**Reviewer’s report**

**Title:** Progressive Optic Nerve Changes in Cavitary Optic Disc Anomaly: integration of copy number alteration and cis-expression quantitative trait loci to assess disease etiology

**Version:** 0  **Date:** 28 Dec 2018

**Reviewer:** Subbaiah Krishnadas

**Reviewer's report:**

Limited genetic studies were explored to understand the clinical and genetic characterization of families with Cavitary Optic Disc Anomaly (CODA). In this manuscript the authors assessed the etiology of cavitary optic disc anomaly using copy number alteration and cis-expression quantitative trait loci. Using four affected and fourteen unaffected family members of a multi-generation pedigree provided evidence for the adult onset phenotype of CODA optic disc rather than congenital. The manuscript is written with care and the clinical and genetic experiments are well designed and the discussion explains the data fully. This manuscript may accept for publication because it add more information to understand the etiology of CODA.

There are following queries in the manuscript which require clarification from the Authors:

1. Among the fourteen unaffected family members 5 were carriers of the disease (Male: female ratio- 3:2). Why the copy number variation is high among the 4 carriers than CODA affected members and explain using in silico analysis the specific gene involvement in the regulation among the four genes for the difference in the copy number.

2. In the six generation pedigree, mostly females are affected and two of females are carriers. Even though CODA is autosomal dominant , Is there any explanation for the cause in female or any nuclear and mitochondrial genome cross talk for the pathogenesis?

3. Methods—Through interview with 18 living family members, we identified deceased individuals who had adult-onset bilateral vision loss and marked these individuals as affected on the pedigree.- Without definite evidence or documentation of clinical features, how is it possible to include the deceased as affected based on retrospective history of bilateral adult vision loss alone- there are several other causes of adult onset bilateral visual decline

**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.

Unable to assess

**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.

I am able to assess the statistics

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

Acceptable

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