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A novel pathogenic variant in the corneodesmosin gene causing generalized inflammatory peeling skin syndrome with marked eosinophilia and trichorrhexis invaginata

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Abstract

Generalized inflammatory peeling skin syndrome (PSS) is a rare autosomal recessive genodermatosis caused by loss-of-function disease-causing variants of the corneodesmosin gene (*CDSN*), resulting in excessive shedding of the superficial layers of the epidermis. We describe a case of generalized inflammatory PSS in an infant, presenting at day two of life with ichthyosiform erythroderma and superficial peeling of the skin. Hair microscopy showed trichorrhexis invaginata. Normal amounts of skin LEKT1, a product of *SPINK5* on immunohistochemical staining excluded a diagnosis of Netherton syndrome. Genetic analysis revealed a homozygous novel complete *CDSN* deletion, estimated 4.6 kb in size, supporting the diagnosis of generalized inflammatory PSS.

KEYWORDS
corneodesmosin, Netherton syndrome, peeling skin syndrome

1 | INTRODUCTION

Generalized inflammatory peeling skin syndrome (PSS), otherwise known as type B PSS, is a rare autosomal recessive disorder caused by homozygous or compound heterozygous pathogenic variants in the corneodesmosin gene (*CDSN*). The biallelic loss-of-function disease-causing variants result in loss of corneodesmosin, a component of corneodesmosomes crucial for cell-to-cell adhesion in the upper epidermis.[1] The result is excessive shedding or detachment of the stratum corneum. Individuals with generalized inflammatory PSS present at birth or in early childhood with widespread erythroderma, peeling and scaling of the skin, severe pruritus, and atopy. Eosinophilia and elevated IgE have also been reported. Generalized inflammatory PSS and Netherton syndrome (NS) have

many overlapping phenotypic features.[2] Trichorrhexis invaginata was previously described as a feature specific to NS[3] and not previously identified in molecularly confirmed cases of generalized inflammatory PSS. We describe a case of generalized inflammatory PSS with a homozygous novel complete *CDSN* deletion, with marked eosinophilia and the presence of trichorrhexis invaginata on hair microscopy.

2 | CASE REPORT

A infant of a non-consanguineous South Asian (Indian) couple was born at 35 weeks of gestation by Cesarean section following premature rupture of membranes and failure to progress. His birth weight was 2.6 kg (75th percentile) and his skin was noted at the time of delivery to be normal apart from "a few red marks" on his face. He is the second child, with no family history of dermatological conditions. By day 2 of life he had generalized mild erythema, fine scaling, and peeling of the skin around his left foot. This was initially attributed to staphylococcal infection and treated with intravenous antibiotics.

Over the following month, he developed a generalized seborrheic dermatitis-like erythroderma with a thicker adherent scale on the scalp (Figure 1). He was admitted to hospital at 4 weeks of age for investigation of eosinophilia (7.7×10^9/L, normal range 0.0–1.0×10^9/L). He was systemically well with no lymphadenopathy or organomegaly. Investigations for immune disorders including Omenn syndrome and severe combined immune deficiency were negative. Specifically, he had mild CD8+ T cell lymphocytosis but otherwise normal proportions of lymphocyte subsets, including naïve CD4+ T and CD8+ T cells, and detectable T-cell receptor excision circles. There was no microthrombocytopenia. Total IgE was normal (30 kU/L). Plasma zinc and amino acids were normal. A skin biopsy of his thigh showed mild acanthosis and spongiosis, as well as intraepidermal neutrophils with microabscesses. There was a mild to moderate mixed inflammatory infiltrate in the upper dermis (Figure 2), consistent with subacute seborrheic dermatitis. He was commenced on regular applications of emollients and topical 1% hydrocortisone.

