Reviewer's report

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

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Reviewer: Linda Reis

Reviewer's report:

Overall, this is an interesting manuscript presenting a possible new mechanism of PITX3 disruption since the majority of dominant mutations result in erroneous extension of the protein. There are several items which should be addressed:

General comments

Throughout the manuscript, the others state that this is the first mutation in the OAR domain. While this is accurate, they should also note that the majority of previously reported mutations also result in loss of the OAR domain as they cause frameshift prior to the OAR domain. Both protein and DNA nomenclature should be given for the mutations (ie, c.797_814del, p.(Ser266_Ala271del))

Co-segregation in two individuals in the family could occur by chance. It would be helpful if a more distant family member could be recruited and tested for co-segregation (ie, II-3, II-5, or II-7).

Background

The authors report that there are four groups of genes that cause cataract, but not all genes fit into one of these 4 groups, so this should be re-phrased to 'four major groups' or something similar. 'Knockdown of PITX3 induced small eyes without lenses': this should be specified to be in mouse and the mouse gene nomenclature, Pitx3, should be used. References need to be given for each of these mutations. I could not find a reference for the c.543delG mutation noted by the authors. In addition, the c.38G>A, p.S13N mutation is left off of the list and another one of the variants included, c.94G>A is a questionable variant only reported in Parkinson's disease, not in cataract as suggested by the introduction and figure.

In addition, the c.657_673dup17 nomenclature is incorrect - it should be c.640-656dup17. It would also be useful to note that the c.640_656del mutation is recessive, while the rest are dominant.
Methods:

The authors should clarify from the start (and throughout the manuscript) that only two members were enrolled. The statement 'a four-generation Chinese family...was enrolled in this study' is misleading. Perhaps the authors could state 'two members of a four-generation Chinese family...' or something similar.

Since the cataracts are inherited from the father, nothing enrollment of III-6 is irrelevant.

Results

gnomAD would represent a better database to cite for absence of the mutation in the general population since this database includes an East Asian subpopulation the authors state that the mutation is expected to disrupt the protein structure, but it is not clear what this is based on. In silico or functional analysis would be beneficial, especially because the mutation is an in-frame deletion.

Discussion

The authors state that PITX3 plays a major role in cataract, but this gene does not explain a large proportion of cases, so this seems to be overstating.

Further comparison of this mutation and other previously reported mutations should be added, along with noting that the majority of the prior mutations also disrupt the OAR domain. Especially of interest is the fact that the majority of dominant alleles result in erroneous protein extension, while this in-frame deletion would not be expected to do so.

Figures:

Figure 4 is very low quality as provided and difficult to read. Figure 2 would also benefit from increased resolution.
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?
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No

Are the conclusions drawn adequately supported by the data shown?
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