

Juvenile Hypoadrenocorticism in the Nova Scotia Duck Tolling Retriever: A recessive monogenic autoimmune disease

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While hypoadrenocorticism, or Addison's disease, can occur in a dog of any breed at any age, certain breeds, including Nova Scotia Duck Tolling Retrievers (NSDTRs), have an increased incidence of the disease. Specifically in the NSDTR, there appears to be at least two forms of Addison's disease in the breed: a juvenile onset form (JADD) occurring in dogs under 1 year of age, and an adult onset form occurring in dogs at 4.5 years of age on average. JADD differs from adult onset Addison's disease, as it can be a multisystemic illness and appears to involve an autoimmune component. This is supported by the identification of a CD3+ T cell infiltrate in histologic sections of a JADD affected adrenal gland sample and that many cases are often affected with other autoimmune diseases, including immune-mediated hemolytic anemia and thrombocytopenia, immune-mediated polyarthritis, and hypothyroidism. To identify a genetic basis of JADD, a genome-wide association study was performed using the Illumina Canine HD 173,000 SNP array with 14 NSDTRs diagnosed with Addison's disease less than 1 year of age and 33 healthy control NSDTRs over 6 years of age. All cases were definitively diagnosed through an adrenocorticotrophic hormone stimulation test. Genome-wide association analysis identified a 1.7Mb associated haplotype on chromosome 27. Whole genome sequencing was performed on 2 NSDTRs with the associated haplotype, as well as 6 unaffected NSDTRs and 11 other dogs from 5 different breeds. Analysis of variants yielded 5 segregating SNPs in the associated region: 1 intergenic, 2 intronic, 1 coding, and 1 in the 3' untranslated region of a gene. The only coding variant, a missense mutation causing an amino acid change from a proline to a leucine, occurs in a currently uncharacterized gene, but is predicted to be damaging and deleterious based on sequence conservation. In summary, genome-wide association and whole genome sequencing analysis has identified a novel gene and mutation implicated in multi-organ autoimmunity and juvenile onset Addison's disease in the NSDTR.