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Case Report

A TRIO CASE STUDY SHOWING NOVEL MUTATION IN *LAMB3* GENE CAUSING JUNCTIONAL EPIDERMOLYSIS BULLOSA [INTERMEDIATE/SEVERE]

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ABSTRACT

Background: Junctional epidermolysis bullosa (JEB) is a type of Epidermolysis Bullosa, a group of genetic conditions that cause the skin to be very fragile and to blister easily. It is categorized into: the Herlitz type and the Non-Herlitz type. JEB is inherited in an autosomal recessive pattern. Most common genetic mutations associated are *LAMB3*, *COL17A1, or LAMC2*, and *LAMA3* genes.
Case presentation: This study reports a consanguineous couple carriers for pathogenic variant for *LAMB3* gene, with an affected child with a homozygous mutation in the *LAMB3* gene causing Herlitz type of Junctional epidermolysis Bullosa/ Non-Herlitz type of junctional epidermolysis bullosa. Furthermore, prenatal diagnosis for the Gravida also showed the same pathogenic variant.
Conclusion: For autosomal recessive genetic conditions, it is advisable to perform genetic testing for the affected individual and further parental segregation which on whole considered as a Trio whole-exome sequencing or next-generation sequencing to detect the genes associated with the disease. Depending on the type of variants involved prenatal diagnosis for the next pregnancy and treatment or management (if available) options can be offered/discussed.

Key Words: Epidermolysis Bullosa, Skin blistering, Trio-exome sequencing, *LAMB3*, Trio study

INTRODUCTION

Junctional epidermolysis bullosa (JEB) is a group of heritable mechanobullous diseases characterized by blistering skin or tissue separation at the lamina lucida. This blistering could be due to little or no trauma. (1,2) EB affects the epithelial lining of the organs and is often termed the “butterfly children” as the skin of the younger individuals is said to be as fragile as a butterfly's wings. Worldwide, about 50 in 1 million live births are diagnosed with Epidermolysis bullosa (EB), out of these 92% are Epidermolysis bullosa simplex (EBS), 5% are Dystrophic epidermolysis bullosa (DEB), 1% is JEB and the rest 2% remains unknown. Incidence in India is estimated to be 54 per million live births (according to National Epidermolysis bullosa Registry) (3). JEB is categorized into two different types Severe JEB(earlier known as Helitz JEB) and Intermediate JEB (earlier known as Non-Herlitz). The H-JEB variant is characterized by the early demise of the individuals affected usually within the first year of life with severe blistering of the skin over the large regions of the body, it could also affect the mucous membranes, such as the moist lining of the mouth and the digestive tract. On the other hand, nH-JEB shows milder phenotypic symptoms with lifelong blistering with a normal life span. (4) As per OMIM three major genes *LAMA3*, *LAMB3*, and *LAMC2* that encode the subunit polypeptides of laminin-5 are associated with JEB. Out of which *LAMB3* accounts for about 80% of all the laminin 5 mutations. (5) JEB represents a group of skin diseases that basically follows an autosomal recessive pattern of inheritance, in which the fetus or the children affected would be born to an obligate carrier parent who doesn't show any phenotypes of the disease. (6)

The present study reports a boy child with a homozygous mutation in the *LAMB3* gene causing Herlitz type of Junctional epidermolysis Bullosa/ Non-Herlitz type of junctional epidermolysis bullosa. Trio sequencing in a specific targeted population especially in cases of consanguineous families or the endogamous populations helps in identifying and understanding the austosomal recessive conditions. Henceforth the risk estimation for the next generations can be evaluated and accordingly the individuals can be guided in paving way for decision making.

CASE DESCRIPTION

A one-month-old boy born to a consanguineous couple presented with clinical indications of skin blistering and excoriation of the skin since birth. He is suspected to be affected with epidermolysis bullosa and has been evaluated for pathogenic variations. Henceforth, the index case was evaluated for whole-exome sequencing (WES) to identify the molecular and genetic basis of suspected genetic conditions. Selective capture and sequencing of the protein-coding regions of the genome/genes are performed. DNA extracted from blood was used to perform targeted gene capture using an exome capture kit. The libraries were sequenced to mean >80-100X coverage on Illumina sequencing platform. GATK best practices framework for identification of variants in the sample using Sentieon (v201808.07) was followed. (7)

The WES analysis showed a homozygous four-base pair duplication in exon 18 of the *LAMB3* gene (chr1:g.209618515dupAGCA; Depth: 150x) resulting in a frameshift and premature truncation of the protein 17 amino acids downstream to codon 950 (p.Ser950AlafsTer17; ENST00000391911.5) was detected. This variant in the *LAMB3* gene was not reported earlier in the 1000 genomes, gnomAD, and the internal databases. However, based on the above evidence this *LAMB3* variation is classified as a pathogenic variant.

