

## Identification of genetic markers for familial subvalvular aortic stenosis in Rottweilers <u>Amanda E. Crofton<sup>1</sup></u>, Eric S. Ontiveros<sup>1</sup>, Kathryn M. Meurs<sup>2</sup>,

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- Aortic balloon valvuloplasty does not significantly increase patient lifespan.<sup>3,4</sup>
- Treatment with beta-adrenergic blockers lowers the patient's heart rate and increases myocardial perfusion but does not alleviate the stenosis.<sup>2</sup>
- This study aims to identify a chromosomal region of interest with candidate genes containing SAS-associated variant(s) in Rottweilers.



**Figure 1.** A) An illustration of a healthy canine heart with the aortic valve and subvalvular region highlighted. B) A gross pathology image of a heart affected with SAS with the subvalvular ridge/ring highlighted. C) 2D, color (upper image) and spectral (lower image) Doppler echocardiogram images of a dog with severe SAS. Note the turbulent blood flow and high aortic flow velocity.

supports an autosomal recessive mode of inheritance.

**Figure 3.** A pedigree of an SAS-affected Rottweiler family.

- 119,526 markers were analyzed.
- The genomic inflation factor ( $\lambda$ ) after EMMAX is 1.02.
- The red line is the Bonferroni threshold for significance, located at 6.38.
- The black line is the suggestive association threshold, located at 4.30.
- The single nucleotide polymorphism (SNP) with the highest suggestive disease association is located on chromosome 31 (p = 7.83e-06).



## Hypothesis

Subvalvular aortic stenosis (SAS) is a heritable condition in Rottweilers with a single significant region of genome-wide association.

	CUI_31_1925/980	2.478-05	T
	Chr_31_20074767	3.06e-05	1
	Chr_31_19116278	5.81e-05	1
2 3 4 5 -log10(Expected P)	Chr_31_18264863	6.10e-05	1

**Figure 4.** A) A Manhattan plot depicting the relative association of each SNP with SAS after EMMAX reduction in population stratification. B) A Q-Q plot demonstrating findings after EMMAX. C) A list of the SNPs with the highest disease association.



## Discussion

- Chromosome 31 contains the SNPs with the highest suggestive association.
- Candidate genes in the suggestive region include ADAMTS1 and ADAMTS5.
- Both play a role in cardiac development.

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- ADAMTS5 is expressed in valvular endocardium and in the aortic wall of the left ventricular outflow tract.<sup>5,6</sup>
- ADAMTS1 and ADAMTS5 degrade versican, a proteoglycan, during heart valve formation.<sup>7</sup>
- This study is underpowered and requires additional samples to draw statistically significant conclusions.



Figure 5. An SAS-affected Rottweiler puppy.



Figure 2. A Rottweiler affected with severe SAS.



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