MPSIIIB

There are now 3 labs testing for MPSIIIB. UPenn was the original one that identified the disease.

UPenn - https://netapps.vet.upenn.edu/PennGen/SampleTesting/default.aspx
MPSIIIB for Schipperkes

VetGen Testing - https://www.vetgen.com/ordertests.aspx?id=Schipperke
MPSIIIB, coat color, coat type, PRA, Bobtail, plus many more

Embark Testing - https://embarkvet.com/
MPSIIIB (Schipperke variant), Breed ID, plus many more

MPSIIIB (Mucopolysaccharidosis type IIIB) in Schipperkes and DNA Testing

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In 2003 the Josephine Deubler Genetic Disease Testing Laboratory at the School of Veterinary Medicine at the University of Pennsylvania identified a genetic disease that 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. Ellinwood, the researcher studying this disease.

What is MPSIIIB

The disease MPSIIIB, also known as Sanfilippo syndrome type IIIB, is an inherited disease. It 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 MPSIIIB 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 MPSIIIB 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 between 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 MPSIIIB is called N-acetyl-a-D-glucoseaminidase (NAGLU).

What are the symptoms of MPSIIIB

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 MPSIIIB inherited?

The inheritance pattern of MPSIIIB is autosomal recessive. 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 MPSIIIB, 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 if so, 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 MPSIIIB. 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 from the inside of the mouth (cheek swabs). Please see the attached documents for instructions on the collections and submission of samples.

How do I go about getting my dog tested?

Create a login here:
https://netapps.vet.upenn.edu/PennGen/SampleTesting/default.aspx

Select the MPSIIIB test. 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. For testing needs, testing materials (swabs and submission forms) can be requested by emailing penngen@vet.upenn.edu

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?

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 MPSIIIB 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. 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 MPSIIIB 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 MPSIIIB are not themselves specific to MPSIIIB, 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 MPSIIIB in any dog. The difficulty 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 MPSIIIB 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 soon can I expect to get results back?

Results will be available in 3-4 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 MPSIIIB. 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.

What do I do if I am planning a breeding?

As we anticipate much of our initial testing is to be done on breeding animals, we feel it impractical to offer a priority testing because a breeding is eminent. In cases where a breeding is eminent, we must regretfully recommend that the planned breeding take place after a diagnosis is provided. We regret the delay this may cause, but in a worst-case scenario, it will only delay breeding by one heat cycle of a bitch.

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. 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 our efforts to find a treatment and a cure for this devastating disease, we encourage you to contact us via e-mail: penngen@vet.upenn.edu

You can also contact the SCA Health and Genetics chair, Shirley Quillen, at imaskip@earthlink.net.