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: Ilja Nolte

Reviewer's report:

Prasad et al. revised their manuscript 'Association of ADPRT1, AKR1B1, RAGE, GFPT2 and PAI-1 gene polymorphisms with chronic renal insufficiency among Asian Indians with type-2 diabetes' and indeed it improved significantly. Most of my comments were answered satisfactorily but still some concerns remained.

Major Compulsory Revisions:

1. After multiple testing none of the associations remained significant. The title should therefore be changed to 'No association of ...' or 'Association analysis of ...'.

2. Although the authors agreed on weakening their statements on the significance of the associations because of multiple testing issues, they still maintained a significance level of 0.05 (p9, line 167) and hence claim to have found significant associations. They mention briefly that 'None of these association observed in the study withstood the Bonferroni correction' (p9, lines 188-189), but they didn't change their conclusions accordingly throughout the manuscript.

3. Table 3 shows that there is no power for most of the SNPs investigated in this study. Therefore the authors should try to increase sample size or select other more frequent SNPs (see also remark 5).

4. Prasad et al. 'attempted to identify putative pathological epistatic interactions between genes from multiple pathways using a combined data set from this study together with data from all our previous studies'. With this in mind it is strange that they only looked at two combinations of genes. This suggests that they looked at more combinations. The choice of which combinations being analyzed and others not should be stated more clearly.

5. The description of the selection of SNPs is still vague (p8, lines 154-157). Why were only functional SNPs selected? Most of them have low MAFs and hence low power (see also remark 3). A tagSNP approach would enable more firm conclusions. In particular when functional SNPs are not associated, the gene cannot be ruled out as a candidate gene.

6. Furthermore concerning the selection of SNPs, in their reply Prasad et al.
mention that they did not select the ADPRT1 SNP Leu54Phe because of low MAF but the MAF of the SNP they did select (Arg940Lys) was only slightly higher. How about LD between these SNPs? If LD is weak there is no reason not to type Leu54Phe (other than power, but that didn't bother them for the other SNPs either). By the way heterozygosity can not be 0.42 when the MAF is 0.03-0.08. Likely this is a typo and it must be 0.042, right?

7. Prasad et al. mention in their reply that HWE was indeed calculated using the control sample only. They should also state this in the manuscript.

8. The p-values of the Fisher's exact test differ much from the p-values of the chi-square test. You should check this, because that must be incorrect.

Discretionary Revisions:

1. Results p10-11, lines 210-217: this is a copy from the introduction. I would suggest to remove it.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests