A Novel Pathogenic Variant of *NECTIN4* Gene in a Child with Ectodermal Dysplasia-Syndactyly Syndrome

Dear Editor,

We describe the case of a 4-year-old Caucasian girl who was referred to our pediatric dermatology unit with several clinical manifestations involving skin, hair, teeth, and nails. She was the third child of healthy non-consanguineous parents.

On physical examination, she showed sparse, brittle, and dry scalp hair [Figure 1a], eyebrows, and eyelashes. The child had small, widely spaced, conical teeth [Figure 1b]. The patient also showed complete proximal cutaneous syndactyly limited to toes 2-3 [Figure 2a], minimal proximal cutaneous syndactyly of fingers 3-4 [Figure 2b], and nail dystrophy. The child had a supernumerary right nipple. She also showed palmoplantar hyperkeratosis with desquamation and diffuse xerosis, heat intolerance, and slightly reduced sweating. Due to the clinical presentation, we suspected a diagnosis of ectodermal dysplasia (ED).

Genetic analysis of genomic DNA extracted from peripheral blood confirmed the diagnosis of ED-syndactyly syndrome 1 (EDSS1). A mutation analysis based on Sanger sequencing of the coding exon of the *NECTIN4* gene was performed, revealing a homozygous missense variant of the *NECTIN4* (NM_030916) gene, c.1117C>T p.Arg373Ter.

To the best of our knowledge, the c.1117C>T variant was never described before in patients with EDSS1 and is absent in the general population genome aggregation database (gnomAD).[1] Family history of skin and genetic diseases was negative and the parents have not been tested. The patient is currently using topical treatments with emollients, urea, and other keratolytic products.

EDs are a heterogeneous group of inherited disorders characterized by alterations in two or more ectodermal structures, with at least one involving hair, nails, sweat glands or teeth.[2]

EDSS1 is a very rare type of ED with autosomal recessive transmission, due to mutations in the *NECTIN4* gene, which encodes the cell adhesion protein nectin-4.[3] Nectins are a class of calcium-independent immunoglobulin-like cell adhesion molecules that cooperate with cadherins to establish cell-cell adhesion, in particular at adherence junctions.[4]

Nectin4 is widely expressed in the epidermis, hair follicles, and cultured keratinocytes and it seems to play a fundamental role in hair morphogenesis and cycling.[3]

The mutation of the *NECTIN4* gene leads to defective ectodermal organogenesis. Nectin-4 is also implicated in the last phases of digit separation in the mouse embryo and for this reason, an impairment of the protein disrupts cell apoptosis in the interdigital tissue leading to cutaneous syndactyly.[3]

Few *NECTIN4* mutations have been described in literature, but three common markers (hair and teeth abnormalities, and cutaneous syndactyly) of EDSS1 were found in all cases.[3,5,6]

EDSS1 commonly involves hair, teeth, nails, and sweat glands with proximal cutaneous syndactyly of the fingers and/or toes.[1,3,6]

Hair alterations include hypotrichosis, sparse and fragile hair, eyelashes and eyebrows with progressive hair loss that can lead to nonscarring alopecia in adulthood. Hair morphology may also be modified with the presence of pili torti and swelling along the shafts with a great possibility of breakage.[1,3,6]

Dental abnormalities may include widely spaced teeth with peg-shaped and conical crowns, enamel defects, and hypodontia; nail dystrophy, hypoplastic nails, palmoplantar hyperkeratosis, variable sweating, and heat intolerance could also be present.[1,3,6]

In patients with suspected ED, clinicians should perform molecular genetic testing in order to achieve the correct diagnosis and to identify the specific syndrome among the heterogeneous group of EDs with possible correlations of genotype-phenotype.

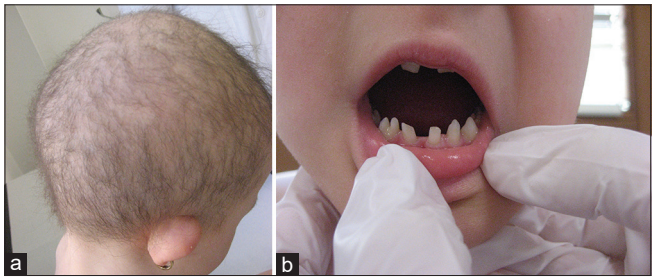

Figure 1: (a) Sparse, brittle, and dry scalp hair. (b) Small, widely spaced, conical teeth

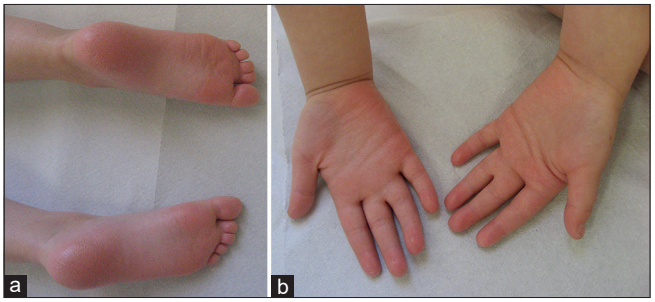

Figure 2: (a) Complete proximal cutaneous syndactyly limited to toes 2-3. (b) Minimal proximal cutaneous syndactyly limited to fingers 3-4

In conclusion, we reported a novel mutation in the *NECTIN4* gene causing EDSS1, contributing to the description of a very rare disease and its clinical manifestations.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Website: www.idoj.in

Quick Response Code

DOI: 10.4103/idoj.idoj_160_22

How to cite this article: Caroppo F, Fagotto L, Fortina AB. A novel pathogenic variant of *NECTIN4* gene in a child with ectodermal dysplasia-syndactyly syndrome. Indian Dermatol Online J 2023;14:110-1.

Received: 13-Mar-2022. **Revised:** 18-Apr-2022.
Accepted: 22-Apr-2022. **Published:** 18-Jul-2022.