Reviewer’s report

Title: Association of ADPRT1, AKR1B1, RAGE, GFPT2 and PAI1 gene polymorphisms with chronic renal insufficiency among Asian Indians with type-2 diabetes

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Reviewer: Goisa Trynka

Reviewer’s report:

In the study of Prasad et al., eight SNPs located in the functionally relevant candidate genes for chronic renal insufficiency (CRI) among Asian Indians with type 2 diabetes have been tested and their frequencies have been contrasted with those in type 2 diabetes patients with normal renal functions. SNPs have been genotyped using RFLP technique. The authors report a moderate association for the polymorphisms tested in this study, within the RAGE and GFPT2 genes (genotype p=0.013 and allelic p=0.047, respectively). However the study is based on the relatively small cohort (196 cases and 225 controls) and its findings need to be interpreted with care.

-Major Compulsory Revisions

1) Authors should specify if the calculated p-values are calculated as one or two tailed

2) Authors should take into account and state in the manuscript the p-values after correction for the number of tests performed e.g. the Bonferroni correction for the seven SNPs tested in this study.

3) P-values in the table 3 should be followed by ORs and confidence intervals

Minor Essential Revisions

1) page 5, introduction, 2nd paragraph. Authors mentioned that the SNPs investigated for the association in this study were chosen based on their significant functional role. I think more information should be added in the introduction or methods section, describing more precisely the criteria for selecting the particular SNPs for this study (e.g. Previously reported associations, bioinformatics predicted strength of the deleterious effect of the SNP on the protein product etc.)

2) Is the polymorphism nomenclature used throughout the manuscript correct (according to the Human Genome Variation Society)? All except two of the tested polymorphisms have the rs ID numbers, it would be more convenient for the reader to use this nomenclature instead.

3) Page 8, paragraph describing association to the GFPT2 gene. Authors state that the significant allelic and genotypic association of the 3'UTR polymorphism was detected. However the p-value for the genotype association, provided in the
table 3 is p=0.11, which is not significant!

4) The same paragraph. The authors state that according to the "Mirbase tool" the miRNAs (has-miR-378 and has-miR-4229) are targeting the sequence that captures variant (rs7725) tested in this study. Given that there are several bioinformatics tools available on-line that can be used for predicting miRNA-target site interaction I would require Authors to provide the reference to the Mirbase tool they have used.

5) Page 10, 5th line of the 2nd paragraph; ‘On the other hand CC genotype of -429 T>C SNP is predisposing (...)’ I would be more careful stating any strong effects of the SNPs tested in the study. Although the SNP that authors are referring to has an OR = 0.11 its confidence are very wide, CI 0.01-0.91, which of course can partly be explained by the small sample size.

Discretionary Revisions

1) Regarding the discussion of the miRNA interactions with the sequence harbouring the rs7725 variation in the GFPT2 gene I was wondering if there is anything known about the genes targeted by has-miR-378 and has-miR-4229, eg. If there are genes known to be regulated by these miRNAs and they would fall into the same pathway as GFPT2 (also relevant for the CRI type 2 diabetes) it could significantly improve the discussion of the current manuscript.

2) Page 11, first paragraph, the authors mention study in the African Americans where a significant association to the rs7725, T allele has been reported. It would be interesting to perform the meta-analysis of that study and the study described in this manuscript (and more if published) and see if the association holds

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests