Reviewer’s report

Title: Association of genetic variants in the promoter region of genes encoding p22phox (CYBA) and glutamate cysteine ligase catalytic subunit (GCLC) and renal disease in patients with type 1 diabetes mellitus

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Reviewer: Solena LE SCOUARNEC

Reviewer’s report:

In their manuscript entitled “Association of genetic variants in the promoter region of genes encoding p22phox (CYBA) and glutamate cysteine ligase catalytic subunit (GCLC) and renal disease in patients with type 1 diabetes mellitus”, the authors describe genotype distributions of three functional SNPs in a cohort of 401 well-phenotyped type 1 diabetes patients with or without associated renal disease. Interestingly two of these SNPs, located upstream of the CYBA and GCLC genes, show association with renal disease in diabetes patients. As stated by the authors, these findings will need to be replicated in larger sample sets. The manuscript is generally well written.

***Major Compulsory Revisions

*Subject and methods
- Are controls age/gender matched?
- Are there different ethnic groups within patients?
- The description of patients with (n=104) or without (n=196) overt DN is unclear as the total adds up to 300 not 401. Is that because overt DN is undetermined for some patients? Please clarify.
- Please replace rs1788390, located on chromosome 21 and not chromosome 6 (GCLC) by the correct dbSNP ID.

*Results
- What are the phenotypes of the few CYBA-A/A and GCLC-T/T patients?
- Did the authors look at the effect of the combination of CYBA+GCLC risk alleles in patients?

*Discussion
- Did the authors look at the effect of the CYBA-T allele on hypertension in this cohort?
- Were other SNPs tested in this cohort of patients, for example polymorphisms found by meta-analyses e.g. Mooyaart et al. Diabetologia 2011?
- Reference [18] is not listed under “References” and there is no reference [17].
***Minor Essential Revisions

*Abstract

- Abstract/Background: “NOX/NADPH oxidase generates...” should be replaced by “NOX/NADPH oxidases generate...”
- Abstract/Background: “encoded by CYBA gene” should be replaced by “encoded by the CYBA gene”
- Abstract/Background: SNP IDs (rs numbers) should be indicated.
- Abstract/Methods: “Patients were sorted according” should be replaced by “Patients were sorted into two groups according”. Define the number of patients in each group.
- Abstract/Results: “in the group carrying the TT genotype” should be replaced by “in the group carrying the T/T genotype”. Please check for consistency across the whole manuscript.
- Abstract/Conclusion: The space should be removed between -> and A.

*Background

- “encoded by CYBA gene” should be replaced by “encoded by the CYBA gene”
- “coded by the GCLC gene” should be replaced by “encoded by the GCLC gene”

*Subject and methods

- “The study was carried out in compliance to the Institutions’ Ethics Committee and to Declaration of Helsinki” should be replaced by “The study was carried out in compliance with the Institutional Ethics Committee and the Declaration of Helsinki”
- “to each subject” should be replaced by “by each participant”
- Please add an alternative description for variants, e.g. in relation to a genomic reference sequence, particularly for the unregistered SNP.
- Provide TaqMan primers and probe sequences for CYBA A/T genotyping.

*Results

- Indicate that “data is not shown” for GPX3 results.

*Discussion

- “We evaluate a different functional...”, this sentence should be reformulated to clarify that it is the proportion of cases with low GFR that is lower in TA or AA cases, not different rates <60.
“the allele T” => “the T allele”
“it is plausible to suppose that” => “it is plausible that”
specify that it is the T allele that was “previously associated to myocardial infarction”
“effect of this SNP at the age of onset” => “effect of this SNP on the age of onset”
“this study widen” => “this study widens”

*Table 1
- TT should be replaced by T/T
- What is the significance of “***” after 73.7% for GPX3-TT in control subjects? Add a footnote if necessary.
- There is an extra space before C/C for GPX3 genotypes.

**“Ackowlegment” should be replaced by “Acknowledgements”**

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

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests