Received: 12 June 2023 | Accepted: 12 June 2023

DOI: 10.1111/age.13341

ANIMAL GENETICS WILEY

BRIEF REPORT

Heterozygous *KRT10* missense variant in a Chihuahua with severe epidermolytic ichthyosis

BACKGROUND

Ichthyoses are a group of heritable cornification disorders. Various different subtypes are known and they can be classified based on the genetic background and underlying molecular mechanisms (Gutiérrez-Cerrajero et al., 2023). A rare form of ichthyosis is termed epidermolytic hyperkeratosis, which is mainly caused by variants in *KRT1* and *KRT10* (Fuchs & Green, 1980; Peter Rout et al., 2019). The encoded proteins, keratin 1 and keratin 10, assemble into intermediate filaments that form the cytoskeleton in differentiated keratinocytes, providing mechanical resilience (Fuchs & Green, 1980; Gutiérrez-Cerrajero et al., 2023; Syder et al., 1994).

Epidermolytic hyperkeratosis in humans predominantly follows an autosomal dominant mode of inheritance, with half of the cases resulting from *de novo* mutation events (Chipev et al., 1994; Peter Rout et al., 2019). In dogs, one occurrence of *KRT10*-associated recessive epidermolytic hyperkeratosis has been described in Norfolk Terriers owing to a homozygous splice-site variant (Credille et al., 2005).

ANALYSES

An 11-month-old male Chihuahua was presented with severe skin lesions gradually progressing from 5 months of age. Clinical examination revealed severe, multifocal hyperkeratosis, mainly affecting paw pads, axillas and the skin around the anus, lips and eyes (Figure 1). Three skin punch biopsies from axilla, lip and paw pad were taken under general anesthesia for diagnostic purposes. All samples displayed similar changes, characterized by marked epidermal hyperplasia and orthokeratotic hyperkeratosis with hypergranulosis, forming papillary

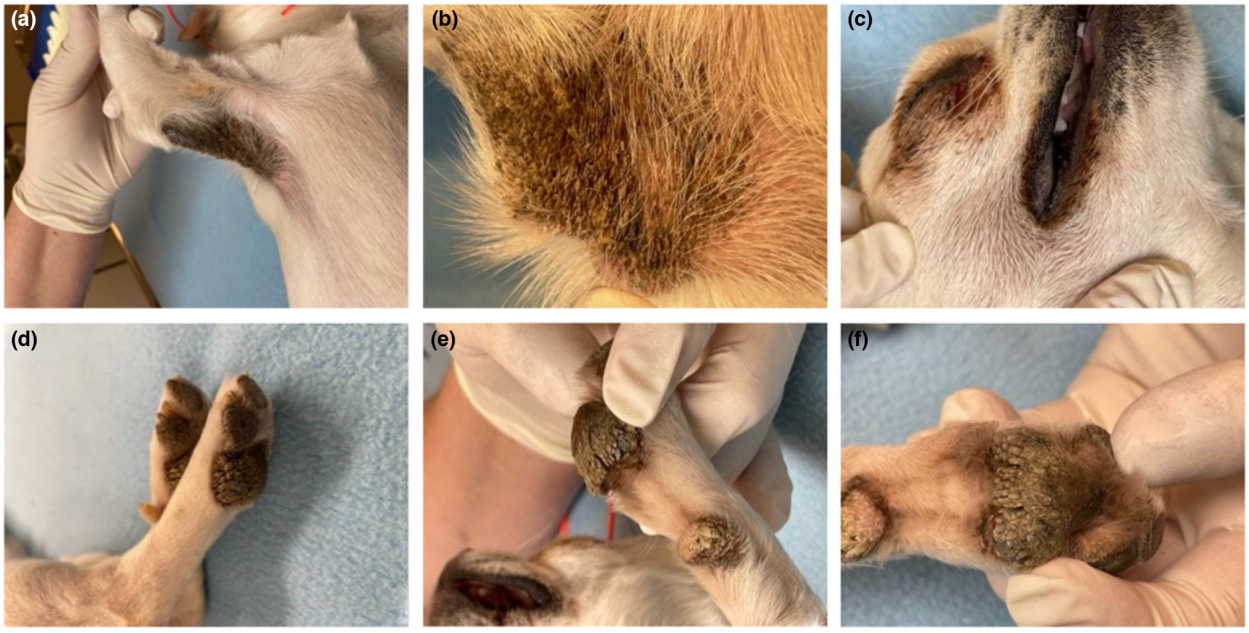

FIGURE 1 Clinical phenotype of the affected Chihuahua. (a) Severe, focal and macroscopically laminar hyperkeratosis in the axillae with concurrent severe hair loss and moderate seborrhoeic changes. (b) Close up of right axilla. (c) Rim of hyperkeratosis around lip commisure and rima. (d–f) Severe paw pad hyperkeratosis and mild palmar and plantar erythema affecting all pads on all four paws.

projections on the skin surface These histopathological findings, together with the anamnesis and clinical findings, were characteristic for an epidermolytic hyperkeratosis.

Whole genome sequencing at 28× coverage was performed on genomic DNA extracted from leukocytes. Data processing was done as previously described (Jagannathan et al., 2019), using the genome reference assembly UU_Cfam_GSD_1.0. We identified 72 heterozygous and five homozygous private protein changing variants in the case by comparing its sequence data with 926 genetically diverse control genomes (Tables S1 and S2). One of these variants was located in *KRT10*, a known ichthyosis candidate gene. The heterozygous missense variant, Chr9:21814695G>A, XM_038547368.1:c.437G>A, was predicted to change an evolutionarily conserved arginine in the coil 1A domain, XP_038403296.1:p.(Arg146His). The presence of the heterozygous genotype at the position of the variant was confirmed by Sanger sequencing. The genotypes of 40 additional Chihuahuas from the Vetsuisse Biobank were homozygous wild type. We speculate that this variant has most likely arisen *de novo* in the affected dog; however, samples from the parents to confirm this hypothesis were not available.

CONCLUSIONS

The identified *KRT10* missense variant is most likely causative for the observed epidermolytic hyperkeratosis in the Chihuahua. The variant affects a conserved CpG dinucleotide within an arginine codon. Heterozygous variants affecting human Arg156, homologous to canine Arg146, have been described in several human patients with epidermolytic hyperkeratosis, suggesting this residue to be a mutational hot spot (Cheng et al., 1992; Chipev et al., 1994; Rothnagel et al., 1992, 1993; Syder et al., 1994).

ACKNOWLEDGEMENTS

The authors would like to thank the dog owner for donating samples and information. The authors also wish to thank the Next Generation Sequencing Platform of the University of Bern for performing whole-genome sequencing experiments and the Interfaculty Bioinformatics Unit for providing high performance computing infrastructure. We acknowledge the DBVDC consortium, the Dog10K genomes project and all researchers who deposited dog or wolf whole genome sequencing data into public databases. Open access funding provided by Universitat Bern.

FUNDING INFORMATION

This study was funded by the Swiss National Science Foundation, grant number 310030_200354.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All underlying raw data are freely available. Accession numbers of the whole genome sequences used in this study are listed in Table S1.

ETHICS STATEMENT

The examinations of the affected dog were done with the consent of the owner in the framework of veterinary care and diagnostics and did not constitute an animal experiment. The collection of blood samples from control dogs was approved by the *Cantonal Committee for Animal Experiments* (Canton of Bern; permit BE94/2022).

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SUPPORTING INFORMATION

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