Reviewer’s report

Title: The mutation spectrum in familial versus sporadic congenital cataract based on next-generation sequencing

Version: 1 Date: 25 Mar 2020

Reviewer: Juan Carlos Zenteno

Reviewer's report:

This is an interesting paper which illustrated the power of NGS for the identification of genetic causes of congenital cataract. The sample size is robust and the results are interesting. However, several points need to be clarified by the authors, specially those related with the identification of variants in non-classical cataract genes (see below).

Abstract: Please change the term "X-linked syndromic proteins" to "proteins associated with X-linked syndromic conditions"

Abstract: Please indicate the NGS approach used for genetic testing (exome, panel, etc)

Page 6, line 130 "also identified a monoallelic mutation in BMP4, which has been associated with isolated hypospadias, a disorder of sexual development.(40)". Please note that BMP4 pathogenic variants are mostly associated with microphthalmia and/or facial clefts. (see https://www.omim.org/entry/112262?search=bmp4&amp;highlight=bmp4)

In my opinion, the analysis of genotype-prognosis correlation is not appropriate. No methods for statistical analysis for this correlation are mentioned nor how a "poor prognosis" vs "good prognosis" classification was considered. In addition, groups of genetically diagnosed vs non-genetically diagnosed are too small for a proper comparison (4 vs 5 cases). I suggest to delete this section.

Caution must be taken for ascribing a cataractogenic effect to some identified variants. For example, BEST1 p.Ser7Asn is present in 9 Asian individuals in Gnomad (https://gnomad.broadinstitute.org/variant/11-61719298-G-A?dataset=gnomad_r2_1). This data in conjunction with the fact that BEST1 has not been previously associated with congenital cataract but with a macular disease indicated that most probably this is not the causative mutation. The same applies for p.Leu107Val in CYP1B1. These and other variants in non-classical cataract genes must be carefully reviewed.

As previously suggested, conclusions on a potential genotype-visual prognosis correlations are not supported and could be eliminated from the discussion.
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.

No

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

No

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:

Not suitable for publication unless extensively edited

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?
I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal.