

April 19, 2010:

**The AMSC and MIT research information release:
Written by Dr. Lisa G. Sarvas and the AMSC Health Committee.**

The AMSC Health Committee is pleased to release the following information about new research on familial renal disease in the Miniature Schnauzers. The details of the research and submission information are included in this release.

In the past 2 years the AMSC HC has continued to receive case submissions of Miniature Schnauzers diagnosed with early renal disease. The continued submissions and concern by AMSC members indicates the need for additional research on this disease. We are also pleased that this project allows us to collect samples prior to committing to any funding request from the researcher.

Please submit case information and sample submission questions directly to the researchers through Michelle in their department. All contact information is listed in the article summary. Please restrict communication with MIT to information directly related to sample submission. Submit any questions about the disease or the research in general directly to the AMSC HC. The AMSC HC will communicate as needed with the researcher, Noriko Tonomura. The committee members will continue to answer individual AMSC member questions where we are able to help facilitate member education and understanding of this complex disease.

The AMSC HC asks that members continue to submit biopsy samples from non-symptomatic dogs to Dr. Brown at the University of Georgia as we have previously recommended. The following MIT work is in addition to the biopsy submissions to Dr. Brown.

INFORMATION FROM MIT:

BRIEF DESCRIPTION OF DISEASE, AND OUR PROJECT:

Juvenile Renal Dysplasia (JRD) affects developmental maturation of the kidney. All dogs are born with developmentally immature kidneys, and then the maturation process is completed within 6-8 weeks after birth. The kidneys of JRD-affected dogs do not go through this process, retaining immature glomeruli and/or tubules, and persistent mesenchyme. Dysplastic kidneys are incapable of efficient water re-absorption and elimination of metabolic waste products, leading to chronic renal failure. How much of the kidneys are affected by JRD varies greatly among affected individuals, and the clinical signs of JRD may not be present unless over 75% of the kidney is affected. When a dog is affected mildly, the first clinical signs are usually elevated BUN and creatinine levels. Other symptoms that may be present are: increased amount of urination (unconcentrated urine), increased intake of water, vomiting, lethargy, and weight loss or delayed growth. This condition eventually leads to kidney failure between age of 6 weeks and 4 years, and currently there is no curative treatment.

Though most commonly reported in Lhasa Apso and Shih Tzu dogs, an elevated disease prevalence is also reported for other breeds, such as Standard Poodles, Soft-Coated Wheaten Terrier, Golden Retrievers, and Boxers. We have initiated a research project to find the mutation(s) associated with JRD in the Boxer dog by comparing the DNA of affected and healthy Boxer dogs using the new single nucleotide polymorphism (SNP) array tool that we have developed at the Broad Institute.

The preliminary genome-wide association has been performed in 17 JRD-affected and 15 healthy boxers, and the result led us to believe that this disease is caused by more than one gene/mutation. In order for us to have the statistical power to find those multiple mutations, we need more individuals (both cases and controls) to participate in the project. Therefore, we are continuing to collect blood samples from JRD-affected and healthy Boxer dogs. For healthy controls, we are recruiting the dam, sire, and healthy sibs of an affected dog. In the second stage of mutation discovery, called “fine mapping” stage (see Figure 1), we will analyze DNA samples from additional breeds that are affected by JRD, which will allow for further pinpointing the regions of DNA where the mutations are to be found. This is where Miniature Schnauzers can help us with this project.

It is possible that Miniature Schnauzers have a slightly different set of risk factors than Boxers. The fine-mapping will show us if Miniature Schnauzer have the same risk factors as Boxers. Since fine mapping is a much cheaper technology, this would be the first step to take. If it turns out that Miniature Schnauzers have different set of risk factors than Boxers we would want to do a complete search of the Miniature Schnauzer genome at a later date.

Our goal of this project is to identify the causative mutations for JRD, which will allow us to develop a genetic test to identify JRD-affected dogs early and accurately. The testing allows providing early interventions for the affected dogs, and implementing better breeding program.

GENOME-WIDE ASSOCIATION MAPPING IN TWO STAGES

Briefly, the process of finding JRD-causing mutations is as follows (Figure 1): The genome-wide association mapping is performed using SNP markers, using the SNP array. The SNP markers are compared between groups of affected and unaffected (healthy) dogs to locate a region where the genomic profile of affected dogs is different from that of unaffected dogs. For the JRD project, we are performing the initial genome-wide association mapping within a single

breed, Boxers. When we find a region that is associated with JRD in the initial screening, we then compare the region by SNP markers across several related breeds. This is where the Miniature Schnauzer breed can help us. We do suspect that at least some of the risk factors (= mutations) are shared between breeds. Since each breed has its own characteristics at any given location of the genome, searching for a smaller region that is shared among JRD-affected dogs across breeds will allow us to rapidly narrow down the region and identify disease-associated mutations.

