Reviewer’s report

Title: Chromosome 7p linkage and association study for diabetes related traits and type 2 diabetes in an African-American population enriched for nephropathy

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Reviewer: Nathalie Vionnet

Reviewer’s report:

For Authors:

Leak TS et coll report results of linkage and association study for diabetes related traits and type 2 diabetes in an African-American population enriched for nephropathy.

This study is a follow-up study of previous reported microsatellite linkage-scan in African-American families with type 2 diabetes enriched with diabetic nephropathy. Evidence of linkage on chromosome 7p in families with early T2D diagnosis, lower BMI and longer duration to ESRD was detected in the initial scan. The present study aims at refining the linkage peak, determining the primary phenotype of association and examining potential positional candidate genes in the resulting region of interest by case/control association studies with common variants.

The linkage fine-mapping involved the genotyping of 11 additional microsatellite markers that confirmed linkage with type 2 diabetes in a subset of families with early onset diagnosis of T2D but not with other traits. The linkage interval falls between 11.5-49.5 cM along chromosome 7p, interval in which positional candidate genes were supposed to be selected.

- Major Compulsory Revisions:

1) It seems there has been a confusion between linkage and physical maps. In the discussion, the authors state that the linkage region is 38 Mb large whereas it is 38 cM large. This makes a difference when considering the selection of potential positional candidate genes. According to figure 1, the linkage region roughly spans the distance between D7S2514 and D7S2846 which are located at 11 cM and 60 cM respectively on the linkage map but at 7.7 Mb and 38 Mb respectively on the physical map. Three out of the 4 so-called positional candidate genes lie outside this interval (GCK at 44.2 Mb; IGFBP1 and IGFBP3 at ~45.9 Mb). Therefore it seems that in the context of positional candidate genes, the study of those 3 genes was not relevant. Please, provide the region of interest on a physical map scale, provide the number of genes lying in this interval and select positional candidate genes within this interval.

2) Linkage was confirmed in a subset of 21% of the families with early onset T2D. How do you explain that the mean age of diagnosis in this subset of
families is 29 +/- 3 years despite the fact that T2D was diagnosed in patients developing diabetes after the age of 35 years. Could those families segregate MODY phenotype? The study of the GCK gene in this context, including sequencing, could be interesting.

- Minor Essential Revisions

References 1 and 16 are the same.

In the article by Bonnycastle LL et coll (ref 32), the association between T2D and GCK markers was not significant with age at diagnosis.

The association with mean age of ESRD onset and GCK markers should be adjusted with age at diagnosis of T2D. The association with shorter duration of diabetes before onset of ESRD is marginally significant and would be contrary to the initial linkage finding with longer duration to ESRD.

**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'