Grant # 01313

Identification of a Genetic Marker for Familial Subvalvular Aortic Stenosis in the Rottweiler

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Start Date: January 1, 2010

Duration of project: 12 months

Progress Report: Final

Objective of the Study: To perform an association analysis using the canine 120K Illumina SNP array and previously collected DNA samples from Rottweilers with and without familial subvalvular aortic stenosis.

Percentage to completion of objective: 100%

Results of tests or experiments
After quality control screening the *Illumina HD SNP Array* yielded 112,782 single nucleotide polymorphism results for each of the 48 Rottweiler DNA samples.

Analysis of samples, tests or experimental results

Genome wide association analysis was performed between affected and normal Rottweilers and significance cut-off was set at $p=5\times10^{-5}$. Affected Rottweiler data implicates the most significant region of genetic variation on chromosome 21 at location 27895300 ($p=8.98\times10^{-6}$; odds ratio 23.39) with 3 other significant surrounding SNPs (25948544−28898527).

Interpretation of analyzed results
Multiple single nucleotide polymorphisms cluster tightly on chromosome 21 with moderate to excellent significance levels. Based upon this analysis we believe a causative mutation for SAS in Rottweilers may exist in this chromosomal region. Further fine mapping and sequencing of genes within and surrounding this region on Chromosome 21 is warranted.

An independently funded study for golden retrievers with SAS revealed the most significant region of genomic variation also on chromosome 21 in a region that overlaps the most significant region in Rottweilers. This data implicates that Rottweilers and golden retrievers may share a causative mutation for this disease on chromosome 21 and further investigation is warranted.

Requests, if needed, to change methods or adjust scientific approaches/techniques for the remainder of the project/grant:
None

Requests, if needed, for a six month no cost extension
None

Requests for CHF to help you (e.g. put out call for samples, issue a press release, connect you with another researcher, etc.)
None at this time since we have completed the work. We may submit a proposal to request funding for the second stage of this study (finemapping and genetic analysis of genes within the region of interest).

Presentations:
Dr. Stern attended the American Rottweiler National Show in Colorado and presented an update on the project at that time.

Lay Summary:

Subvalvular Aortic Stenosis is a common canine heart defect characterized by a fibrous ridge located below the aortic valve. Affected dogs are at risk of developing heart valve infections, congestive heart failure or sudden death and severely affected dogs have an average lifespan of 19 months. We are trying to identify a genetic marker associated with this disease but it is very important that we have a small blood sample from affected and unaffected Rottweilers that have been evaluated by a cardiologist.

The national Rottweiler organization and many, many Rottweiler owners have provided us with a small blood sample from their dog to help us identify a genetic region that may be associated with the development of aortic stenosis.

DNA from 28 SAS affected Rottweilers and 20 normal Rottweilers was selected to perform a single nucleotide polymorphism array. This test provides the DNA sequence for over 170,000 points in the dog genome. Differences between the normal and affected Rottweilers are utilized (genome wide association analysis) to identify regions of the Rottweiler genome that may contain a causative genetic mutation for SAS. Through statistical analysis a region of chromosome 21 was indicated as the most likely to contain a causative mutation for SAS. Through an independently funded study these results were paralleled in golden retrievers with SAS. This implicates the possibility for a shared causative mutation between Rottweilers and golden retrievers with SAS. Evaluation of genes within this region on chromosome 21 is the next step toward discovery of the genetic mutation responsible for SAS in Rottweilers.