Reviewer's report

Title: A Possible Founder Mutation in FZD6 Gene in a Turkish Family with Autosomal Recessive Nail Dysplasia

Version: 0 Date: 13 Sep 2018

Reviewer: Liesbeth Vossaert

Reviewer's report:

Abstract:

- Background: make clear that there are already seven mutations reported within this FZD6 gene.
- Results: also a sentence about the 3D modeling should be included - as a large part of the manuscript is dedicated to that; and not just mention it in the conclusion
Try to highlight was this study is adding to the already existing knowledge

Main text:
1) Clinical information:
More clinical information can be given about this family. The index case was diagnosed at birth; are all nails affected, and if so, all similarly or are there differences? Are there any differences between her and her affected sisters? If compared with the families described in the Kasparis et al. paper (2016), are all symptoms comparable? Did they also report on ocular tuberculosis? Why was she only referred to genetic counseling for her second pregnancy? Additionally, it might be good to transfer the clinical assessment to the Results section instead of the Methods part.
The first two sentences within the Results section fit more appropriately in the Methods section.

2) Also more information could be included (in the Discussion) on whether there are any possible treatments or measures to be taken. It is indicated in the abstract and the title that this is a possible founder mutation and that it definitely needs to be taken into account for the diagnosis of nail dysplasia - but this is not repeated in the main text, even though it would serve to make your point more clear.

3) Different tools for pathogenicity estimations are mentioned in the Methods section, yet no results are shown for this. Why were all these different tools used?

4) When explaining expression patterns of FZD6 (page 13-14), expand a bit more on the studies in mice that have been done before, which mutations were induced, how and where is FZD6 normally expressed, etc. Are there any expression data available on FZD6 with specific frameshift mutation? Did the authors do any experiments for this?

5) As mentioned before, try to highlight sufficiently what this manuscript adds to the already existing knowledge. In support of the hypothesis that the change in structure this frameshift
induces leads to altered interactions of FZD6 with other players in its pathway, a figure could be added more clearly showing in which pathway FZD6 is involved, and which interactions are thus influenced, so that is how nail dysplasia is established

6) Figures:
Figure1: There seem to be a few errors within that figure:
- The mutation described throughout the manuscript is listed as p.Glu... instead of p.Gly...
- The mutation on position 620 is listed as p.Glu620... instead of p.Ser620... (according to the Supplementary Table)
- This last one is also highlighted in orange, which seems unnecessary? I believe it is the p.Gly559Aspfs*16 that is supposed to be highlighted. This can also be mentioned on the Figure legend.

Figure 2: it is mentioned in the Methods section that the index case had given birth to an unaffected offspring before, so two children should be indicated for her.

References to figures does not seem correct
- Page 3, line 58: Figure S2 --> Suppl Table 1
- A reference to Figure 1 on Page 4 first paragraph can be included
- Page 9, first sentence: Figure S3 --> S2
- Page 9, line 42: Figure S1 --> Figure 4

In terms of language, grammar and style, a thorough review is advised to get a better flow in the text.
Some specific remarks:
- Consistency of writing numbers in full versus as a figure. Generally, numbers <10 are written in full, but the authors need to make sure it is used consistently throughout the whole manuscript
- Consistency of writing gene names in italic
- Consistency in using abbreviations; Add RMSD and RMSF to abbreviations list + write in full at first use
- The use of articles should be revised; they are not used where they should and vice versa.
- There are several errors in correct verb conjugation; for example page 2, line 49: "grow" should be used instead of "grows"; page 4, line 49: "are" instead of "is"
- Miscellaneous:
Page 5, line 34: "... nine months of anti-tuberculosis [fill in]"
Page 9, line 59: "KTxxxW motif flexibility could" instead of "KTxxxW motif could"
Page 9, line 42: "than" should be used instead of "then"
Page 12, line 49: should this be "homozygosity" instead of "homozygous" ?
Page 13, first sentence: "five out of [fill in] mutations"
Page 13, line 51: "existing" instead of "existed"
Page 15, line 20: should this be "FZD6" instead of "FZD5" ?
"C-terminal" is an adjective, "C-tail" or "C-terminus" is the noun, adjust where necessary
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Unable to assess

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

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Are the conclusions drawn adequately supported by the data shown?
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Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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