RESEARCH ARTICLE

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Heterozygous *DSP* in-frame deletion in a poodle with syndromic ichthyosis involving additional hair and tooth abnormalities

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Abstract

Ichthyoses comprise a large heterogeneous group of skin disorders, characterized by generalized scaly and hyperkeratotic skin. We investigated a miniature poodle with early onset generalized scaling, dry and irregularly thickened skin, paw pad hyperkeratosis and abnormalities in hair and teeth. The clinical signs of ichthyosis were confirmed by histopathological examination, which revealed mild epidermal hyperplasia and lamellar orthokeratotic hyperkeratosis. A hereditary condition was suspected and a genetic investigation was initiated. We sequenced the whole genome of the affected dog and searched for potentially causative variants in functional candidate genes for the observed phenotype. The analysis revealed a heterozygous in-frame deletion in *DSP*, NC_049256.1:g.8804542_8804544del resulting from a de novo mutation event as evidenced by genotyping leukocyte DNA from both parents. The 3 bp deletion is predicted to remove one aspartic acid without disrupting the open reading frame (XM_038584124.1:c.1821_1823del, XP_038440052.1:p.(Asp608del)). The *DSP* gene encodes desmoplakin, a desmosomal plaque protein, responsible for cell–cell adhesion to provide resistance to mechanical stress in epidermal and cardiac tissues. We hypothesize that the deletion of one amino acid in the N-terminal globular head domain acts in a dominant negative manner and thus impairs the proper connection with other proteins. Several variants in *DSP* in humans and cattle have been described to result in different phenotypes associated with hair and skin abnormalities, sometimes in combination with variable cardiac and/or dental manifestations. In conclusion, we characterized a new syndromic ichthyosis phenotype in a dog and identified a de novo 3 bp deletion in the *DSP* gene as causal variant.

KEYWORDS
Canis lupus familiaris, dermatology, dog, genodermatosis, precision medicine, skin, whole genome sequencing

INTRODUCTION

Hereditary skin cornification disorders include the heterogeneous group of ichthyoses. These are characterized by abnormal scaling, dryness and thickening of the epidermis (Oji et al., 2010). Both non-syndromic ichthyoses, with phenotypic changes limited to the skin, and syndromic forms, affecting additional organs, exist (Gutiérrez-Cerrajero et al., 2023; Mauldin & Elias, 2021). In humans, at least 69 genes have been associated with different forms of ichthyosis (Gutiérrez-Cerrajero et al., 2023; Uitto et al., 2020). These can be molecularly classified, based on

the underlying genes and pathophysiology. Affected components encompass the intracellular protein network, lipid metabolism or intercellular junctions (Gutiérrez-Cerrajero et al., 2023). The latter, specialized structures that facilitate cell adhesion include desmosomes fundamental to maintaining tissue integrity, enabling resistance to mechanical stress and environmental challenges. The core components of the desmosome consist of members from three protein families (Johnson et al., 2014). Desmogleins and desmocollins, belonging to the cadherin superfamily, play a key role in mediating adhesion at desmosomes. Cytoplasmic components of the desmosome, including plakoglobin and the plakophilins from the armadillo gene family, interact with the desmosomal cadherin tails, facilitating the recruitment of intermediate filaments to sites of desmosome assembly. Desmoplakin, an intermediate filament binding protein, links the desmosome to the cytoskeleton and associates with both plakoglobin and plakophilins (Delva et al., 2009). Genetic aberrations in many of these desmosomal proteins have been linked to diverse inherited skin disorders (Hegazy et al., 2022; Johnson et al., 2014).

This aim of this study was to characterize the clinical and histopathological phenotype in a miniature poodle with ichthyosis and to elucidate the underlying genetic defect.

METHODS

Animal selection

This study included a miniature poodle affected with ichthyosis and its unaffected parents. We further included 270 control poodles from the Vetsuisse Biobank, comprising a grandmother and an aunt of the affected dog, and 926 control genomes of genetically diverse dogs (Table S1). Genomic DNA was isolated from ETDA blood samples with the Maxwell RSC Whole Blood Kit on a Maxwell RSC instrument (Promega, Dübendorf, Switzerland).

