Whole-genome sequencing identifies a candidate pathogenic variant for osteogenesis imperfecta in a Miniature Schnauzer.

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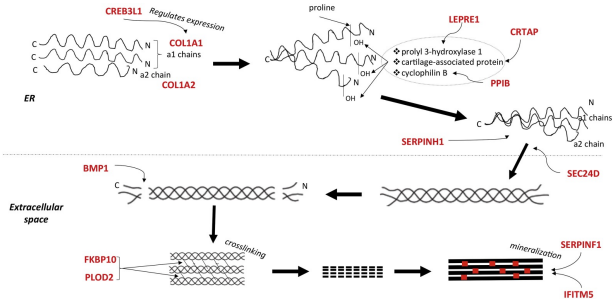
Osteogenesis Imperfecta

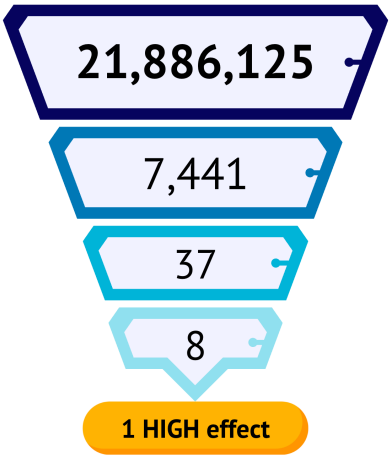
Osteogenesis imperfecta (OI), or brittle bone disease, in dogs is a genetic disorder characterised by fragile bones and loose joints due to poor collagen formation, leading to spontaneous fractures and other health issues. Breeds known to be affected by this disease include Beagles, Dachshunds, Poodles, Bedlington Terriers, Golden Retrievers and Norwegian Elkhounds.

Human versions of OI have shown to be genetic with causal mutations located, primarily, in genes involved in the collagen synthesis pathway. There are 19 recognised forms of OI in humans with varying patterns of inheritance – recessive, X-linked and dominant.

Symptoms of OI include spontaneous fracturing of the bones and teeth, loose joint, sclera of the eye maybe appear blue, stunted growth, loss of hearing and malformation of bones due to progressive healing of fractures.



Analysis Steps



- A single adult male miniature schnauzer (MS) presented with clinical signs of OI, including cryptorchidism and generalized osteopenia of the jaw.
- Potential known genetic causes were excluded so whole-genome sequencing (WGS) was undertaken by Wisdom.
- FASTQ files were shared with the Canine Genetics Centre for alignment and analysis.
- Data from the individual case were incorporated into a cross-breed joint-called dataset of 53 toy breeds, including an additional 15 MS (number of variants[n]=21,886,125).
- Variants were filtered by recessive segregation (n=7,441) followed by predicted HIGH or MODERATE impact (n=37).
- Remaining variants were further restricted by comparison to the Dog 10K dataset of ~1900 samples (n=8).
- The genes affected by the remaining variants were prioritised using VarElect[1] for phenotypes *"Ostegeneis Imperfecta"* OR *"Dentinogenesis Imperfecta"*

Secreted Protein Acidic And Cysteine Rich (SPARC)

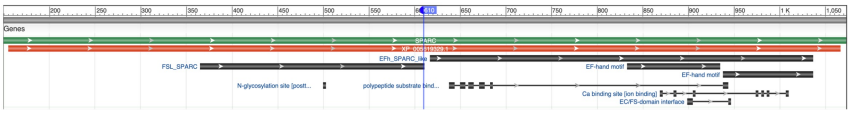
Our analysis yielded one directly related gene with a high disease-likelihood score – ***SPARC*** (Secreted Protein Acidic And Cysteine Rich).

SPARC has been associated with human recessive forms of OI[2,3,4], including a case where the proband was cryptorchid.

The HIGH impact variant is a 1bp insertion [T/TC] in exon 7 which results in a frame-shift and the inclusion of a premature termination codon within eight amino acids.

SPARC is not structural itself but is thought to act as a chaperone for collagen, to assist the correct assembly and cross-linking. The protein is required for the collagen in bone to become calcified *(refseq, June 2015)*.

Our variant truncates the final protein, removing the functional extracellular calcium (ES) and EF-hand binding domains.



Future Work

- Complete the follow-up on the other seven MODERATE variants.
- Genotype our primary variant of interest on a cohort of USA MS samples.
- Develop and launch a DNA test for breeders.

Acknowledgments

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References

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