

## Canine von Willebrand's Disease

Canine von Willebrand's Disease is an inherited deficiency in one of the clotting factors of the blood. It is similar to haemophilia in some respects, but may appear in either male or female. "Carriers" may show no overt symptoms of the disease, but their progeny can have severe bleeding problems. Dogs affected with vWD may have symptoms varying from very mild to severe or lethal. These bleeding problems include prolonged bleeding from toenails cut too short, hemorrhage from even minor surgical procedures, lameness, hematomas, stillbirths or early death of newborn puppies, intestinal bleeding, and so on. The bleeding primarily involves mucosal surfaces (gastrointestinal tract, nose- bleeds, blood in the urine, vaginal or penile bleeding) and is aggravated by stress situations (other physiological, pathological, emotional or hormonal conditions).

Selected recent references:-

Meyers, K., Wardrop, K.J., and Meinkoth, J., " Canine vWD: Pathobiology, diagnosis, and short-term treatment", Compendium on Continuing Education for the Practicing Veterinarian, 1992, Vol 14(1), pp.13-23

Stokol, T. & Parry, B.W., "Canine von Willebrand Disease: a review", Australian Vet. Practitioner, 1992, Vol 23 (2), pp. 94 - 103

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The article below is by George J. Brewer who is a Professor at the Department of Human Genetics and Internal Medicine, University of Michigan Medical School and is Co-Founder of VetGen LLC

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### **DNA studies of von Willebrand's disease in the Doberman Pinscher - DNA test developed**

Our research team is very excited about our discovery of the mutation that causes von Willebrand's disease (vWD) in the Doberman Pinscher. Credit for the discovery must include my colleagues, Dr.'s Patrick Venta, Vilma Yuzbasiyan-Gurkan, and William Schall, of the College of Veterinary Medicine at Michigan State University, and to Dr. Jianping Li, who works in my laboratory at the University of Michigan as well as at VetGen LLC, and who did all the DNA sequencing. This discovery is a nice example of the productive cooperation between the two universities and the company mentioned, as well as four funding organizations that provided support, The Doberman Pinscher Foundation of America, Inc., The Orthopedic Foundation for Animals, the Morris Animal Foundation, and the American Kennel Club.

The mutation itself has some interesting aspects. For one thing, precisely the same mutation has occurred in some human patients with vWD. It is a little unusual to see mutations be identical across species. This shows how closely we are related to our canine brethren! Second, the mutation is of a type such that completely normal von Willebrand's factor (vWF) is made about 5-10% of the time. Technically, the mutation is called a splice site mutation, with alternative splicing occurring about 90-95% of the time. That jargon won't mean much to the average breeder or owner, but let me explain what is happening in layperson language. It may be useful to understand the mutation to a certain extent, because its nature explains why it was so confusing to understand for a long time, and it also explains why affected Dobermans have a milder disease than, say, affected Scotties.

To try to understand the effects of this mutation, let's use an analogy common to general experience. Imagine that a freight train is supposed to go from point A to point B following a railroad track. There is a point where a sidetrack goes to point C. However, normally the train never goes to point C, because the switch to point C, connecting the track up to the main track, is never thrown. Then the switch breaks (this is the mutation) such that the lock holding the switch from connecting the track to point C is no longer effective. The switch can now jiggle back and forth, sending some trains to point B, and others to point C. As freight trains rumble towards the switch, 95% of the time it jiggles over and causes the train to end up at point C. This is useless because point C ends at a cliff. The trains rumble over the cliff and are never heard from again. A minority of the time, maybe about 5%, the switch jiggles the other way and the trains end up at their normal destination. So, only 5% of the freight is delivered.

This is exactly what happens in the Doberman affected animal. These animals have two doses (two trains in the above example) of the mutated gene. Each gene is capable of making 5-10% of normal vWF (that is, going down the main track to point B), because the normal splice site is used a little. The 90-95% of the time the mutated splice site is used (going down the side track to point C), no useful vWF is produced. Since each of the two mutated genes is producing 5-10% of normal vWF the affected Doberman ends up with twice that, or 10-20% of normal vWF in their blood.

So, one of the mysteries of Doberman vWD that has puzzled scientists for years, how affected dogs can end up with a small amount of completely normal vWF, is cleared up by understanding this type of mutation. A second mystery is also cleared up. Doberman owners and breeders have had their dogs tested for vWF for years using the protein assay of vWF, and have often discovered low values in dogs without a bleeding history, even at surgery. The reason is, such dogs have 10-20% of normal vWF. If the bleeding stress isn't too great, the 10-20% of normal vWF that is present can prevent undue bleeding. Part of the time uneventful surgery fits that criterion, and unusual bleeding does not occur.

I hasten to add that this should not be taken to mean that vWD in the Doberman is clinically harmless. The literature is full of reports of Doberman's bleeding and dying from vWD. There are a number of factors, known and unknown, which will affect the clinical outcome in a given case. First coagulation factors, such as vWF, are consumed during blood clotting. The more the bleeding, from injury or surgery, the more the consumption, and the more likely the limited supply of vWF in an affected Doberman will be used up, leading to renewed bleeding, now from vWF deficiency. Second there is also variation in the amount of vWF in affected Dobermans. A dog with a 5% value is at greater risk than one with 15%. Of course, other factors, such as other coagulation and tissue factors that we aren't measuring, will certainly vary from one affected dog to another, and change the risk of bleeding up or down in a given situation.