Clinical and histopathological examinations

A detailed clinical and dermatological examination of the affected dog and its parents was performed by a veterinary dermatologist (GL). Skin biopsies from hyperkeratotic skin of the affected dog were taken under sedation and local anesthesia according to standard procedures. The biopsies were routinely processed and stained with hematoxylin and eosin, prior to histological evaluation.

Whole genome sequencing and variant calling

A PCR-free DNA library with ~400 bp insert size was prepared from genomic DNA of the affected miniature poodle and sequenced on an Illumina NovaSeq 6000 instrument at 18× coverage. The reads were mapped to the UU_Cfam_GSD_1.0 reference genome assembly and variant calling was done as described (Jagannathan et al., 2019). The SnpEff software was used together with NCBI annotation release 106 to predict the functional effects of the called variants (Cingolani et al., 2012). The sample accession number of the sequence data from the European Nucleotide Archive is SAMEA110175540. Accession numbers from this dog and 926 controls are listed in Table S1.

Sanger sequencing

The candidate variant was confirmed by Sanger sequencing of PCR amplicons. We also used Sanger sequencing to genotype additional poodles. Using the forward primer 5′-TCT TGT CGG TCA TGC TAT GG-3′ and the reverse primer 5′-AGG GTA CTT GGC CTC AAC CT-3′ together with the AmpliTaqGold360Mastermix (Thermo Fisher Scientific, Waltham, MA, USA) we amplified a PCR product from genomic DNA. After treatment with exonuclease I and alkaline phosphatase, the sequencing reactions were performed using the forward PCR primer and an ABI BigDye v3.1 sequencing kit (Thermo Fisher Scientific, Waltham, MA, USA). The purified products were sequenced on an ABI 3730 DNA analyzer, and the sequence data were analyzed using the SEQUENCHER 5.1 software (GeneCodes, Ann Arbor, MI, USA).

Parentage verification

The parent–offspring relationship between the affected dog and the presumptive parents was investigated using a panel of 12 microsatellite markers (Table S3).

RESULTS

Family anamnesis, clinical examinations and histopathology

A 10-month-old miniature poodle was presented with mild pruritus and a lifetime history of pronounced generalized scaling, coarse skin at the neck and thickened paw pads. The parents were clinically unremarkable. Clinical examination of the affected dog revealed mild generalized hypotrichosis and non-curly (atypical for a poodle) hair coat, moderate to severe dry seborrhea, with scales of various size adhering to the hair coat. Severely affected areas showed bilaterally symmetrical alopecia extending from the ventrolateral neck to the buccal region, where the skin was rough, dry, inelastic and irregularly thickened, giving a cobble stone pattern (Figure 1a). On dermatoscopy thick adherent plate-like scales were visible on the skin surface and

dilated follicular ostia showed frond-like projections (Figure 1b). All paw pads showed marked hyperkeratosis with secondary fissures (Figure 1c). Several claws were mildly dry, rough, and showed longitudinal ridges, which was interpreted as trachyonychia. Trichography and skin scraping showed no abnormalities. Cytology samples from body skin and ear canals showed the presence of 3+ malassezia (Budach & Mueller, 2012), which was interpreted as an overgrowth secondary to a presumed congenital cornification disorder (Bond et al., 2020). Only five mandibular incisors were present, with wide interdental spaces and signs of periodontal disease (Figure 1d). Clinical keratoconjunctivitis sicca had been diagnosed earlier at 4 months of age by a veterinarian experienced in ophthalmology. The initial Schirmer test results were not available. Since the original diagnosis, the dog had been under treatment with topical cyclosporine and tear replacement. Repeated Schirmer tear test results during this investigation were between 15 and 18 mm/min for both eyes (reference value ≥15 mm/min). Apart from these findings, the clinical examination revealed no further abnormalities.

