Reviewer’s report

Title: Differential methylation in rare ophthalmic disorders: a systematic review protocol.

Version: 0 Date: 09 Nov 2018

Reviewer: Sebastien Kenmoe

Reviewer's report:

Kerr et al. want to conduct a systematic review to summarize data on the association between DNA methylation and rare ophthalmic disorders. This review has a significant impact for physicians and researchers working in this field. This protocol is well written, but I have major concerns. I believe that the following points are important and deserve further clarification.

Background

Background: The introduction needs restructuring and it can be shortened by avoiding irrelevant details, example genetic details at line 72-87. Two pages are sufficient for both Background and objectives. A long Background section can reduce the readability of the paper.

Line 75. It's not interventional studies which find association between the level of DNA methylation and the disease. They are rather observational studies.

Line 102 and 103. Give more information on key articles that have worked on the DNA methylation association with rare ocular diseases or the usefulness of DNA methylation as a biomarker of rare ophthalmic diseases.

Are there any studies that compare the methylation level in rare ocular diseases compared to common ophthalmic diseases? Please you should describe in the introductive part if yes?

Is there enough specificity to discriminate rare ophthalmic diseases from common ophthalmic diseases? Could you get information on the level of Specificity, Sensitivity, predictive values in differential diagnosis of rare ophthalmic diseases compared to healthy patients using methylation? Are there any studies that have defined a threshold in the expression of methylation for the differential diagnosis of rare ocular diseases? Are these thresholds variable according to age, according to the type of ocular infection?

Please clearly address above questions in the introductive part.

Background subheadings are confusing as observational studies will be examined. It would be nice if you could eliminate and keep only background and objectives.
Objectives

Authors should clearly describe the objectives of the study.

Methods

Line 131. Give more details on the type of studies that will be included (cohort, control case, cross-sectional????). Quantitative studies as you indicate is unclear. The remaining part (line 131-134) on qualitative studies should not be mentioned in this section because it is the manual search for articles to include.

Line 137. The authors plan to work on human patients, animal models and in vitro models. Physiopathology generally, including DNA methylation patterns, is variable in these environments. I will recommend to the authors to consider a protocol for several meta-analyses according to these different environments.

Line 142. These are not interventional studies that will be included. The studies treated will be observational that compare the level of methylation observed in patients with and without rare ocular diseases. The author should eliminate all statements that suggest interventional studies throughout the document.

Line 144. The authors plan a comparative study of the level of methylation of subjects with rare ophthalmic diseases compared to common ophthalmic diseases. Please include data on this topic in the introduction if there are any.

Line 158. Selection bias due to language selection. Consider using Google Translate for other languages.

Line 161. Pubmed is the search interface in the Medline database. You must consider only one or the other.

Line 170 (Appendix one). Authors should be more specific about rare ocular diseases to consider. Many of these diseases have not yet been studied for correlation with methylation so authors should eliminate these diseases from the list by researching cases by cases in databases. Conversely they will also identify those who return the most results in order to focus only on those rare ophthalmic diseases.

Line 168. Specify the software that will be used.

Line 221. Data synthesis. Is there a difference in methylation in individuals according to the type of rare ocular disease, age, sex, comorbidities... The authors should plan for subgroup analyzes if yes.

Line 225. The interpretation of the results of the meta-analysis will be difficult due to the heterogeneity of rare ophthalmic disease case definitions, disease prevalence, comparative information, small sample size, and lack of uniformity in the threshold values according to the selected studies.

Line 244. The comparison involving patients with common ocular diseases in relation to rare ocular diseases is not mentioned here.
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Please indicate how interesting you found the manuscript:

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**Quality of written English**
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