

International Windsprite Club Board Statement

The frequency of the ATP7B (ATP7B:c.4358G>A) risk variant, impacts on breeding choices, and Copper Associated Hepatopathy in the Breed

As of Dec 10, 2024, Atp7B and/or Atp7A genotype data has been submitted for 113 IWC registered Windsprites. For Atp7B the genotype frequencies reported to-date are 19% NN, 58% NM, and 23% MM. The variant risk allele frequency is 52% meaning that 52% of the alleles in this tested population are the risk allele. Atp7B data from 115 European Windsprites tested through Feragen are not drastically different (the variant risk allele frequency in that population is 54%). For Atp7A (the gene that has the ‘attenuating variant’) the genotype frequencies reported to-date are (for females), 23% NN, 68% NM, and 9% MM and for the males who have only one copy of this X-linked gene, 67% N and 33% M.

Atp7B Variant Allele and the Risk of Copper-Associated Hepatopathy.

As IWC board members, we are concerned about the high frequency of this Atp7B risk variant in the breed. The allele frequency of Atp7B has very likely been high in Windsprites since the early days of Windsprites. Although ~23% of Windsprites have two copies of the risk variant and 58% have one copy, there are no indications that copper-associated hepatopathy (CAH, pathologic copper accumulation in the liver over time) is prevalent in the breed. A definitive diagnosis is not trivial and requires an invasive and costly liver biopsy. Two Windsprites to-date have been diagnosed formally with CAH by a liver biopsy after notice of abnormal high liver enzyme values with routine bloodwork. Late stage/untreated CAH results in liver dysfunction with symptoms that can include (for example) jaundice, weight loss, lethargy, excessive thirst, fluid accumulation in the abdomen, neurological problems, and diagnostic abnormal blood test results. It is not at all apparent that Windsprites are experiencing liver dysfunction in significant numbers despite the high numbers of Atp7B MM individuals. However, the board will task the newly formed IWC Health Committee with inclusion of information on general liver health when regularly collecting data on the overall health of the breed.

With regards to the role of the Atp7B risk allele in CAH, several points should be noted. In Labrador retrievers, the presence of the Atp7B risk allele was associated with increased liver copper levels while the variant in Atp7A was associated with lower liver copper levels (Fieten *et al.* 2016). Fieten *et al.* 2016 found that these two variants together only explained 12.5% of the genetic variation in liver copper levels hence the designation of Atp7B as a “risk” allele and not a “causative” allele such as the mutant allele that causes MDR1. There are other factors (including diet, see below) involved in determining whether a dog will in fact develop CAH. A recent study at Michigan State (Langlois *et al.* 2022) that studied 90 Labrador retrievers did also conclude that the Atp7B variant contributed to CAH. However, 47% of the CAH dogs in the study did not have an Atp7B risk allele, and 25% of the dogs without CAH did have the variant risk allele. In summary, there are risk variants in other (unknown) genes that contribute to this disease, at least in Labs, and the environment also likely plays a significant role.

Diet and Copper-Associated Hepatopathy.

In addition to the contribution of genetics to CAH, much research has focused on the role of diet in the accumulation of excess copper in dog livers. In a 2018 study of 546 dogs of various breeds, a significant increase in liver copper levels was noted in samples collected between 1982

and 2015 (Strickland et al. 2018) and coincides with changes made to the type and amount of copper added to commercial dog foods. These changes are speculated to be one of the main drivers of the increased CAH/CT cases seen today across breeds (Center et al. 2021). In “[Copper hepatopathy and dietary management](#)” published online by the Riney Canine Health Center at the Cornell University of Veterinary Medicine, ~1.8 mg/1000 kcal of copper is recommended for adult dogs and ~3.1 mg/1000 kcal for growing puppies.

Board Recommendations.

The Atp7B risk allele has been found in significant numbers across many breeds (Haywood et al. 2023). Given the high frequency of the Atp7B variant in Windsprites along with the absence of data to-date demonstrating that it is contributing significantly towards CAH in the breed, the board at this point in time is recommending that (in general) breeders not prioritize Atp7B genotype information when making breeding decisions. The board recommends that breeders take care to not breed Atp7B MM x Atp7B MM dogs. Removal of all MM dogs from the breeding pool would constrict the genetic diversity of the breed and could easily backfire and inadvertently cause another untested, and more serious ‘disease’ allele to become more abundant.

If you have not yet gotten your Windsprite tested for Atp7A and Atp7B we urge you to consider doing so. Knowledge regarding the Atp7B genotype of intact males will be useful for those with MM females in their breeding programs. And conversely knowledge regarding the Atp7B genotype of your breeding female should affect your choice of a sire if she is MM. Importantly, knowing whether your Windsprite has this risk variant will help guide you and your veterinarian with regards to the scheduling of regular bloodwork to monitor basic liver function.

References

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