The patient has been followed up until 3.5 years of age and the preparation of this article. Pruritus has mainly been present at the axillae, face, ventrolateral neck and pinnae during spring, summer and early autumn, but entirely absent during the winter months. At the latest examination in February 2024, the majority of the lesions were in remission, using oral essential fatty acids and biweekly topical sebolytics and moisturizer. However, moderate generalized xerosis and mild dry seborrhea persisted throughout the year. Palpatory normal periocular skin remained alopecic and hyperpigmented, presumably partially secondary to mild remaining pruritus. Additionally, the periocular skin showed fine folds and creases, reminiscent of rhytids. The paw pads had partially improved. Cutaneous projections were effectively trimmed regularly using scissors. The hair coat kept growing non-curly for approximately 1–1.5 years (Figure 1e), and from then on became more curly (Figure 1f). Interestingly, the almost exclusively anagen hair, verified on trichography, could be depilated extremely easily. The eyes were treated with daily topical cyclosporine, and on ocular examination the cornea remained pigmented, being fluorescein negative. Schirmer tear test were repeatedly within normal limits. Conjunctivitis flares were synchronous to the seasonal pruritus, suggesting a coexisting atopic
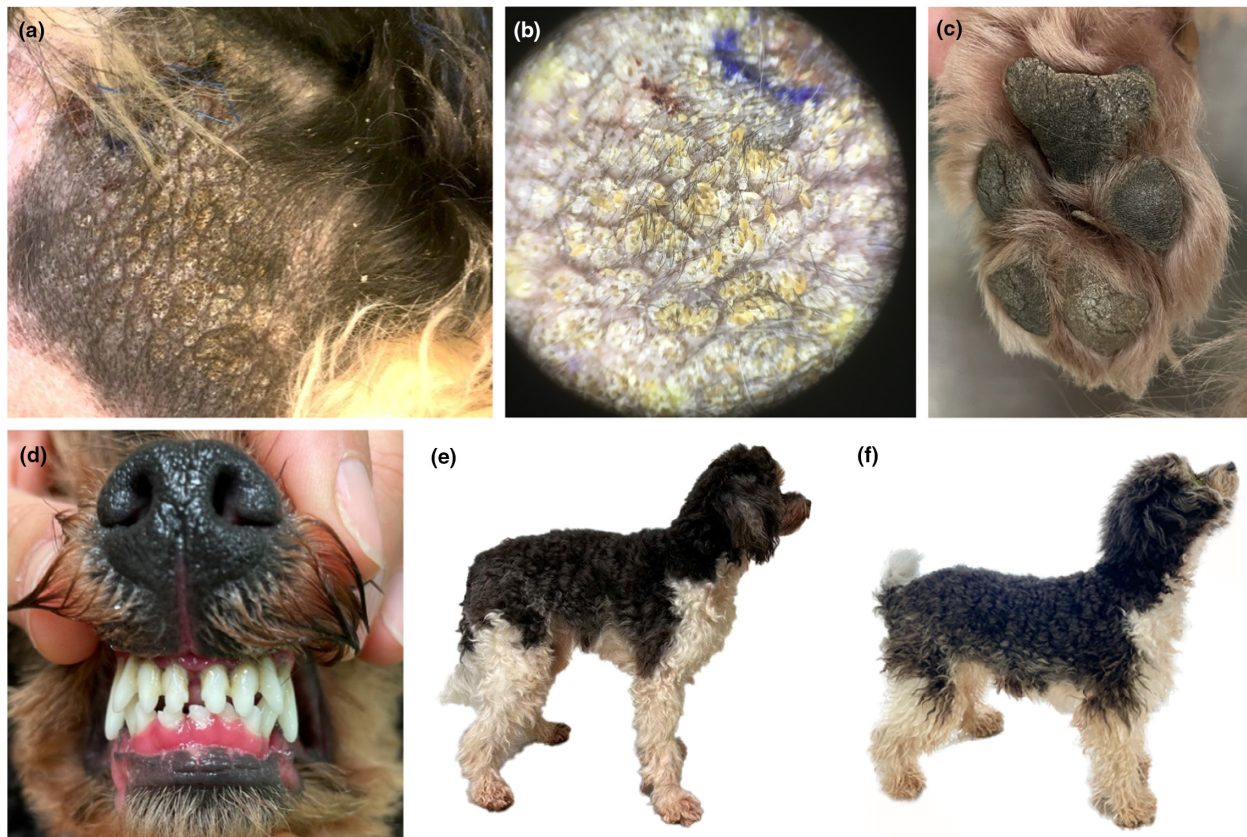

FIGURE 1 Details of the clinical phenotype of the affected miniature poodle. (a) Rough, dry and thickened cobble stone patterned skin. (b) Dermatoscopic image showing thick adherent scales on the skin surface. (c) Paw pad hyperkeratosis. (d) Front teeth of the affected dog showing large interdental spaces, non-inflammatory periodontal disease and only five mandibular incisors at 10 months of age. (e) Affected dog at 10 months of age with mostly straight hair, different from the breed-specific curly coat standard. (f) Affected dog at 3 years of age with a curlier coat, but still not consistent with breed standard.

disease. At 15 months of age the dog underwent a dental intervention, owing to loose incisors. All incisors were extracted by the primary veterinarian.

