ABCF MESSENGER

Official Newsletter of the American Boxer Charitable Foundation, Inc.
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2009 RESEARCH UPDATES

In this issue of the *Messenger*, we're featuring research updates from Dr Kate Meurs of Washington State University on ARVC; Dr Joan Coates of the University of Missouri on DM; and Dr Kerstin Lindblad-Toh of the Broad Institute on a wide range of genetic research projects in which she and the Broad Institute have participated this year.

Comments, questions or suggestions? Email vzboxers@aol.com.

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First, ARVC: In April, shortly before the annual ABC specialty, Washington State University announced that Dr Kate Meurs had discovered a gene that causes Boxer Cardiomyopathy, more formally known as Arrhythmic Right Ventricular Cardiomyopathy (ARVC), and was developing a test that would allow boxer breeders to breed away from the disease (see the April *Messenger* for the announcement).

By the time the ABC had rolled around in May, Dr Meurs had perfected the DNA test, and the ABC Health & Research Committee had arranged to collect DNA blood samples for Dr Meurs to take back to her WSU Cardiac Genetics Lab to be tested. The ABCF paid for three days of a vet tech's services and the ABC helped by providing a room for three days, plus all the paperwork copying, tubes, needles, syringes, etc. In addition, Dr Meurs brought a supply of cheek swab test kits to distribute, so those of us who had dogs at home could test them, too, as soon as we returned from the ABC.

On Tuesday, May 5, Dr Meurs made a half-hour presentation to ABC attendees between the selection of the Grand Prize Futurity Winner and the start of the regular puppy classes. After her talk, Dr Bill Truesdale, president of the American Boxer Charitable Foundation, presented Dr Meurs with a plaque commemorating her many years of service to the Boxer breed and the ABC, and the large audience gave her a standing ovation.

At the ABCF Auction Dinner later that evening, ABC President Larry Hughes announced that the ABC Board had unanimously voted to make Dr Meurs an honorary member of the ABC. Dr Meurs also received a beautiful and unique medallion from Dr Joyce Campbell, chair of the ABC Health & Research Committee, in gratitude for all she had accomplished for our dogs in the battle against Boxer heart disease.

Dr Meurs has promised to provide breeders with a statistical report when her lab has processed 1000 ARVC tests, and they are very close to that number at this time. In the meantime, as of 9/18/09, the owners of 341 boxers have elected to list their dogs' results publicly on the WSU website. Those results and an explanation of the different test results can be viewed here (please copy and past the following URLs into the address bar of your browser):
http://www.vetmed.wsu.edu/deptsVCGL/Boxer/TestResults.aspx.
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Place an online order for cheek swab test kits here: http://www.vetmed.wsu.edu/deptsVCGL/Boxer/test.aspx.

As might be expected with a brand new genetic test, in the four months since the inception of the WSU ARVC testing program, there have been reports of unexpected/anomalous test results in some quarters, especially among UK imports, but from the owners of a number of North American boxers, too. We will continue to publish updates on Dr Meurs' ARVC research and the new test as we receive them.

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Summary of the Degenerative Myelopathy Study for the ABC
August 24, 2009
Joan R. Coates, DVM, MS, Diplomate ACVIM (Neurology)

We continue to characterize the phenotype for Degenerative Myelopathy (DM) in the Boxer and other breeds using sequential neurodiagnostic testing and neuropathology. We are concentrating on morphometric studies (quantitative evaluations) of the spinal cord and peripheral nerves and muscles. This will provide further data to assess the relation of DM to amyotrophic lateral sclerosis (ALS – Lou Gehrig's disease) so that we can better establish collaborations with the ALS researchers and develop potential treatment strategies. A small subset of 6 of the proposed 10 dogs has been characterized by the principal investigator monitoring the clinical progression. Clinical progression was followed with neurodiagnostic testing and histopathologic studies of the spinal cord, and peripheral nerves and muscles. In total so far, we have collected 31 spinal cords from the Boxer and of those 9 dogs have come to the University of Missouri for necropsy. We still are in need of spinal cords from older (> 9 years of age) unaffected ('normal') dogs so that we can have control tissues. Also, we still need spinal cords from dogs that are DM affected so that we can do these quantitative evaluations. We offer to send a kit with paid postage so that the spinal cord, nerves and muscle tissues can be properly collected.

We are pursuing investigations for biomarkers which are like yard markers to follow disease progression. This is very important because we need a way to see if the potential therapies will slow or halt disease progression. Potential biomarkers will be gathered from pathologic studies of the spinal cords and nerve tissue, the spinal fluid and from clinical evaluations. We are getting nearer to developing an electrodiagnostic technique (motor unit number estimation) in normal dogs which has been used in ALS patients to follow disease progression. In addition, we videotape the gait and are evaluating a scoring system.

I stay in contact with an ALS researcher at Washington University in St. Louis. We are organizing a pilot study to investigate a potential therapy – this is called developing a 'proof of concept' study. In addition, I have arranged to travel to an ALS meeting in Quebec in September and to the International ALS/MND meeting held in Berlin, Germany in December. I will be giving oral and poster presentations sharing the disease discovery in dogs with other ALS researchers.

We continue to identify dogs at risk in collaborations with the Animal Molecular Genetics Laboratory, MU Veterinary Medical Diagnostic Laboratory and Orthopedic Foundation for Animals (OFFA).
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As of 8/21/2009, we have tested 10,695 dogs of which the mutated allele has been found in 85 breeds. Twelve breeds and the mixed breed dog have been histopathologically confirmed for DM. We have tested approx. 1300 Boxers. The genotype total includes 158 clears (13%), 410 carriers (33%), and 690 (55%) AT RISK. The allelic frequency takes into account the number of chromosomes with the mutation. About 71% of the chromosomes in Boxers have the mutant allele.

