Author's response to reviews

Title: Polymorphism rs547984 on human chromosome 1q43 is not associated with primary open angle glaucoma in a Saudi cohort

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Reviewer reports:

Reviewer #1

Abstract:

Line 36: What does "numbers of anti-glaucoma medication" mean?

Reply: It represents the number of medication(s) the patient is receiving.

How many different medications a given patient is taking?

Reply: The numbers vary from 1 to up to 4 depending on the clinical condition of the disease and as recommended by the clinical Ophthalmologists/surgeons.

Line 44ff: How do the authors distinguish between association of rs547984 with clinical parameters
Reply: We analyzed the association of SNP with certain clinical parameters such as IOP and cup/disc ratio in the POAG group only (Table 3 results) and with the SNP being a risk factor for POAG?

Reply: We analyzed the association of SNP with the POAG (vs. controls) (Table 2 results)

Introduction:

Line 15: should read: "the general population" and "the polygenic nature"

Line 33: should read: "GWAS"

Line 50ff: Do the authors refer to the same SNP? Then it should read: "rs547984"

Reply: All the above corrections have been included

Methods:

P. 5, line 15: should read: "DNA samples were obtained"

P. 6, line 19: should read: "Kolmogorov Smirnov"

P. 6, line 21: should read: "significant difference"

Reply: All the above corrections have been included

Results:

P. 6, line 41: Should that read: "No significant difference in age and gender distribution…"?

Reply: Yes

If not, it is not clear how a distribution can be significant.

Discussion:

The authors did not find an association of the SNP rs547984 with POAG. Can the authors speculate or do they know of any studies, if the other SNPs may be associated with POAG? What was the rational to pick that specific SNP out of all the other suggested ones? Did this one have the strongest association in the initial GWAS study? May be the rational why looking at this SNP should be explained in the introduction.
Reply: The comment is well taken. The ‘Introduction’ section has been expanded accordingly in the light of other SNPs/studies in POAG with additional references.

Table 3:

Row "Female": Third column should read "9 (50.0)"

Reply: Rectified.

Reviewer #2: This is an interesting paper in which the ZP4 SNP rs547984 was found not to be associated with POAG in a Saudi cohort. The design is straightforward and the study well conducted. The paper is written with clarity.

A major concern is the small sample size (90 cases vs 95 controls) so that the statistical power may not be enough to rule out false negative association. The statistical power should be calculated and discussed.

Only one SNP was included in the study. Therefore it is not powerful enough to rule out the ZP4 gene in POAG. A hyplotype tagging SNP association analysis should be a preferred way to fully assess the role of the gene. Otherwise, the authors should discuss the limitation of single SNP analysis.

Reply: We appreciate the comments from the reviewer. The limitation of sample size and the possible role of other polymorphism(s) in this gene as suggested by the reviewer have been specified in the ‘discussion’ section.

In this study, we calculated the sample size based on the difference in clinical indices between cases and control. Since the major difference is IOP (POAG versus Normal) and given that; Effect Size (d) = 0.5, α error = 0.05, Confidence Interval = 95%, the minimal target power is 80%, an exact total sample size of 172 (86 cases and 86 controls) are required. However, there is always a contingency of 15% in these types of studies to cover any potential loss due to incomplete data. It is important in these studies to achieve a coverage rate of 85% for the precision of the findings, the matter that has been successfully achieved in the current report. Software used for calculations is GPower (Version 3.0; Universitat Kiel, Germany).

Thank you.

Prof. Khaled K. Abu-Amero