

American Kennel Club Canine Health Foundation 2017 Clinician-Scientist Fellowship Report

Fellow: Jennifer M. Reinhart, DVM, PhD, DACVIM

Mentor: Lauren A. Trepanier, DVM, PhD, DACVIM, DACVCP

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I am very thankful to the AKC-CHF for awarding me the 2017 Clinician-Scientist Fellowship. I have used these funds to further my research and to share our findings with the veterinary community. The fellowship funds were the primary financial support for our study entitled “A single nucleotide polymorphism in the canine cytochrome *b₅* reductase (*CYB5R3*) gene is associated with sulfonamide hypersensitivity and is overrepresented in Doberman Pinschers,” which has been accepted for publication in the Journal of Veterinary Pharmacology and Therapeutics.

This study investigated a variant in the gene encoding cytochrome *b₅* reductase (*CYB5R3*), an enzyme that detoxifies sulfonamide drug metabolites. This variant has previously associated with hypersensitivity to sulfonamide antibiotics (“sulfa allergy”) in dogs. We found that this variant is also overrepresented in Doberman Pinschers, a breed that is predisposed to this adverse drug reaction. Thus, it is possible that the variant contributes to a genetic predisposition to sulfonamide hypersensitivity in Dobermans. We also investigated whether the genetic variant reduces enzyme production or function, which would provide a causal link between the variant and sulfonamide hypersensitivity. These experiments were performed in both canine liver samples (banked from a previous, unrelated study) and in an *in vitro* cell transfection system. No differences in mRNA transcription, protein translation, or enzyme function were seen in samples containing the wildtype vs. the variant. Given these findings, it was concluded that the *CYB5R3* is not causative for sulfonamide hypersensitivity in dogs, but may be in linkage disequilibrium (coinheritance) with another variant that does affect drug phenotype. Therefore, this study paves the way for future investigations for other genetic causes of sulfonamide hypersensitivity in dogs.

The Clinician-Scientist fellowship was the major funding source for this study. Specifically, funds were used to collect, ship, and genotype DNA samples (buccal swabs) from Doberman Pinschers in collaboration with Doberman Pinscher owners, breeders, and interest groups. The fellowship also funded mechanistic investigations of the variant: examining differences in *CYB5R3* mRNA transcription (RT-qPCR), protein translation (immunoblotting), and enzyme function (SMX generation detected by HPLC) between samples with and without the variant. The travel funds were used, in part, for my attendance of the American Academy of Veterinary Pharmacology and Therapeutics (AAVPT) Biennial Symposium (May 2017), where abstract presentation of this work was awarded the AAVPT Resident/Graduate Student Award. Funds were also used for travel to the American College of Veterinary Internal Medicine Forum (June 2017), where this work was presented in the poster session and as a part of a podium session entitled “Pharmacogenetics of Idiosyncratic Drug Reactions: Sulfonamide Hypersensitivity and Beyond.” Finally, this work was presented in poster form at the University of Wisconsin Phi Zeta Day (April 2017) and the International Conference on Canine and Feline Genetics and Genomics (May 2017, unfunded travel).

Abstracts, Presentations, and Manuscripts Featuring this Work:

1. Reinhart JM, Ekena J, Cioffi AC, Trepanier LA. A single nucleotide polymorphism in the canine cytochrome *b₅* reductase (*CYB5R3*) gene is associated with sulfonamide hypersensitivity and is overrepresented in Doberman Pinschers. *J Vet Pharmacol Ther*. Forthcoming 2018.
2. Pharmacogenetics of Idiosyncratic Drug Reactions: Sulfonamide Hypersensitivity and Beyond. ACVIM Forum Invited Speaker, Washington, DC, Jun 2017.
3. Reinhart JM, Cioffi AC, Trepanier LA. A Polymorphism in the Cytochrome *b₅* Reductase Gene is associated with Sulfonamide Hypersensitivity and is Over-Represented in Doberman Pinschers. University of Wisconsin Phi Zeta Research Day, Madison, WI, Apr 2017. AAVPT Biennial Symposium, Potomac, MD, May 2017. International Conference on Canine and Feline Genetics and Genomics, Minneapolis, MN, May 2017.
4. Reinhart JM, Ekena J, Trepanier LA. Functional evaluation of the canine *CYB5R3* A729G single nucleotide polymorphism associated with sulfonamide hypersensitivity. ACVIM Forum, Washington, DC, Jun 2017.