PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Heritability of glaucoma and glaucoma-related endophenotypes: Systematic review and meta-analysis protocol
AUTHORS	Asefa, Nigus; Neustaeter, Anna; Jansonius, Nomdo; Snieder, Harold

VERSION 1 – REVIEW

REVIEWER	Moulinath Acharya National Institute of Biomedical Genomics, India
REVIEW RETURNED	14-Nov-2017

GENERAL COMMENTS	The protocol manuscript authored by Asefa et al on systematic review and meta-analysis of glaucoma endophenotypes and heritability described a detailed methodology of glaucoma text-mining considering established databases such as MEDLINE, EMBASE, Web of Science and Science Direct. While the idea is interesting, a few clarifications are needed to understand the manuscript in greater depth for its consideration in the BMJ Open journal. 1. Seemingly, authors are interested in primary glaucoma only. In that case is there any specific reason not to include congenital glaucoma in their study design? 2. While heritability will be more in case POAG in comparison with PACG, there will definitely be large variations in each group due to population structure and environmental parameters. The authors have also mentioned this in the “Strengths and limitations” section. What strategy the authors will adopt to overcome this issue? 3. Page 4, line 47-51: Genetically determined open angle glaucoma cases show autosomal dominant mode of inheritance for most of the candidates found from genome-wide linkage analyses. The authors should clarify these sentences with further information. 4. It is not very clear why the authors intend to do the systematic review on heritability and endophenotypes separately. Do they have any intention to join these two analyses to obtain some new information that would be beneficial for glaucoma researchers? 5. Why angle opening distance (AOD) and trabecular iris space area (TISA) are not included in Table 1. Why the authors not considering those quantitative parameters as endophenotypes for PACG?

REVIEWER	Yu-Hung Lai Department of Ophthalmology Kaohsiung Medical University Hospital Kaohsiung Medical University Kaohsiung

	Taiwan
REVIEW RETURNED	09-Dec-2017

GENERAL COMMENTS	1. Page 5, lines 18 to 20. The authors stated, ”glaucoma can be defined as, [a multifactorial optic neuropathy associated with characteristic structural changes to the optic nerve and visual function]”, and cited 2 references (reference 13 and 14). However, in the reference 13 (by Casson et al. 2012), their concise definition of glaucoma is “a group of ocular disorders with multi-factorial etiology united by a clinically characteristic intraocular pressure-associated optic neuropathy”. Additionally, there was a long discussion regarding to intraocular pressure in Casson’s article. The former one (the reference 14) ignored the traditional definition, i.e. intraocular pressure. I would recommend the authors further clarify their definition in this section. 2. The authors will study the endophenotypes of glaucoma. In introduction section, I realize their endophenotypes includes intraocular pressure, optic cup area, vertical cup-to-disk ratio (page 7, lines 14 to 16), could the authors please explain what candidate traits are considered as endophenotypes in their methods and materials section? Minor points 1. Table 1. [Tiab] in Step #1 should have footnote. 2. Page 11, line 16. If the 45 in parenthesis redundant?

VERSION 1 – AUTHOR RESPONSE

Dear editor,
Thank you for considering our manuscript entitled “Heritability of glaucoma and glaucoma-related endophenotypes: Systematic review and meta-analysis protocol”, manuscript ID bmjopen: 2017-019049 for publication in BMJ Open. In the attached file, you will find a point-by-point reply to the issues raised by the reviewers. However, we have also put the responses below in short. We would like to thank the editor and reviewers for their valuable time and useful comments, which helped us to improve the manuscript significantly. All changes made in the manuscript are in a red-colored font.

I look forward to hearing from you.

Sincerely, Nigus Gebremedhin Asefa

REVIEWER #1
1. Thank you for asking to clarify this point. We actually included not only primary open-angle glaucoma (POAG) but also congenital glaucoma and primary angle closure glaucoma (PACG), pigment dispersion glaucoma, exfoliation glaucoma, etc., but apparently made this insufficiently clear. We updated the text to clarify that congenital glaucoma and PACG were included; they were already mentioned in the search string.
2. It is true that there will be a large variation in heritability estimates (or heterogeneity), basically due to population and environmental variability.
For this reason, we will use a random-effects model for the meta-analyses, different combinations of subgroup and sensitivity analyses and meta-regression. The protocol is modified accordingly.

3. Indeed, glaucoma can be inherited as a Mendelian autosomal-dominant or recessive trait, typical for the rare early-onset disease (before age 40). However, adult-onset glaucoma does not usually follow a clear Mendelian inheritance pattern, suggesting that inherited risk factors can result in a susceptibility to the disease but alone are not necessarily causative. (Wiggs, J. L. , 2007, Archives of ophthalmology, 125(1), 30-37). The manuscript is modified to clarify this point.
4. The primary purpose was to perform a comprehensive review on the heritability of any type of glaucoma. However, glaucoma-related endophenotypes (where endophenotype is defined as any trait that is associated with a disease but is not a direct symptom of the disease), are powerful tools in the identification of genes contributing to glaucoma. Currently, a number of GWAS studies are targeting SNPs associated with these endophenotypes (e.g. intraocular pressure, central corneal thickness, cup and disc parameters, etc.), in addition to glaucoma itself. Therefore, rather than looking for glaucoma heritability alone, we believe that an inclusion of these endophenotypes would be a better approach to obtain broad information that would be beneficial for glaucoma genetic research. However, meta-analyses will be separately conducted, as these phenotypes differ from each other.
5. Thank you for pointing to this omission. We have now included angle opening distance, trabecular iris space area and angle recess area (Table 1, step #4)

REVIEWER #2
1. Here, we followed the ISGEO definition of glaucoma as developed for epidemiological research by Foster et al, 2002. They stated that a statistically increased IOP is no longer a defining characteristic for glaucoma diagnosis. For this reason, we will exclude “intraocular pressure” as part of the definition of the disorder. The definition is now updated.
2. The type of endophenotypes were listed in the search string (Table 1), but we agree that it would be better if they were added to the materials and methods section, as well.
3. Thank you for the careful look of the manuscript. The footnote was inserted on step#2, instead of step#1. It is now updated.
4. Thank you also for this. Definitely, it was redundant. Now, it is modified.

VERSION 2 – REVIEW

REVIEWER	Moulinath Acharya National Institute of Biomedical Genomics, India
REVIEW RETURNED	18-Jan-2018

GENERAL COMMENTS	The authors have answered all the queries. No further comment.