VON WILLEBRAND'S DISEASE

And how it affects Manchester Terriers

This paper was written by RG Benton, with information taken from veterinary and scientific papers. The information presented in this paper is not prejudiced by commercial interests or pressure from any other interested party.

What is von Willebrand's Disease

Canine von Willibrand's Disease (vWD) was first reported in 1970, it is a deficiency of one of the several clotting factors in the blood, a plasma protein known as von Willebrand's Factor. It is caused by a gene mutation, so is an inherited disorder.

The mutation causes a reduction in the production of the von Willebrand's Factor. Put quite simply this means that a dog born with the mutated gene will produce less than the normal quantity of the von Willebrand blood clotting factor.

Dogs affected by von Willebrand's Disease can have symptoms which include: prolonged bleeding from, for example, toe nails cut too short, haemorrhage from even minor surgical procedures, haematoma, lameness, stillbirth or early death of newborn puppies, intestinal bleeding or nose-bleeds. These symptoms can be further aggravated by stress.

Clearly this disease must be taken seriously, because there is a very real possibility that affected dogs can bleed to death from relatively minor injuries or surgical procedures, because their blood does not clot with sufficient speed.

The disease is quite similar to haemophilia and can appear in either males or females.

Dogs in around 50 breeds are known to have been affected by Von Willebrand's disease.

It is however common in a number of dog breeds, including Dobermans, Manchester Terriers, Poodles, Scottish Terriers, Shetland Sheepdogs and both Pembroke and Cardigan Corgis.

Researchers in the USA, at Michigan State University, the University of Michigan have identified the gene mutation that causes von Willebrand's Disease. So far three, apparently breed specific, variations of this gene mutation have discovered.

The three known variations of this gene mutation are as follows:

**Type I.**

Which occurs in Dobermans, Manchester Terriers, Poodles, Pembroke and Cardigan Corgis.

This is considered a mild form of the disease.

**Type II.**

Which to date is known to occur in Shetland Sheepdogs.

This is considered to be a severe form of the disease.

**Type III.**

Which to date is known to occur in Scottish Terriers.

This is considered to be a severe form of the disease.
Details of the Genetics

It is helpful for Manchester Terrier owners and essential for breeders to know about the gene mutation that causes this disease. Understanding its nature helps explain why von Willibrand's Disease causes so much confusion.

Dobermans are prone to the same variation of the disease that affects Manchester Terriers and most of the research into this variation of vWD has been done with Dobermans in the USA, so much of the information presented here comes from that work.

Genetically, each dog carries two genes controlling production of von Willebrand's Factor, one inherited from each parent. Each normal gene is capable of producing only 50% of the total amount of von Willebrand's Factor produced by a cell. Two normally functioning genes are required to produce a normal amount of this vital blood clotting factor.

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. Second, with the Type I mutation (the variation that affects Manchester Terriers and Dobermans) completely normal von Willebrand's Factor (vWF) is made about 5 to 10% of the time.

One of the mysteries of Canine vWD that had puzzled scientists for years, is how some affected dogs could end up with this small amount of completely normal vWF. Technically, the mutation is called a splice site mutation, with alternative (incorrect) splicing occurring about 90 to 95% of the time. Affected animals have two copies of the mutated gene. When the normal splice site is used, each mutated gene is capable of making 5 to 10% of normal vWF, but, 90 to 95% of the time the mutated splice site is used. When this occurs no useful vWF is produced. Since each of the two mutated genes is responsible for producing 5 to 10% of normal vWF the affected animal ends up with twice that, or 10 to 20% of normal vWF in their blood.

This should not be taken to mean that vWD in the dog is clinically harmless. Although dogs affected by the Type I mutation are less likely to suffer from spontaneous bleeding as has been known to happen dogs more severely affected by the disease, veterinary literature offers many reports of Doberman's bleeding and dying from vWD. It should also be noted that there are unsubstantiated reports from the USA of Manchester Terriers dying on the operating table as a result of von Willebrand's Disease.

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 dog will be used up, leading to renewed bleeding, now from vWF deficiency.

Second there is also variation in the amount of vWF in affected animals. 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 are not part of this discussion, 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 Canine vWD in Dobermans, that is now better understood, is the actual frequency of vWD in the breed. Dobermans have been said to have a 70% plus frequency of this disease, but that is not correct. It is nearer to 35% of Dobermans are 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.

Research data suggests the mutant gene is common in Dobermans. A small scale test of Manchester Terriers in the UK suggests the frequency of the mutated gene in the UK population is low.

Carriers, that is dogs with a single copy of the mutant vWD gene, have a very low risk of bleeding from vWD, but will transmit the mutant gene to their offspring about 50% of the time.

