Reviewer’s report

Title: The genetic susceptibility to type 2 diabetes may be modulated by obesity status: implications in association studies

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Reviewer: Vincenzo Trischitta

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In this study Cauchi et al have investigated whether the association between 11 candidate genes and type 2 diabetes (T2D) is modulated by the presence of obesity. This was tested by performing two case-control studies for T2D, one comprising non obese individuals (i.e. BMI< 30Kg/m2; 1283 controls and 1581 cases) and on obese patients (i.e. 3189 controls and 1244 cases). Some variants (i.e. HNF1A I27L, GCK -30G>A, SLC30A8 R35W), were significantly associates only in the non obese sample while others (i.e. PPARG Pro12Ala, ADIPOQ -11,377 C>G, ENPP1 K121Q) were associated only among obese patients. The only variant which was associated in both subgroups – although with a different strength (OR=1.89 and 1.30, in non-obese and obese sample, respectively)– was TCF7L2 rs7903146. The authors like to suggest that genetic variants affecting insulin secretion or insulin resistance modulate the risk of T2D in non-obese or obese individuals, respectively and that this scenario may be the cause of lack of replication in association case-control studies with a different design as far as BMI status is concerned. The paper is clear and concise and is focused on an important issue.

Major points

1. In order to say that a gene variant acts differently in non-obese vs- obese individuals, a formal significant interaction has to be observed. As the authors clearly state, this is the case only for the ENPP1 K121Q and the TCF7L2 rs7903146 SNPs. Thus the Abstract and the entire first part (i.e. first page) of the Discussion, has to be re-written using more caution. In general, when discussing their own data the authors should stress those on ENPP1 and TCF7L2 rather than keep saying that also the effect of HNF1A, GCK, SLC30A8, PPARG and ADIPOQ is modified by the absence/presence of obesity.

2. Previous studies are not always properly quoted. In details,

a) When referring to ENPP1 (Background, lines 6, 7) the very recent study of Mc Ateer et al (Diabetes. 2008, 57:1125-30) has to be quoted. This is the largest meta-analysis so far carried out and, of note in this specific context, suggests that the gene effect is mediated by BMI.

b) When referring to PPARG the study by Florez et al (J Clin Endocrinol Metab. 2007, 92:1502-9) has to be quoted. In this paper which analyzed the prospective DPP study, the authors clearly show that the protective effect of the Ala12 variant is larger in leaner people. A finding which is in line with the meta-analysis by
Ludovico et al (reference 4 of this paper). Since both papers suggest just the opposite of what suggested by the authors, this issue has to be deeper discussed.

3. Given the important role mediated by obesity on the risk of T2D determined by both ENPP1 and TCF7L2, it would be important to understand whether these two genes have any effect on BMI itself either in the 4 different groups singly examined (NG non obese, NG obese, T2D non obese, T2D obese) or in the NG (non-obese + obese) and the T2D (non-obese + obese) groups. What one could expect to find is that, because of ascertainment bias (virtually always present in case-control design); variants which increase the risk of T2D by interacting with obesity would be associated with lower BMI in controls and vice versa.

Minor points
1. In the abstract, it would be better to show also the OR in the non-obese group for ENPP1 (as done for TCF7L2). Once again, these are the two genes showing interaction with obesity and, therefore, data should be clearly shown in the abstract.
2. Background line 2: “pathology” should be changed with “disease”.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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 below.