

A novel mutation in *LAMA3A* gene in a child with laryngo-onycho-cutaneous syndrome from the Indian subcontinent

Sir,

Laryngo-onycho-cutaneous or Shabbir syndrome (OMIM 245660) is a rare autosomal recessive epithelial disorder confined to the Punjabi Muslim population.¹ Herein, we present a child with laryngo-onycho-cutaneous syndrome demonstrating a new mutation in *LAMA3A* gene.

A 2-year-old Bangladeshi girl, born out of non-consanguineous parentage, presented with a history of hoarse cry since birth and spontaneous blistering, automatic reddish growths from eyelids, wounds on the body and discoloration of nails since 6 months of age. On examination, we noted superficial erosions and ulcers with exuberant granulation tissue (ranging in size from 7× 4 to 15× 4 cm) on the right cheek, upper chest and left shoulder [Figure 1a]. Multiple hyperpigmented to violaceous papules and plaques with central erosions and crusting were noted on the trunk and limbs [Figure 1b]. We also observed fleshy growths from both upper eyelids without any bleeding, discharge or matting. Brownish discoloration of teeth was observed along with few dystrophic nails [Figure 1c and d]. Ear, nose and throat referral was made and laryngoscopy revealed multiple tense bullae in the larynx [Figure 1e]. There was no history of breathing difficulty. Parents denied any history of recurrent skin or respiratory infections or similar complaints in any family member. Developmental milestones were

adequate for her age. Routine blood investigations and serum immunoglobulin levels were normal. Absence of hair or sweating abnormalities, ichthyosis, palmoplantar keratoderma, photosensitivity and acantholysis on skin histopathology ruled out ectodermal dysplasias and other genodermatoses associated with blistering. Ultrasonogram of the abdomen revealed a fatty liver with borderline splenomegaly.

We identified three different mutations in different exons of the *LAMA3A* gene on chromosome 18 by molecular analysis of the child's blood sample. A heterozygous two base pair deletion in exon 47 of the *LAMA3* gene resulted in a frame shift and premature truncation of the protein, 5 amino acids downstream to codon 1967 (p. Ser1967GlnfsTer5; ENST00000313654) was detected [Figure 2]. A heterozygous missense mutation was detected in exon 13 of the *LAMA3* gene (chr18:21390398C>T; depth: 164×), which led to substitution of amino acid tryptophan for arginine at codon 558 (p. Arg558Trp; ENST00000313654). This observed variation lies in the lamin in epidermal growth factor domain of the *LAMA3* protein. Another heterozygous missense variation in exon 28 of the *LAMA3* gene (chr18:21422480G>A; depth: 74×) was found which resulted in amino acid substitution of glutamine for arginine at codon 1153 (p. Arg1153Gln; ENST00000313654).

Based on clinical findings and mutations in the *LAMA3A* gene, we made a diagnosis of laryngo-onycho-cutaneous syndrome. We advised daily dressing of the wounds, topical steroids and antihistamines. Parents were taught about wound care and ophthalmologic intervention was sought for excision of conjunctival granulation tissue and amniotic membrane transplant. The child expired after 6 months following respiratory distress.

Laryngo-onycho-cutaneous syndrome is a localized variant of junctional epidermolysis bullosa. It starts in infancy with chronic erosions affecting the face (predominantly perinasal and perioral). The nails are involved with marked periungual and subungual inflammation. Hoarseness is a universal feature characterized by altered cry at birth. The teeth may be notched. Exuberant skin and mucosal granulation tissue formation can impair wound healing and result in laryngeal obstruction and blindness.² Although these findings are common to all types of junctional epidermolysis bullosa, the erosions

and bullae are much extensive in generalized junctional epidermolysis bullosa whereas minimal blistering with excessive granulation tissue formation is characteristic of laryngo-onycho-cutaneous syndrome. Conjunctival eye lesions, characteristic of laryngo-onycho-cutaneous syndrome, are rare in other subtypes of junctional epidermolysis bullosa.¹

