Reviewer’s report

Title: A novel PLEC nonsense homozygous mutation (c.7159G>T; p.Glu2387*) causes epidermolysis bullosa simplex with muscular dystrophy and diffuse alopecia: a case report

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Reviewer: J Uitto

Reviewer's report:

This manuscript describes a patient with epidermolysis bullosa simplex with muscular dystrophy due to a novel homozygous nonsense mutation in PLEC. The patient has characteristic skin, nail and tooth abnormalities which accompany late onset muscular dystrophy. A somewhat unusual feature is diffuse alopecia which, however, has been reported previously in association with EBS-MD.

I have a few comments for improvement:

1. A somewhat unusual feature in this case is the reported "diffuse non-scarring alopecia" which is not particularly impressive in this 28 year-old patient as shown in Fig. 1a. The manuscript states (line 92) that "…at an early age, she…showed extensive nail dystrophy and hair weakness". Can the authors be more precise of the age? What is meant by hair weakness: Is it fragility and brittleness of the hair or extensive shedding which might lead to diffuse non-scarring alopecia? Was there any attempt to examine the morphologic features of the hair shaft or determine the hair cycle stage by examination of the hair bulb (anagen/telogen/catagen ratio)? The authors are also hedging their interpretation that the diffuse alopecia is a result of PLEC mutation bringing up the possibility of "environmental factors". It is not clear what such factors might be, but the authors should also consider hormonal influences and state specifically whether this patient had any hormonal imbalance or not. Also, it would be of interest to know if there is familial history of alopecia particularly in the females.

2. The mutation analysis is competently performed and demonstrates a homozygous stop codon mutation. However, the interpretation of the consequences of this mutation is muddled. For example (line 120) the authors state that this stop codon results in down regulation of the corresponding mRNA through nonsense-mediated mRNA decay. While this may be true, it was not documented in this study and should not be stated as a fact.
3. The authors conclude (line 140) that since the mutation is located in exon 31 this mutation probably causes the disease by the expression of shortened plectin polypeptide, i.e., the rodless truncated isoform of plectin. The authors should clarify this interpretation by indicating that the disease is due to lack of full-length variant of plectin, and the rodless variant which is devoid of exon 31 due to alternative splicing may explain the relatively mild phenotype noted in this patient, including late onset of muscular dystrophy. In this context, the authors should note that a previous publication (Pulkkinen et al., Hum. Mol. Genet. 5L1539-46, 1996), reported Japanese sisters with EBS-MD whose muscle involvement was not noted until in their 40s.

Minor points:

* Line 38: "…plectin, a protein expressed in epithelial, muscles and fibroblasts". This statement mixes tissue types, organs and cells, and should be corrected to define the cell or tissue types.

* Line 42: "…28-year-old girl…” should be changed to "female"

* Line 50: The statement "This mutation predicts the expression of shortened plectin polypeptides" is confusing. The mutation does not predict synthesis of the rodless truncated form of plectin, which is constitutively expressed. Rather the mutation predicts the absence of the full-length isoform.

* Line 61: The archaic descriptives, epidermolytic, lucidolytic and dermatolytic, should be deleted.

* Line 162: The description of the compound heterozygous mutations in two patients is confusing and should be modified to indicate both mutations in one patient first followed by indication of the mutations in the second patient.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Needs some language corrections before being published

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