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EPIDERMOLYSIS BULLOSA SIMPLEX WITH MUSCULAR DYSTROPHY ASSOCIATED WITH PLEC DELETION MUTATION

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Epidermolysis bullosa simplex with muscular dystrophy (EBS-MD; OMIM #226670) is an autosomal recessive disorder characterized by neonatal blistering and later-onset muscle weakness.

EBS-MD is caused by mutations in the *PLEC* gene located on 8q24 which encodes plectin-1, a giant (>500 kDa) multifunctional cytolinker abundantly expressed in tissues subjected to great mechanical stress, that plays a crucial role in cytoskeleton stability, cell and tissue integrity, and regulating signal complexes.¹

The mutated protein leads to disruption of the myofibrillar intermediate apparatus and aberrant binding of hemidesmosomes to intermediate filaments with consequent muscle loss and skin blistering, respectively.^{2,3}

We report a homozygous in-frame deletion mutation in the *PLEC* gene related to EBS-MD.

Case report. A 29-year-old woman was referred for slow progressive muscle weakness and hoarseness starting at her early 20s. She reported trauma-induced blisters since she was born that diminished as she grew older. Examination revealed diffuse alopecia, blisters in various stages of healing, and limb-girdle muscle weakness. Shoulder abduction strength was modified Medical Research Council grade 3–/5, elbow flexion-extension 3/5, wrist flexion 4+/5, wrist extension 3/5, hip flexion and abduction 4–/5, knee flexion-extension and ankle dorsiflexion 5/5, and head extension 4+/5.

Muscle MRI T1 sequences showed fatty degenerative changes predominantly in deltoids, gluteus maximus and minimus, and both fascia-latae tensors. EMG showed myopathic changes and repetitive stimulation without decremental response. Creatine kinase levels ranged from 381 to 686 U/L. Skin biopsy exhibited intraepidermal blisters and dermal mononuclear inflammatory infiltration. Muscle biopsy demonstrated characteristic dystrophic changes comprising extensive lipomatosis, moderate variation in fiber size with isolated angulated fibers, increased internal nuclei, some

regenerating rounded fibers, endomysial and perimysial fibrosis, and histochemical predominance of type 1 fibers and occurrence of type 2C fibers. Spirometry parameters, cardiologic evaluation, and cardiac ultrasound were normal. There is no known muscle disease in the family or consanguinity known by parents.

DNA sample of the patient was used for enrichment of a sequencing library using the HaloPlex Target Enrichment System protocol (Agilent Technologies, Santa Clara, CA). The enrichment was performed using the probes of MYOcap gene panel version 2 that is targeted to the exons of 236 genes that are known or predicted to cause muscular dystrophy or myopathy. The enriched library was sequenced using the Illumina MiSeq Sequencer (Illumina, San Diego, CA). The acquired sequencing data were filtered against 1000 Genomes and NHLBI Exome Sequencing Project databases so that variants with population frequency less than 1% remained. In the results, there was a previously unknown homozygous *PLEC* mutation c.2594_2596delTCT p.F865del (according to transcript NM_201380). The finding was verified by Sanger sequencing.

Discussion. Mutations in the *PLEC* gene have been shown to cause EBS-MD as well as EBS with pyloric atresia (OMIM #612138), EBS Ognia type (OMIM #131950), limb-girdle muscular dystrophy type 2Q (OMIM #613723), and the recently described EBS with nail dystrophy (OMIM #616487).⁴ All reported mutations in the *PLEC* gene are recessive, apart from the mutation p.R2110W that causes dominant Ognia type EBS. Most mutations causing EBS-MD have concentrated on exons 32 and 33, but pathogenic mutations have been reported from every part of the gene. It is not known why certain mutations cause certain phenotypes. It has been postulated, however, that the phenotypic variability could be related to perturbed interactions between plectin and its counterparts and/or differences in the size of the truncated polypeptides.⁵ It has also been suggested that in-frame insertions and deletions, like the deletion in our patient, could cause milder phenotypes than other mutations.⁶ Amino acid p.F865 deleted in our patient is part of the spectrin 3 repeat of the complete protein. The functional

importance of p.F865 is not known, but p.F865 is evolutionarily highly conserved, and therefore, it is likely to cause a disease when mutated.

We report a case of EBS-MD related to a homozygous in-frame deletion mutation in the *PLEC* gene.⁷ Hoarseness and alopecia, rarely reported, were main complaints.⁷ Neither cardiac nor respiratory compromise was evident. The clue to diagnosis was the patient's history of neonatal blisters. Muscle MRI was concordant with strength clinical evaluation and could be helpful for future comparisons with other myopathies.

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