The Genetics of Degenerative Myelopathy in BMDs

What do we know?

I'm going to start with some assumptions:

1. There is still more to learn about the genetics of DM, we don't yet know the full story
2. I have indicated my beliefs or conclusions where applicable, they are not stated as facts

There are two genetic mutations linked to Degenerative Myelopathy (DM), both are found on the SOD1 gene. Here are some key vocabulary terms that will be used:

Chromosome – a long string of genes, think of it as a necklace of beads, with each bead a different specific gene. Dogs have 39 pairs of chromosomes, one set of 39 from the father, the other set of 39 from the mother.

Gene - a unit of heredity that is transferred from a parent to offspring and is held to determine some characteristic of the offspring. The gene we will be discussing is the SOD1 gene on chromosome 31.

Allele - an alternative form of a gene.

Research done by the University of Missouri found a mutation linked to DM in 98 different breeds of dogs. They found the mutation SOD1:c.118, which I am going to refer to as SOD1-A, the common mutation found in all breeds. Subsequent to that finding, they also discovered a mutation SOD1:c.52 which I am going to refer to as SOD1-B, the mutation found only in Bernese.

What makes most sense to me is that the SOD1-A mutation occurred at some point before the breeds were segregated into separate breed groups, and that mutation has been found in 56 out of the 222 breeds tested by the U of MO. Because the SOD1-B mutation has only been found in Bernese, I believe that it was a more recent mutation that occurred sometime after Berners were established as a breed – and that mutation occurred on a normal allele, not the allele that held the SOD1-A mutation. If that is true, then there would be no cases of a Berner that is at risk for SOD1-A with a copy of the SOD1-B mutation; likewise there would be no cases of a Berner that is at risk for SOD1-B with a copy of the SOD1-A mutation. What this would mean is that there are three alleles for Berners that are of concern, one that is clear of any mutation, one that has the SOD1-A mutation, and one that has the SOD1-B mutation.

The researchers at U of MO tested 1,613 dogs – these included 701 mixed breeds, 912 Berners, and 55 other pure breeds found to have the mutation for DM. The only dogs in which the SOD1-B mutation was found were 61 out of the 912 Bernese. 59 of the Berners had one copy of the SOD1-B mutation, and two had two copies of the mutation, giving an allele frequency of 3.5%. [For the math geeks: total number of alleles = 2 x 912 = 1824. Total number of mutations = 59 + (2 x 2) = 63. Frequency = 63/1824 = 0.0345]

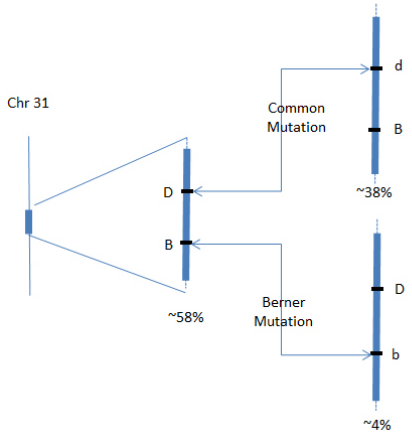
Of the 912 Berners tested for both mutations, the U of MO researchers found none of the 136 at-risk SOD1-A dogs that also had the SOD1-B mutation. There were only two Berners with two copies of the SOD1-B mutation, and they were both clear of the SOD1-A mutation. 24 of the Berners carried both mutations.

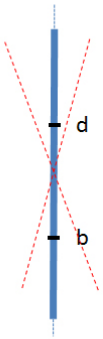
Table 1: Berners Tested for both SOD1 mutations

	SOD1-A status		
SOD1-B status	clear	carrier	at risk
clear	316	399	136
carrier	35	24	0
at-risk	2	0	0

All of these results provide support for my supposition that we have two different independent mutations. We can represent the gene and the alleles the following way.

Diagram 1: Chromosome 31, gene SOD1, three alleles





Not yet seen

What can we do about it?

If we use the representation D for the normal copy of the common mutation, and a d for the common mutation, then use B for the normal copy of the common mutation and a b for the Berner-only mutation, we have the three different alleles DB (normal), dB (common mutation, SOD1-A), and Db (Berner only mutation, SOD1-B). Since each dog gets two copies of the gene, we have these possible combinations (this is a Punnet square):

Table 2: Breeding combinations

	DB	dB	Db
DB	DDBB clear	DdBB carrier	DDBb carrier
dB	DdBB carrier	ddBB at risk	DdBb at risk
Db	DDBb carrier	DdBb at risk	DDbb at risk

From Berner-Garde we can find two dogs that were diagnosed as affected with DM on necropsy that were clear of the SOD1-A mutation but had two copies of the SOD1-B mutation. There were three additional Berners in Berner-Garde that had one copy of each mutation; two were diagnosed as affected with DM, and one was diagnosed as having a possible variant of DM.

Using the current knowledge and tools available, we have the ability to avoid producing puppies that will be at risk of developing DM. Dogs that test as carriers or at-risk for the two combined mutations can be bred to a clear dog. Each one of the genetic tests looks for the presence of a specific mutation. So a dog that is clear of the SOD1-A mutation is not necessarily clear of the SOD1-B mutation. If we look at the table of test results again:

Table 1 again

	SOD1-A status		
SOD1-B status	clear	carrier	at risk
clear	316	399	136
carrier	35	24	0
at-risk	2	0	0

we can see that 37 of the dogs that were clear of the original mutation were carriers or at-risk for the SOD1-B mutation, and another 24 dogs were carriers of both mutations. We don't have many of the SOD1-B mutations in the breed, and we certainly want to keep it that way! We now have a test available commercially for both mutations, GenSol here in the US, and SSV in Germany.

Given that only 35% of the dogs tested were clear of both mutations, it would be a severe bottleneck to eliminate 65% of the Berners from the gene pool. The beauty of a genetic test is that it allows breeding selections to be made with knowledge of the actual genetics. We may learn more in the future to enable us to make even better selections, but for the time being we have to use the tools available in order to reduce the incidence of affected dogs.

What do we not yet know?

Not every at risk Berner will get DM. That means that the mutation has incomplete penetrance, and it's why we use the term '*at risk'* instead of *'affected'* for dogs that have two copies of a mutation. We don't know if 5% or 95% of the at risk Berners will get DM, and knowing that would certainly be helpful. Determining that percentage would involve studying a statistically significant number of at risk Berners that live long enough to have signs of the disease, and then doing necropsies to determine whether or not each dog has DM or not.

The more interesting question is why don't all of the at risk Berners get DM? I believe that it is most likely that there are other genes involved in the disease, perhaps a modifier gene that suppresses the disease, or one that allows the disease to be expressed. More research is needed to better understand the underlying genetics of the disease.

One affected Bernese Mountain Dog in the research study had only one copy of a mutation. Out of a total of 173 dogs (30 pure breeds and several mixed breeds), there were 115 that were confirmed to have DM. Of those, one affected German Shepherd Dog had no mutation found, and 7 dogs were found to have only one mutation (1 Alaskan Husky, 1 BMD, 2 Chesapeake Bay Retrievers, 2 GSDs, and 1 Rhodesian Ridgeback). Either there is a slight risk that carriers can become affected, or as I believe – it is more likely that there are other mutations at play. DM has been likened to ALS (amyotrophic lateral sclerosis, or Lou Gehrig's disease) which at last count has been associated with about 144 mutations on 6 genes. There is undoubtedly more to learn about the genetics of DM in canines.

The best that we can do is to work with the tools we have. If there is a compelling reason to breed a carrier to another carrier, it would be beneficial to know that there are no known cases of DM anywhere in the near pedigree, the hope being that whatever modifier genes are needed to prevent the disease from being expressed are also present in the family. It's still a difficult explanation to make to the owners of the puppies 6 or more years down the road when some of their dogs start stumbling or dragging their rear paws. If I were a breeder I would want to be able to explain to any of my owners with a symptomatic dog that I used the genetic tests available at the time to make the best choices possible. Breeders can't control everything, but they have always tried to use a number of tools to stack the genetic deck in their favor. We now have two more tools – which also makes the selection process that much more challenging.