European Journal of Human Genetics (2017) 25, 161

www.nature.com/ejhg

NEWS AND COMMENTARY

A canine model of EAST syndrome

Of dogs and men

Detlef Bockenhauer* and Robert Kleta

European Journal of Human Genetics (2017) **25,** 161; doi:10.1038/ejhg.2016.161

Perhaps you will be surprised to find a paper on a canine disease in a journal of human genetics. As indeed, in this edition you will find an article by van Poucke *et al.* about four Malinois dogs, who presented with neurological abnormalities, including ataxia, myokymia (involuntary, spontaneous, localized quivering of muscles) and generalized seizures.[1] Further investigations of brainstem auditory evoked potentials revealed also abnormalities in hearing. Genetic investigations subsequently identified a homozygous variant in kcnj10 as the cause of the problem. So, can we learn something from these observations in 'man's best friend'? Indeed, medical care for animals, at least in some parts of the Western society, has reached similar sophistication as for humans, including professional subspecialization.[2] And this includes genetics: OMIA (www.omia.org), the veterinary equivalent of OMIM (www.omim.org), lists at present 202 gene records relevant for dogs.

So, what can we learn from Snoopy and his peers? Recessive mutations in KCNJ10 are the cause of EAST syndrome (also described as SeSAME syndrome), a rare disorder characterized by epilepsy, ataxia, sensorineural deafness and tubulopathy.[3] To date less than 30 patients with 14 different mutations have been reported.[4–6] It is the neurological aspects that are typically most debilitating in this disorder, with severely affected patients being almost completely restricted in their ability to communicate either verbally or in written form due to their speech apraxia and ataxia. In addition, they suffer from recurrent seizures.[7] There is no specific treatment for EAST syndrome, and animal models are needed to identify and test potential drugs.[8] It is in this context that the finding of a canine equivalent of EAST syndrome is of interest. And perhaps, this also illustrates the artificial gulf between human and veterinary medicine. These authors have a strong personal interest in EAST syndrome, but were not aware of a previously described canine model, as it had been published in a veterinary journal.[9] It is only the submission to this journal of human genetics that alerted us to its existence. Yet, collaboration between these disciplines is highly desirable as insights from one species can inform the treatment and understanding of the disease in others. For instance, one of the dogs reported in this edition had a postmortem examination, showing a myelopathy in the central nervous system affecting the cerebellum, brainstem and spinal cord. Interestingly, changes were not obvious on macroscopic examination, but only on histology. This reflects our experience with MRI imaging of human patients, which were initially reported as normal,[3] and only after careful examination of imaging from multiple patients were subtle changes in the cerebellum and spinal tract noted.[7] This also parallels the experience of the previous report of kcnj10 mutations in Jack Russell Terriers, as MRI images were reported as normal, yet histopathological investigations revealed spinocerebellar myelopathy.[9]

However, there are also limitations to the comparability of manifestations of kcnj10 disease between dogs and men. A cardinal feature of the human disease is a specific salt-wasting tubulopathy.[10] Curiously, this has not been demonstrated in dogs, although it was not examined in the Jack Russell Terriers and blood tests were obtained in only two of the Malinois dogs, yet without concomitant urine studies. Nevertheless, the blood tests showed a normal electrolyte profile, suggesting that kcnj10 potentially has less relevance in renal tubular function in dog than in man.

Yet, given that it is the neurological abnormalities that are most debilitating, these dogs could still prove a valuable model for the testing of any compounds identified for instance in zebrafish screening, prior to testing in man.

Moreover, the apparent absence of electrolyte abnormalities is also helpful information. To this day, patients with EAST syndrome often receive large doses of potassium and magnesium supplementation in an attempt to normalize plasma levels, as the abnormal electrolytes are erroneously thought to contribute to or even cause the neurological complications. In patients with renal electrolyte wasting it is exceedingly difficult to normalize plasma levels, as the briefly increased levels in the glomerular filtrate lead to increased losses in the urine. Physicians sometimes respond with ever-increasing doses of supplementation, which can cause complications such as diarrhea (worsening the electrolyte profile) and gastric irritation. In this context, the experience in dogs, that neurological manifestations occur in the apparent absence of electrolyte abnormalities, further confirms that seizures and ataxia are a primary manifestation of the disorder and not electrolyte imbalance, and that attempts at normalizing plasma levels are thus not necessarily helpful.

Besides providing a much needed diagnosis to the dogs' owners and breeders, we thus welcome further detailed observations from our veterinary colleagues to inform the understanding and management of EAST syndrome.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

D Bockenhauer and R Kleta are at the UCL Centre for Nephrology & Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK
E-mail: d.bockenhauer@ucl.ac.uk

1 M VP, KS, Bhatti SFM *et al*: The novel homozygous kcnj10 variant c.986C>T; p.(Leu329Pro) variant is pathogenic for the SeSAME/EAST homologue in Malinois dogs. *Eur J Hum Genet* 2016 (this issue).
2 Jonathan E, Gregory G.*BSAVA Manual of Canine and Feline Nephrology and Urology*, 2nd edn. British Small Animal Veterinary Association. Wiley: Hoboken, USA, 2007.
3 Bockenhauer D, Feather S, Stanescu HC *et al*: Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ10 mutations. *N Engl J Med* 2009; **360**: 1960–1970.
4 Abdelhadi O, Iancu D, Stanescu H, Kleta R, Bockenhauer D: EAST syndrome: clinical, pathophysiological, and genetic aspects of mutations in KCNJ10. *Rare Dis* 2016; **4**: e1195043.
5 Abdelhadi O, Iancu D, Tekman M, Stanescu H, Bockenhauer D, Kleta R: Founder mutation in KCNJ10 in Pakistani patients with EAST syndrome. *Mol Genet Genomic Med* 2016; **4**: 521–526.
6 Freudenthal B, Kulaveerasingam D, Lingappa L *et al*: KCNJ10 mutations disrupt function in patients with EAST syndrome. *Nephron Physiol* 2011; **119**: 40–48.
7 Cross JH, Arora R, Heckemann RA *et al*: Neurological features of epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome. *Dev Med Child Neurol* 2013; **55**: 846–856.
8 Mahmood F, Mozere M, Zdebik AA *et al*: Generation and validation of a zebrafish model of EAST (epilepsy, ataxia, sensorineural deafness and tubulopathy) syndrome. *Dis Model Mech* 2013; **6**: 652–660.
9 Gilliam D, O'Brien DP, Coates JR *et al*: A homozygous KCNJ10 mutation in Jack Russell Terriers and related breeds with spinocerebellar ataxia with myokymia, seizures, or both. *J Vet Intern Med* 2014; **28**: 871–877.
10 Bandulik S, Schmidt K, Bockenhauer D *et al*: The salt-wasting phenotype of EAST syndrome, a disease with multifaceted symptoms linked to the KCNJ10 K+ channel. *Pflugers Arch* 2011; **461**: 423–435.