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Hier der Abstract des Papers:

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Exclusion of RPGRIP1 ins44 from Primary Causal Association with Early-Onset Cone-Rod Dystrophy in Dogs.

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Abstract

Purpose. Canine cone-rod dystrophy 1 (cord1) has been previously mapped to CFA15, and a homozygous 44-bp insertion in exon 2 (Ins44) of canine RPGRIP1 (cRPGRIP1(Ins/Ins)) has been associated with the disease. However, from the recent identification of a significant discordance in genotype-phenotype association, we have reexamined the role of cRPGRIP1 in cord1. Methods. Retinal structure and function was assessed by clinical retinal examination, noninvasive imaging, electroretinography, and histopathology/immunohistochemistry. cRPGRIP1 splicing was analyzed by RT-PCR. Retinal gene expression was determined by quantitative RT-PCR (qRT-PCR). Five markers spanning the entire cRPGRIP1 were identified and used for haplotyping. Results. Electroretinography demonstrated that cone responses were absent or present in cRPGRIP1(Ins/Ins) individuals. Moreover, performance in vision testing and optical coherence tomography (OCT) were comparable in cRPGRIP1(Ins/Ins) dogs, regardless of the cone ERG status. While histologic changes in retinal structure were minimal, immunohistochemistry demonstrated a lack of cone opsin labeling in cRPGRIP1(Ins/Ins) dogs. cDNA analysis revealed that Ins44 disrupts a putative exonic splicing enhancer that allows for skipping of exon 2, while retaining the functional RPGR-interacting domain (RID) of the protein. New cRPGRIP1 sequence changes were identified, including a 3-bp deletion affecting the 3' acceptor splice site of alternative exon 19c. The extended haplotype spanning cRPGRIP1 was identical in cRPGRIP1(Ins/Ins) dogs with and without retinal degeneration. Gene expression analysis showed that expression levels were not associated with Ins44 genotype. Conclusions. The results indicated that cRPGRIP1 Ins44 is an unlikely primary cause of cord1, and that the causal gene and mutation are likely located elsewhere in the critical disease interval.