American Cocker Spaniel Cataract Genetic Study

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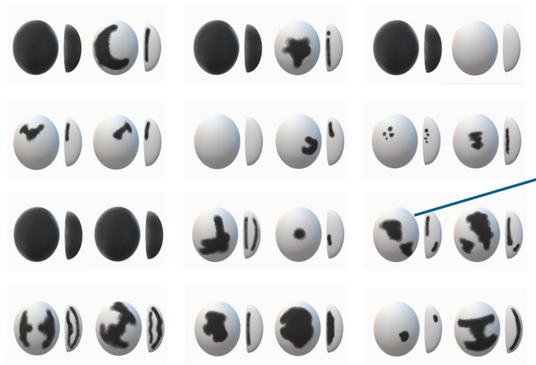
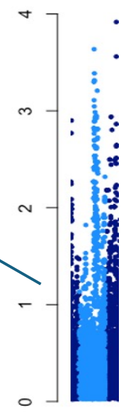
Our group aims to identify the genetic causes of inherited cataract in American Cocker Spaniel.
We encountered issues related to the complex inheritance of the disease, the SNP platform used, and the overall variability of the phenotype.
In addition of manifesting in different ways, we soon discovered that the **age of onset** of cataract in American Cocker can occur early in the dog's life (2-5 years) or later (5-8).



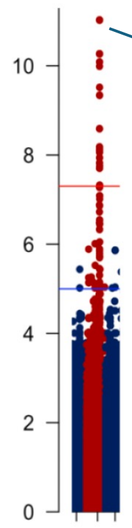
Each case can look very different, with smaller or larger cataracts which can be full, anterior or posterior.
Some cocker develops a cataract in the second eye years after the first eye manifested one.

Old GWAS analysis. Low power.



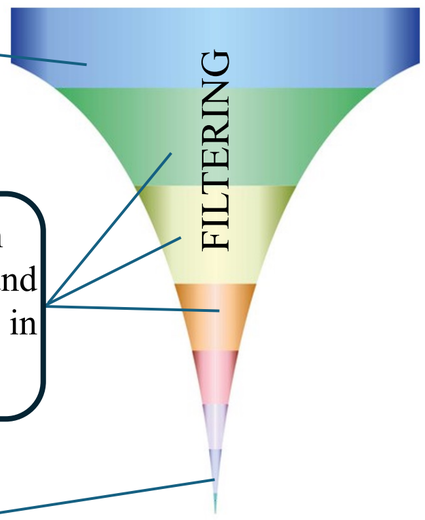
We used the novel low-pass whole genome sequencing, a technique carried out by the company Neogen, named "Skimseek".
The principle of this technique is to create a dataset comparable to a very "dense" marker chip, which is, therefore better than what we used for our analyses carried out in previous years.
The result was VERY IMPRESSIVE for our late-onset cataracts, pointing out clear associated regions.

On the right, a "major" peak discovered with this technique, pointing out at associated genes in the region.



Each dot is a marker.
The highest the dots have the strongest association with late-onset cataracts.
The markers within the "peak" are used as coordinates for the gene search.

All the markers



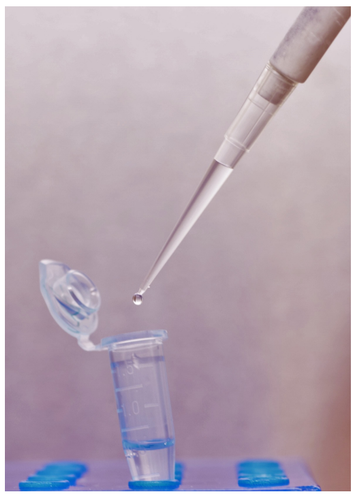
Progressive exclusion (marker that are found to frequently occur in healthy dogs)

Our candidates

As a next step, we decided to analyze the later-onset cataract-affected dogs we sequenced with the "complete" ("deep") whole genome sequencing. We searched in the region highlighted by the analysis above.
Focusing on such region, we found a small number of variants after all the proper analysis and filtering, reducing their number (<20), falling within within plausible candidate genes.

We therefore think that a potential putative marker for late-onset cataracts will be among these.

This approach (Skimseek + classic whole genome sequencing) was more effective than our previous attempts with early-onset cataract, which didn't lead to a definitive result so far.



Of these 20 variants, the five best were selected for a first round of genotyping in the larger available cocker population.
We used two primary criteria to rank and select these variants:
1) Their overall rarity of the variant, calculated using the available dataset
2) How much of a plausible candidate for cataract the gene affected is (from available literature)

We think that this reduced the number of candidate markers for later-onset cataracts to a handful of variants, and we are optimistically closer to selecting a test-suitable marker.

Skimseek analysis above detected additional peaks, for other chromosomes; while the association is less strong, we are now repeating this procedure in search of secondary markers, which could explain the disease complexity.

After this striking progress in the later-onset cataracts, we decided to carry out a similar analysis in the early-onset cataracts. While the same technique didn't yield the same result, suggesting that early-onset cataracts are more diverse.

We are currently building a better pipeline to explore these regions, using all the material gathered, and the data generated so far. We are currently waiting for a new Postdoc to replace of the current one leaving, which caused some delay in the genomic analysis.

Once again, we stress the critical importance of updates and new cases. We also ask any owner of non-affected, older dogs to send samples for the study.
We wish to thank all the breeders who contributed with samples and updates. The project couldn't have progressed without you! Contact: jniggel@vet.upenn.edu

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