‘The Bullmastiff Health action group’

Together we are stronger!

Who are the bullmastiff action group?

The answer is quite simple, its each and every one of you. Anyone who is actively involved within the breed, whether it is the show scene, breeding, tracking, agility, therapy dogs, or just pet owners. In fact, anyone who wants healthier bullmastiffs for future generations to enjoy. All of us who breed have a duty of care to make sure they are breeding the healthiest dogs possible. If we sweep our health issues under the carpet you can be assured that one day, they will come and bite you in the BUTT!

Our small team comprises of Deborah Morgan of Optimus bullmastiffs, Magda Porter of Araucaria Bullmastiff and myself. Magda does a great job in looking after the admin and distributing information on Facebook and other social media Bullmastiff platforms. However, our group is not exclusive, and we welcome anyone who would like to be involved. This is no time for petty differences or rivalries, we should all agree that we have one common goal, and that is healthy disease-free bullmastiff dogs for future generations to love and enjoy. We want to reach out to everyone who owns a bullmastiff to come on board and help the research to bring this horrendous disease to an end.

Our group is currently focusing on bringing in a DNA test for Cerebellum Ataxia, and the geneticists involved at the university of Berne will also look at Retinal Dysplasia, which often is found in dogs with cerebellum Ataxia. It is sight or lack of it, that is usually the first sign to owners, breeders, and vets that there is a possible issue. There is often a sequence that appears alongside Cerebellum Ataxia and if we can develop a DNA test for Cerebellum Ataxia then hopefully a DNA test for retinal dysplasia will not be far behind. In the future the group will look at what else we can do to improve the health of the dogs we love so much.

My Story

The majority of people reading this know the hard work that goes into raising a litter, I’m not just talking about the physical and mental challenge of having a litter on the ground, and the sleepless nights, endless feeds and poop!!!! We are all too happy to stress ourselves out to the limit for the sight of a beautiful bundle of pups in the whelping box. We will have spent a lot of time on selection, worrying about predicted seasons that never come when they should! The logistics of the actual mating and then the agonising four week wait for the scan to hopefully be positive. Is she, isn’t she? the agony goes on. Well picture this, our mum has amazing litter of fourteen, all are superb, no issues and they grow and grow. Then they are up on their feet, weaned and become more and more beautiful and active every day. At 6 weeks the first vet check comes and they all pass with flying colours, no hernias, no heart murmurs, absolutely nothing abnormal detected, as a breeder you are thrilled and proud. Puppies new owners are contacted, and the eight-week goodbye is arranged. One by one they go to their new homes and everyone is delighted. Puppies are then taken to their own vet for checks as per contract, and again all pass with flying colours. At 10 weeks the second vaccination is given with no issues.

Then it starts, usually with a phone call 'This puppy is so clumsy and keeps bumping into the patio doors." The usual response is to discuss the pup and joke "what are bullmastiffs like???" nothing to be worried about or is it? A few days later another puppy is bumping into things. This sparks my concern, and I advise to be on the safe side to go to vet. The vet says that he is a little worried about the puppy's eyesight although nothing abnormal is detected. However, we ask for a referral to an eye specialist. This is where the bombshell explodes. Confirmed diagnosis of Retinal Dysplasia! questions of how? What? When? Consume you. As we are trying to answer all these questions the puppy then becomes wobbly on back end and the MRI confirms Cerebellum Ataxia, and then real horror begins. One by one puppies start to become symptomatic; nine out of the fourteen puppies are affected. Owners are distraught with questions of "I thought I was buying a well-bred healthy puppy". Well you did, right? You keep asking yourself I did everything right didn't I? The planning the generations of health testing. I have always health tested and done the best I could, right? The questions keep coming but the answers of what went wrong still allude you. The simple fact of the matter is that at the moment there is no test and no way of knowing whose litter is next. Take it from me that taking 16-week-old puppies to be euthanized is the single hardest thing I have ever had to do; my heart broke each and every time. For the owners who chose to try treatment but eventually had to make the trip to the vets to euthanize their pup themselves, I felt totally responsible. No amount of refunds and paid vets' fees by me will ever heal the hurt and distress they must have felt. Since then I have vowed not to breed another litter of Bullmastiffs until a DNA test for this heart-breaking disease is found.

So, I wanted to do something about it, I looked at the condition in other breeds and how they had dealt with it, some already had a DNA test so I asked why don't we? After some failed attempts with commercial labs, I came into contact with the Animal Health trust and the discussion began. I can't tell you how happy it made me feel that I had finally found some people who wanted to help our beautiful breed. However, as some of you will know in early 2020 the devastating news emerged that the Animal health Trust was to close. This came as a real blow and pushed our research back, but not to be defeated the search went on, and after what felt like an eternity of emails and calls, I eventually found The Institute of Genetics, University of Bern, Switzerland, who agreed to assist us in our quest.

What is Cerebellum Ataxia

The cerebellum receives information from the sensory systems, the spinal cord, and other parts of the brain and then regulates motor movements. The cerebellum coordinates voluntary movements such as posture, balance, coordination, resulting in smooth and balanced muscular activity.

