Mucopolysaccharidosis type IIIB

Update

10/20/2006

Now that over 1900 MPS 111B tests have been run and they are being checked by breedings and testing the offspring, a few errors in results have been discovered. While the test for MPS 111B is very accurate, as with any laboratory testing a certain percentage of error is expected due to human error. Errors can be made anywhere from sample collecting and identifying the dog, through the testing process, to reporting the results. So far the reported error percent is 0.23% which is well below the accepted and even expected error rate.

Because of this the following recommendations are being made:

Reviewed and approved by Dr. Urs Giger, Professor of Medical Genetics
University of Pennsylvania

1. All animals must be permanently identified by either tattoo or microchip at time of sample taking/testing.
2. Test all breeding stock. Exception; when the individual, its sire, and its dam have been DNA identity profiled and parentage of the individual has thus been verified plus the individual has three generations of ascendants (parents, grandparents and great-grandparents) that are normal by testing.
3. Test all offspring of a mating involving a carrier. Exception: The normal parent is the dam and has three generations of normal ascendants and she, her sire and her dam have been DNA identity profiled and parentage verified.
4. All schipperkes that need to be DNA profiled for AKC litter registration requirements should be MPS111B tested.

If anyone notices discrepancies in their test results, it would help if you would send the details to Shirley Quillen, Chairman of the SCA Health and Genetics Committee at imaskip@earthlink.net.

General Information

Mucopolysaccharidosis type IIIB (MPS IIIB) in Schipperkes and DNA testing

This recently identified genetic disease is present in Schipperkes and in humans. When a dog is affected it is ultimately lethal. The gene has been identified in many of our dogs in the current population. It is imperative that we learn about this disease and test all dogs prior to using them for breeding from this point forward. Read the information below furnished by Dr. Matthew Ellinwood, one of the original researchers studying this disease at the Josephine Deubler Genetic Disease Testing Laboratory at the University of Pennsylvania School of Veterinary Medicine

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MPS IIIB Testing Kits can be requested by calling (215) 898-3375. For instructions, see the Submission Form.

If you are a breeder and find that you have an unplaced affected pup, or if you are an owner of an affected dog, and you would like to know how you can help to further efforts to find a treatment and a cure for this devastating disease, we encourage you to contact: the Josephine Deubler Genetic Disease Testing Laboratory at the University of Pennsylvania School of Veterinary Medicine under the direction of Dr.Urs Giger.

WHAT IS MUCOPOLYSACCHARIDOSIS TYPE IIIB (MPS IIIB)?

The disease MPS IIIB, also known as Sanfilippo syndrome type IIIB, is an inherited disease classified as a lysosomal storage disease (LSD). Lysosomes are "bags" within cells of the body, filled with special enzymes which disassemble molecules in an orderly manner. If one of the enzymes is missing, due to mutations in the gene for that enzyme, the disassembly stops, and undegraded molecules accumulate in lysosomes (hence the term LSD), and the cells become sick or die, which leads to disease. The compound accumulating in MPS IIIB is heparan sulfate and the affected enzyme is N-acetyl-a-D-glucoseaminidase (NAGLU).

The disease MPS IIIB, is one of a group of eleven different genetic diseases known as the MPS disorders. The MPS disorders are all classified as lysosomal storage diseases. Other better-known lysosomal storage diseases that occur in humans include Tay-Sachs disease and Gaucher disease. The feature that unites lysosomal storage diseases is that they have abnormal lysosomal function. The lysosome is an important structure of virtually all cells in the body, and serves as the "garbage disposal" of the cell. In humans MPS IIIB is seen in approximately one out of 73,000 live births.

