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Joint Formal Comment for PLGE and Commentary for G3

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Two recent papers by Gustavo Aguirre's and Hannes Lohi's groups have been published describing the genetics of Progressive Retinal Atrophy (PRA) in Miniature Schnauzers. This recessively inherited condition is a serious problem in companion animals, and also is a model for human retinitis pigmentosa. The first paper by Murgiano *et al.* 2019 (G3) proposed a complex structural variant affecting the coding region of the *PPT1* gene as causal, but some dogs were apparently homozygous for the variant and did not exhibit disease, suggesting incomplete penetrance. A more recent study by Kaukonen *et al.* (PLoS Genet 2020) identified the same locus, but identified a different candidate causal variant—a SNV in an intron of the *HIVEP3* gene, which lies ~1.5 Mbp away from *PPT1*. In the Kaukonen *et al.* study, the candidate causal variant appeared completely penetrant, although the Murgiano *et al.* study reported 5 cases that were not homozygous for the *HIVEP3* variant, but were homozygous for the *PPT1* risk haplotype.

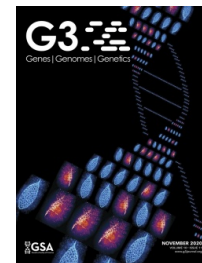
The different conclusions drawn in the two published papers have facilitated discussions and comparisons of the datasets between the groups, and some re-analyses have been conducted to test the presented alternate hypotheses of the causal candidate genes and variants. Importantly, these re-analyses reveal new insights which affect the interpretation of the data and related conclusions. We take this opportunity to summarize our analyses in a joint statement.

Key observations affecting the interpretations and conclusions in both studies relate to: (1) discovery of the non-mutated risk haplotype as described by Kaukonen *et al.*; and (2) the realization that is challenging to determine the zygosity of the complex *PPT1* structural variant without high quality WGS data.

In the work from Kaukonen *et al.*, a heterozygous obligate carrier dog was found to be homozygous for SNV markers previously described by Murgiano *et al.* as associated with the condition, revealing that the PRA mutation is recent, with both mutant and non-mutant chromosomes with the same haplotype segregating in Miniature Schnauzers.

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This same obligate carrier was originally inferred to be homozygous for the *PPT1* structural variant based on SNV genotyping; however, a new coverage-based analysis of WGS data revealed that the dog is actually heterozygous for the *PPT1* structural variant (and is also heterozygous for the *HIVEP3* variant).

Thus, the *genetic* evidence is unable to distinguish between the *HIVEP3* and *PPT1* variants as potential causes of PRA. Furthermore, the SNV markers initially proposed in Murgiano *et al.* are not reliable to determine the zygosity of the complex *PPT1* structural variant, or to reach conclusions regarding its potential penetrance. Although functional considerations favor causality of the coding *PPT1* structural variant over the intronic *HIVEP3* SNV, an efficient and inexpensive means of genotyping the *PPT1* structural variant has not been developed, limiting our ability to reach final conclusions about the true causal gene. It is also possible but unlikely that PRA is caused by a different variant in the mapped interval that could not be identified by whole genome sequencing.

For the purposes of diagnosis by breeders and veterinarians, the *HIVEP3* variant may be used in a genetic testing environment until final conclusions of the causal variant are made and a robust method to genotype the *PPT1* structural variant becomes available. 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.

Sincerely yours,

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