Reviewer's report

**Title:** Linkage Disequilibrium Analysis Reveals an Albuminuria Risk Haplotype Containing Three Missense Mutations in the Cubilin Gene with Striking Differences Among European and African Ancestry Populations

**Version:** 2  **Date:** 14 May 2012

**Reviewer:** Jose L Gorriz

**Reviewer's report:**

Review report

Identification of genetic risk factors for albuminuria may alter strategies for early prevention of CKD progression. It is important to know the possible influence of common genetic variants on albuminuria in both general and diabetic populations. Given the importance of cubilin in the process of endocytotic reabsorption of albumin, any finding related to cubilin gene is of interest to the clinicians, because it would help to understand the mechanisms of albumin excretion and explain the differences between different populations. The availability of genomic sequences databases help us to carry on these investigations.

The most relevant finding of the study from Tzur et al. is the difference in linkage disequilibrium patterns found between Africans and European ancestor populations.

Using linkage disequilibrium search, the authors showed the association between a missense variant (I2984V) in the cubilin gene and showed the difference between African and European populations. This variant has not been previously reported. This finding is added to the other two variants previously described by (Böger CA et al JASN 2011).

The article can be accepted for publication with discretionary revisions, but I suggest to the authors to perform it, especially in the description of methods:

- Although it is described in a "diffuse" form, it would be of interest for them to define better the objective of the study. It can be read in the abstract, but is not clearly defined at the end of the introduction section.

- It would be interesting a better description of the methods. Since BMC Nephrology is a journal with a major clinical content and read by many clinicians, it is suggested to make a very brief description of the methodology used. For example, brief description (three lines) of Haploview, more detailed description in how they identify the haplotypes in different populations examined and how did they examined the frequency of single nucleotide polymorphisms.

- It is suggested to end the article with a paragraph that will mention the work's
conclusion.

The results should be shown separately from the discussion. The presentation form, that the authors used, can be confusing.

It is of interest to analyse the differences between the African and African American population.

Limitations:

The authors do not mention the study limitations. It would be of interest that they will mention them on the discussion section.

This is not an association study of genetic variants with development of albuminuria, but a study of detection of cubilin gene variants. Given the implication of cubilin in the process of endocytic reabsorption is assumed to be associated with further development of albuminuria. This should tested in major studies biobanks.

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I haven’t any financial interest with a company whose product was used in the study or referred in the manuscript. Neither any financial interests of arrangement with a competing company or any other financial connection, direct or indirect, or other situation that might raise the question of bias in the work reported or conclusion, implications or opinions stated