Skin histology revealed a mild epidermal hyperplasia and a moderate to severe lamellar orthokeratotic hyperkeratosis (Figure 2). The lamellae of the excessive stratum corneum were exfoliating multifocally. Occasional malassezia were observed in the stratum corneum. There was also mild intercellular edema and lymphocytic exocytosis. In the superficial dermis a mild perivascular infiltrate composed of mainly mast cells and lymphocytes and a mild edema were present.

Genetic analysis

We compared whole genome sequencing data of the affected dog with 926 genetically diverse control genomes to search for candidate causative variants for the observed phenotype. Several filtering steps were performed to narrow down the resulting lists of variants (Table 1, Table S2).

Variants private to the affected dog were further prioritized by focusing on variants with a SnpEff predicted impact of 'high' or 'moderate' (protein-changing variants). Only one of the private protein-changing variants was located in a known ichthyosis candidate gene (Gutiérrez-Cerrajero et al., 2023). This was a heterozygous in-frame deletion in *DSP*, NC_049256.1:g.8804542_8804544del. The 3 bp deletion, XM_038584124.1:c.1821_1823del, is predicted to delete one aspartic acid from the encoded protein, XP_038440052.1:p.(Asp608del).

The heterozygous presence of the deletion was confirmed by Sanger sequencing (Figure 3). Genomic DNA from blood leukocytes of both parents was genotyped as homozygous wildtype, confirming a de novo mutation event that happened either in the germline of one of the parents or during early embryonic development of the affected dog. The correct parentage was experimentally confirmed (Table S3).

The disease allele was also absent from 270 additionally genotyped poodles, including one grandmother and an aunt of the affected dog.
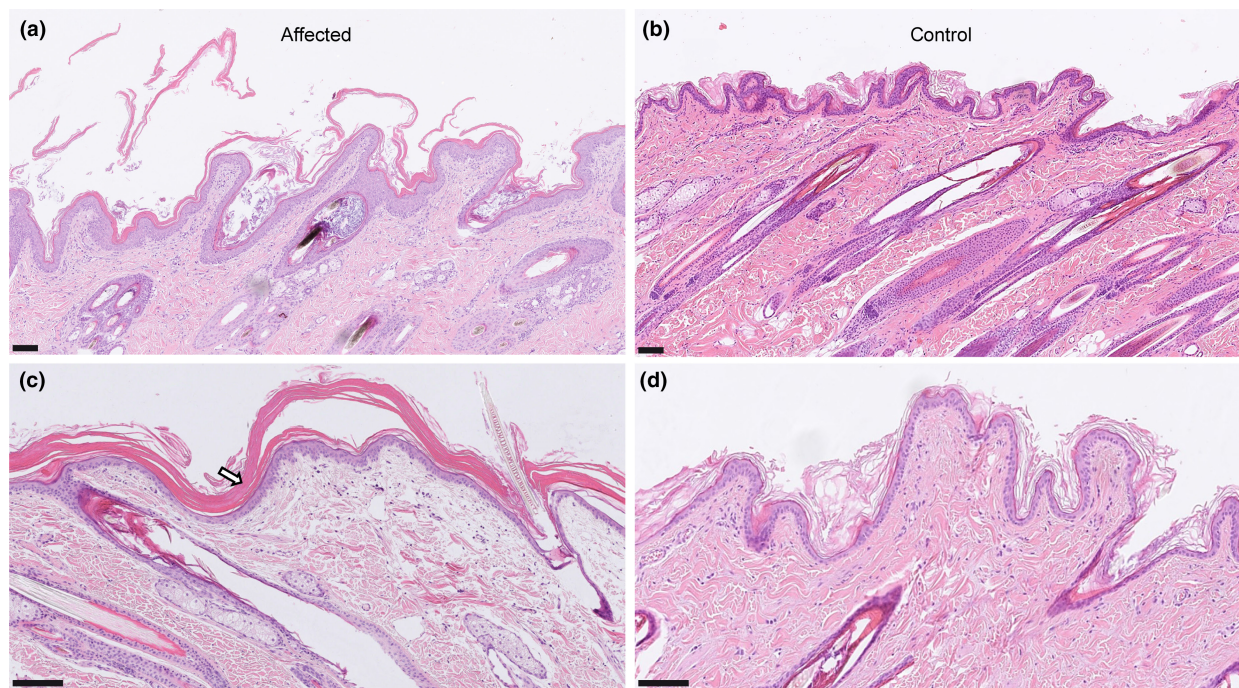