Going forward parental segregation was performed for the carrier status of pathogenic variants in the *LAMB3* gene by Next generation sequencing (NGS). The targeted analysis revealed both the parents to be carriers of a pathogenic variant in the *LAMB3* gene (p.Ser950AlafsTer17). However, the p.Ser950AlafsTer17 variant has not been reported in the 1000 genomes database and has a minor allele frequency of 0.006% in the internal database. Later on prenatal diagnosis was done for the fetus to evaluate for the same gene mutation. The fetus also presented with the pathogenic variant in the *LAMB3* gene.

DISCUSSION

Intermediate junctional epidermolysis bullosa 1A (OMIM#226650) and Severe junctional epidermolysis bullosa 1B

(OMIM#226700) are caused by homozygous or compound heterozygous mutations in the *LAMB3* gene (OMIM*150310). Intermediate junctional epidermolysis bullosa 1A (JEB1A) is a blistering disease of the skin and mucous membranes. Generalized trauma-induced blistering occurs from birth. Blistering is less severe than in severe JEB, usually without the tendency for developing chronic granulation tissue. The plane of skin cleavage is through the lamina lucida of the cutaneous basement membrane zone. Nail dystrophy or loss and dental enamel defects are present. Scarring or nonscarring alopecia and diffuse hair loss may occur. Blistering does not affect the life span of affected individuals. Severe junctional epidermolysis bullosa 1B (JEB1B) is a skin blistering disorder characterized by extreme fragility of the skin and epithelia of various extracutaneous tissues. Blisters and erosions are present at birth. Blister formation occurs within the dermal-epidermal basement membrane zone. (8,9). The *LAMA3*, ***LAMB3***, and *LAMC2* genes each provide instructions for making one part (subunit) of a protein called laminin 332. Laminins are a family of network-forming trimeric proteins that are significant constituents of the basal lamina, an extracellular matrix layer of the basement membrane. Henceforth any mutations in these genes would be associated with the defective or non-functional version of the protein causing JEB. (10). As per the study by Aoi Nakano *et.,al*, we see mutations primarily found in the **β**3 chain of the laminin 5, the *LAMB3* gene is associated with the HEB. They studied the *LAMB3* gene in about 22 families out of which 8 novel mutations were identified. Six out of 8 have created a downstream PTC (premature termination codon), and the other two showed an effect in the intron-exon borders potentially resulting in aberrant splicing. (15)

As per the study by Aoi Nakano et al., 54 mutations were identified in a cohort of 24 patients, 22 of them novel. Mutations were identified in all three laminin 5 genes, with the majority in *LAMB3*. The common hotspot of *LAMB3* gene, R365X is seen in 14 of 36 *LAMB3* gene mutations. Thirteen of 15 Herlitz JEB patients were homozygous or compound heterozygotes for PTC mutations, while in eight of 12 non-Herlitz JEB patients a PTC mutation was combined with a missense or splicing mutation.The other four of non-HJEB showed compound heterozygous for PTC mutations. (4)

CONCLUSION

In this study we did a Trio Exome sequencing (ES) initially for the affected child and later targeted analysis was performed in both the parents for the gene *LAMB3* which is associated with Epidermolysis bullosa, Trio ES helps in aiding parental counseling and decision making in many cases. We have demonstrated that using medical trio ES followed by a targeted panel for prenatal diagnosis allows detection of autosomal recessive genetic conditions. Further which this helps in early detection and the management of the condition, if available.

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Conflict of Interests The authors declare there is no conflict of interest.

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Authors Contribution: Shaile Bandla has conceived the idea, done with literature search, and wrote the initial draft, Srinadh.B provided the framework and edited the manuscript, Soumya Peruchala helped with the clinical data, Shaile Bandla contributed to the literature search, and finalized the manuscript. All the authors have read and approved the manuscript.

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