Reviewer's report

Title: Common variants of the TCF7L2 gene are associated with increased risk of type 2 diabetes mellitus in a UK-resident South Asian population: a case control study

Version: 1 Date: 30 August 2007

Reviewer: Jana van Vliet-Ostaptchouk

Reviewer's report:

Since the original report of the association of the TCF7L2 gene with the susceptibility to type 2 diabetes by Grant et al (Nat Genet 2006), multiple replication studies in different populations confirmed that TCF7L2 is a major determinant of type 2 diabetes risk. In this study Rees and colleagues provide evidence that the TCF7L2 SNPs are associated with type 2 diabetes in Indian Asians of North Indian origin, using a set of 831 patients and 436 controls. This is the third study in the Indian population to date. Moreover, they investigate the correlation between odds ratio and mean age of control group and demonstrate that the association with the disease becomes stronger with an increase of the mean age of controls.

The results of this paper are of the interest for researchers in the field of genetics of type 2 diabetes, since it provide additional information to the previous observations in the genetically diverse Indian population.

- Major Points

1. It is unclear whether unrelated type 2 diabetes patients were used in the study or not.
2. The authors do not provide power calculation which gives an estimation of the effect sizes their study is powered to detect. That will help in the interpretation of the data.
3. Please include more details on genotyping accuracy in Methods, e.g. genotyping success rate.
4. One of the snps, rs12255372 didn’t follow the multiplicative genetic model (in disagreement with the original observation of Grant et al as well as with the previous study in the Indian population by Chandak et al.) The controls were not in HW (p=0.02). The authors have performed extra genotyping using the exactly same method, to exclude genotyping mistakes and did not find any inconsistency with the original results. They concluded that the departure from HW was due to the chance sampling.

Since the authors observe too many homozygotes for the minor allele, this observation may also point to a systematic genotyping error. It would be helpful to retype the SNP in ALL control samples with a completely different method to
rule out this possibility, or to sequence a subset of the alleles.

5. In Table 2 the results of genotyping for rs7901695 in controls is: 226+169+42 =437 which is in disagreement with total number of 436 controls used in the study.

- Minor Points

1. Please include the 95% confident interval in the Abstract.

2. Methods, page 5. “Mendelian consistency” should be changed to “Hardy-Weinberg equilibrium”.

3. Results. At page 7 the authors state: “To further explore the effect of including young control subjects on the strength of association, we compared the allelic ORs calculated for each SNP using subsets of our control group defined by different minimum age thresholds. When increasing minimum age thresholds were applied, there was a corresponding increase in OR up to an age cut-off of 46 years (Figure 2). When the minimum age was increased beyond this point, the relationship with OR deteriorated, although regression analysis still revealed a significant positive relationship (p < 7.11 x10-3) for all variants when the minimum age threshold was increased to 65 years (data not shown). “

It would be helpful to rephrase the statement as it is difficult to follow the author’s argumentation.

4. It should be mentioned in Table 1 that BMI, waist circumference and blood pressure measurements were available for only 252 controls.

5. “A case control study” can be omitted in the title of the paper.

What next?: Accept after minor essential revisions

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 declare that I have no competing interests.