FIGURE 2 Histopathological findings. (a) Affected poodle. The abundant stratum corneum is compacted and exfoliates as scales. (b) Histopathological image of haired skin of a healthy poodle. The stratum corneum presents as a basket weave layer. (c) Higher magnification of the affected skin. The arrow marks the start of a split in the stratum corneum, where a large scale is beginning to form. (d) Higher magnification of normal haired skin. Hematoxylin and eosin stain; scale bars = 100 μm.

TABLE 1 Variant filtering steps in the affected dog against 926 control genomes.

Filtering step	Heterozygous	Homozygous
All variants	3 574 495	2 668 035
Private variants	5809	605
Protein-changing private variants	44	6
Protein-changing private variants in ichthyosis candidate genes	1	0

(a)

(b)

(c)

(d)

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Dog       550 SLVSWHYCMIDIEKIRAMTIAKLKTMRQEDYMKTISDLELHYQEFIRNSQGSEMFGDD D KRKMQSQFTDAQKHYQTLVIQLP 631
Human     546 ...............................................A............. . ...I.................... 627
Chimp     546 ...............................................A............. . ...I.................... 627
Monkey    546 ..........................................T..A............. . ...I.................... 627
Cow       556 ...........................K............................. . .......T............ 637
Mouse     558 ...................................E.......D..K............. . ..R................... 639
Rat       553 ...................................E.......D..K............. . ..R................... 634
Chicken   553 ..........................K...Q.I.T...I....L...........E. . ....I.T...............I.... 634
Zebrafish 561 ..I..Q..LR..QH.NSL.LSM.TQ..P.E.RQ..KN..I....L...L........ . ....EL.YAG..S..DQ...... 642
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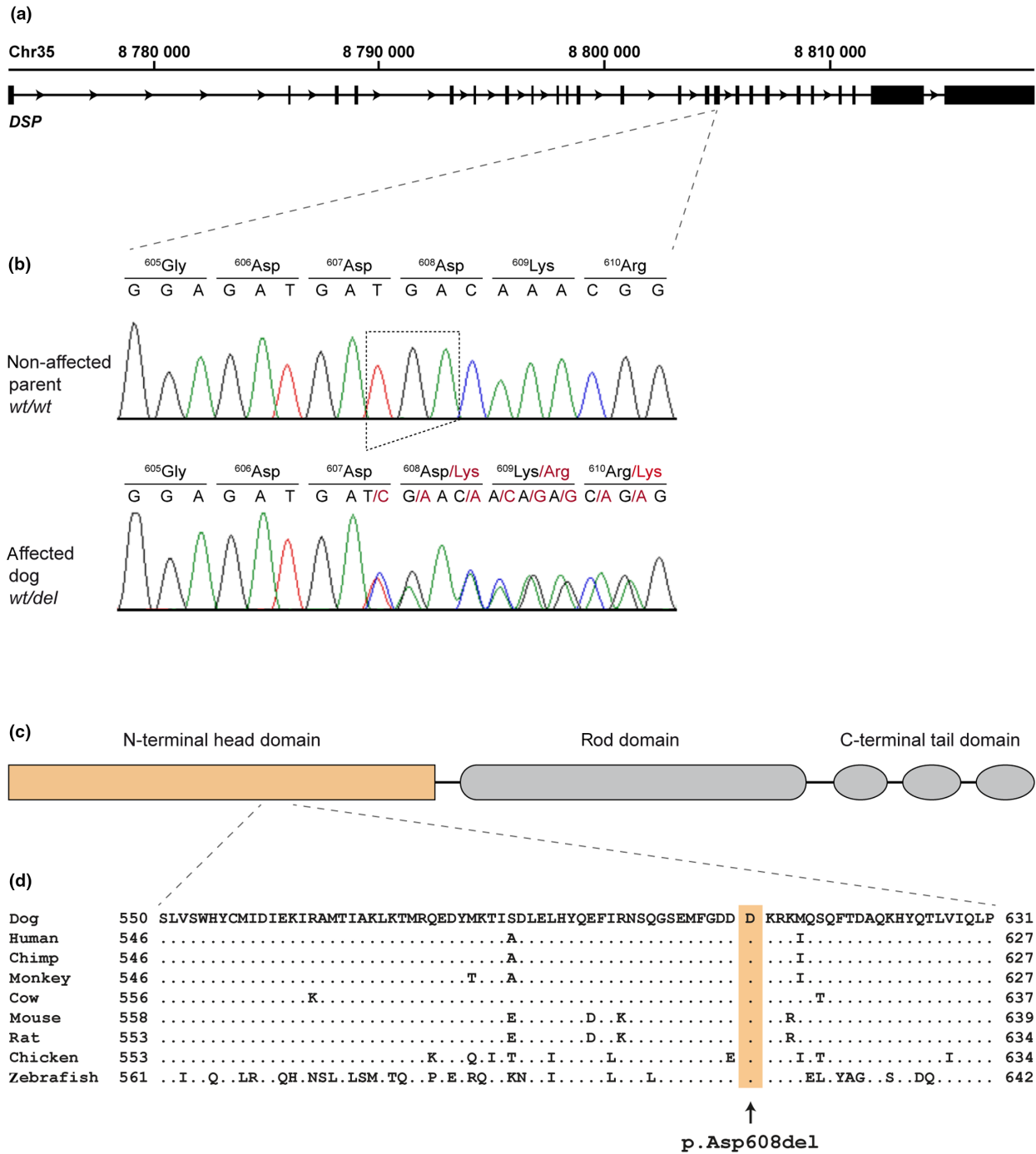   p.Asp608del