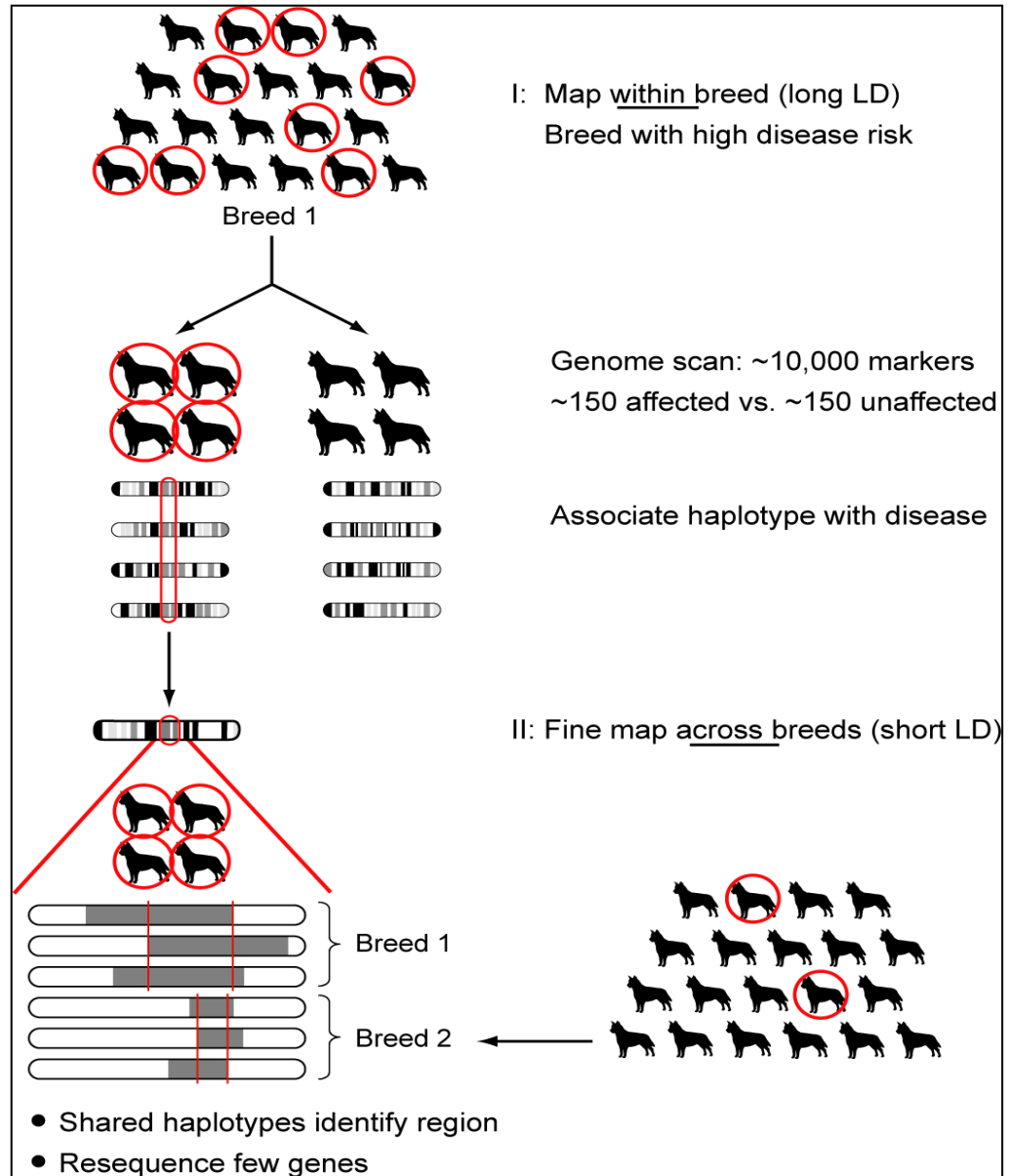


Figure 1: Mutation discovery (mapping) strategy

In order for us to successfully identify a gene (or genes) that is associated with any given disease, it is very important to recruit a sufficient number of participants. We are encouraging Miniature Schnauzers that fall into any of the following categories to participate in this project:

- 1) Has elevated kidney values at young age (birth to ~4 years)
Other clinical signs may include to, but not limited to:
excess drinking/urination, dilute urine, vomiting, lethargy, irregular and/or abnormally small kidneys by ultrasound
- 2) Dam, sire and healthy siblings of the affected individual
- 3) Over 5 years old and without any kidney problems

To obtain a DNA sample, we only need ~10 ml (= 2 teaspoon) of blood in a purple top tube (EDTA tube) from each individual. When mailing in the sample, please make sure the tube is well protected against potential breakage, especially since the tube is made of glass. If it is during the hot summer season, please pack the tube with ice packs in an insulated container. We need a consent form signed by the owner to be sent in with the sample. For the participant, we are asking for health information and pedigree information if available. You can provide the pedigree info as a printout of the pedigree (if available), and if your dog is registered with any organization (ie, AKC), please make sure to provide us the registration number and organization. If the participating dog is not registered but any of his/her parents/siblings are, then you can provide the pedigree info of a closely related dog and tell us how they are related. The consent form can be found at www.DogDNA.org by clicking on the link "Printable brochure (PDF)". We are asking for pedigree information only because we are looking at genes that are all inherited from the parents, and we would like to analyze the mode of inheritance of JRD. All the information regarding your dog is kept strictly confidential, and the genetic disposition of any dog is never to be made public. The details of "how to" can be found at www.DogDNA.org, but please feel free to contact us by e-mail at dog-info@broad.mit.edu. We are looking forward to your participation.

We would also like to characterize the type of JRD the Miniature Schnauzers have to evaluate the similarity of the disease to that of Boxers. In order to do so, we would like to ask you to consider donating either a wedge biopsy of affected kidney, or the whole kidneys to the research. The wedge biopsy option is not always doable, since a dog with compromised kidney cannot tolerate anesthesia. The whole kidneys can be donated at the time of necropsy. The details/arrangements for sample submission are available by contacting Michele Perloski at Broad Institute. Any questions intended for the researchers can be submitted through Michele.

Sample should be sent to:
c/o Michele Perloski
Broad Institute
7 Cambridge Center
Cambridge, MA 02142

It would be great to let Michele that the sample is coming by email (preferred), or phone
email: perloski@broadinstitute.org
phone: 617-714-7792