Genetic background of focal junctional tachycardia with isorhythmic atrioventricular dissociation in Labrador retrievers

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Focal junctional tachycardia with isorhythmic atrioventricular dissociation is a known arrhythmia in Labrador retrievers. Because of breed specificity of this type of arrhythmia, genetic background is also strongly suspected in the dog. Recently, we diagnosed the disease in several Labradors including a family with three consecutive generations.

The aim of our study was to describe the inheritance pattern and to identify potentially causative gene mutations in our population.

Study population consisted of 12 Labradors. Eight dog was diagnosed with different severity of the disease, one was a 13 years old healthy littermate in an affected family, three dogs (>10 years old) from different breed lines served as controls. Clinical diagnosis was made by electrocardiography and echocardiography. Inheritance pattern was studied by pedigree analysis. Genomic DNA was isolated from EDTA-anticoagulated blood samples using a commercial kit. Whole exome sequencing (WES) of healthy and diseased littermates was used to identify candidate mutations (Illumina HiSeq2500 next generation sequencing system, Agilent Sure Select Canine All Exon 54Mb library-kit, 50x-coverage, CanFam3.1 annotation). Selection of target mutations in genes related to calcium transport was based on clinical experience with calcium channel blocker diltiazem, that could effectively control the disease. Sanger-sequencing was used to validate WES results in the study population and in controls (ABI3500 capillary-sequencing system, BigDye3.1 chemistry).

The disease was present in all generations (affecting both genders) of the affected Labrador family, although the symptoms varied among the individuals. Sudden death at young age occurred in the offsprings of parents that were both clinically affected. Development of congestive heart failure between 5 and 8 years of age due to tachycardiomyopathy was another observed phenotype, while there were also some clinically asymptomatic dogs with or without the arrhythmia. Comparison of the WES data of the healthy and diseased littermates resulted in 1629 differences in coding regions. After filtering for calcium turnover related targets a homozygous single nucleotide variant (c.[3019C>A]; [Gln1007Lys]) in Ryanodine receptor-2 (RyR2) gene and a heterozygous insertion (c.246_247insCAG; p.Gln92_Ser93insGln) in the calcium activated potassium channel gene (KCNN2) were identified. Both were confirmed to be present in all of the clinically affected (related and unrelated) dogs and absent in healthy controls by Sanger-sequencing.

Pedigree analysis suggests an autosomal dominant inheritance pattern with strong but incomplete penetrance and variable expression in the affected Labrador family. The identified RyR2 and KCNN2 mutations may have a causative role in the disease development in Labrador retrievers.