FIGURE 3 Details of the *DSP*:C.1821_1823del variant. (a) Overview of the genomic organization of the canine *DSP* gene. (b) Representative Sanger electropherograms confirm the heterozygous 3 bp deletion in the affected dog. The amino acid translations of the wildtype and mutant alleles are indicated. (c) Schematic representation of the desmoplakin protein comprising 2879 amino acids. The N-terminal domain consists of six spectrin repeats (SR3-6, SR8-9; Choi & Weis, 2011). The position of the dog variant is indicated together with a selection of five variants identified in human patients with autosomal dominant dilated cardiomyopathy with wooly hair, keratoderma and tooth agenesis (OMIM #615821; Boulé et al., 2012; Boyden et al., 2016; Chalabreysse et al., 2011). (d) Multiple species alignment of the amino acid sequence of the SR6 in the N-terminus of desmoplakin, harboring the p.Asp608del variant.

DISCUSSION

In this study we investigated a miniature poodle affected with a syndromic form of ichthyosis. A congenital cornification disorder was the top differential diagnosis. Using a whole genome sequencing approach, we identified a candidate causal variant in an excellent functional candidate gene for ichthyosis, a heterozygous in-frame deletion in the *DSP* gene. *DSP* encodes desmoplakin, a desmosomal plaque protein. Desmosomes are present in epidermal and myocardial tissue where they play an important role in cell–cell

adhesion and provide resilience to mechanical stress (Rasmussen et al., 2013).

In domestic animals, there is only one report of an autosomal recessive form of *DSP*-associated ichthyosis in cattle. The affected Scottish Highland calf presented with syndromic ichthyosis involving alopecia, acantholysis of the tongue and corneal defects. The calf had to be euthanized at 2 weeks of age owing to the severity of the lesions. The causative homozygous variant, p.Ala2298Asp, affected a conserved residue in the C-terminal plakin domain, a region mediating binding to intermediate filaments (Häfliger et al., 2022).

