50/50% Carrier/Clear	25/50/25% Clear/Carrier/Affected	50/50% Carrier/Affected
Affected Female	100% Carrier	50/50% Carrier/Affected	100% Affected

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Von Willebrand's Disease

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are available for 18 breeds through VetGen, a diagnostic laboratory in Ann Arbor, Mich., affiliated with the University of Michigan and Michigan State University. VetGen has tested 76,267 Doberman Pinschers for vWD since the genetic test became available in 1996. More than 60 percent of tested Dobermans were found to carry the gene mutation that causes vWD, with 17 percent being affected of those tested dogs. Affected dogs are defined as homozygous for the mutation, but does not imply they are clinically affected or bleeders.

Besides Dobermans, other breeds for which there is a type 1 genetic test are: Bernese Mountain Dog, Coton de Tulear, Drentsche Patrijshond, German Pinscher, Kerry Blue Terrier, Manchester Terrier, Papillon, Pembroke Welsh Corgi, and Poodle. A type 2 genetic test is available for Boxer, Deutch Drahthaar, German Shorthaired Pointer, German Wirehaired Pointer, and Pointer. A type 3 test is available for Kooikerhondje, Scottish Terrier and Shetland Sheepdog.

Von Willebrand's disease occurs when a clotting factor called von Willebrand's factor is reduced in concentration, as seen in type 1 vWD; functionally abnormal, as noted in type 2 vWD; or missing, as occurs in type 3 vWD. An abnormally low production of vWF blood protein, which aids in the clotting process of a damaged blood vessel, results in blood failing to clot normally at the site of injury. Mild to severe bleeding can occur.

Signs of vWD include bleeding from the nose or gums, bruising, swelling, red spots on a puppy's abdomen, bloody feces or urine, lengthy bleeding episodes during nail clipping, teething and whelping, prolonged estrous, stillbirth or fading puppies, and hemorrhaging during surgery.

Erick von Willebrand, a Finnish physician, discovered von Willebrand's disease in the 1920s in humans. He observed that blood vessels need to clot in order to heal an injury, and when a blood vessel is injured, von Willebrand's factor enables the blood cells to bind to the injured area, seal the hole and stop bleeding. When vWF is decreased or absent, blood cannot clot as well. In dogs with type 3 vWD, minor bleeding episodes can turn into major health risks.

The direct DNA test, available from VetGen, is 100 percent accurate in identifying a gene mutation associated with low plasma vWF. (See "Applying Good Breeding Practices" on page 1 for information on breeding strategies for dogs with vWD.)

The disease has an autosomal recessive mode of inheritance, meaning that affected dogs inherit a copy of the gene mutation from both parents.

Carriers inherit one copy of the causative allele and thus are not affected by the disease but can pass it on to their puppies. With the genetic test, breeders can test their dogs and eventually eradicate vWD from their bloodlines. Doberman Pinschers identified as carriers can be bred to normal dogs that do not carry the gene mutation, thereby not perpetuating the disease prevalence and also maintaining genetic diversity.

The vWD genetic test was developed by George Brewer, M.D., professor of human genetics and internal medicine at the University of Michigan School of Medicine, and researchers at Michigan State University. They found three separate autosomal recessive mutations in various breeds of dogs.

Type 1, the mild form found in Dobermans, is due to an autosomal recessive splice-site mutation that hinders from 5 percent to 10 percent of the functioning level of the gene responsible for normal clotting factor blood protein. In comparison, the severe type 3 form of vWD is an autosomal recessive mutation that results in virtual absence of the vWF protein in the plasma of affected dogs.

Results from the genetic test indicate a dog's status as a carrier, affected or clear. Carriers are not usually at risk of bleeding, but they pass the mutant gene to 50 percent of their offspring. Affected dogs have two causative genes, and clear dogs have two normal genes.

To encourage owners and breeders to test their dogs, the Doberman Pinscher Club of America (DPCA) arranges health clinics at the National Specialty and other national events. The club encourages owners to register and make public their dogs' test results with the Orthopedic Foundation for Animals (OFA) and the Canine Health Information Center (CHIC). Doing so helps the parent club track statistics on vWD in the breed and informs breeders on the status of potential dogs to use for breeding.

Functional Tests for vWD

The two new collagen binding assay tests, developed at the University of Guelph and Cornell University, look at the function of the clotting factor blood protein and tell how much is present. "In some cases, the protein can be present but doesn't work well," says Darren Wood, D.V.M., DACVP, of the Department of Pathobiology at the University of Guelph, who developed the CBA test over the past three years with graduate student Hiliary Burgess, D.V.M.

The researchers at Guelph also evaluated the use of a platelet function analyzer, called PFA-100, in screening for vWD. "The PFA-100 result is abnormal in dogs with low vWF antigen concentration," Wood says. "The PFA-100 mimics a blood vessel defect and relies on fully functioning platelets to close an aperture in a membrane. The result is the time in seconds it takes for platelets to close off the aperture and essentially form a blood clot. Platelet function is highly dependent on the presence of vWF."

Though neither CBA nor ELISA are genetic tests or intended to be used solely for diagnosing vWD, "they serve as part of a panel of tests that can be used to screen for or determine the type of vWD," Wood says.

"It helps to use a panel of tests to pinpoint different aspects of the disease. Not only can affected dogs be more effectively identified, but also types of vWD with different clinical risks and inheritance patterns can be identified."

The Cornell group, led by Catalfamo, used the CBA to examine vWF function in the plasma of 293 dogs, including 58 Doberman Pinschers with type 1 vWD. In contrast to other breeds with type 1 vWD, Doberman Pinschers have a slight increase in vWF activity related to vWF concentration and a significant decrease in the mean ratio of vWF concentration to vWF activity, they observed.

"The lower ratio is consistent with increased amounts of the more active forms of vWF in the plasma of Dobermans with type 1 vWD," Catalfamo says. "The importance of this observation to the synthesis, processing, or bleeding risk in Dobermans with type 1 vWD requires additional study."

The good news for Doberman Pinscher owners and breeders is that multiple tests are available to help understand von Willebrand's disease in their dogs. What's more, research continues to learn more about the bleeding disorder. With proper testing, no Doberman should be at risk of bleeding profusely during nail clipping as did Steinberg's Doberman Greta many years ago. The best part of all is that breeders can use the genetic test to selectively breed vWD out of their bloodlines and help reduce the incidence of von Willebrand's disease in Doberman Pinschers. ■

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