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BRIEF REPORT

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Heterozygous *ASPRV1* frameshift variant in a Pembroke Welsh Corgi with ichthyosis

BACKGROUND

Ichthyoses comprise a large, heterogeneous group of inherited cornification disorders. They are characterized by generalized scaly and hyperkeratotic skin (Oji et al., 2010). In humans, over 69 genes have been associated with different forms of ichthyosis, grouped into non-syndromic ichthyoses with the phenotypic expression of the disorder only seen in the skin, and syndromic ichthyoses that show additional organ involvement (Gutiérrez-Cerrajero et al., 2023; Uitto et al., 2020). Further subdivision into epidermolytic and non-epidermolytic ichthyoses is based on the presence or absence of light microscopic findings of vacuoles and

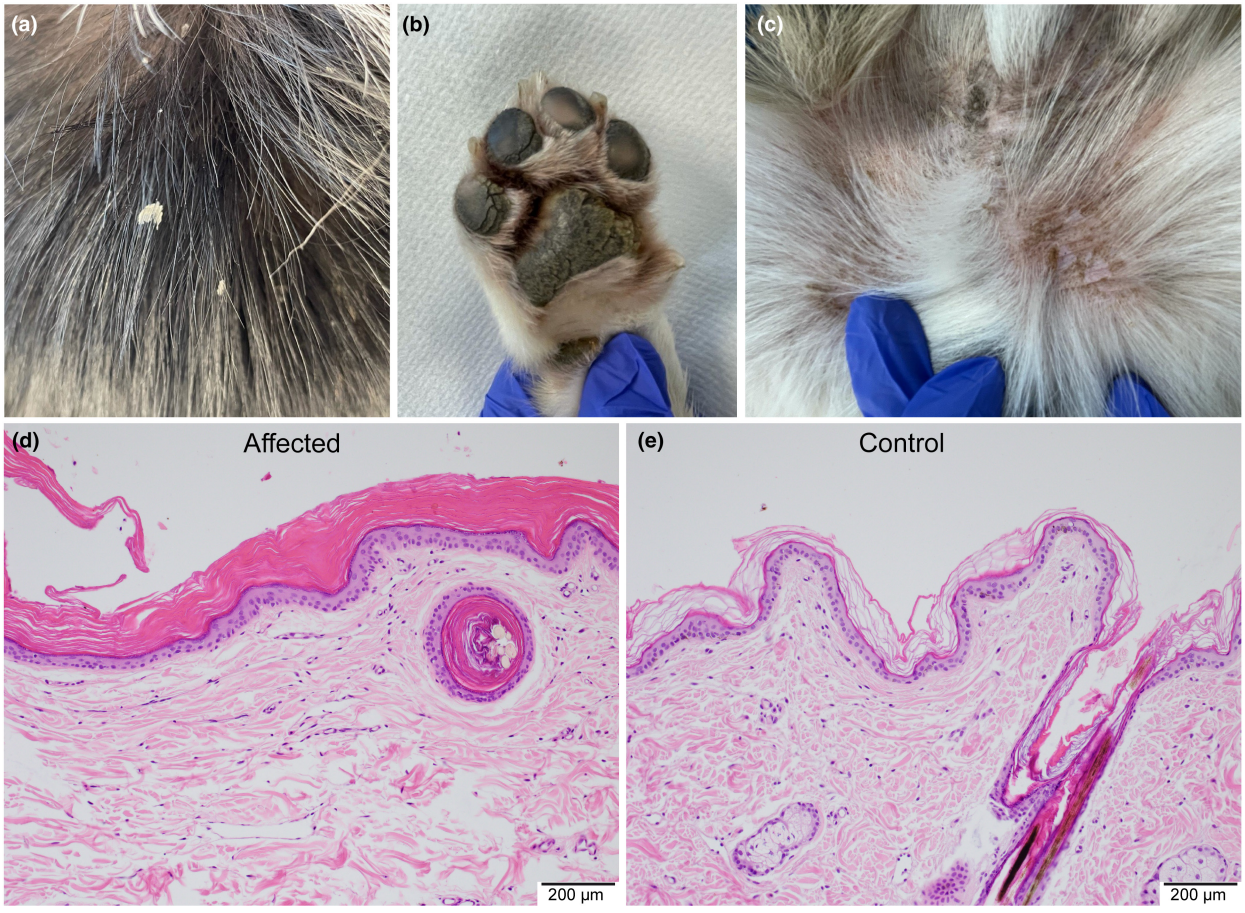

FIGURE 1 Clinical and histopathological phenotype of the affected Pembroke Welsh Corgi. (a) Large scales flaking from the skin and adhering to the hair coat. (b) Paw pad hyperkeratosis. (c) Brown-red discoloration and fish-skin-like scales with mild erythema in the inguinal region. (d) Haired skin of the ichthyotic dog exhibiting an increased amount of compact to lamellar orthokeratotic keratin covering the epidermis. Hematoxylin and eosin stain. (e) Skin of a 6-month-old unaffected control dog for comparison. Note the basket-weave structure of the keratin covering the epidermis. Hematoxylin and eosin stain.

lysis of keratinocytes (Mauldin, 2013). In dogs, several breed-specific ichthyoses have been described, and, to date, causal variants in nine different genes have been identified (Affolter et al., 2022; Bauer et al., 2017; Briand et al., 2019; Casal et al., 2017; Credille et al., 2005, 2009; Grall et al., 2012; Kiener et al., 2022; Kiener, Åhman, et al., 2023; Kiener, Castilla, et al., 2023; Metzger et al., 2015). These genes are mainly involved in the biosynthesis, metabolism, and transport of lipids required for skin barrier function or the intracellular protein network responsible for the integrity of skin structure (Gutiérrez-Cerrajero et al., 2023).

ANALYSES

A 6-month-old Pembroke Welsh Corgi was presented with non-pruritic severe scaling (large 5–10-mm scales; Figure 1a), hyperkeratotic paw pads (Figure 1b), and fish-skin like flakes and erythema in friction areas (Figure 1c), present since shortly after birth. Histological examination of biopsies taken from haired skin and paw pads showed prominent compact to lamellar orthokeratotic hyperkeratosis (Figure 1d). The observed changes were compatible with non-epidermolytic ichthyosis.

