Reviewer's report

Title: AlphaA-Crystallin R49C Mutation Influences the Architecture of Lens Fiber Cell Membranes and Causes Posterior and Nuclear Cataracts in Mice

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Reviewer: Jon Martin Collinson

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This paper describes that mice carrying 1 or 2 alleles of the R49C mutation of aA crystallin, but which also retain the floxed neo cassette in intron 1, show a posterior cataract phenotype that is nevertheless less severe than R49C mutants in which the neo cassette has been removed by Cre. It's an interesting and worthwhile study.

Major revisions

1) The author postulates that the reduced severity of the phenotype is due to suppression of transcription and/or processing of the mutant allele by the neo cassette. This makes sense and is quite likely, but no evidence for the hypothesis is presented here in respect of aA crystallin protein levels, comparing WT with R49Cneo with R49C. This evidence should be presented.

2) I am not sure how the insolubility assay is performed as no details are given here, but there should probably be some sort of loading control in figure 3. Also the author should perhaps explain why introduction of the neo cassette would reduce the solubility of the protein, if it is in an intron and should be spliced out. It is possible that the neo cassette acts at the level of mRNA processing and creates a protein that retains the intron, but there is no evidence presented for this either - and this would be simple to assay with Western blot.

Minor revisions.

1) Spelling of solubility in Fig 3 legend.

2) Describe genetic background of Cre-EIIA mice. Is it possible that breeding R49Cneo with these leads to mice on a mixed genetic background that affects the severity of the cataracts independently of the change in the R49C allele. A control would have been to report any cataracts in WTneo x CreEIIA mice.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests