

The Future of DM Research

by Marjorie Zimmerman

Now that a DNA marker has been discovered for Degenerative Myelopathy, how will this affect our DM research? One would think we have found the key to unlock the DM mystery, but sadly, that is not the case. Just because a dog carries the marker for DM (aka GSDM or CDRM) does not necessarily mean the dog will, indeed, develop the disease. In fact, a large percentage of dogs that carry the marker do not go on to develop Degenerative Myelopathy. Therefore, we must realize there is more to developing DM than simply possessing the DM marker.

If we choose to eliminate all dogs from the German Shepherd Dog gene pool that possess the DM marker, we may need to eliminate approximately 75 percent. Eliminating such a large number of dogs based solely upon the presence of the DM marker, especially at this stage of research, would be foolhardy.

Research cannot end with the discovery of a DM marker. This is the tip of the iceberg when looking for a cause. DM is a far more complex disease process than one gene or marker. The development of DM is brought about by many factors, and there is no such thing as one cause as to why a dog with the marker will develop DM, and another with the same marker/gene will not.

Research must now turn in the direction of imprinting and "dark DNA," the concept that other genes influence the expression of the main genes thought to control genetic disease transmission. This is also the concept of gene *imprinting*, where some genes turn on or off, thereby influencing whether other genes function, creating consequences. Finding a DM marker does not explain who actually gets the disease, so the discovery of a DNA marker is only **PART** of an answer. If we cannot find which other genes determine whether or not the primary gene acts, we will never find the answer.

That is why the search cannot stop now. We have opened the door so we can begin to explore, but we are still quite a distance from our goal. It is imperative that we find what is acting as a trigger, for the development of DM, as the development of DM is not controlled by one factor. We need to concentrate on finding the imprinted genes to explain why some get the disease and others do not, and why some respond to therapy and others do not. Those are the most important questions for the dogs – and the real focus of the research. Treatment probably has to focus on stem cells, but we have to break the canine adult cell maturation issue for that to succeed.

Different paths have been traversed by different researchers in the quest to track the causes of Degenerative Myelopathy. Dr. Clemmons believes, and has found supporting evidence, that German Shepherd Degenerative Myelopathy (GSDM) is like the human disease Primary Progressive Multiple Sclerosis. Other researchers believe GSDM is more like Amyotrophic lateral sclerosis (even though ALS may not occur in dogs), which is a motor unit disease. GSDM as a pure motor unit disease does not fit all of the available data.

However, here are the facts:

DM Corgis, Boxers: Auto-immune disease not proven, but no motor unit disease proven either
DM GSD: Auto-immune disease

DM Corgis, Boxers: Protein is normal in the AO CSF
DM GSD: Protein is normal in the AO CSF, but protein is elevated in the **Lumbar** CSF

DM Corgis, Boxers: Oligoclonal bands of IgG have not been examined
DM GSDS: Oligoclonal bands of IgG are common (as in MS)

DM Corgis, Boxers: No proof it affects cell bodies of neurons
DM GSDS: Does not affect cell bodies of neurons

DM GSDS: no muscle spasms

DM Corgis, Boxers: EMG is normal
DM GSDS: EMG is normal

ALS is associated with early EMG changes, loss of neuronal cell bodies either in the spinal cord or the central nervous system. ALS is not associated with an increase in CSF protein nor changes in CSF IgG levels or nature. ALS does not present with sensory changes (such as conscious proprioceptive dysfunction [scuffing toes or standing on the top of the foot] or unconscious proprioceptive dysfunction [picking the leg up too high like goose stepping]).

DM does not have EMG changes. Motor neurons in the spinal cord and brain are not affected. There are changes associated with altered immunity including elevations of circulating immune-complexes and elevations of inflammatory mediators in the CSF. CSF protein is elevated in the lumbar CSF and this is due to the production of inflammatory mediators into the CNS. There are elevated IgG and oligoclonal bands of IgG in CSF. DM is associated with sensory changes and these are the earliest neurologic signs that are seen.

All of these changes and the pathology of the disease are consistent with the human disease PPMS. They are not consistent with ALS. It is possible that DM in Boxers and Corgis is different from GSDM, but they are probably more similar than different. As such, DM is more likely to be PPMS and the gene change in the SOD1 region merely the trigger for why the immune system attacks the dog's own nervous system. More work needs to be performed, not just in the GSD breed but in other breeds who get DM as well.

It is imperative that we support Dr. Clemmons, as he is the researcher who has made DM his life work. It is imperative that we support Dr. Clemmons, as he has a history of always making himself available to those whose dogs suffer from DM. It is imperative that we support Dr. Clemmons so he can continue to be able to move research forward - not sideways or backward. Dr. Clemmons was the true pioneer who **FIRST** discovered the DM markers, with no help from the AKC-CHF. Others have merely followed in his footsteps, and some have admittedly taken his work from his website.

The only way to ensure that DM research **advances** is by supporting Dr. Clemmons. The future of DM research is Dr. Clemmons, period.