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BRIEF REPORT

Heterozygous *COL5A1* deletion in a cat with classical Ehlers–Danlos syndrome

Classical Ehlers–Danlos syndrome (cEDS) represents one of 14 subtypes of EDS, hereditary connective tissue disorders characterized by skin hyperextensibility, poor wound healing and, especially in human patients, joint hypermobility (Bowen et al., 2017; Malfait et al., 2020). cEDS is frequently inherited as an autosomal dominant trait and caused by pathogenic variants in the *COL5A1* gene encoding the α-1 subunit of collagen type V (Mak et al., 2016; Symoens et al., 2012). Collagen type V represents only a small percentage of the total collagen content in most tissues but plays a key role in regulating collagen fibrillogenesis (Malfait et al., 2020). In cats, five different causative variants for cEDS have been reported in the *COL5A1* gene so far (Kiener et al., 2022; McElroy et al., 2023; Spycher et al., 2018; OMIA:002165-9685). In this study, we investigated a female Maine Coon cat with suspected EDS due to complications in wound healing.

The 10-month-old female Maine Coon was presented to a specialty dermatology practice for referral and consultation regarding a nonhealing spay incision. The wound had shown minimal bleeding but had not resolved after multiple attempts at corrective surgery. On initial physical examination, the cat showed bilateral alopecia of the concave and multiple small wounds at the base of the pinnae from self-trauma. Scarring was present on the base of neck and the preauricular region. The wound associated with the spay incision was healed at the time of presentation, but a white scar persisted. Skin elasticity index was determined to be 23% (Figure 1a). The remaining physical examination was unremarkable.

Histopathological examination of a skin biopsy from the cat revealed mildly decreased dermal thickness. Collagen fibers were of variable size and width and increased numbers of fibroblasts were present in some regions (Figure 1b). The epidermis was of normal thickness and the hair follicles and adnexa present in adequate number.

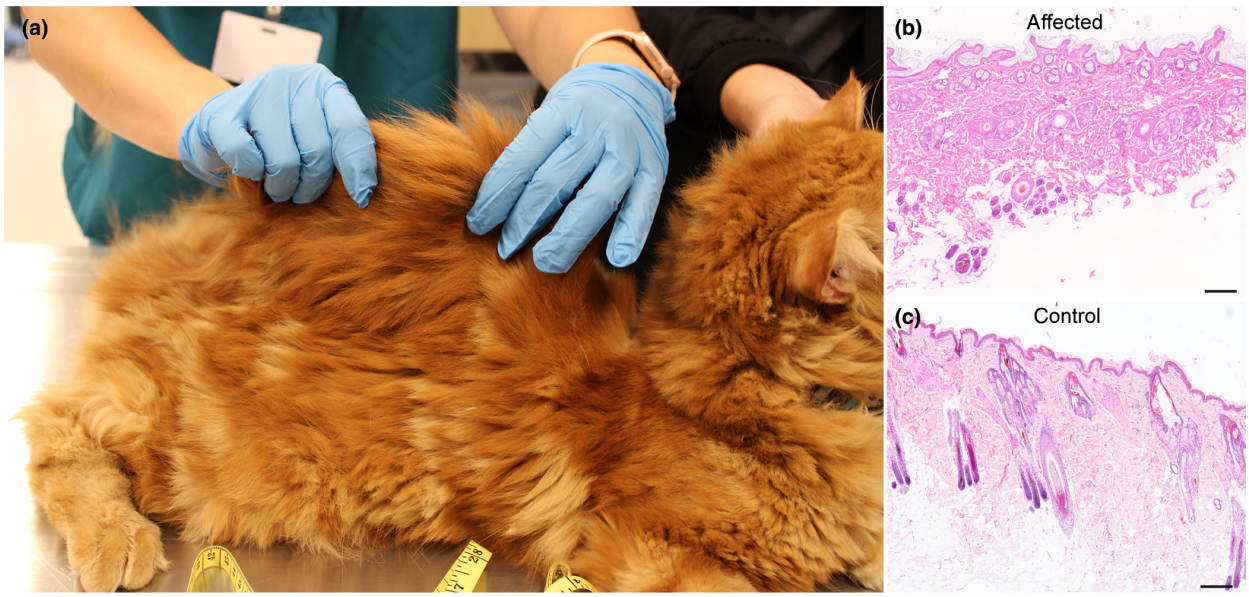

FIGURE 1 Clinical and histopathological phenotype of the affected cat. (a) Hyperextensible skin. (b) Histopathology of a skin biopsy showed reduced dermal thickness and irregularly arranged collagen fibers in the affected cat. (c) Skin of an unaffected control cat. Hematoxylin and eosin staining, scale bars = 200 μm.