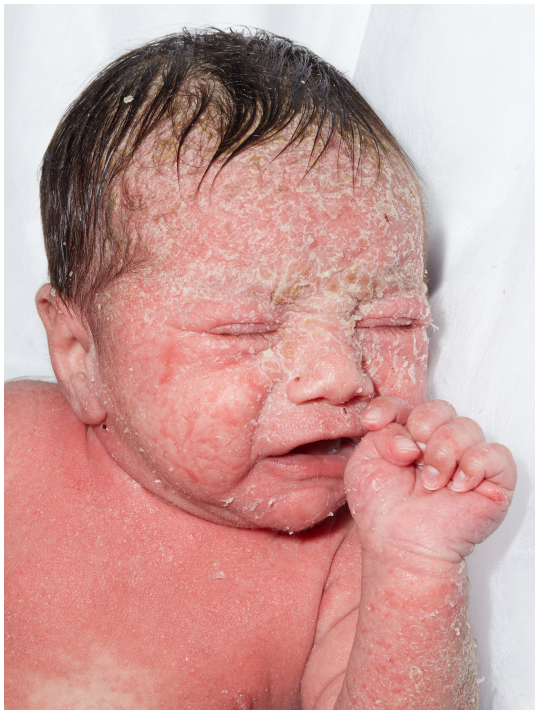

FIGURE 1 At 3 weeks of age with generalized seborrheic dermatitis-like erythroderma with a thicker adherent scale on the scalp

Hair clippings taken at 5 months of age showed trichorrhexis invaginata (bamboo hair shaft) on light microscopy (Figure 3). Based on this finding, NS was thought likely. Targeted genetic testing by Sanger sequencing detected a heterozygous pathogenic variant in *SPINK5* (NM_006846.3: c.2459delA, p.(K823Rfs*101)). Dosage analysis using high-density SNP-array (Affymetrix CytoScan Optima, Hg19) did not detect the second causative allele or loss of heterozygosity in the chromosomal region involving *SPINK5*.[4] Immunofluorescence staining showed the presence of LEKT1, predicted in the normal amount within the epidermis, excluding the working diagnosis of NS.

At 19 months, he was noted to have no improvement in his skin despite regular emollients and trials of moderate potency topical corticosteroids. Thick curly scalp hair was noted. The dermatological phenotype evolved, now characterized by areas of superficial peeling with underlying erythema (Figure 4). He had significant pruritus resulting in sleep disruption and areas of lichenification around his wrists and ankles. He had ongoing marked eosinophilia (up to 15.24×10^9/L). Total IgE had increased significantly to >3000 kU/L and this was accompanied by increases in the levels of allergen-specific IgE to common food allergens that he had been avoiding. He had no symptoms of other atopic conditions such as asthma and allergic rhinitis. In infancy, his weight was in the second percentile. By age 5 years, his weight and height were in the 25th percentile.

Based on the skin phenotype, a targeted exome-based panel including genes implicated in epidermolysis bullosa and ichthyosis was performed. Homozygous deletion of the entire *CDSN* was detected. The deletion was estimated at 4.6 kb in size with loss of the entire coding region of *CDSN*. The parents are heterozygotes for this *CDSN* deletion. They have normal scalp hair and skin. The novel *CDSN* deletion is classified as pathogenic (Class 5) according to ACMG variant classification guidelines.[5]

3 | DISCUSSION

Similarities between generalized inflammatory PSS and NS can be attributed to a shared mechanism of rapid breakdown of the stratum corneum. This results in impaired skin barrier function. In generalized inflammatory PSS, this is due to the impaired cell-to-cell adhesion from the absence of corneodesmosin, whereas the increased break down in NS is due to the increased activity of proteases such as kallikrein 5 (KLK5), resulting from the loss of inhibition by LEKT1,

