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Genome-wide study in Labradors reveals a modifier gene for copper toxicosis

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Wilson disease is a genetic disorder in which copper accumulates to toxic levels in tissues, leading to neurological symptoms and liver disease. Diagnosis of the disease is challenging because symptoms can vary widely across patients. The mechanisms underlying this clinical heterogeneity are unclear. Using a genome-wide approach in a new dog model for copper toxicosis, a team of researchers led by Hille Fieten have now revealed that mutations in a copper transporter gene, ATP7A, can ameliorate symptoms of the disease. This work, which is published in *Disease Models and Mechanisms*, could pave the way for early detection and treatment of hereditary copper metabolism disorders.

Copper is an essential metal in many cellular processes but its levels have to be carefully regulated to avoid deficiency or toxic overload. In Wilson disease, mutations in the copper transporter ATP7B result in the build-up of copper in the brain and liver, leading to irreversible damage to these tissues. Affected individuals demonstrate neuropsychiatric symptoms and fatal liver failure if left untreated. Despite the fact that a single gene (ATP7B) causes the disease, the age of onset and severity of symptoms are believed to be influenced by modifier genes, which confound diagnosis. The identification of these modifier genes has proven to be challenging in humans, largely because the disease is very rare.

Genetic studies in purebred dogs are an important tool in disease research because dogs often display the same clinical symptoms as humans and disease-associated genes can be mapped relatively easily. Dr

Fieten and colleagues recently discovered that, like humans, Labrador retrievers can be affected by hereditary copper toxicosis. Affected dogs display liver abnormalities that mimic those seen in Wilson disease patients, making them good models in which to explore the complex biology of the human condition. In their new study, the team performed a genome-wide association study (GWAS) on a cohort of 235 Labrador retrievers, together with an independent replication cohort. By mapping candidate single nucleotide polymorphisms (SNPs) and performing detailed functional analyses, they show that mutations in the Wilson disease gene ATP7B are associated with copper accumulation in the liver, validating the use of these dogs as a model for the human disease. Intriguingly, Dr Fieten and colleagues also found that mutation of a second copper transporter gene, ATP7A, protected dogs against hepatic copper accumulation. This suggests that ATP7B and ATP7A play antagonistic roles in copper homeostasis, and that attenuation of copper accumulation by mutation of ATP7A could ameliorate symptoms of Wilson disease in humans.

This work illustrates how the study of inbred canine populations can provide new insights into the genetic underpinnings of complex disease, bridging the gap between small rodent models and humans. "The dog is an invaluable model for exploring hereditary copper-storage diseases, and observations made in this study will benefit both canine and human patient populations." said Dr Fieten, explaining the implications of their findings.

More information: H. Fieten et al. The Menkes and Wilson disease genes counteract in copper toxicosis in Labrador retrievers: a new canine model for copper-metabolism disorders, *Disease Models & Mechanisms* (2016). DOI: 10.1242/dmm.020263