Update for breeders: Intrahepatic portosystemic shunts in the Nova Scotia Duck Tolling Retriever

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Congenital portosystemic shunts (CPSS) are inappropriate hepatic vascular connections between the portal and systemic circulation [1]. Normally, venous blood is delivered to the liver by the portal vein and its tributaries where it disperses into the hepatic sinusoids before draining back into the systemic circulation via the hepatic veins. In dogs with CPSS, however, the main portal vein (or branch of portal vein) connects directly to the systemic circulation, bypassing the liver sinusoids; thus depriving the liver of oxygen and nutrients and allowing toxins and bacteria to accumulate in the systemic circulation. CPSS can be subcategorized as intrahepatic portosystemic shunts (IHPSS) or extrahepatic portosystemic shunts (EHPSS). IHPSS result when the portal vein connects directly to systemic vasculature within the liver, whereas EHPSS result when the abnormal connection occurs outside the liver parenchyma. A number of dog breeds are predisposed to CPSS [2]. Specifically in Irish Wolfhounds and Cairn Terriers, test matings have been used to show a genetic basis of CPSS in those breeds [3, 4]. Subsequent to the development of IHPSS in a number of NSDTRs and the likelihood of heritability demonstrated in other dog breeds affected with CPSS, we aimed to investigate a genetic cause of IHPSS in a large group of NSDTRs with extensive family and pedigree data available.

Whole blood and saliva samples were obtained from NSDTRs and submitted to the Bannasch lab at the UC Davis School of Veterinary Medicine to be used for genome-wide single nucleotide polymorphism (SNP) genotyping on the Illumina Canine HD 174,000 SNP array (Illumina, San Diego, CA). In total, samples were collected from 12 NSDTRs with IHPSS and 47 unaffected relatives (sire, dam, siblings). Genome-wide association analysis was performed using this cohort of affected dogs and 53 unaffected NSDTRs (includes related and previously collected unrelated samples). Potential regions of association with IHPSS in the genome were determined by a chi square statistic, with a threshold of $p<0.05$ indicating genome-wide significance. Despite ample statistical power and a minimally stratified sample population, there were no genome-wide significant associations for IHPSS ($p_{Bonferroni}>0.05$) in the NSDTR (Figures 1 and 2). These results suggest that if inherited, IHPSS is potentially a complex trait with a non-simple inheritance pattern, making eventual development of a useful genetic test problematic. Sample collection is on-going. It is possible that with additional samples, the complex pattern of inheritance of IHPSS may be elucidated. Please contact Emily Brown at eabrown@ucdavis.edu if you are interested in submitting a sample from an IHPSS affected NSDTR.

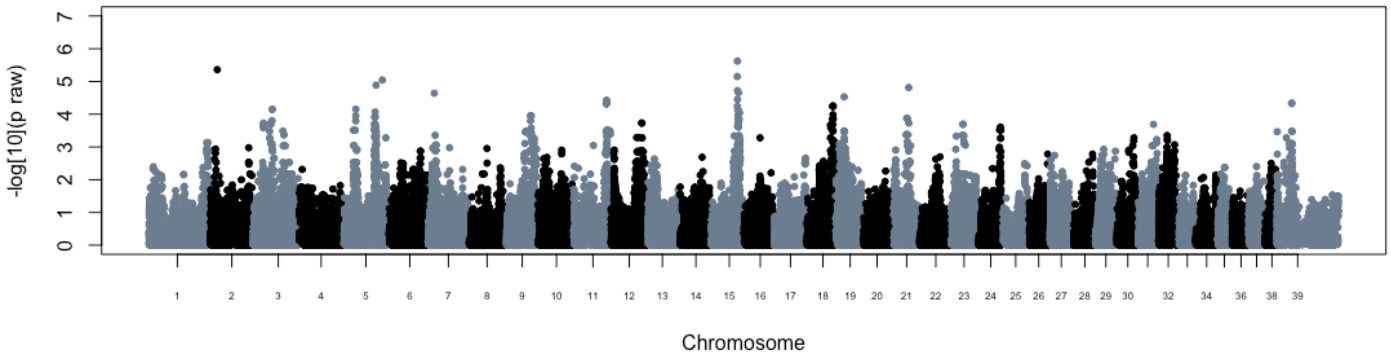

Figure 1. Manhattan plot of -$\log_{10}$ of the raw p-values (y-axis) for each of the genotyped single nucleotide polymorphisms by chromosome (x-axis).

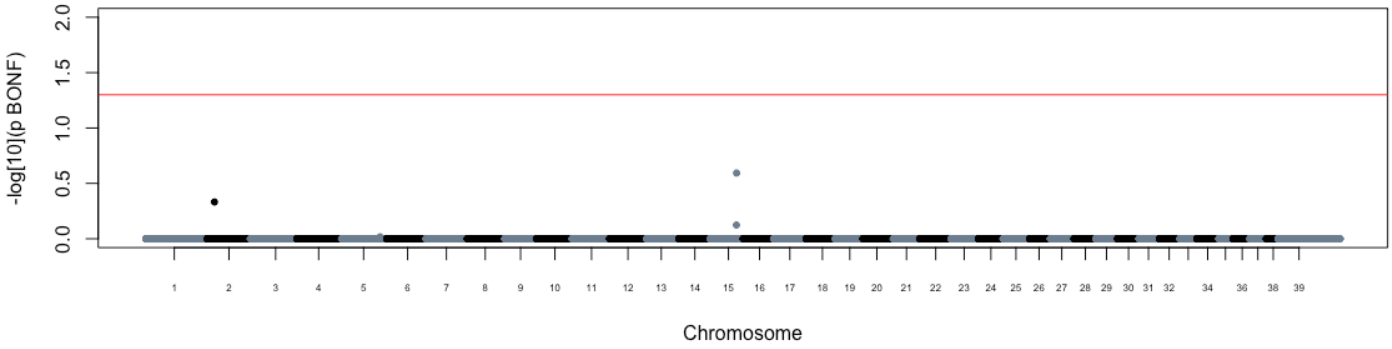

Figure 2. Manhattan plot of -$\log_{10}$ of the Bonferroni-corrected p-values (y-axis) for each of the genotyped single nucleotide polymorphisms by chromosome (x-axis). The red line indicates significance at the threshold of p=0.05. There are no genome-wide significant SNPs.

References:

1. Nelson, R.W. and C.G. Couto, *Small animal internal medicine*. 2014: Elsevier Health Sciences.
2. Hunt, G.B., *Effect of breed on anatomy of portosystemic shunts resulting from congenital diseases in dogs and cats: a review of 242 cases.* Australian veterinary journal, 2004. **82**(12): p. 746-749.
3. Van Steenbeek, F., et al., *Evidence of inheritance of intrahepatic portosystemic shunts in Irish Wolfhounds.* Journal of veterinary internal medicine, 2009. **23**(4): p. 950-952.
4. Straten, G.v., et al., *Inherited congenital extrahepatic portosystemic shunts in Cairn terriers.* Journal of veterinary internal medicine, 2005. **19**(3): p. 321-324.