The lysosome is essentially a "bag" within cells of the body, which is filled with special enzymes. The lysosome's function is to disassemble large molecules of a cell that need to be recycled or disposed of. The way in which molecules are dissembled in the lysosomes involves a series of steps, something like an automobile assembly line, but in reverse. In place of the "disassembly" line workers who each do one specific job, the lysosome employs many different enzymes, which again have just one job each. These enzymes, when all are present, disassemble molecules in an orderly and efficient manner. When one of the enzymes is missing, due to mutations in all copies of the gene for that specific enzyme, the orderly processes of disassembly stops, and large undegraded molecules begin to accumulate in the lysosomes, hence the name lysosomal storage disease. Eventually the lysosomes of a cell become so large, that it interferes with the normal job of a cell, and the cells become sick or die, which leads to the clinical signs and symptoms of the disease.

In MPS IIIB the compound which is stored is called heparan sulfate. Heparan sulfate is one of a number of compounds known as glycosaminoglycans (GAGs), which are themselves long strings of chemically modified sugar molecules important in structures like bone and cartilage and in the

communication machinery betweens cells in the body, especially in the brain. The term mucopolysaccharide is actually on old-fashioned term for GAG, hence the name mucolpolysaccharidosis. The enzyme that is not functioning appropriately in MPS IIIB is called N-acetyl-a-D-glucoseaminidase (NAGLU).

WHAT ARE THE SYMPTOMS OF MPS IIIB?

The clinical signs in the dogs are related to brain disease, appear between 2-4 years of age, and include tremor, and difficulty in balancing, walking, and negotiating obstacles such as stairs. The disease is progressive, and owners have chosen euthanasia, usually 1-2 years after recognizing clinical signs.

In humans the signs and symptoms of MPS IIIB are related to the mental deterioration that is seen. By the age of 3-6 years, affected children start to show delayed development. The mental deterioration progresses through mental retardation and finally to dementia. As part of this progression the children may show behavioral abnormalities which can include hyperactivity, poor sleeping patterns, and aggressive and destructive behaviors. If the children have acquired speech and toilet training skills these are eventually lost. In the last stages of the disease the children lose the ability to walk or feed themselves. Most do not see their third decade of life. At this time there is no proven and effective treatment for this disease. To learn more about this condition in children one can visit www.mpssociety.org

The clinical signs in the dogs are in many ways similar to the children, in that the clinical signs are related to the brain disease. However, the dogs differ from children in two important ways. The age of onset is seen in the dogs during early adulthood, and the clinical signs are related to a particular part of the brain called the cerebellum. The cerebellum plays an important role in balance and smooth and coordinated movement. The clinical signs in the dogs have been reported to appear between 2-4 years of age, and include tremor, difficulty balancing, walking, negotiating obstacles such as stairs, head tilts, falling to both directions, and other clinical signs associated with the generalized balance problems. Some have reported a change in coat color from black to auburn; however, coat changes can be associated with many other diseases and illnesses. In the dogs the disease is progressive, and the initial problems with balance become worse until the dogs cannot stand, walk, eat, etc., without a great deal of difficulty. Owners have eventually chosen to have their dogs euthanized. This was usually chosen within 1-2 years after clinical signs were first recognized. Affected bitches are fertile, and can have pups. We expect that affected males may also be fertile, but we have not observed this.

HOW IS MPS IIIB INHERITED?

The inheritance pattern of MPS IIIB is autosomal recessive. . Both males and females are equally capable of having the disease, or of being carriers. Carriers are absolutely normal, and will not have signs of the disease.

As is the case with all autosomal genes (genes not found on the sex-chromosomes), an individual has two copies of a specific gene, one copy on each of a pair of autosomes. With MPS IIIB, if an individual is affected with the disease, both of the NAGLU genes that the affected dog inherited

were the mutant form of the gene. Both males and females are equally capable of having the disease, in other words the disease in not sex-linked, and inheritance of the mutant copy of the gene must come from both the sire and dam. Carriers, or individuals that have inherited one normal copy and one mutant copy the NAGLU gene are absolutely normal, and will not have signs of the disease. Parents of an affected animal are what is called "obligate carriers", in other words, since an affected was produced from them, they must both be carriers of a mutant copy of the NAGLU gene.

