Reviewer's report

Title: Genetic variation of Glucose Transporter-1 (GLUT1) and nephropathy in 10,278 Caucasian and African-Americans: a case-control study in the Atherosclerosis Risk in Communities (ARIC) Study

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Reviewer: Samy HADJADJ

Reviewer's report:

C. Hsu et al, have examined the relationship between GLUT1 genetic variations and albuminuria in a large sample of Caucasian and African-American people. The study is interesting because, as mentioned by the authors, it is the largest examination to date of the GLUT1 genetic variations according to albuminuria.

Major comments:

1. In the title and along the manuscript, the authors refer to nephropathy. In fact, they should mention albuminuria. Nephropathy is not certain in non diabetic microalbuminuric patients.

2. The abstract is not so self comprehensive. Indeed, the notion of stage 1 and stage 2 are clearer in the text but are not very easy to understand in the abstract. Thus, a more appropriate term as primary sample and replication sample could be used.

3. The greatest concern I have is that the genotypic frequencies among Caucasians or African-Americans, are very different as seen in Figure 1. It is thus very complicated to consider both ethnicities all together.

4. Although diabetes duration is not available, it is clearly unexpected to have only 6 proteinuric patients among 1095 type 2 diabetes people. Thus, a selection bias is likely and makes the conclusions on type 2 diabetes and nephropathy very questionable.

Minor comments:

In the “GLUT1 Enh2 Risk Genotype and Insulin” section, the authors explained that the excluded people with microalbuminuria. This is not clearly stated why they made such a choice. It could be suggested to present the data with albuminuria first and then with only macroalbuminuric patients.

The discussion is quite long and could be shorten.

In the discussion, the speculations about the Enh2 SNP effects are not very clear to me. Two alternate speculations are indeed presented: - high insulin is associated with high intracellular glucose concentrations, leading to glomerulosclerosis.

- the alternate hypothesis is that insulin in podocytes prevents albuminuria via GLUT1.
It is not very easy to me to reconcile both hypotheses.
The data on estimated GFR according to MDRD formula should be added in the tables, as they are cited in the method section.

**Level of interest:** An article of importance in its field

**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' below