In humans, variants at different positions of the *DSP* gene have been described to result in differing phenotypes associated with hair and skin abnormalities, and/or variable cardiac manifestations (Cheong et al., 2005). A heterozygous splice site and a heterozygous nonsense variant both leading to premature termination codons within the N-terminal domain were identified in patients with autosomal dominant striate palmoplantar keratoderma (Keith et al., 1999; Whittock et al., 1999). Autosomal dominant arrhythmogenic right ventricular cardiomyopathy has been reported in patients caused by variants in either the N- or the C-terminus of desmoplakin (Christensen et al., 2010; Rampazzo et al., 2002; Yang et al., 2006). Autosomal recessive defects in either of the N- or the C-terminus result in Carvajal syndrome, characterized by epidermolytic palmoplantar keratoderma with wooly hair and dilated cardiomyopathy (Alcalai et al., 2003; Al-Owain et al., 2011; Carvajal-Huerta, 1998; Norgett, 2000; Rasmussen et al., 2013; Uzumcu, 2005; Vahlquist et al., 2014; Whittock et al., 2002). A second autosomal recessive disorder, lethal acantholytic epidermolysis bullosa, is associated with homozygous *DSP* variants resulting in truncation of the desmoplakin tail (Bolling et al., 2010; Hobbs et al., 2010; Jonkman et al., 2005). Heterozygous variants clustering within the spectrin repeat 6 in the N-terminus of desmoplakin have been described in patients with dilated cardiomyopathy with wooly hair, keratoderma, and tooth agenesis (OMIM #615821; Boulé et al., 2012; Boyden et al., 2016; Chalabreysse et al., 2011; Norgett et al., 2006). In the same globular head domain, a de novo missense variant resulting in an amino acid substitution was identified in one patient with severe dermatitis, multiple allergies and metabolic wasting syndrome (McAleer et al., 2015).

The heterozygous p.Asp608del variant identified in the dog described herein is located in spectrin repeat 6, which is altered in many autosomal dominant disorders with overlapping clinical features previously reported in human patients (Paller et al., 2018). Spectrin repeat 6 forms part of the N-terminal globular head domain of desmoplakin, which is responsible for the interaction with the desmosomal proteins plakophilin and plakoglobin that associate with the transmembrane cadherins, desmogleins and desmocollins (Favre et al., 2018). As desmoplakin forms homodimers in its mature form

(Green et al., 1992), we hypothesize that the deletion of Asp-608 acts in a dominant negative manner and affects the correct formation of the desmoplakin dimer and/or its interaction with binding partners. This mechanism has also been discussed in a patient with syndromic ichthyosis owing to a heterozygous variant resulting in the insertion of 10 amino acid residues in the N-terminal domain of desmoplakin (Norgett et al., 2006).

According to the ACMG/AMP consensus criteria for human diagnostics (Richards et al., 2015), we compiled the following arguments for the pathogenicity of the p.Asp608del variant in the affected poodle: the variant resulted from a de novo mutation event (PS2) and is located in a known mutational hotspot associated with highly specific clinical phenotypes in human patients (PM1). The mutant allele was absent from a cohort of 270 unaffected poodles (PM2) and involves shortening of the protein (PM4). Taken together, this evidence is sufficient to designate the p.Asp608del variant as pathogenic.

The clinical ichthyosis in the affected miniature poodle was histologically confirmed to represent a non-epidermolytic ichthyosis. The observed dermal infiltrate and the lymphocytic exocytosis were compatible with the atopic dermatitis and the yeast infection in this dog. Comparable with the phenotype seen in human patients with corresponding *DSP* variants, the affected dog also showed impaired hair quality, clinical and histopathological signs of atopic dermatitis, and tooth abnormalities. It did not present any overt clinical signs of heart disease up until the age of 3.5 years; however, no detailed cardiac examination was performed. Extrapolating from the genotype–phenotype correlation in human patients, the affected dog has an increased risk of developing cardiac problems later in life.

In summary, we characterized a new syndromic ichthyosis phenotype in a miniature poodle and identified the underlying genetic defect. To the best of our knowledge, we provide the first characterization of a *DSP*-related disease in a dog.

computing infrastructure. We acknowledge the DBVDC consortium, the Dog10K genomes project and all researchers who have deposited dog or wolf whole genome sequencing data into public databases.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The genome sequence data were submitted to the European Nucleotide Archive. All accession numbers are listed in Table S1.

ETHICS STATEMENT

The affected dog in this study was privately owned and skin biopsies and blood samples for diagnostic purposes were collected with the consent of the owners. The collection of blood samples from healthy control dogs was approved by the 'Cantonal Committee for Animal Experiments' (Canton of Bern; permit no. BE94/2022). A control biopsy of non-lesional canine skin was retrieved from archival diagnostic material at the Institute of Animal Pathology, Vetsuisse Faculty, University of Bern.

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SUPPORTING INFORMATION

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