We continue to offer the genetic test at no cost in dogs presumptively diagnosed with DM by a veterinarian. Thus, we have performed 60% of the tests in Boxers at no costs.

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Broad Boxer Study Update
Dr Kerstin Lindblad-Toh

Dear boxer folks,
It is time for another Broad Institute update. We seem to be making progress on many studies for different breeds, although most are not yet published. Still in our most recent paper, published together with Tosso Leeb from Switzerland, we found a gene for osteogenesis imperfecta, a disease characterized by extremely fragile bones and teeth and found in Dachshunds.

Now to a summary of the status of our boxer projects:

Degenerative myelopathy:

Together with Drs. Coates and Johnson at the University of Missouri we have identified a mutation in the superoxide dismutase 1 (*SOD1*) gene that confers a major risk to degenerative myelopathy. We did however see some indications that additional genes might be involved in the disease, so we are currently continuing the search for additional loci. Additional samples from both DM affected dogs and old healthy dogs are necessary for this study, and we have so far not received as many samples as we need. **PLEASE help us by submitting more samples**.

Cardiomyopathy:

Together with Dr Meurs at Washington State University we have searched the boxer genome for risk factors for cardiomyopathy. We have found several candidate loci, and have found a mutation in a gene at one of these loci. This gene has a relevant function and we can see that the protein's function is affected by the mutation. A paper describing this finding has been submitted for publication. Dr Meurs is now offering a test and together we are following up to see if we can find additional genes with mutations to fully explain the risk factors involved in the disease.

Juvenile Renal Dysplasia:

As you might remember, we have searched the genome for genetic risk factors for juvenile renal dysplasia using 12 cases and their parents (or
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equivalent relatives), as part of a collaboration with Dr Hedhammar in Uppsala, Sweden. Unfortunately we did not find a clear region of association. This might suggest that multiple loci are involved in the disease and that we need more dogs to find these risk factors. Thus, we are now in a phase of renewed samples collection to ensure we get enough samples to identify the disease genes. We **STILL NEED MORE SAMPLES** to reach the magic number of 50 samples required to perform the next genome-wide screen.

Hemangiosarcoma:

In collaboration with Dr Azuma at Tufts University we have performed a SNP scan and found six candidate regions in the Golden retriever that appear to confer a risk to hemangiosarcoma. Further study of these regions suggests that one of these regions may be a risk factor also in the boxer breed, although analysis with more boxer dogs may potentially suggest association at more loci. We are currently looking for the actual mutations at these loci. The mutation screen has been ongoing for some time, but we have not yet found the causative, perhaps since the mutations seem to be of the trickier kind that does not break the protein, but rather regulate how MUCH protein is produced. We would very much like to receive more samples from boxers with hemangiosarcoma. We are also looking for tumor tissue to study the effect of potential mutations on the nearby genes. **If you are able to submit tissue in addition to a blood sample please contact dog-info@broad.mit.edu prior to taking the sample.**

Osteosarcoma:

Together with Dr Comstock at University of Michigan we have performed SNP scans in both the Rottweiler and Greyhound breeds and found three potential loci in each breed. Follow-up analysis of these regions has been done in multiple breeds and is currently ongoing in the boxer breed. We are also in the process of searching for the actual mutations. **Again tissue samples would be of real value for follow-up work.**

Mast cell tumors:

In collaboration with Dr London we have identified have identified four candidate regions by SNP scanning the Golden Retriever breed. None of these appear to be present in the boxer. However, we have already collected over 30 cases, so if we continue to collect samples, we could very well envision a separate genome scan in the boxer breed. We currently have no funds for this study, so while we are still accepting samples, we are also looking for funds for this project. Among several options we are exploring the possibility to perform this study as part of the LUPA project, a European collaborative effort to map many different diseases.

Lymphoma:

Together with Matthew Breen, we have just performed a preliminary B cell lymphoma scan in golden retrievers and are finding at least one plausible candidate locus. We expect to include boxers in the fine-mapping stage shortly.

FOR ALL CANCER STUDIES we really need more samples, because it is evident that in canines, as is likely in humans, there are multiple genes involved. This means that a larger sample number will give us more power to find all genes working together to trigger the disease.

In conclusion, I hope that you are as excited as we are about the progress we are making. We also ask you to keep in mind that when performing any of these studies it is critical for us to have the most updated status for all dogs. We therefore request owners who have previously submitted samples to us to contact us if the health status of their dog changes in any way.

Kind regards,
Kerstin Lindblad-Toh
Scientific Director, Vertebrate Genome Biology
Broad Institute of MIT and Harvard
Professor, Uppsala University, Sweden

JOIN THE FOUNDATION!

For as little as $25 a year, YOU can join the American Boxer Charitable Foundation and claim your share of the credit for supporting and funding the fantastic research described above, which is already benefiting both our Boxers and OURSELVES! Human beings suffer from ARVC, DM/ALS (Lou Gehrig's Disease), too, and most of us have experienced the untimely loss of a friend or family member to cancer.

Just go to the opening page of the ABCF website (www.abcfoundation.org), and on the left side of the page, click on **Join or Renew ABCF Membership**, where you will find a printable form or a link to PayPal for a credit card payment. If you prefer to receive a print copy of the *Messenger* through the mail, just add $10 to your membership fee and let me know that you want a print copy.
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