The laminins are a family of heterotrimeric molecules, responsible for structural and functional integrity of basement membrane. Through the study of blistering skin diseases, it is now well-established that the $\alpha 3$ subunit of laminins-332, -321 and -311 plays an important role in mediating epidermal-dermal integrity and is essential for the skin to withstand mechanical stress.³ Most mutations in both Herlitz and non-Herlitz forms of junctional epidermolysis bullosa disease are restricted to three genes, *LAMA3*, *LAMB3* and *LAMC2*, that encode the α , β and γ subunits of laminin 332, respectively.⁴

The human *LAMA3* gene encodes 76 exons from 318 kb of genomic DNA at chromosomal location 18q11.2 and has two transcripts *LAMA3A* and *LAMA3B* (B1 and B2).³ In most laryngo-onycho-cutaneous cases of Punjabi origin, a homozygous recessive mutation has been detected in exon 39 of *LAMA3A* which encodes laminin 3A leading to the fore-shortening of a critical portion of the N terminus of the $\alpha 3$ chain of laminin-5 trimer.³ Studies suggest altered homeostasis of extracellular matrix due to secretion of abbreviated $\alpha 3$ chain by the basal keratinocytes.^{5,6}

In our patient, we detected a novel heterozygous 2-base pair deletion in exon 47, not reported till date, leading to premature truncation of protein, which could be the possible pathogenic mutation. Absence of the N-terminal region of



Figure 1a: Erosions with exuberant granulation tissue seen on the cheeks and chest



Figure 1b: Hyperpigmented papules and plaques with erosions on the surface present in the gluteal region



Figure 1c: A fingernail showing dystrophy



Figure 1d: Great toenail showing dystrophy



Figure 1e: Intact bullae seen in the larynx on laryngoscopy

laminin alpha 3a in laryngo-oncho-cutaneous syndrome results in excessive granulation tissue production at wound sites.⁵

We also found heterozygous missense mutations in exon 13 and exon 28, however, further studies are needed to highlight its significance. The different mutations reported in laryngo-oncho-cutaneous syndrome till date are described in Table 1.⁵⁻⁷

Declaration of patient consent

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

Table 1: Reports of mutations in laryngo-onycho-cutaneous syndrome

Authors (year)	Number of patients	History of consanguinity (yes/no)	Country of origin/descent	Clinical diagnosis	Type and site/locus of mutation
Mclean <i>et al.</i> (2003) ⁵	15 families	Yes	Muslim population in Punjab region of Pakistan and India	JEB-LOC	Homozygous recessive mutation Single nucleotide insertion151insG in exon 39 of <i>LAMA3A</i> This frame shift mutation causes premature truncations of N-terminal
Figueira <i>et al.</i> (2007) ⁶	1 case	No	Irish descent	Overlapping features of JEB and LOC	Paternal <i>LAMA3</i> splice mutation which would have affected the C terminus common to the <i>LAMA3A</i> and <i>LAMA3B</i> variants and a maternal exon 39 117N missense mutation affecting only the <i>LAMA3A</i> variant causing JEB-LOC features
Barzegar <i>et al.</i> (2013) ⁷	5 cases from 2 families	-	Iran	JEB-LOC	Homozygous nonsense mutations in the last codon of exon 39 of the laminin α 3a (<i>LAMA3</i>) gene (p. Gln57X) and a donor splice site mutation in <i>LAMA3</i> (IVS57+5G>A) in the first and second family, respectively
Our case (2020)		No	Bangladesh	JEB-LOC	A heterozygous two base pair deletion in exon 47 of the <i>LAMA3</i> gene resulting in a frame shift and premature truncation of the protein 5 amino acids downstream to codon 1967 was detected

JEB: junctional epidermolysis bullosa, LOC: laryngo-onycho-cutaneous syndrome, *LAMA3*: lamininA3

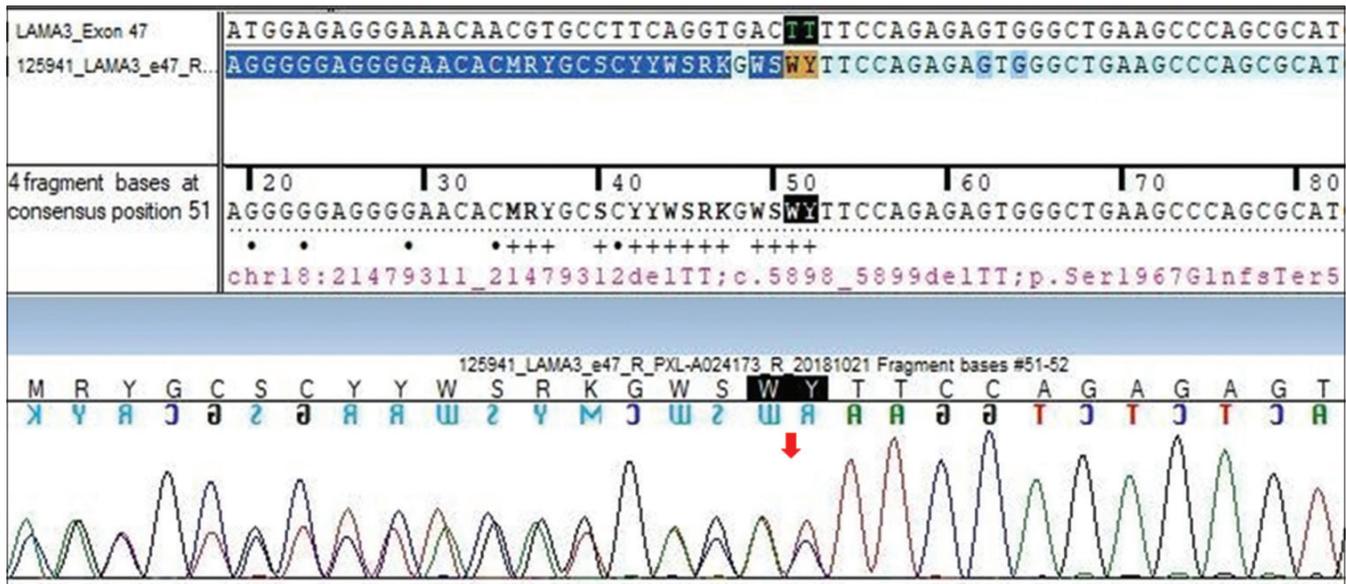


Figure 2: Sequence chromatogram and alignment to the reference sequence showing the variation in exon 47 of the *LAMA3* gene (chr18:21479311_21479312delTT; c.5898_5899delTT; p. Ser1967GlnfsTer5) detected in heterozygous condition

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Conflicts of interest

There are no conflicts of interest.

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References

- Cohn HI, Murrell DF. Laryngo-onycho-cutaneous syndrome. *Dermatol Clin* 2010;28:89-92.
- McGrath JA. Genetic blistering diseases. In: Chalmers R, Barker J, Griffiths C, Bleiker T, Creamer D, editors. *ROOK's Textbook of Dermatology*. 9thed. West Sussex, UK: John Wiley and Sons, Ltd.; 2016. p. 71.14.
- Hamill KJ, Paller AS, Jones JC. Adhesion and migration, the diverse

- functions of the laminin alpha3 subunit. *Dermatol Clin* 2010;28:79-87.
4. Varki R, Sadowski S, Pfendner E, Uitto J. Epidermolysis bullosa. I. Molecular genetics of the junctional and hemidesmosomal variants. *J Med Genet* 2006;43:641-52.
 5. McLean WH, Irvine AD, Hamill KJ, Whittock NV, Coleman-Campbell CM, Mellerio JE, *et al.* An unusual N-terminal deletion of the laminin alpha3a isoform leads to the chronic granulation tissue disorder laryngo-onycho-cutaneous syndrome. *Hum Mol Genet* 2003;12:2395-409.
 6. Figueira EC, Crotty A, Challinor CJ, Coroneo MT, Murrell DF. Granulation tissue in the eyelid margin and conjunctiva in junctional epidermolysis bullosa with features of laryngo-onycho-cutaneous syndrome. *Clin Exp Ophthalmol* 2007;35:163-6.
 7. Barzegar M, Mozafari N, Kariminejad A, Asadikani Z, Ozoemena L, McGrath JA. A new homozygous nonsense mutation in LAMA3A underlying laryngo-onycho-cutaneous syndrome. *Br J Dermatol*. 2013 Dec;169(6):1353-6.

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