We performed Illumina short-read whole-genome sequencing at 26× coverage on genomic DNA isolated from leukocytes to investigate potential causal genetic variants. The data were processed as previously described (Jagannathan et al., 2019) with respect to the genome reference assembly UU_Cfam_GSD_1.0. Subsequent comparison of the whole-genome sequencing data of the affected dog to 960 genetically diverse canine genomes (Table S1) revealed 76 heterozygous and eight homozygous protein-changing private variants (Table S2). Among them was a heterozygous two base-pair deletion variant in the ichthyosis candidate gene *ASPRV1*, XM_038551592.1:c.594_595del or Chr10:NC_049231.1:69888722_69888723del, leading to a frameshift and altering 48% of the wildtype protein sequence, XP_038407520.1:p.(Leu199Argfs*342). The predicted mutant protein contains 539 compared to 381 amino acids in the wildtype protein. *ASPRV1* encodes the retroviral-like aspartic protease 1, which is responsible for cleavage of the multimeric profilaggrin into filaggrin monomers, which are essential for the structural integrity of the outermost, cornified layer of the epidermis. The identified c.594_595del frameshift variant is most likely to be the result of a de novo mutation event and probably leads to a complete loss of ASPRV1 function.

CONCLUSIONS

A whole-genome sequencing approach in a Pembroke Welsh Corgi with clinically and histopathologically diagnosed ichthyosis enabled us to identify a candidate causative variant in *ASPRV1*. The gene has previously been reported to cause an autosomal dominant form of ichthyosis in a German Shepherd and in human patients (Bauer et al., 2017; Boyden et al., 2020). Our study highlights the potential of precision medicine for investigating genodermatoses in veterinary medicine.

AUTHOR CONTRIBUTIONS

Sarah Kiener: Conceptualization; investigation; visualization; writing – original draft; writing – review and editing. **Susanne Åhman:** Conceptualization; investigation; visualization; writing – original draft; writing – review and editing. **Robert Cikota:** Investigation; writing – review and editing. **Vidhya Jagannathan:** Data curation; writing – review and editing. **Sohvi Blatter:** Investigation; visualization; writing – original draft; writing – review and editing. **Iva Cvitas:** Investigation; writing – review and editing. **Sara Soto:** Investigation; visualization; writing – original draft; writing – review and editing. **Tosso Leeb:** Conceptualization; funding acquisition; visualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The accession numbers of 961 dog genomes are listed in Table S1. Private variants in the sequenced Pembroke Welsh Corgi affected with ichthyosis with respect to 960 control geneomes are listed in Table S2.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.