A Novel Missense Variant in the *PVRL4* Gene Underlying Ectodermal Dysplasia-Syndactyly Syndrome in a Turkish Child

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Keywords

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Abstract

Ectodermal dysplasia-syndactyly syndrome is a rare autosomal recessive congenital disorder caused by mutations in *PVRL4* coding for nectin-4. Five different mutations in the *PVRL4* gene, including 3 homozygous missense mutations, have been reported. Here, we present an unreported missense variant (c.247C>T, p.His83Tyr) in a consanguineous Turkish family.

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Ectodermal dysplasia-syndactyly syndrome (EDSS1; OMIM 613573) is a rare form of ectodermal dysplasia. It is a clinically and genetically heterogeneous group of disorders characterized by alterations in 2 or more ectodermal appendages. [Freire-Maia, 1971; Brancati et al., 2010; Raza et al., 2015].

EDSS1 typically affects hair, nails, teeth, and sweat glands with cutaneous syndactyly of the fingers and/or toes. Abnormalities in the hair morphology include pili torti and swelling along the shafts with a tendency to

break [Brancati et al., 2010]. Eyebrows, eyelashes, and body hair are also sparse. The nails are hypoplastic. Dental findings consist of abnormally widely spaced teeth, with peg-shaped and conical crowns. Patients may have hypo- or hyperhidrosis.

The disease is very rare, and so far only 5 families are reported worldwide. Since the identification of the first causative mutation in the poliovirus receptor-related 4 gene (*PVRL4*; OMIM 609607) by Brancati et al. [2010], only 5 mutations have been reported to date [Brancati et al., 2010; Jelani et al., 2011; Fortugno et al., 2014; Raza et al., 2015].

Here, we report clinical and genetic data in a sixth family with this very rare disorder.

Case Report

The patient is the first child of healthy parents of Turkish descent. The parents are related, first cousins once removed. Family history is negative with regard to congenital malformations or similar disorders as seen in the child.

The girl was referred for etiologic diagnosis at the age of 2.5 years. Her psychomotor development and growth were normal. Biometrics were normal; the girl's weight was 11.9 kg (−0.9 SD), height 88.3 cm (−0.8 SD), and head circumference was 48 cm (−0.4 SD). She had dry, sparse scalp hair and eyebrows, with slightly increased hair

Table 1. Cases previously reported and present case

Reference	PVRL4 variant	Mutation type	Protein	Family/origin	Clinical features
Brancati et al. 2010	c.851G>A (exon 4)	homozygous missense mutation	p.Arg284Gln	Algerian, 4 siblings, consanguineous parents	partial cutaneous syndactyly, variably involving fingers and toes; sparse and coarse hair, with a tendency to break; identical abnormalities of eyebrows, eyelashes, and body hair; progressive hair loss that resulted in complete alopecia; abnormally widely spaced teeth, with peg-shaped and conical crowns; normal sweating
	c.554C>T (exon 3)	compound heterozygous: missense	p.Thr185Met	Italian, 2 siblings, nonconsanguineous parents	
	c.906delT (exon 5)	frameshift	p.Pro304HisfsX2		
Jelani et al. 2011	c.635C4G (exon 3)	homozygous missense mutation	p.Pro212Arg	Pakistani, consanguineous family, with 10 affected individuals	sparse scalp hair, sparse to absent eyebrows and eyelashes; conical- and cylindrical-shaped teeth with ill-defined surface morphology and enamel hypoplasia; hypoplastic finger and toe nails with nail plate degeneration and hyperkeratosis over the palms; bilateral cutaneous syndactyly of fingers and toes; no hypo- or hyperhidrosis
Fortugno et al. 2014	c.724G4A (exon 3)	homozygous missense mutation	p.Val242Met	Afghan, consanguineous parents with 3 affected individuals	cutaneous syndactyly, involving fingers 2–4 and toes 2–5; pili torti; progressive hair loss, leading to complete alopecia in the second decade of life; abnormally widely spaced and hypoplastic teeth; heat intolerance in individuals
Present case	c.247C>T (exon 2)	homozygous missense mutation	p.His83Tyr	Turkish, consanguineous parents	dry, sparse hair; small widely spaced teeth with conical crowns; small, thin, and brittle nails; dry skin with irregular regions of hypopigmentation; normal sweating; cutaneous syndactyly of toes 3–5 and mild webbing between the fingers 2–3