Ataxia is a term for a group of disorders that affect co-ordination and balance. Any part of the body can be affected, but canines with ataxia often have difficulties with balance and walking.

(Neuronal ceroidlipofuscinosis) NCL

NCL can cause a cerebellar ataxia. But cerebellar ataxia itself is a huge term with many diseases that can cause it. It means not being able to fine-tune different kinds of movement or being unable to coordinate balance etc., as the cerebellum (small brain) is the part of the brain that is responsible for this kind of movements. A striking symptom of cerebellar ataxia in dogs is that it gets worse when focusing on something (intentional tremor), for example eating. I have a youtube link for you in which you can see a litter of dogs (Belgian Shepherds in this case) in which four of the dogs were affected by cerebellar ataxia. In this litter, the four dogs sadly had to be euthanized because the

ataxia was so strong that they could not even eat properly. However, the symptoms can range from a small, almost invisible tremor up to this life-threatening tremor that can be seen in the videos of this playlist:

https://www.youtube.com/watch?v=mTpTX5rdJqk&list=PLvxEhTJk7-5iDbiYivA6qBISokaJKMsgi&has_verified=1

Why does cerebellar ataxia happen?

There are a lot of reasons why it can happen, some of the more important reasons are intoxication (including food intolerances etc.), trauma and genetics.

Aside for genetic reasons, no disease-causing factor for NCL. Everything starts with substances that the own body produces. Those substances are mainly protein and fat, which become visible in the cell as the pigment's 'ceroid' and 'lipofuscin' (hence the name of the disease). Normally those side products can be degraded by the body, but in animals with a genetic defect, they can for different reasons (e.g. Faulty cellular transportation mechanisms) not be degraded by the cell and slowly start to accumulate. This accumulation leads to an alteration in the cellular environment, so that the cell becomes 'poisoned' and dies. For reasons that are not completely known until now, this accumulation and cell death happens mainly in nerve cells.

What can I do if my dog is affected/ what is the prognosis for affected animals?

This depends strongly on the cause and the severity of the ataxia. Some of the symptoms can be alleviated by proper supplementation of vitamins, through proper feeding or through medication. But sometimes you cannot do anything and must hope that the ataxia is not so strong that it affects the quality of the dogs. It is sad to say, but until now, neither in humans nor in animals, any effective therapy for NCL is known. A dog owner can do everything to make the life for his/her dog as comfortable as possible (e.g. Epilepsy medication and good food) but must keep in mind, that the lifespan of the dog is very limited, as most NCL patients die at the age of 4 years. For this time, it is important, that regular visits at the vet are planned, to customize a treatment program for the symptoms that can be treated. Because of this sad outcome, it is of utmost importance to find the genetic cause for those diseases, (which differ in each breed), so that the disease can be eradicated with good breeding programs.

What is Retinal Dysplasia?

There are various causes for retinal dysplasia, the most common cause being inherited. RD may also result from viral infections, and exposure to toxins. In some cases, retinal folds may be seen in young puppies around 6 to 8 weeks of age. It is thought that this is a growth-related problem, in that the sclera (coat of the eyeball) and the retina are growing at different rates. Within 4 to 6 weeks the retinal folds resolve as the retina and sclera (coat of the eyeball) are then growing at the same rate. This is not thought to be inherited. However, dogs can have lots of retinal folds and this may be a sign of RD. In breeds that are affected with RD, growth related retinal folds may confuse the diagnosis of inherited RD. In some cases, we recheck these puppies later on once they has finished growing to see if the retinal folds have disappeared. RD will not disappear. (Animal Eye Clinic)

What are the symptoms?

In the beginning, most affected dogs get a bad vision and eventually go blind (which is why the disease can be confused with RD), because cells in the eye are the ones that die first. Later, neurological symptoms such as hind limb weakness and seizures start to be more and more pronounced, until the quality of life for the dog is eventually so bad, that it must be euthanized.

What will the university do once they receive my dogs blood sample?

Research protocol & Mapping.

Ok guys let us get technical with Matthias Christen, you may want to grab yourself a large glass of red or your favourite tipple for this part. I do not think a cup of tea will cut it!

The first phase of sample collection and phenotype determination.

This will also continue during the rest of the research period. Sending of Samples for a SNP-Chip array (single nucleotide polymorphism) are sent. Those are about 220'000 markers on the genome that get genotyped for all dogs we send. For a first marker determination, DNA samples of 10 cases and 10 controls are sent (for a recessive inherited disease). Those 220'000 markers are spread across the whole genome of a dog and they are used because this approach is much cheaper then directly whole genome sequencing the dogs (which costs about 10 times as much as a SNP-array).

