July 12, 2019
Subject: Norwich Terrier Upper Airway Syndrome

Dear NTCA Members,
A recently published paper *An ADAMTS3 missense variant is associated with Norwich Terrier upper airway syndrome*, by Marchant et al., has prompted some discussion amongst breeders of Norwich Terriers and confusion about what the results actually mean in terms of the cause of UAS in our dogs, with some suggesting that we push for a genetic test. Because the paper may be difficult to understand without a genetics background, I asked Bryden to provide us with a lay summary to distribute. The full paper is available here:
https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1008102

SUMMARY PROVIDED BY DR. BRYDEN STANLEY:

The study reported by Marchant et al. used a population of Norwich Terriers that had been scored on an upper airway examination as unaffected, borderline, mild, moderate or severe for upper airway disease using a series of 10 criteria. Using a subset of these phenotyped dogs they performed a genome wide association study and looked for association of any SNPs on the array with each of the 10 scoring criteria for upper airway disease. Four of these criteria (eversion of the laryngeal saccule, edema of the cricoid mucosa, edema of the oropharynx and cartilage position) had significantly associated SNPs mapping to the same chromosomal location. Further fine mapping combined with whole genome sequencing and long read sequencing (needed because of an assembly error in the canine genome) resulted in the identification of a missense mutation in the ADAMTS3 gene (p.R929H). This variant is predicted to be deleterious by prediction software. **Genotyping of all of the Norwich Terriers showed that the missense mutation did not show complete segregation with disease status.** However, dogs homozygous for the variant had a significantly higher upper airway disease score than dogs that were heterozygous for it or homozygous for the normal allele. Two dogs homozygous for the variant were considered to be normal.

So we think this variant appears to be a **"risk allele"** that is associated with more severe airway disease, rather than a causative gene mutation. The gene does not appear to be an obvious candidate for upper airway disease, as the NTs affected with severe upper airway issues do not have any other systemic lymphedema issues. The authors try to make their case as to why this variant could contribute to Norwich Terrier upper airway disease. In mice, knockout of the gene is embryonic lethal. In humans, mutations in ADAMTS3 are associated with Hennekam lymphangiectasia-lymphedema syndrome-3 which is a syndrome characterized by widespread lymphedema, facial dysmorphism and protein-losing enteropathy of variable severity. This is quite a different phenotype from the upper airway disease in Norwich Terriers. Marchant et al suggest that the pharyngeal and laryngeal edema in Norwich Terriers somehow correlates with the generalized edema in human patients who are double heterozygotes for missense mutations in ADAMTS3. **It seems most likely that the ADAMTS3 missense variant in Norwich Terriers is a modifying factor and that the main gene mutation underlying the condition remains to be discovered**.

Dr. Stanley's team has confirmed that ADAMTS3 is also a risk allele in North American NTs. They are progressing with the genetic study at Michigan State University and currently genotyping several severely affected and several virtually unaffected dogs. Dr. Stanley maintains contact with researchers around the world, including Dr. Schoenebeck and others. We will continue to keep you informed as new discoveries are made.

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NTCA Health Committee Co-Chairs