Reviewer’s report

Title: A novel elastin gene frameshift mutation in a Russian family with cutis laxa: a case report

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Reviewer: Zsolt Urban

Reviewer's report:

The authors investigated a frameshift mutation in the elastin (ELN) gene discovered in a Russian family with cutis laxa. The mother and son both presented with loose, inelastic skin with a prematurely aged appearance. This mutation was detected by exome sequencing and confirmed by Sanger sequencing in both subjects. This mutation was novel and unreported in ExAC, 1000 Genomes Browser, and Genotek samples (65,000+). Full patient medical summaries were provided allowing for the analysis of possible links between these diseases and the primary phenotype of cutis laxa. These phenotypes can be seen in several disorders including progeria, congenital cutis laxa, wrinkly skin syndrome, and geroderma osteodysplasticum, however, it is necessary to molecularly identify the root cause of the disease to target the specific disease to ensure proper treatment of patients.

Strengths

1. Novel ELN mutation adds to the reported literature of mutations.
2. Full medical details provided to show which concomitant disease may be seen with this disease.

Major Comments

1. Analysis of the text (excluding the bibliography) by iThenticate reveals 42% similarity to previously published work. To ensure that the text is not plagiarized, the authors will need to perform their own text similarity searches and rewrite sections of the manuscript that have high similarity to previously published work.
2. The content of the manuscript is repetitive and redundant. In particular, whole sentences in the abstract are repeated verbatim in the text. Repeated sentences need to be rewritten or eliminated.
3. Word use and sentence structure are incorrect at places. The organization of the text into paragraphs is also poor. We recommend that the authors seek help from an English editor to improve the language and clarity of the manuscript. Many of the use errors are listed as minor comments.

4. The ELN gene is subject to extensive alternative splicing. The use of different transcripts to number mutations creates a great deal of confusion in the literature on ELN. The authors contribute the confusion by using a transcript (NM_001278915.1) that is not used in any other prior publications. Ideally, the best transcript to use is one that includes the most exons. The most commonly used transcripts to report mutations in prior publications are ENST0000358929 (NM_0012789391) or NM_000501. The authors should use one of these transcripts to report their mutation and convert other mutations cited in the paper to the same transcript for better comparison. Mutation c.2156delG cited on page 4 of the manuscript is consistent with numbering using ENST0000358929

Minor comments:

1. Abstract: Bold Background, Case Presentation, and Conclusions

2. Abstract, page 2, line 7: Abbreviate "cutis laxa" after first use. "Cutis laxa (CL) is a rare…"

3. Abstract, page 2, line 11: Change "Autosomal dominant cutis laxa characterized" to "Autosomal dominant cutis laxa is characterized"

4. Abstract, page 2, line 12: Change "sagging inelastic skin associated in some cases with…" to "sagging, inelastic skin and in some cases is associated with internal organ involvement."

5. Abstract, page 2, lines 14-15: Combine First two sentences with the linker "which includes": "We report a familial case of autosomal dominant cutis laxa which includes a 33-year-old woman and her 11-year-old son…"

6. Abstract, page 2, line 17: Change "In both patients we identified…" to "In both patients, we identified…"

7. Abstract, page 2, line 19: Replace "33 exon" with "exon 33". Note that the exon numbering depends on the reference transcript used. If the authors switch to using ENST0000358929, this phrase will need to be changed to "exon 34".

8. Abstract, page 2, line 20: Change "reported previously" to "previously reported"
9. Abstract, page 2, line 23: Change "Our results show novel frameshift mutation" to "Our results show a novel frameshift mutation"

10. Abstract, page 2, line 24: The last sentence of the abstract does not capture the main conclusion of the manuscript. Instead the main conclusion would be that there are some diseases with similar phenotypes which need to be identified properly by using molecular techniques (like WES) to ensure proper treatment is provided.

11. Background, page 2, line 30: Change "Cutis laxa (CL), or elastolysis is a…" to "Cutis laxa (CL), or elastolysis, is a…"

12. Background, page 2, line 31: Change "characterized by loose redundant skin folds." to "characterized by loose, redundant, wrinkled skin."

13. Background, page 2, line 32: Change "X-linked form caused by…" to "Th formerly classified X-linked form, caused by mutations…"

14. Background, page 2, line 36: Reference 2 used here is incorrect. Use instead more relevant papers showing that X-linked cutis laxa (occipital horn syndrome) is allelic with Menkes disease (eg. Das et al. 1995. Am J Hum Genet 56:570-576 or Moller et al. 2005 Hum Mutat 26:84-93).