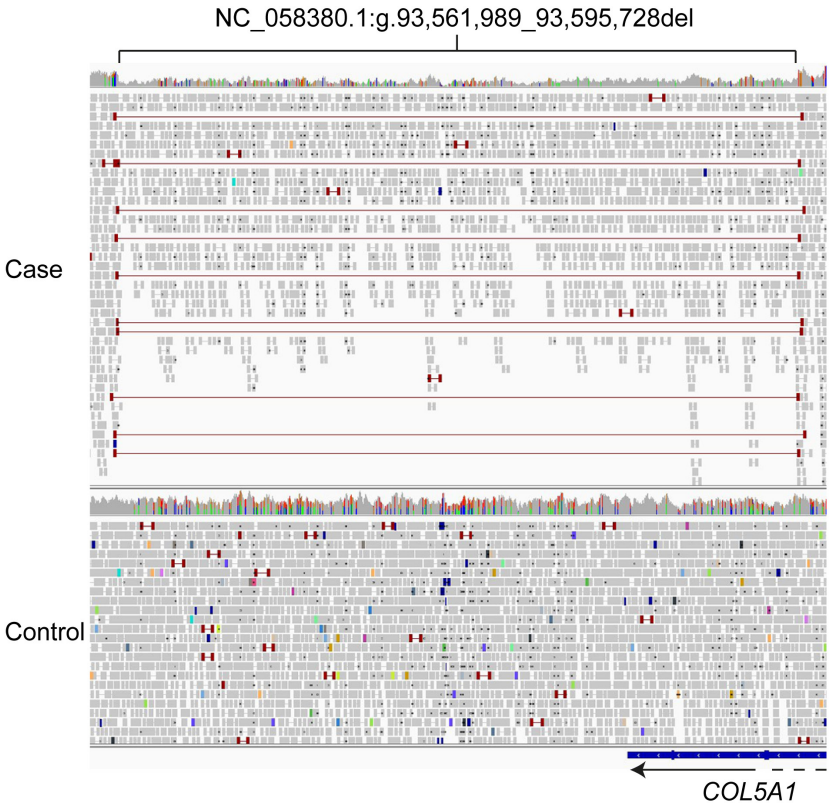

FIGURE 2 Details of the genomic variant. Integrative Genomics Viewer short-read alignments show the heterozygous deletion harboring the last two exons of *COL5A1* in the affected cat.

Genomic DNA of the cat was isolated from an EDTA-blood sample. A PCR-free library was prepared and sequenced with 2×150-bp reads at 22× coverage. The sequencing reads were aligned to the F.catus_Fcat126_mat1.0 reference assembly and variant calling was performed as described (Jagannathan et al., 2019). Comparison to 87 control genomes (Table S1) yielded three homozygous and 182 heterozygous private protein changing variants (Table S2). However, none of these variants were located in any of the 20 known functional candidate genes for EDS that were analyzed (Table S3).

Therefore, the short-read alignments of the affected cat were visually inspected for structural variants in the same 20 candidate genes using the Integrative Genomics Viewer (Robinson et al., 2011). This led to the discovery of a heterozygous deletion spanning 33 740 base pairs including the last two exons of *COL5A1* (Figure 2). The variant can be designated as NC_058380.1:g.93561989_93595728del. It was not present in any of the 87 control genomes.

COL5A1 is a well-established candidate gene for autosomal dominant cEDS (Symoens et al., 2012). The loss of the last two exons removes 127 codons from the wild-type open reading frame. It is therefore unlikely that the mutant allele with the genomic deletion results in a functional collagen type V α-1 subunit. In accordance with the clinical and histopathological examination, these findings substantiate and refine the diagnosis of cEDS in the investigated cat. This highlights the potential of whole genome sequencing as a tool for precision medicine and diagnostics in veterinary medicine.

AUTHOR CONTRIBUTIONS

Stefan J. Rietmann: Investigation; visualization; writing – original draft; writing – review and editing. **Sarah Nowell:** Conceptualization; investigation; visualization; writing – original draft; writing – review and editing. **M. Kelly Keating:** Conceptualization; investigation; visualization; writing – original draft; writing – review and editing. **Cynthia Bauer:** Conceptualization; investigation; writing – original draft; writing – review and editing. **Vidhya Jagannathan:** Data curation; 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 conflicts of interests.

DATA AVAILABILITY STATEMENT

All data are freely available. Accessions for the whole genome sequence data are given in Table S1.

ETHICS STATEMENT

The cats in this study were privately owned and samples were collected with the consent of their owners. The collection of blood samples from control cats was approved by the 'Cantonal Committee For Animal Experiments' (Canton of Bern; permit 94/2022; Approval date: 30-11-2022). The collection of samples from the affected cat was performed for diagnostic or therapeutic reasons and did not constitute an animal experiment in the legal sense.

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SUPPORTING INFORMATION

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