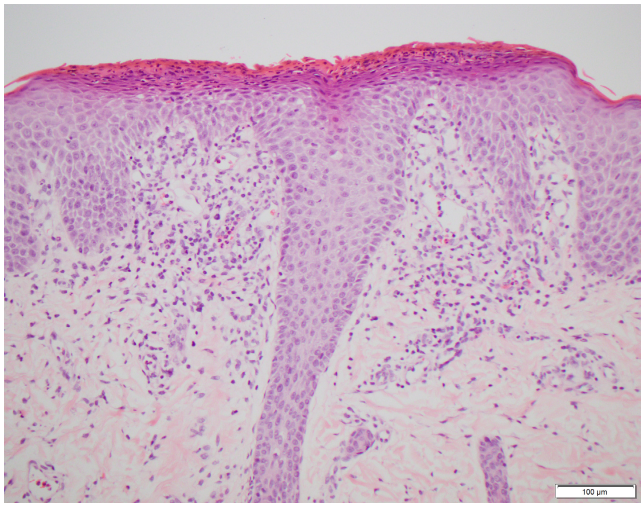

FIGURE 2 Punch biopsy of our patient's thigh H&E stain. Mild acanthosis and spongiosis were found, as well as intraepidermal neutrophils with microabscesses. There was a mild to moderate mixed inflammatory infiltrate in the upper dermis

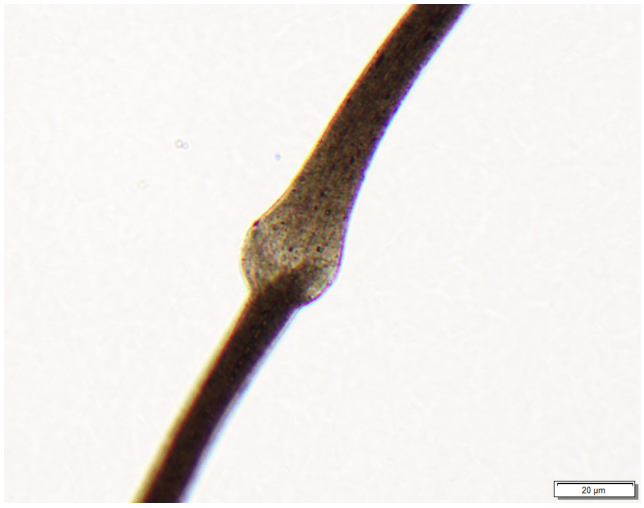

FIGURE 3 Our patient's hair with trichorrhexis invaginata found on light microscopy

a serine protease inhibitor.[6] The clinical overlap is predominantly limited to skin findings accompanied by laboratory features of eosinophilia and elevated total IgE.

Netherton syndrome can be associated with very sparse fragile hair, whereas generalized inflammatory PSS is traditionally associated with macroscopically normal hair. Detection of trichorrhexis invaginata in NS can be difficult and require multiple hair samples. We would expect similar difficulty in detecting trichorrhexis invaginata in generalized inflammatory PSS. This may explain this feature not having been previously detected in individuals with PSS, and if detected may have resulted in a clinical diagnosis of NS instead. We highlight the clinical utility of targeted next-generation sequencing-based multi-gene panels in the diagnosis of genodermatoses that are genetically and phenotypically heterogeneous.

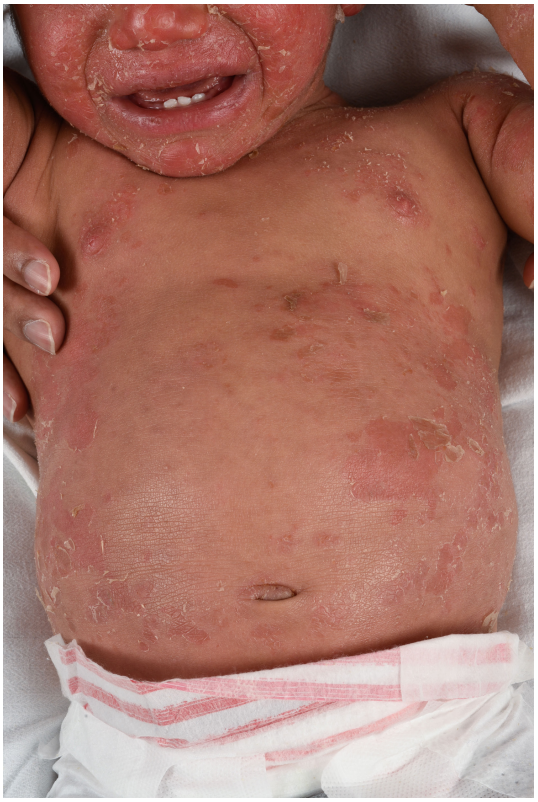

FIGURE 4 At 19 months of age a clinical finding of areas of superficial peeling with underlying erythema