Another mystery about Doberman vWD that we now understand better is the actual frequency of vWD in Dobermans. Dobermans have been said to have a 70% plus frequency of this disease, but that is not correct. It's more on the order of 35% affected, with an additional large group being carriers, but free of any bleeding risk. The disease is an "autosomal recessive", which means that affected animals have two doses of the mutated gene, and a mild to moderate risk of bleeding, for reasons explained earlier. Based on very preliminary data, we believe the mutant gene has a frequency of about 0.6 (60% of the genes are mutant) which translates into about 36% of all Dobermans being homozygous affected (two doses of the abnormal gene and at risk for bleeding), 48% being carriers (one abnormal and one normal gene, no risk of bleeding), and 16% being homozygous clear (two doses of the normal gene). If the gene frequency turns out to be closer to 0.5, the frequencies for affected will be 25%, carriers 50%, and clear 25%. Of course, our small sample comes from a limited region of the country. The gene frequencies may vary some in different parts of the country, but the bottom line will remain the same. This is a very common disease and a very common mutant gene.

Carriers of the mutant vWD gene are at no risk of bleeding from vWD, but of course, will transmit the mutant gene to their offspring 50% of the time. Roughly, the ranges of vWF factor levels are 5 to 20% for affected, 30-100% for carriers, and 50-130% for homozygous normal. Note the major overlap between carriers and normals for vWF levels. This overlap accounts for the extreme unreliability of the vWF assay in trying to identify Doberman carriers of vWD.

In summary, Doberman pinscher breeders are now in the advantageous position of being able to begin eliminating one of the significant diseases in their breed, because of the discovery of the mutation producing vWD in this breed, and the development of a vWD DNA test by VetGen (<http://www.vetgen.com> ).

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### **The Mutation Discovered**

by George J. Brewer, Professor, Department of Human Genetics and Internal Medicine, University of Michigan Medical School, Co-Founder of VetGen LLC

Our research team is very excited about our discovery of the mutation that causes von Willebrand's disease (vWD) in the Doberman Pinscher. Credit for the discovery must include my colleagues, Dr.'s Patrick Venta, Vilma Yuzbasiyan-Gurkan, and William Schall, of the College of Veterinary Medicine at Michigan State University, and to Dr. Jianping Li, who works in my laboratory at the University of Michigan as well as at VetGen LLC, and who did all the DNA sequencing. This discovery is a nice example of the productive cooperation between the two universities and the company mentioned, as well as four funding organizations that provided support, The Doberman Pinscher Foundation of America, Inc., The Orthopedic Foundation for Animals, the Morris Animal Foundation, and the American Kennel Club.

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To try to understand the effects of this mutation, let's use an analogy common to general experience. Imagine that a freight train is supposed to go from point A to point B following a railroad track. There is a point where a sidetrack goes to point C. However, normally the train never goes to point C, because the switch to point C, connecting the track up to the main track, is never thrown. Then the switch breaks (this is the mutation) such that the lock holding the switch from connecting the track to point C is no longer effective. The switch can now jiggle back and forth, sending some trains to point B, and others to point C. As freight trains rumble towards the switch, 95% of the time it jiggles over and causes the train to end up at point C. This is useless because point C ends at a cliff. The trains rumble over the cliff and are never heard from again. A minority of the time, maybe about 5%, the switch jiggles the other way and the trains end up at their normal destination.

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So, one of the mysteries of Doberman vWD that has puzzled scientists for years, how affected dogs can end up with a small amount of completely normal vWF, is cleared up by understanding this type of mutation. A second mystery is also cleared up. Doberman owners and breeders have had their dogs tested for vWF for years using the protein assay of vWF, and have often discovered low values in dogs without a bleeding history, even at surgery. The reason is, such dogs have 10-20% of normal vWF. If the bleeding stress isn't too great, the 10-20% of normal vWF that is present can prevent undue bleeding. Part of the time uneventful surgery fits that criterion, and unusual bleeding does not occur.

I hasten to add that this should not be taken to mean that vWD in the Doberman is clinically harmless. The literature is full of reports of Doberman's bleeding and dying from vWD. There are a number of factors, known and unknown, which will affect the clinical outcome in a given case. First coagulation factors, such as vWF, are consumed during blood clotting. The more the bleeding, from injury or surgery, the more the consumption, and the more likely the limited supply of vWF in an affected Doberman will be used up, leading to renewed bleeding, now from vWF deficiency. Second there is also variation in the amount of vWF in affected Dobermans. A dog with a 5% value is at greater risk than one with 15%. Of course, other factors, such as other coagulation and tissue factors that we aren't measuring, will certainly vary from one affected dog to another, and change the risk of bleeding up or down in a given situation.