There is no cure for an affected dog. Some treatments may help improve clotting time, but it's unclear how effective they are or how long affected dogs generally live. In all circumstances great care would have to be taken to avoid even minor injuries.
Testing for von Willibrand's Disease

Until recently the only way to test for the presence of von Willebrand's Disease was through the use of a protein-based test called a "von Willebrand's Disease Factor Assay Test". This test measures the amount of von Willebrand's Factor the dog is able to produce and compares it to the 'normal amount' found in a dog presumed to be clear of the disease. The dogs are then classified accordingly. A low reading, around 5 to 20%, indicates the dog is producing less than normal amounts of von Willebrand's Factor, and can be considered to be affected by the disease.

Higher readings of around 30 to 100% would indicate a strong possibility that the dog is carrying the mutated gene.

Readings in the range 50 to 130% show greater quantities of the factor are present, indicating that the dog is homozygous clear, so would almost certainly not be carrying the mutated gene.

Note the major overlaps for vWF levels, which show that the Factor Assay Test can establish if the subject is affected by the disease or not, but cannot show with certainty if an animal is carrying a single copy of the mutated gene, that can be passed on to its offspring. The Factor Assay Test has many variables that can affect the resulting readings, including thyroid hormone levels, condition of the liver, breeding cycles, improper blood handling and variations within the protein-based tests themselves.

As a result of the research mentioned earlier, a DNA test to detect the presence of the gene mutation causing von Willebrand's Disease has been developed.

This test has several advantages over the Factor Assay Test, the most important of which is accuracy. The test looks at an individual dog's DNA, and results are not subject to change due to any of the variables that affect the Factor Assay Test.

So no matter how many times the dog is tested during its life the results will always be the same. A dog is either carrying the gene mutation or it is not.

There are three possible test results from a DNA test:

**CLEAR, CARRIER, or AFFECTED.**

**CLEAR.** This finding indicates that the mutated gene is not present in the dog. Therefore, when used for breeding will not pass on the mutated gene.

**CARRIER.** This finding indicates that one copy of the mutated gene is present in the dog. It will not exhibit clinical symptoms of vWD nor have medical problems as a result but **will often** pass on the mutated gene to its offspring.

**AFFECTED.** This finding indicates that two copies of the mutated gene are present in the dog. The dog will be medically affected by the disease and **will** pass on the mutated gene to its offspring. Appropriate treatment should be pursued by consulting a veterinarian.

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. This is in contrasted to the factor assay, in which the levels could change drastically over time.
Breeding Strategies

The Manchester Terrier breeder and owner should view vWD as a significant health risk. Now the DNA test is available, breeders can definitively know if any of their stock is affected by vWD or is likely to pass it on to its offspring. The test results allow a breeding strategy that, if implemented by all breeders, could eliminate the disease from a bloodline, and ultimately from the UK population of Manchester Terriers.

The chart provided below, outlines the implications of various breeding pair combinations.

<table>
<thead>
<tr>
<th>Parents</th>
<th>Statistical probability for each individual puppy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>Clear X Clear</td>
<td>100% Clear</td>
</tr>
<tr>
<td>Clear X Carrier</td>
<td>50% Carrier 50% Clear</td>
</tr>
<tr>
<td>Clear X Affected</td>
<td>100% Carrier</td>
</tr>
<tr>
<td>Carrier X Clear</td>
<td>50% Carrier 50% Clear</td>
</tr>
<tr>
<td>Carrier X Carrier</td>
<td>25% Clear, 50% Carrier, 25% Affected</td>
</tr>
<tr>
<td>Carrier X Affected</td>
<td>50% Carrier, 50% Affected</td>
</tr>
<tr>
<td>Affected X Clear</td>
<td>100% Carrier</td>
</tr>
<tr>
<td>Affected X Carrier</td>
<td>50% Carrier, 50% Affected</td>
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<tr>
<td>Affected X Affected</td>
<td>100% Affected</td>
</tr>
</tbody>
</table>

*It must be stressed that these are only statistical probabilities applying to each individual puppy in a litter.*

*For example; if breeding a Carrier to a Carrier the statistics do NOT mean that 25% of a litter will be Clear, 50% will be Carriers and 25% will be Affected.*

*It does mean that for each individual puppy in the litter their is a 25% chance it will be clear, a 50% chance it will be a carrier and a 25% chance it will be affected.*

As can be seen some breeding pair combinations present high levels of risk for producing affected stock, that the wise breeder would avoid. Clearly, it is only acceptable to breed "Clear to Clear". If followed by all breeders, this strategy would result in the elimination of this disease from Manchester Terriers in the UK.

All imported dogs should not bred from unless DNA tested clear of the disease.