Paroxysmal Dyskinesia in the Norwich Terrier

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Paroxysmal Dyskinesia

- Paroxysmal dyskinesia (PxD), which in the past has been referred to as Canine Epileptoid Cramping Syndrome (CECS), is a neurological condition that manifests as periodic muscle cramps/contractions.
- A study carried out by Luisa De Risio (published 2016) characterised PxD in the Norwich Terrier.
- The survey included 198 Norwich terrier dogs, of which 26 (13%) were classified as affected.
- The onset of episodes is typically from three years of age.
- Episodes occur weekly or daily in the most severe cases, lasting from a few seconds to up to thirty minutes.
- Stress, anxiety, excitement, and variation in daily routine can be triggers for episodes in some cases.
- Dogs are neurologically normal between episodes.

Paroxysmal Dyskinesia

- The underlying cause of the disease is unknown.
- Pedigree analysis was suggestive of it being an inherited disease.
- No genetic variants associated with PxD have been identified in the Norwich Terrier to date.
- There is presently no known treatment or cure for the disorder.

Genetic Research In Other Breeds

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- Cavalier King Charles Spaniel – Episodic Falling (*BCAM*)
  - "paroxysmal exertion-induced dyskinesia" – autosomal recessive inheritance
  - GWAS with 31 cases, 38 controls. Used 91,427 markers across the genome.

- Soft Coated Wheaten Terriers – Paroxysmal Dyskinesia (*PIGN*)
  - Autosomal recessive inheritance
  - Whole genome sequences of 2 affected dogs compared to 100 controls

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Border Terrier Paroxysmal Dyskinesia

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- A previous genetic study was unable to find the underlying cause
  - A GWAS carried out using dogs from Finland, The Netherlands, and Germany (110 cases and 120 unaffected dogs) did not identify any regions of the genome associated with PxD.
  - Lack of positive results could have been caused by the broad case definition.
  - Suggests mode of inheritance could be complex
- AHT research in collaboration with Mark Lowrie
  - Paroxysmal Gluten Sensitive Dyskinesia
  - Very specific case definition – affected dogs tested for serum antibody levels
  - Based on previous findings
  - Sample recruitment currently underway with the aim to perform a GWAS including 96 affected dogs and between 96 and 192 unaffected controls

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Previous AHT Norwich Terrier Research

- GWAS: 38 cases 38 controls (some of which were from Finland)
- The study identified a number of suggestive associations, but these could not be replicated.
- Relaxed inclusion criteria for affected dogs
- Genotyped for a relatively low density of markers across the genome (~50,000)
- Analysis suggested that the set of unaffected dogs were not representative of the affected dogs ("population stratification")

Our Current Study So Far

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- A genome-wide association study (GWAS) using 24 well characterised cases and 24 unaffected dogs over six years of age (controls) has been carried out
- The paroxysmal dyskinesia cases were either diagnosed at the AHT, or their diagnosis was confirmed by Luisa De Risio through owner reported questionnaire
- The controls used were chosen using an extended pedigree – each case had a related control
- The cases and controls were genotyped using the new high density Axiom Canine HD array, which types over 710,000 markers across the genome

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GWAS Results

- After filtering for quality, there were 233,987 markers available for analysis.
- Unfortunately there were not any regions of the genome that were significantly associated with paroxysmal dyskinesia

GWAS Results

- Our findings support the hypothesis that paroxysmal dyskinesia has a complex mode of inheritance
- Interestingly we have not replicated any of the regions suggested to be associated with the disease in the previous research – confirms that they were most likely not real

Norwich Terrier Data from Collaborator

- We are collaborating with Jeff Schoenebeck at the University of Edinburgh, to make use of the dataset of 233 presumably PxD-unaffected Norwich Terriers previously used to investigate upper airway syndrome
- We will take the top tier of markers from our analysis and look at them in this large set of additional dogs

Next steps for the Norwich Terrier

- Imputation
  - The data from Jeff Schoenebeck is at a lower resolution than our GWAS
  - Imputation is a clever statistical approach that will allow us to fill in the gaps
- As mentioned previously, once we have filled in the gaps in the additional data, we will look at the most promising regions in these dogs
- We will then want to follow up any regions that are associated in additional affected and unaffected Norwich Terriers
- The work in this new study has been funded by a Dogs Trust pump priming grant
- We need additional funding for:
  - The collection of DNA from additional unaffected and affected dogs
  - Genotyping suggestive variants in these new sets

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