SHORT COMMUNICATION

The Candle Spot: An Unreported Sign of SULT2B1-nEDD

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Congenital ichthyosis (CI), characterized by abnormal scaling often associated with erythroderma, is now classified within the group of epidermal differentiation disorders (EDD). This group comprises palmo-plantar keratoderma (pEDD), syndromic (sEDD) and non-syndromic (nEDD) forms of ichthyosis. EDDs are named based on the gene and grouped based on the function of the gene product (e.g. cholesterol metabolism enzyme-associated disorders including *SULT2B1*-nEDD) (1).

SULT2B1 encodes a sulfotransferase that converts cholesterol into cholesterol sulfate. Loss of function of this enzyme results in the accumulation of toxic cholesterol metabolites and disruption of normal cornification (2). Only a few patients with *SULT2B1*-nEDD have been reported in the literature (2, 3) and the clinical description remains lacking. Here, we report a new case involving a novel variant associated with a distinctive phenotype of "candle spot like" lesions.

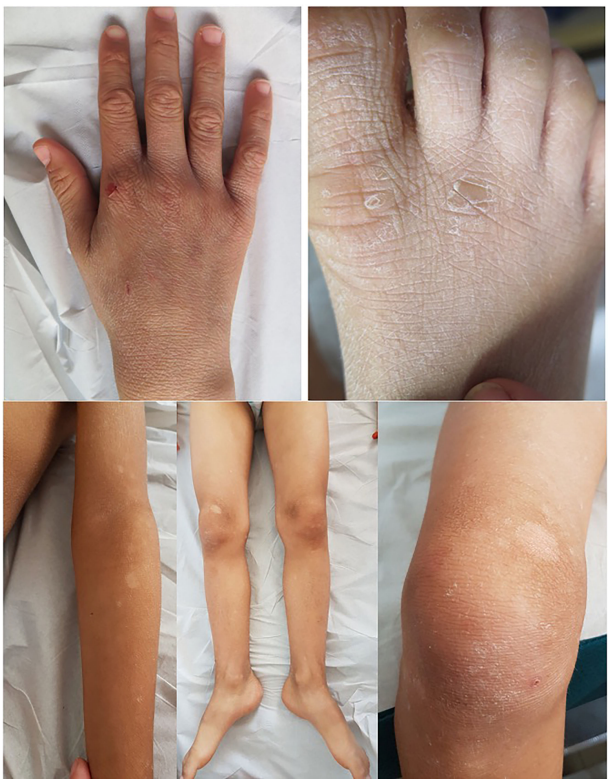

Fig. 1. Clinical presentation of the patient. Marked skin thickening and scaling, predominantly on the extensor surfaces of the legs and dorsal aspects of the hands. Small (5–10 mm) round white patches with a "candle-spot" appearance are visible in these areas.

CASE REPORT

A young boy originally from Tunisia was referred to our department for evaluation of skin anomalies. He had no personal or family medical history (three siblings, non-consanguineous parents). He presented at birth with scaling, which gradually worsened with age. By the age of 11, he exhibited generalized skin thickening and scaling (sparing the skin folds) with more pronounced involvement on the extensor surfaces of legs and the dorsal aspects of hands. In these areas, small (5 to 10 mm in diameter) round white patches with an appearance of "candle-spots" were observed (**Fig. 1**), which, according to the parents, were due to skin fragility. Erythema was very subtle, and no pruritus was reported. Additional findings included pectus excavatum, recurrent onychomycosis (with otherwise normal-appearing nails) and mild learning disabilities.

Using a next-generation sequencing (NGS) panel of 108 genes involved in EDD, we identified the c.102C>G (p.(Tyr34Ter)) variant in exon 2 of *SULT2B1 gene* (NM_177973.2) in a homozygous (or possibly hemizygous) state. Immunofluorescence analysis of SULT2B1 expression in a skin biopsy revealed a complete loss of the intense staining observed in the granular keratinocytes, in contrast to healthy control skin (**Fig. 2**).

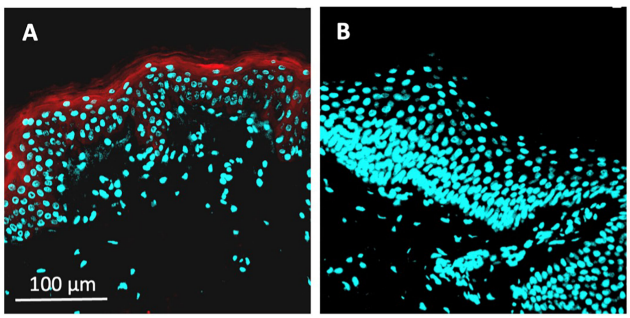

Fig. 2. Analysis of SULT2B1 expression by immunofluorescence in the patient's skin. Immunofluorescence staining of a skin section from a healthy control (A) and the patient (B) using an antibody specific to SULT2B1 (red), showing the complete absence of SULT2B1 protein in the *stratum granulosum* of the patient's epidermis. Nuclei are countersained with DAPI (blue).