As soon as we receive the marker data (probably 2-3 months): First tests can be done. This is where my research really starts. I will use the marker data to try to narrow down the possible region on the genome as much as possible. In concrete terms, this means that I will look for regions where all cases look the same, and are at the same time different from all controls (this mapping step is the reason, why phenotypes have to be characterized very precise). If this works with the 10/10 animals that have been sent in, which I strongly hope it will, we will have enough evidence to move on to the next step. Otherwise, we will have to go back to the sample collection. I do not think it will be difficult to find healthy controls, but the number of cases can become a problem.

With our Bullmastiffs I will send in the DNA of one dog with a well described phenotype (so far this would be DOG L, but even better if we get a case where an MRI was done) for a whole genome sequencing. I will do this even before we have the 10 cases for SNP, because a WGS takes forever to make and we can also do some stuff with this alone. We still have some time though, because we need a certain number of samples (from other projects) before we can send them in.

Whole genome sequencing: Here, the complete genome is sequenced from one of the cases. For a dog, this means that the previous 220,000 markers are expanded to 2'400'000'000 billion markers. Accordingly, it unfortunately takes an exceptionally long time until we get the data. We must reckon with a waiting period of about 6 months. I can then compare the sequenced dog with all other dogs of different breeds that we have in our database (currently about 900 dogs and some wolves). I hope that I will be able to identify a single mutation that is private to our case. The problem with this approach is, that we can only identify variants where between one and 20 of the bases (those are the markers I was writing about) are changed. For bigger variants, we need the mapping approach.

In case we don't find a small variant: This means I need to go visually through the whole genome of the sequenced dog, to see if there are bigger changes. This is absolutely impossible for 2.4 billion markers, that is why I need the mapping approach that I described before, so that the time I need is reduced greatly. I will then confirm the found variant(s) in the laboratory with some experiments. I

will for example compare the case to all the Bullmastiffs we have in our database. This is also the step where a gene test can be developed.

What stage are we at with developing a DNA test?

Earlier this year we appealed for blood samples from healthy dogs and affected dogs to begin the mapping process and this is where we are to date. Without everyone's help and commitment to provide samples we simply cannot develop a DNA test; we **urgently** need your samples for research. We are not testing dog**s** for anything else and only the university knows what samples belong to what dog. All information is totally confidential and retained by the university. So please for the future of our beautiful Bullmastiff Breed please get involved. You have nothing to lose only everything to gain. Think about it, next time it could be you!

So the first focus of the group will be to develop a DNA screening test for Cerebellum Ataxia and if possible Retinal dysplasia, as often but not always these diseases will develop at the same time

What can I do to help the Bullmastiff?

To help bullmastiffs all you need to do is Download the submission form from http://magdaporter7.wixsite.com/bullmastiffhealth

Please then ask your vet to take a sample of 5ml of blood, all the instructions for your vet are on the submission form, tell your vet this is for research, some vets will do this for free. Enclose the blood sample form, a 3-generation pedigree and send to the university. We desperately need affected cases to come forward. We have some but need more. In the case of an affected sample please enclose all relevant history from vet and referral practice. We need samples from all around the world, the protocol is the same whatever country you live in.

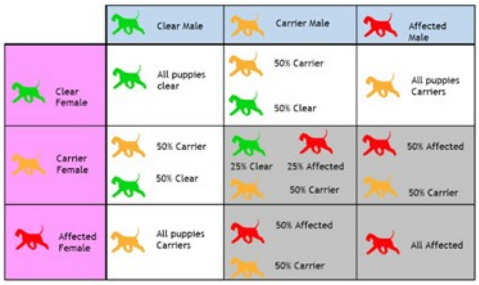
What can the test do for future breeding programmes?

Normally those disease are caused in a recessive matter, meaning that the dog is only affected if it inherits one affected allele of both mother and father. In this way: no healthy allele is present in the puppy and it gets sick. This means to breed animals without the disease you should only do mating's, in which one of the parents is completely free of the disease causing allele, so that the puppies can only inherit maximum of one 'sick' allele. In this way they are carriers, but they will not get sick and you can breed with clear animals. No longer will we breed blind we will have a new tool that will allow us to make educated choices when selecting dogs in our breeding programme, we do not need to 'throw the baby out with the bathwater'. There is a way a new way and only by us all pulling together can we make this happen. The table below explains the possible outcomes once we develop a DNA test.

How will the DNA test work?

Once the test is developed you would take a sample from your dog and send to a commercial lab. We do not know at this stage what lab will run the test, what sample they require and cost. Below is a table of possible outcomes Clear, Carrier and Affected and what this means when mated together.

There is only one thing standing in the way of a better future for our dogs and that's us please send your samples Bullmastiffs need you.



Planned Future event.

We would love to invite Matthias Christen from the Institute of genetics, University of Bern, Switzerland to speak at our seminar, hopefully this could be combined with a sample draw BUT we are living in difficult times and this may be a little while away. We will keep you posted on our page.

Further reading

https://journals.plos.org/plosgenetics/article…

https://www.g3journal.org/content/7/8/2729.long

https://www.g3journal.org/content/7/2/663.long

Compiled by Sonja Oliver-Hicks (Nashbank Bullmastiffs UK)

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