Genome-wide Association Study of Protein-losing Nephropathy in Soft-coated Wheaten Terriers

Claire A. Wiley, Meryl P. Littman, Michael G. Raducha, Paula S. Henthorn
University of Pennsylvania School of Veterinary Medicine
clwiley@vet.upenn.edu, merylitt@vet.upenn.edu, henthorn@vet.upenn.edu

Protein-losing nephropathy (PLN) affects 5-15% of Soft-coated Wheaten Terriers (SCWT). The SCWT Open Registry, which lists hundreds of SCWT with PLN diagnosed since 1997, shows no limitation for age of onset nor evidence of predictive biologic markers. The mode of inheritance appears complex.

Samples from the PennVet SCWT DNA Bank were used in a genome-wide association study (GWAS) using 177,000 single nucleotide polymorphisms (SNPs), of which 81,097 SNPs were informative. Disease status was defined by blood, urine, and histopathologic criteria. Because the average age of onset for PLN is 7.1 years, control dogs were unaffected SCWT aged 14-18 years. The GWAS showed strongest support for association of PLN to a locus on chromosome 1 that contains two significant candidate genes encoding the podocyte slit diaphragm proteins nephrin and Neph3 (filtrin). DNA sequencing of the genes encoding these proteins identified a novel canine SNP in the nephrin gene (NPHS1) changing a glycine to arginine in the nephrin protein that is associated with PLN-affected SCWT. The gene encoding canine Neph3 (KIRREL2) contains a novel SNP responsible for a proline to arginine substitution in the Neph3 protein, also associated with PLN.

DNA samples of 753 dogs representing 114 other breeds were assayed for the NPHS1 SNP using an MspA1I restriction enzyme digest. The KIRREL2 SNP in 190 dogs of other breeds was analyzed through sequencing. One bloodhound was heterozygous at only the KIRREL2 SNP. Only 1 dog, an Airedale Terrier, was heterozygous for both polymorphisms. The only dog homozygous at both SNPs was also an Airedale and had been diagnosed with PLN. Eight additional PLN-affected dogs of other breeds lacked the novel alleles.

Both nephrin and Neph3 are found in the podocyte slit diaphragm, a fundamental component of the glomerular filtration barrier in the kidney. Mutations in nephrin have been associated with PLN in humans. While no mutations in Neph3 have been identified, decreased glomerular expression of Neph3 has been observed in humans with PLN. The amino acid changes caused by these SNPs may have pathologic effects on the glomerular filtration barrier and warrant further investigation. In addition, these studies indicate that the availability of DNA-based tests for these SNPs could lead to a decrease in the incidence of PLN in the SCWT breed through selective breeding.