In all cases, the affected domain is the second immunoglobulin-like domain of nectin-4.

growth on the back. She had small widely spaced teeth with conical crowns. The nails were small, thin, and brittle, especially on the toes. She had dry skin with irregular regions of hypopigmentation. In addition, she had a cutaneous syndactyly of toes 3–5 and mild webbing between the second and third fingers (Fig. 1). She sweated normally. The nipples were slightly hypoplastic.

Method and Results

Genetic Analysis

To unravel the genetic defect of EDSS, targeted sequencing of the *PVRL4* gene in the patient was performed. All coding exons of the *PVRL4* gene (NM_030316 NP_112178) were amplified by PCR and subsequently analyzed by direct sequencing. The resulting sequences were aligned to database reference sequences and scanned for mutations. A single homozygous C to T substitution in exon 2 was identified in the patient (c.247C>T), resulting in a missense mutation (p.His83Tyr).

This variant was neither found in population databases (ExAC, 1000 Genome, and Exome Variant Server) nor in disease databases (OMIM, ClinVar). The variant is predicted to be pathogenic by in silico predictive algorithm (MutationTaster).

The mutated His83 residue is located in the second immunoglobulin-like V-type 1 domain of nectin-4 and is highly conserved among species (5 species among 6).

Discussion

EDSS1 is a very rare autosomal recessive disorder, with only 5 families reported to date.

EDSS1 is caused by recessive mutations in the *PVRL4* gene. This gene contains 9 exons and encodes a 510-amino acid nectin-4 protein, an emerging class of molecules acting in cooperation with cadherins to form cell-cell adhesion, especially at adherens junctions. Brancati et al. [2013] proposed the term “nectinopathies” for disorders caused by mutations in nectins. Besides EDSS1 (nectin-4 ectodermal dysplasia), this would also encompass nectin-1 ectodermal dysplasia (cleft lip/palate ectodermal dysplasia; CLPED1; OMIM 225060) [Brancati et al., 2013].

Fig. 1. Clinical features of ectodermal dysplasia-syndactyly syndrome. **a** Dry and sparse hair and eyebrows. **b, c** Small widely spaced teeth with conical crowns. **d, e** Bilateral webbing between the 2nd and 3rd fingers. **f** Bilateral cutaneous syndactyly of toes 3–5.

In the literature, 3 homozygous missense, 1 homozygous nonsense, and 1 compound heterozygous (missense and frameshift) mutations of this gene have been described in 5 families. Clinical and genetic data are summarized in Table 1 [Brancati et al., 2010; Jelani et al., 2011; Fortugno et al., 2014; Raza et al., 2015].

The missense mutation described here (p.His83Tyr) is novel and affects a highly conserved amino acid in the V-type1 immunoglobulin-like segment of the PVRL4 protein, the same domain where the other missense mutations have been described before. Our patient shows the characteristic phenotype described in the other families. However, as outlined in Table 1, there is variability in phenotypic expression. For instance, sweating is highly variable with a different intolerance to heat. In our case, the main distinctive feature is lack of hair loss; however, the girl is still very young, and in some cases, hair loss was described in the third decade of life.

In conclusion, we confirm a novel *PVRL4* mutation in the present family leading to the characteristic features of EDSS1.

Statement of Ethics

Genetic analysis for the patient was performed after obtaining parental informed consent, in a clinical diagnostic setting. Permission was granted for the publication of this paper and the accompanying patient's photographs. This study was approved by the KU Leuven University Hospitals Ethical Committee (B322201010111-S52853).

Disclosure Statement

The authors have no conflicts of interest to declare.

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