Trichorrhexis invaginata has been previously described in a Jordanian boy with erythematous, scaly, and peeling skin, and short lusterless scalp and eyebrow hair.[7] Hair abnormalities described as trichorrhexis invaginata-like and pili torti-like were detected under light microscopy. The authors considered this boy had phenotypically generalized inflammatory PSS. However, this case was not confirmed by genetic testing. Netherton syndrome was not excluded by molecular testing and immunohistochemistry.

Heterozygous *CDSN* truncating variants resulting in abnormal corneodesmosin protein are associated with hypotrichosis simplex of the scalp (HYPT2).[8–10] The truncated corneodesmosin is found accumulated in the inner root sheath as well as in the superficial dermis.[8] The truncating variants cluster in exon 2 of *CDSN* and the aggregation of truncated proteins are proposed to exert a dominant-negative effect contributing to the phenotype.[9,11] This condition is associated with normal skin and progressive hair loss from the middle of the first decade of life until complete baldness, typically in the third decade of life. Corneodesmosin can normally be found in the inner root sheath of hair follicles, where it is thought to be involved in hair attachment. The phenotypically normal *CDSN* deletion-carrier parents may be explained by the absence of truncated protein due to whole gene deletion.

Generalized inflammatory PSS is caused by loss of the CDSN protein encoded by *CDSN*. Six homozygous disease-causing variants have been previously described in the literature.[1,12–20] Homozygous and compound heterozygous frameshift, nonsense, missense, and splice-site variants have been described (see Table S1). A founder

59.1 kb contiguous gene deletion (6p21.3), encompassing *CDSN* and 5 other genes was responsible for five unrelated cases of generalized inflammatory PSS in Japan.[14,16,17] The parents of probands were reported to be phenotypically normal and are assumed to be non-consanguineous. Affected probands have no additional phenotypic features apart from dermatological manifestations. These cases and the absence of the whole gene deletion in the population databases further strengthen the pathogenicity of the novel complete *CDSN* deletion in our case.

Our patient had peripheral eosinophilia and elevated circulating levels of total IgE and allergen-specific IgE also observed in other reported cases of generalized inflammatory PSS. The mechanisms driving this systemic immune dysregulation remain poorly understood. It is possible that exposure to external stimuli and allergens via defective skin barrier leads to activation of the innate immune system through the release of alarmins such as interleukin (IL)-33.[21] Type 2 innate lymphoid cells can be induced by alarmins, leading to the secretion of cytokines including IL-4, IL-5, IL-9, and IL-13 which polarize lymphocytes to T-helper 2 cells and may contribute to the development of an atopic diathesis in patients with generalized inflammatory PSS.

Effective treatment starts with an accurate diagnosis. In a mouse model, PSS CDSN^{iep}–/– mice were treated with anakinra, an IL-1 receptor antagonist, with significant improvement in clinical findings and histological inflammation.[22] A recent study explored using a liposomal delivery system for topical application of recombinant CDSN.[23] These studies pave the way for a potential treatment for *CDSN*-related generalized inflammatory PSS.

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We would like to thank our patient and his family for publication consent, and Blueprint Genetics for providing commercial sequencing and Sanger confirmation of the disease-causing variants. Open access publishing facilitated by The University of Auckland, as part of the Wiley - The University of Auckland agreement via the Council of Australian University Librarians. [Correction added on 30 May 2022, after first online publication: CAUL funding statement has been added.]

CONFLICT OF INTEREST

No conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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