Reviewer's report

Title: Analysis of common PTPN1 gene variants in type 2 diabetes, obesity and associated phenotypes in the French population

Version: 1 Date: 17 January 2006

Reviewer: DW Bowden

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General
Cheyssac et al report an extensive analysis of PTPN1 gene polymorphisms in a variety of case-control and family collections with the goal of evaluating association with type 2 diabetes, related metabolic traits, and obesity. This systematic study adds to the available data addressing the significance of PTPN1 genetics in diabetes and obesity. Strengths of the study are fairly large collections of subjects that are evaluated and presentation of estimates of power to detect effects. The major challenge of a manuscript such as this is distilling the large number of analyses and comparisons into a consistent presentation of results and then relating those to the existing literature.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. LD structure of the PTPN1 gene. The authors state that the LD structure is consistent with previously reports that the PTPN1 gene encompasses a single haplotype LD block. It is therefore puzzling that figure 1 presents a haploview block structure that clearly has two haplotypes blocks--this needs to be explained.

2. the abstract is not a very good reflection of the data reported in the body of the manuscript. For example it states that none of the 14 SNPs show evidence of association in the case-control study, however rs6020563 does have a P-value of 0.04 D1/CI. It is also puzzling that the results for rs914458 are presented for the dominant model with T2DM in the abstract, but these data are not shown in the tables. In addition, in the abstract the summary of associations with HOMA-B, HDL, etc. are reported as two P-values. It should be clarified that the P-values are under dominant and recessive models.

3. Haplotypes are reported numerically (1221). This presents a major challenge to even a motivated reader to ascertain which base is actually making up the haplotype. This makes it especially difficult to assess haplotypes from different studies. The base designations should be used.

4. It is also puzzling that the text states that no haplotypes show evidence of association with diabetes or obesity but in the tables the 2112 haplotype does show evidence of association with both T2D and obesity.

5. The follow-up assessment of the polymorphisms in the French Canadian families that originally gave evidence of linkage on 20q is appropriate, but as presented is somewhat misleading. In this study the total family sample did not provide evidence for linkage in the PTPN1 gene region and this should be noted. A subset of the families (I believe 55 early onset sib pairs) appeared to drive the evidence of linkage in Zouali et al. Have these SNP adjustment analyses been performed in this subset of the family collection?

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. There are a significant number of typographical errors in the text
2. There are quite a few places where results for T2D analysis with the dominant or recessive models is quoted in the text, but these data are not shown in tables. The text should state "data not shown" or the authors should include this data in tables.

Discretionary Revisions (which the author can choose to ignore)

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

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:
'I declare that I have no competing interests'