15. Background, page 2, line 36: Change "Cutis laxa caused by…" to "Cutis laxa is caused by…"

16. Background, page 2, lines 38-40: Change to "…extracellular matrix structures responsible for properties of resilience and elastic recoil in all elastic tissues including lungs, large blood vessels, and dermis.", and delete the last sentence

17. Background, page 2, line 48: the authors write that CL forms differ in severity and then describe ADCL. Instead, we recommend the following in line 48: "ADCL is generally considered as a milder disease without severe involvement of internal organs and normal neuromotor development whereas ARCL is more severe with many involved systems and poor prognosis.", or something to this effect.

18. Background, page 2, line 52: Replace "exones" with "exons".

19. Background, page 2, line 53: Change "Also mutation in exon…" to "Also, a mutation in exon…"
20. Background, page 2, lines 54-55: Replace "Other disease-causing mutations" with "Other ADCL-causing mutations".

21. Case Presentation, page 3, line 4: Change to "The two patients are the proband and her son from Kazakhstan who are Russian by nationality." The current form makes it seem like there are two female probands.

22. Case Presentation, page 3, line 7: Change to "negative for similar clinical conditions, indicating de novo mutation occurring in the proband or incomplete penetrance in previous generations."

23. Case Presentation, page 3, line 7: Is the age of the patients listed in the introduction (33 yo and 11 yo) the same age as the patients in the photos? If so, state in the text or the figure legend.

24. Case Presentation, page 3: Was DNA from maternal grandparents available to test for the presence of the mutations? If not, state in the paper to justify why this was not tested.

25. Case Presentation, page 3, line 10: Change to "Figure 1. Clinical photograph of proband and her son, ages __ and __, respectively." Move the figure legends to the end of the manuscript.


27. Case Presentation, page 3, line 24: Lungs don't have departments. They have lobes or compartments.

28. Case Presentation, page 3, line 26: State the aortic root diameter and Z-score.

29. Case Presentation sentences don't flow. Can be merged together to be more concise.

30. Case Presentation, page 3, line 34: State the purpose of the Levothyroxine sodium treatment. Eg. "to treat goiter".

31. Case Presentation, page 3, line 34: It is unclear how blood glucose and cholesterol measurements are relevant to the differential diagnosis of cutis laxa vs. progeria. Explain the justification and interpretation of these results better. Be specific about which type of progeria is excluded by these measurements with appropriate literature references.

32. Case Presentation, page 3, line 35: 4.7 mmol/L and 5.7 mmol/L
33. Case Presentation, page 3, line 40: Give the height and weight percentiles in addition to the actual measurements.

34. Case Presentation, page 3, lines 43-44: The following sentence is unclear: "Physical development was above average, not harmonious with a small deficit in weight." Clarify as follows: "Height was above average in contrast to a small deficit in weight." Inclusion of percentiles in this sentence would make it more exact.

35. Case Presentation, page 3, line 46-47: As echocardiography was performed on the son, state the aortic root diameter and Z-score.

36. Discussion and conclusions, page 4, lines 4-20: state what other pathogenic variants were found and what CNVs, if any, were found.

37. Discussion and conclusions, page 4, line 6: Replace "FATQS" with "FASTQC".

38. Discussion and conclusions, page 4, line 7: Replace "Best Practices DNA-seq" with "Best Practices for DNA-seq".

39. Discussion and conclusions, page 4, line 8: Replace "conservativism" with "conservation".

40. Discussion and conclusions, page 4, line 12: Replace "this type of mutations" with "this type of mutation".

41. Discussion and conclusions, page 4, lines 31-34: Make this all one sentence "This mutation was not previously reported in literature, nor in the 60,706 subjects in ExAC, the 2,535 subjects in the 1000 Genomes browser, or the 2000 Genotek patients."

42. Discussion and conclusions, page 4, line 36: Change to "We discovered a novel frameshift mutation in a two-patient Russian family with cutis laxa, presenting with phenotypes consistent with those previously reported. Although novel, this mutation is similar to frameshift mutations previously reported in ELN…"

43. Discussion and conclusions, page 4, line 46-49: This sentence is incorrect. Replace with the following: "The location of the mutation correlates with the phenotype of the patients. Mutations in exon 32 cause fewer cardiovascular and pulmonary abnormalities than mutations elsewhere [6, 8]."
44. Discussion and conclusions, page 4, line 55: Change to "This is especially characteristic of the autosomal recessive form, however, inguinal hernias, emphysema, aortic aneurysmal disease and root dilation has also been described in the autosomal dominant form of cutis laxa."

45. Discussion and conclusions, page 4, line 57: Replace "could lead to" with "can lead to".

46. Discussion and conclusions, page 5, line 4: Replace "which indicates a" with "consistent with a".

47. Figure 2: If there are multiple Gs in a stretch, and one is deleted, it is typically considered to be the last G in that stretch that was deleted. The numbering is consistent for this mutation, however, the arrow should be drawn three spaces to the right above both sequence traces.

**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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Please indicate the quality of language in the manuscript:

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