Table I. SULT2B1 cases in literature

Family, Patient, Origin	Skin examination		Extracutaneous anomalies	*SULT2B1*[a] nucleotide variant	SULT2B1[b] protein variant	ClinVar reference	Pathogenicity	Publication
	At birth	During infancy						
Family1, P1, Tunisian	Collodion baby	Moderate to severe lesions made of skin thickening and scaling (lamellar aspect) sparing face and folds	None	c.[446C>T];[446C>T]	p.[Pro149Leu];[Pro149Leu]	VCV000426107.5	5 (pathogenic)	(2)
Family1, P2, Tunisian	Collodion baby	Not described	None	c.[446C>T];[446C>T]	p.[Pro149Leu];[Pro149Leu]	VCV000426107.5	5 (pathogenic)	(2)
Family1, P3, Tunisian				c.[446C>T];[446C>T]	p.[Pro149Leu];[Pro149Leu]	VCV000426107.5	5 (pathogenic)	(2)
Family2, P4, Turkish	Collodion baby	Skin thickening and erythema	None	c.[364dupA];[821G>]	p.[Met122AsnfsTer73];[Arg274Gln]	[VCV000426109.5];[VCV000426108.5]	5 (pathogenic) (bot alleles)	(2)
Family3, P5, Kurdish	Scaling and erythema	Skin thickening and scaling sparing face and folds	None	c.[71+2T>A];[71+2T>A]	p.[?];[?]	VCV000426110.5	5 (pathogenic)	(2)
Family3, P6, Kurdish		Skin thickening and scaling sparing face and folds, mild erythroderma		c.[71+2T>A];[71+2T>A]	p.[?];[?]	VCV000426110.5	5 (pathogenic)	(2)
Family4, P7, Pakistani	Collodion baby	Skin thickening and scaling (lamellar type) sparing face and folds. Eclabion Ectropion	Allergic rhinoconjunctivitis	c.[419C>T];[419C>T]	p.[Ala140Val];[Ala140Val]	Absent	3 (uncertain significance)	(3)
Family4, P8, Pakistani				c.[419C>T];[419C>T]	p.[Ala140Val];[Ala140Val]	Absent	3 (uncertain significance)	(3)
Family4, P9, Pakistani				c.[419C>T];[419C>T]	p.[Ala140Val];[Ala140Val]	Absent	3 (uncertain significance)	(3)
Our patient	Dry skin	Generalized skin thickening and scaling (sparing folds) with more pronounced involvement on the extensor surfaces of legs and the dorsal aspects of hands.	Pectus excavatum, Recurrent onychomycosis, Mild learning disabilities.	c.[102C>G];[102C>G]	p.[Tyr34Ter];[Tyr34Ter]	SCV006310947	4 (likely pathogenic)	This report

[a] Reference sequence SULT2B1 NM_177973.2. [b] Reference sequence SULT2B1 NP_814444.1

Based on previous evidence of toxic cholesterol metabolites accumulation in *SULT2B1*-nsEDD, a combination therapy consisting of 2% topical lovastatin and 2% cholesterol alongside regular emollients was applied to one side of the body over a period of more than two months. No skin clinical improvement of the skin was observed.

DISCUSSION

To date, nine patients with nEDD carrying *SULT2B1* variants have been reported; their characteristics are summarized in **Table I**. Seven of them were born as collodion babies, while the remaining two presented at birth with scaling and erythema. During childhood, ichthyosis was only briefly described by the authors and/or inconstantly documented through photographs. The condition ranged in severity and was characterized by skin thickening and variable scaling patterns, including white scales or brown thick scales of lamellar appearance with occasional erythroderma. Lesions were diffuse, often sparing the face and soles. None of the reported cases exhibited the particular "candle spots" appearance seen in our patient, which may reflect a certain degree of skin fragility, similar to that observed in epidermolytic ichthyosis caused by *KRT2* variants (*KRT2*-nEDD).

The nonsense variant identified in our patient has not been previously reported in the literature or in genomic databases (*dbSNP*, *GnomAD*). Immunostaining confirmed the absence of SULT2B1 expression in the patient's skin, likely due to nonsense-mediated mRNA decay. Given that previously reported loss-of-function variants in *SULT2B1* have been established as causative of ns-EDD (OMIM#617571) (2), we classified this novel variant as likely pathogenic.

In conclusion, we reported here a case of *SULT2B1*-nEDD caused by a novel variant, presenting with a previously unreported distinctive "candle-spot" phenotype. This clinical feature may aid in the suspicion of *SULT2B1* involvement in cases of EDD and could support the interpretation of variants of uncertain significance.

The authors have no conflicts of interest to declare.

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