Reviewer's report

Title: Polymorphisms near EXOC4 and LRGUK on chromosome 7q32 are associated with Type 2 Diabetes and fasting glucose; The NHLBI Family Heart Study

Version: 1 Date: 8 February 2008

Reviewer: Martine Vaxillaire

Reviewer's report:

The paper by Laramie et al. reports an interesting study focusing on the genetic variation (deletion and SNP polymorphisms) in a 1.08 Mb region on chromosome 7q32 which was shown to be linked to metabolic syndrome and obesity in the Family Heart Study.

The study design and the methodology used are correct, albeit a very limited statistical power due to the low number of diabetic patients (207 diabetics) included in the genetic association analysis.

Major Compulsory Revisions:

One more general concern with this study is that the original linkage was obtained for another disease status, and particularly obesity related traits, and there is no attempt to replicate the present findings in other cohorts of patients outside the FHS participants. Moreover, T2D in this study sample was defined based on participants' self report (as well as BMI at age 25).

Probably, all these limitations are reflected by the rather moderate association found between T2D and the TCF7L2 SNP, the one which was largely and reproducibly replicated in most of the reported association studies. Thus, the sentence in the abstract and in the discussion, where it is stated that the evidence of association to T2D for the deletion is comparable to that of TCF7L2 SNP, is somewhat ambiguous and should be changed.

One interesting finding is that the non-diabetic male homozygous deletion carriers may have lower fasting glucose levels, though the polymorphism does not seem to overlap with the EXOC4 gene, but is located downstream of that gene and just upstream of the LRGUK gene. There is no strong evidence for a functional effect of the deletion polymorphism; and to my view, in this paper it is difficult to make a link between the deletion polymorphism and the other SNPs tested, and more importantly with the putatively associated SNPs: in the abstract (but not in the Results section), it is reported that six SNPs are significantly associated to diabetes. This needs to be improved in the current report.

Specific points:

1- the deletion polymorphism has to be clearly indicated (sequence and number
of nucleotides) in the text of the manuscript.

2- does the description of the genotype cluster assignment (in page 5) mean that about 30% of genotypes are missing for the deletion polymorphism?

3- In the results for SNP association: the number of polymorphisms with evidence of association should be indicated in the text on page 9. Indeed, from the Table 5, we can not easily identified which are the six SNPs (as reported in the Abstract). Please clarify this point.

4- the p-values given throughout the manuscript should be as nominal p-values, as no correction for multiple testing (number of polymorphisms and number of statistical tests) was made.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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