IS THERE A DNA TEST AND WHAT DO THE DNA TEST RESULTS MEAN?

There is now a DNA test available. We have found a mutation in the NAGLU gene in the Schipperke breed and the test for this mutation is offered through the Josephine Deubler Genetic Disease Testing Laboratory at the School of Veterinary Medicine at the University of Pennsylvania. The DNA diagnosis will report a result as either affected (affected with the disease-both genes are mutant), carrier (clinically normal-one mutant and one normal gene), or normal (clinically normal-both genes normal). This test is the most efficient way to diagnose affected animals with MPS IIIB. It is also the only way to be sure of whether a breeding animal is a carrier or a normal dog. This DNA test can be run from DNA extracted from either EDTA blood (lavender top tube) or from special cytology brushes used to get a sample of cells form the inside of the mouth (cheek swabs). Please see the attached documents for instructions on the collections and submission of samples.

HOW DO I GET MY DOG TESTED?

If you would like to have your dog tested, please see the submission form, and attached instructions and check list. A 2-3 day delivery service which provides the ability to track the progress of the delivery, is recommended. Samples to submit can be either 1-2 ml of EDTA blood or 2 cheek swabs. Testing materials for cheek swab submissions includes 2 cheek swabs and a submission form. Owners can take cheek swab samples at home and send samples in according to submission instructions. Testing materials (swabs and submission forms) can be requested by calling (215) 898-8894.

WHO RECEIVES NOTIFICATION OF THE DNA TEST RESULTS?

It is the policy of the Josephine Duebler Genetic Disease Testing Laboratory that all results are kept completely confidential. No results are released to anyone other than the individual that submitted the sample. This may be the veterinarian, the owner, or an agent for the owner. No result that is identified as being from a specific dog is made in scientific communications or publications unless by the written consent of the owner. Results will be sent out within 3-4 weeks from the receipt of samples.

HOW COMMON IS THIS DISEASE AND HOW LONG HAS IT BEEN IN THE SCHIPPERKE BREED?

The mutant gene may be as far back as eleven generations, and hence may be very broadly distributed in the Schipperke population. The carrier frequency is unknown, but judging from similar diseases in cattle, it may be as high as 15%.

We cannot be certain of how common this disease is in the Schipperke, either in terms of how many affecteds there are or how many carriers there are. We had initially seen two cases of this disease, which we diagnosed from samples submitted for analysis to the school's metabolic genetic screening laboratory. Since then we have documented MPS IIIB affected dogs in a total of five different families. From comparisons of the pedigrees of these dogs we can say that the nearest and most likely common ancestor was an animal found as far back as eleven generations in some pedigrees. This would mean that the mutant gene may be very broadly distributed in the Schipperke population. We cannot predict what sort of frequency of carriers there may be in the population at large without a controlled study. However a similar lysosomal storage disease, called ß-mannosidosis, which was seen in the Salers breed of cattle was shown to have a carrier frequency of 15%. If a similar carrier frequency was to be seen in the Schipperke breed this would mean that on average, up to one out of every seven dogs could be a carrier.

IF THE MUTATION IS SO OLD, WHY HAS THIS NOT BEEN SEEN BEFORE?

Although it is impossible to prove, we feel that this disease has been seen before, but was just not recognized. Factors contributing to this including a low frequency of cases, non-specific clinical signs, an adult onset, a lack of post-mortem examinations, and very limited knowledge among medical professionals.

