OPEN LETTER TO THE MINIATURE SCHNAUZER FANCY

In two recent papers published by the Aguirre[1] and Lohi[2] research groups, the clinical and genetic aspects of progressive retinal atrophy (PRA) in Miniature Schnauzers were studied. The two papers described partly conflicting results concerning the causality of the disease and testing implementation. To this end, we have continued to compare our datasets and together found new important aspects on the subject, which we briefly discuss below and in the accompanying published Joint Formal Comment to the original journals ("Joint Formal Comment for PLGE and Commentary for G3").

Background

Progressive retinal atrophies (PRA) are a group of inherited, blinding eye diseases that affect many dog breeds, including the Miniature Schnauzers (MS). Many genes and variants have been implicated, and some breeds, such as the MS, are even affected by multiple genetic forms of PRA.

There are several subtypes of PRA. In the MS, photoreceptor dysplasia (PD[3]) was initially reported as an early-onset autosomal recessive disease and was considered a specific entity within the PRA group of diseases. Several attempts were made to identify its genetic cause[3,4,5]; among these include identification of a phosducin gene variant that later was been found **not** to be disease-associated, although some commercial DNA testing companies still carry out the test (Aguirre, unpublished information).

Additionally, a study by the Aguirre group including mixed breed dogs of MS origin reported a form of chromosome X-linked PRA (XLPRA2) to be caused by mutations in the RPGR gene[6]. XLPRA2 carrier females were also mildly affected, indicating X-linked dominant inheritance. A gene test named "Type A PRA" was commercialized by OptiGen, LLC. However, the Type A PRA seems extremely rare: during the 17 years that the test has been available, not a single positive case in MS has been identified. A reanalysis of the data published in the PD and XLPRA2 studies by the Aguirre group[1,3], and of archival DNA samples, indicated that PD **is** XLPRA2, and the disease should not be considered a separate entity. This has led to a search for additional genetic causes of PRA in the breed.

Present

The 2019 article by the Aguirre research group reported a complex structural variant in the PPT1 gene located in chromosome 15 to be associated with PRA in MS[1]. Based on the results, a gene test named "Type B PRA" was commercialized by OptiGen, LLC. Recently, a separate report by the Lohi research group was published, mapping the disease to the same chromosomal region, but proposing a putative regulatory variant in the HIVEP3 gene as causative for the disease they named "type 1 PRA"[2].

The different conclusions have facilitated discussions and comparisons of the datasets between the groups, and some re-analyses have been conducted. These have revealed the difficulty of genotyping the PPT1 variant reliably on large-scale, thus preventing us from drawing final conclusions on the causal disease association of this variant. To our current understanding, only whole-genome sequencing can be utilized to reliably genotype PPT1 and determine disease status; however this is too costly for large scale population screening. Although functional considerations would favor the disease causality of the coding PPT1 variant over the regulatory HIVEP3 variant, an efficient and inexpensive means of genotyping the PPT1 variant has to be developed to establish the identity of the true causal gene. In the meantime, we prefer to refer to

the disease as **HIVEP3/PPT1-PRA**, and discourage the use of either Type B PRA or type 1 PRA to refer to this form of PRA in MS.

Testing recommendations

Until final conclusions on the genetic cause of PRA in MS are made, the HIVEP3 variant should be used in a genetic testing environment. The markers initially proposed to associate with the PPT1 variants[1] are not reliable to determine conclusively PPT1-genotype on a population wide basis, and should not be used in genetic testing. Importantly, when testing the HIVEP3 variant one should bear in mind that if HIVEP3 is not the causal gene, recombination between HIVEP3 and the causal variant would produce incorrect test results.

Lastly, we kindly ask any questions or comments to be addressed to all the undersigned authors for a joint response.

Sincerely yours,

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