Reviewer's report

Title: A novel mutation in the OAR domain of PITX3 associated with congenital posterior subcapsular cataract

Version: 2 Date: 03 Jan 2019

Reviewer: Linda Reis

Reviewer's report:

The manuscript is much improved but would benefit from a few additional minor revisions. Overall, there are still some awkward or difficult to understand phrases (for example- Pg 5, line 13- 'two of them were associated with…' should be 'two of them were affected with'; pg 7, lines 15-17 the sentence beginning with 'Finally, according to' and pg 9, line 26-27 starting with 'for the downstream' are poor English and difficult to understand).

Background:

References are missing for some statements, such as the assertion that 8.3-25% of congenital cataracts are hereditary

For consistency, please use the HGNC approved gene names in paragraph 2 (ie, ABCA3 rather than 'ATP-binding cassette protein A3') since this is what is used elsewhere in the manuscript

Results

When family is first described on Page 6, lines 25-27, authors should note that only the proband and her parents were enrolled. It would also be helpful to specify this on Figure 1, perhaps with an asterick (*) added to indicate enrolled individuals.

I suggest deleting Supplementary Table 1 (14076 raw variants) as this is excessive and impossible to interpret without additional annotation.

It would be helpful to provide frequency info in Supplementary Table 2.

The authors state that the variant meets ACMG criteria to be classified as likely pathogenic (pg7, line 23) - they should note which criteria they used to make this determination. In my opinion, the variant meets criteria PM2, PM4, and PP1, which would classify it as uncertain significance.
Discussion

Page 8, line 12, the authors call the variant 'a novel pathogenic deletion variant', but this is not certain. While the uncertainty is expressed elsewhere in the discussion, this phrase should also acknowledge the uncertainty.

Page 8, lines 27-page 9 line 2: the mutation nomenclature needs to be consistent. In some, the distance to stop codon after the frameshift is given, for others only fs is noted. In some, * is used to indicate the stop, in others X is used. In some, parentheses are applied to the protein name, in others this is omitted, etc.

Pg 8, line 28-pg 9 line 1: Two mutations are incorrectly listed as delT, but are actually delC (c.573delC and c.669delC). If the review reference cited lists incorrect nomenclature, I suggest going back to the original article or find a different review article.

Pg 9, line 3: the authors state- 'all these mutations are in exon 4 and are frameshift', but the p.Ser13Asn mutation is not.

Pg 9, line 26- I think the authors mean to use the word 'deletion' rather than 'disruption of the OAR domain, since later in the sentence they state this deletion would not do so, yet they claim that this mutation does disrupt…

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
Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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