There is a report in the scientific literature that describes a case of a lysosomal storage disease in a Schipperke that was published in 1993. The authors were unable to say exactly which lysosomal storage disease it was. Their findings however were nearly identical to what we have seen in two cases from the late 1990s. Many factors may have contributed to MPS IIIB not having been recognized earlier. It may be that the mutant gene is rare enough in the population at large, that the chances of two carriers being mated and producing offspring was low, and such sporadic cases escaped the attention of veterinarians, breeders, and owners. The clinical signs of MPS IIIB are not themselves specific to MPS IIIB, but can be caused by a host of other illnesses. The disease is seen in adulthood, which is not usually the case with such severe genetic diseases. Many owners may have declined a post-mortem examination. Unless a post-mortem examination was conducted, it is unlikely that anyone who had a case of this disease would have known about it. Even if a post-mortem examination was conducted all that could be determined was that the patient had a lysosomal storage disease. Knowledge of these sorts of diseases is limited among medical professionals. Very few veterinarians will have ever heard of this disease, and if so, never in a dog, since the Schipperke breed is the first case of the diagnosis of MPS IIIB in any dog. The difficult in finding an accurate diagnosis is not a situation that is unique to veterinary medicine, as families whose children have this disease are not infrequently given other diagnoses before a definitive diagnosis of MPS IIIB is made. We believe a combination of all these factors may have served to obscure earlier cases of this disease.

WHO SHOULD HAVE THEIR ANIMALS TESTED?

Considering the fact that the disease is progressive, cannot be treated, is fatal, and devastating to the dogs and their families, we would recommend that every breeding animal be DNA tested for this disease. Additionally, all pups that are waiting to be placed in permanent homes should be considered for testing, to spare their new owners a great deal of anguish and anxiety. Any non-breeding animal that is under three years of age may be a candidate for testing to identify if it is affected and will develop clinical signs. However it must be mentioned that there is no treatment for this disease, hence testing of such animals is probably useful only to relieve the anxiety of owners who know that their pet is at risk, i.e. an animal whose parents are known to be carriers.

HOW MUCH DOES TESTING COST?

Testing costs $75/dog.

HOW SOON CAN I EXPECT TO GET RESULTS BACK?

Results will be available in 4-6 weeks from the time of receipt of samples. Because DNA testing is usually for planned breedings, we do not have a policy of accepting rush diagnostics for genetic diseases, unless it is an animal with clinical signs of disease for which there is a treatment available, which is not the case for MPS IIIB. Please do not contact the Laboratory to inquire whether samples have arrived. If you wish to be able to confirm that samples have been delivered we suggest that you use a delivery/mail service that allows you to track the shipments progress, arrange for a return receipt which acknowledges delivery, or include a stamped self addressed card for the acknowledgement of receipt of samples. Because we are in the first stages of diagnosing this disease with a DNA test, there may arise an overwhelming response to the testing in the first few months, which may delay the reporting of results. If such a situation occurs, we will keep the Schipperke Club of America's Health and Genetics Chairperson appraised of any change in the normal turnaround on test results.

IS RUSH TESTING PROVIDED OR SPECIAL BULK OR LITTER PRICES?

Rush testing is not available. There are also no bulk submission or litter submission price adjustments.

WHAT SHOULD I DO IF I HAVE AN AFFECTED DOG?

Unfortunately there is no treatment for this disease. Once an animal has begun to show clinical signs, all that can be done is to provide a safe environment, such as one without stairs, or obstacles, which might lead to falls or make getting around difficult. The decision of when to elect euthanasia for a sick pet is a difficult one, and must be made by balancing the importance of the bond between the owner and their pet, and the quality of life of their pet. Under no circumstances can we recommend that non-symptomatic animals be euthanized. Although the

lifespan of dogs with this disease is much shorter than normal, until they become clinically affected, they are absolutely normal, and depending on the clinical course of the disease in the individual, they can have many months of quality life after clinical signs appear. The difference between owning an affected versus and unaffected dog, is that the owner has a very good idea of when and why they may face the decision to elect euthanasia for their pet.

Article Links :

http://www.mpssociety.org/gran-res-update1.html

http://www.mpssociety.org/gran-res-update1.html

http://w3.vet.upenn.edu/research/centers/penngen/services/allforms.cfm?form=12