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BRIEF REPORT

Renal dysplasia in Leonberger dogs – An emerging recessive congenital disorder?

Renal dysplasia (RD) is a complex congenital disease characterised by abnormal differentiation of renal tissue (Greco, 2001). Several forms of inherited RD have been reported in various animal species, including dogs (OMIA:001135-9615). The canine RD phenotype can range from asymptomatic to severe chronic kidney disease and the genetic etiology remains unclear (Cavalera et al., 2021; Dillard et al., 2018; Safra et al., 2015). Similar secondary kidney damage can also result from recessive metabolic disorders such as xanthinuria, known in dogs (OMIA:001283-9615) or cattle (OMIA:001283-9913). Leonbergers globally suffer from various diseases, with cancer, orthopedic and neurological conditions being the most frequent (Letko et al., 2020). However, in the owner-reported health survey, 0.44% of dogs were diagnosed with 'renal system issues' (Letko et al., 2020). The underlying cause of RD has not yet been described in this breed.

In a litter of eight purebred Leonbergers, one puppy was diagnosed with a congenital form of RD and euthanised at 11 weeks of age owing to worsening clinical signs. For diagnosis confirmation and histopathological examination, the kidneys were collected and fixed in 10% buffered formalin and embedded in paraffin. Sections of 1.5 µm were cut and compared with a kidney sample of a control dog (Figure 1a). Histological lesions were present in both kidneys. The cortex and medulla had areas of fetal glomeruli featuring small glomeruli with peripheral nuclei and inapparent capillaries. Some tubuli appeared small and immature and were lined by closely packed cuboidal epithelial cells while others were ectatic and sometimes contained birefringent greenish crystals and occasional mineralisation. Additionally, some tubuli contained intraluminal eosinophilic droplet material. The interstitium showed multifocal areas with mild fibrosis and aggregates of lymphocytes, plasma cells, a few neutrophils and macrophages, some of which were laden with hemosiderin (Figure 1b).

Samples for genome sequencing of the affected dog or his littermates were not available. Therefore, parental whole-genome sequencing (WGS) data were utilised to gain insights into the genetic basis of RD. Blood samples and the DNA of the unaffected dam and sire of the case were previously donated to the Vetsuisse Biobank for diagnostic purposes. Whole-genome sequencing was performed at ~20× read depth using Illumina NovaSeq6000 and variants were called as described previously (Letko et al., 2023). The pedigree records supported a recessive mode of inheritance (Figure S1). Therefore, the WGS data were queried for variants heterozygous in both parents with respect to canine reference UU_Cfam_GSD_1.0. A global cohort of 1541 dogs, including 85 unrelated adult Leonbergers not known to be RD affected (Table S1), was used to evaluate allele frequency of the 1 090 859 shared variants. Based on the impact predicted by SNPEFF v5.0e, considering no homozygotes among control dogs, and an allele frequency below 1% in other breeds, 29 protein-coding (only 16 of

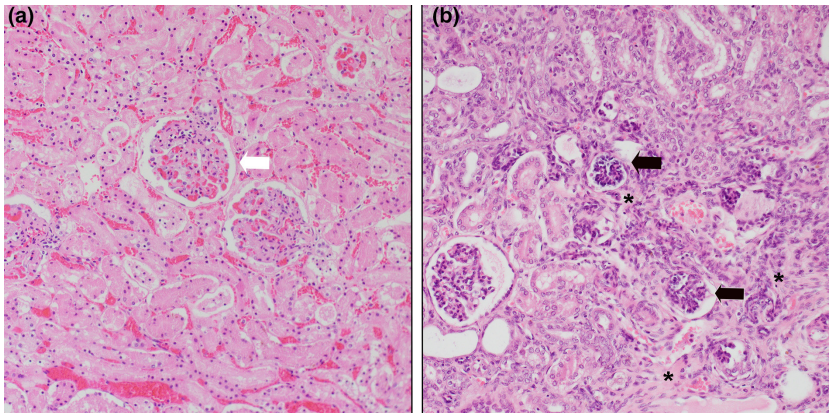

FIGURE 1 Histopathological phenotype of the RD-affected Leonberger. (a) Kidney of an unrelated control (10-week-old male St Bernard dog that died of verminous pneumonia) for comparison purposes, showing mature glomeruli (white arrow). (b) Kidney of an affected dog showing fetal glomeruli (black arrows) and interstitial fibrosis (asterisk). Haematoxylin and eosin staining, 40× magnification.

these variants affected genes with human orthologues) and 1106 non-coding variants were left (Table S2). Although no protein-changing variant was present in an obvious RD candidate gene, three were prioritised as warranting further investigation: a splice site variant in *SLC15A2* known to be associated with renal protein reabsorption (Rubio-Aliaga et al., 2003), a missense variant in *SPOCK2* that influences risk of end-stage kidney disease (Ngo et al., 2020) and a missense variant in *TRABD2B* that is implicated in organogenesis through the Wnt-signaling pathway with high expression in kidney (Reis et al., 2014).

This study presents the first histopathological description of RD in a purebred Leonberger and offers a list of putative pathogenic variants potentially contributing to the disease phenotype based on parental WGS. However, samples of RD-affected Leonberger dogs and of healthy controls are essential to find the causal variant(s) and decrease the occurrence of RD in this breed.

AUTHOR CONTRIBUTIONS

Anna Letko: Conceptualization; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Corinne Gurtner:** Investigation; methodology; visualization; writing – original draft; writing – review and editing. **Vidhya Jagannathan:** Data curation; software. **Cord Drögemüller:** Funding acquisition; project administration; resources; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The WGS data is available under study accession no. PRJEB16012 at the European Nucleotide Archive (www.ebi.ac.uk/ena; sample accessions of all dogs are detailed in Table S1).

ETHICS STATEMENT

The dogs in this study were privately owned and samples were collected with the consent of their owners for diagnostic reasons and did not constitute an animal experiment.

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