The Doberman breeder and owner should view vWD as a significant health risk, and a fault, and strive to get rid of the mutated gene. The discovery of the mutation, and the recent development of a DNA test, now provides just that opportunity.

Another mystery about Doberman vWD that we now understand better is the actual frequency of vWD in Dobermans. Dobermans have been said to have a 70% plus frequency of this disease, but that is not correct. It's more on the order of 35% affected, with an additional large group being carriers, but free of any bleeding risk. The disease is an "autosomal recessive", which means that affected animals have two doses of the mutated gene, and a mild to moderate risk of bleeding, for reasons explained earlier. Based on very preliminary data, we believe the mutant gene has a frequency of about 0.6 (60% of the genes are mutant) which translates into about 36% of all Dobermans being homozygous affected (two doses of the abnormal gene and at risk for bleeding), 48% being carriers (one abnormal and one normal gene, no risk of bleeding), and 16% being homozygous clear (two doses of the normal gene). If the gene frequency turns out to be closer to 0.5, the frequencies for affected will be 25%, carriers 50%, and clear 25%. Of course, our small sample comes from a limited region of the country. The gene frequencies may vary some in different parts of the country, but the bottom line will remain the same. This is a very common disease and a very common mutant gene.

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The new DNA test for Doberman vWD is offered by VetGen LLC (3728 Plaza Drive, Suite 1, Ann Arbor, Michigan 48108; (313) 669-8440, (800) 4-VETGEN; Fax (313) 669-8441). It is very easy to do the test.

You can order the test kit from VetGen by phone or letter. Each test kit costs \$5 and contains three soft brushes and instructions. Following the instructions, the dog owner brushes the inside of the dog's mouth. Some of the cells lining the inside of the mouth stick to the brush, and provide the DNA for the test. No blood is required. The brushes are replaced in their envelope and mailed back to VetGen. Each vWD DNA test costs \$135.

VetGen will supply test results within two weeks of receiving the DNA.

Test results will come back as "clear," "carrier," or "affected." As stated earlier, clear means both vWF genes are normal, carrier means one is normal and one is defective, and affected means both genes are defective. It is important to realize that this DNA test is very different from the old protein-based factor assay. The DNA test is definitive and final, a lifelong, permanent determination of the vWD status of each dog tested as contrasted to the factor assay, in which the levels could change drastically over time. We can now say in hindsight that the old test probably correctly identified some affected Dobermans (values under 20), but it is completely unreliable for carrier detection.

What should a breeder do with the test results, once they are obtained, in terms of breeding decisions? The problem facing the Doberman breeder is that it appears that only 15 to 20% of Dobermans are clear of the vWD gene. If one breeds mostly clear to clear, it narrows the breeding pool so much that there is risk of losing some of the Doberman's genetic heritage, i.e., some of the genes determining valuable positive characteristics of the Doberman might be lost, or highly diluted.

Therefore, as a first priority, we advise breeding clear to clear and clear to carrier, at least for the next two or three generations. Over time, as the frequency of clear dogs increases, it should be possible to breed mostly clear to clear, and to eventually eliminate the mutant vWD gene.

As a second priority, we suggest that it is reasonable to breed carrier to carrier, if an acceptable clear dog is not available for breeding. This type of mating will produce 25% clear, 50% carrier, and 25% affected, on average. The puppies should be tested and the affected puppies not used for breeding.

Breeding carrier to affected and affected to affected should be avoided if at all possible. The first breeding produces 50% affected on average, and the second produces 100% affected animals. In my opinion, there should be two initial objectives of the Doberman vWD breeding program. One objective should be to produce as few affected animals as possible, because each is a health risk. That doesn't mean we believe affected Doberman puppies should be put down. Most of them can live normal lives. If possible, we believe it would be a good idea to neuter affected animals. The second objective of the breeding program should be to gradually reduce the gene and disease frequency. The kinds of breedings involving the mating of an affected, as listed at the first of this paragraph, tend to increase the disease gene frequency, whereas clear to clear and clear to carrier breedings tend to decrease frequency. [Click here](#) for further information on Breeding Strategies.

To further raise the awareness and standards of Doberman breeders, VetGen is helping the Orthopedic Foundation for Animals (OFA) establish a vWD registry for Dobermans. By registering the results of the vWD DNA test on their dogs, breeders stand to benefit at the point of sale when selling either carrier or clear puppies as established by the vWD DNA test.

In summary, Doberman pinscher breeders are now in the advantageous position of being able to begin eliminating one of the significant diseases in their breed, because of the discovery of the mutation producing vWD in this breed, and the development of a vWD DNA test by VetGen. The test is remarkably easy to get done, and is reasonably priced, considering that it is a definitive lifetime determiner of the vWD genetic type of the dog tested. We urge Doberman breeders to get their breeding stock tested, so that we can get on with eliminating this disease.

For further information, or to order test kits, contact VetGen at:  
3728 Plaza Drive, Suite 1, Ann Arbor, Michigan 48108  
800-4-VETGEN (800-483-8436) / fax 313-669-8441  
For further info contact: <http://www.vetgen.com>