Whole genome sequencing of an Old English Sheepdog with multiple-ocular defect identifies a candidate causal variant with a probable dominant mode of inheritance in a collagen-type gene

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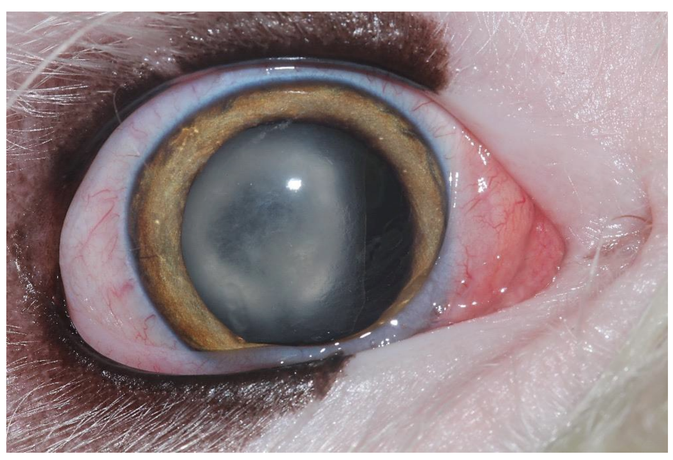
Background and Aims

Multiple-ocular defect (MOD) is an inherited ocular syndrome that has an increased prevalence in a number of breeds including the Old English Sheepdog (OES)[1-3]. Affected dogs typically present with multiple and various ocular abnormalities that can include: cataracts, microphakia, lens coloboma, macroglobus, vitreal degeneration and retinal detachment. The disease can lead to blindness and in severe cases requires enucleation.

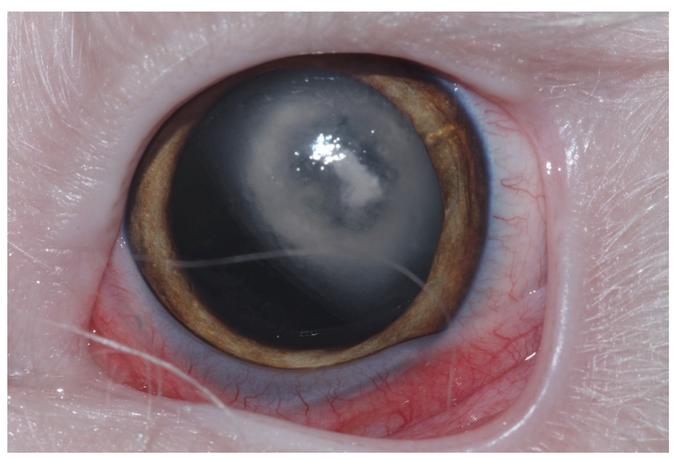
The objectives of this project were to describe the clinical presentation of MOD in the OES breed and to identify the causal variant using whole genome sequencing analysis.

Clinical Presentation of a male 2 yr 5mnth MOD Case

Right Eye



Left Eye



Ophthalmic investigation revealed:

- Bilateral macroglobus
- Bilateral microphakia
- Bilateral lens coloboma
- Bilateral cataracts
- Bilateral vitreal degeneration

Whole Genome Sequencing Analysis

A seven year old female OES exhibiting hereditary cataracts, bilateral vitreal degeneration, macroglobus, flattened lenses and reduced photoreceptor function was diagnosed with MOD by a board certified veterinary ophthalmologist. The dog was whole genome sequenced (WGS). The WGS was aligned to canine genome build Canfam3.1 and variants filtered based on predicted functional consequence and against 867 control genomes of varying breeds not previously reported to be affected with MOD.

- 17 variants private to the case and flagged as deleterious (Sift) were genotyped in a small cohort of six OES MOD cases and controls (dogs certified clear of inherited eye disease).
- Only one variant, located in the *COL11A1* gene, segregated correctly. Further validation of the variant was carried out by genotyping a further 74 OES and nine dogs of different breeds.

OES *COL11A1* Genotyping Results

Phenotype	+/+	+/-	-/-
MOD Cases		**7**	**12**
HC Unaffected (BVA certificate/Litter screen)	38	8*	
HC Affected (BVA certificate/Litter screen)	5	2*	4
Other Cataracts	1	3	
	44	**20**	**16**

* Ophthalmologist comments refer to additional abnormal phenotypes

HC (Hereditary Cataracts) is the only inherited eye disease for which OES are certified under the British Veterinary Association/Kennel Club/International Sheep Dog Society Eye Scheme (https://www.bva.co.uk/canine-health-schemes/eye-scheme/).

We have identified several HC-affected OES under the BVA/KC/ISDS Scheme, that are homozygous for the reference allele. We therefore postulate that HC in the OES is genetically distinct from MOD.

Collagen-Type XI Alpha 1 Chain

A single exonic nucleotide variant (T>C) causes a missense amino acid change in *COL11A1* predicted to be damaging (PolyPhen-2). *COL11A1* mutations have been reported to cause autosomal dominant forms of Stickler Syndrome and Marshall Syndrome in humans[4,5], both of which share clinical features with MOD in OES.

The mode of inheritance of the mutation is dominant as seven MOD cases carry one copy of the mutant allele as illustrated in the table opposite.

Acknowledgements

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