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Background and Aims

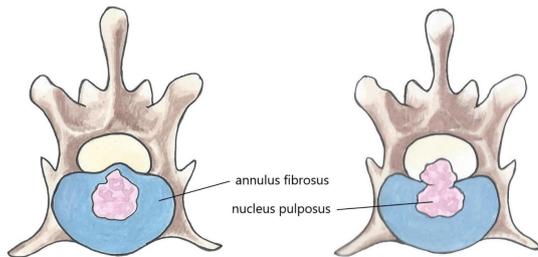
Intervertebral disc disease (IVDD) is a common cause of spinal injury in dogs. It is very painful for the affected dog and can cause irreversible paralysis. IVDD can occur in all breeds and tends to be an age-related, degenerative condition. However, chondrodystrophic ("short-legged") breeds are at a higher risk and may suffer at an earlier age.

An inserted FGF4 (fibroblast growth factor 4) retrogene on chromosome 12 (12-FGF4R) has been shown to contribute to both the short-legged morphology and an increased IVDD risk¹. However, despite this shared genetic risk factor, individual dogs and breeds vary significantly with respect to age and clinical presentation of IVDD, indicating additional genetic, environmental and conformational risk factors are involved.

We aim to identify these extra risk factors in three high-risk breeds, with the goal being to offer breed-specific breeding and lifestyle advice to reduce the incidence of this debilitating disease.



Intervertebral discs



Intervertebral discs are located between the vertebrae in the spine acting as shock absorbers for the body. They are made up of an outer fibrous layer (annulus fibrosus) and a jelly-like centre (nucleus pulposus). Over time the nucleus pulposus can become calcified, reducing their shock-absorbing capabilities. As the centre of the disc becomes harder there is increased strain on the disc and can lead to a tear in the annulus, through which the nucleus pulposus is squeezed out, termed a disc **herniation** or **extrusion**.

Study Proposal

We have recently submitted a grant application to the Pet Plan Charitable Trust (PPCT) to fund an 18-month project to identify additional risk factors for IVDD in three popular and high-risk breeds – Dachshunds, French Bulldogs and Cocker Spaniels.

Objectives

1. Obtain, and analyse, owner-reported responses to online surveys to determine environmental and lifestyle risks.
2. Generate whole genome sequence (WGS) data from 10 robust IVDD cases and 10 controls of all three breeds.
3. Interrogate the WGS data to identify IVDD candidate risk variants and use bioinformatic tools to prioritise those variants based on frequency, genomic context and their candidacy for disease involvement.
4. Genotype those prioritised candidate variants in 100 additional IVDD cases and 100 controls of each breed to identify validated IVDD risk variants.
5. Determine 12-FGF4R allele frequency in the UK populations of each breed to gauge the potential for selective breeding to reduce disease incidence.

We will undertake both within- and across-breed analysis of our WGS data, utilising our in-house, mixed-breed WGS dataset of over 100 other breeds, to identify both breed-specific and shared genetic risk factors.

Work to date

Dachshunds

- As part of the DachsLife 2015 survey², owner-reported data helped identify conformational and lifestyle risk factors.
- Known to be fixed for the 12-FGF4R mutation.
- DNA from 3 IVDD cases and a related control has been submitted for WGS, to enable preliminary investigations to proceed.

Cocker Spaniels

- We have undertaken a breed-wide survey, similar to DachsLife, for which we received in excess of 13,500 responses and analysis is currently underway
- We have identified 159 dogs affected with IVDD from which DNA can be obtained.

French Bulldogs

- A similar breed-wide survey will be sent to owners of all Kennel Club registered French Bulldogs at the beginning of April.

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References

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2. Packer, R.M., I.J. Seath, D.G. O'Neill, et al., DachsLife 2015: an investigation of lifestyle associations with the risk of intervertebral disc disease in Dachshunds. *Canine Genet Epidemiol*, 2016. 3: p. 8.