**Reviewer's report**

**Title:** Polymorphisms of superoxid dismutases and catalase and diabetes mellitus

**Version:** 2  **Date:** 26 November 2007

**Reviewer:** Su-Chi Lim

**Reviewer's report:**

**General**
The authors need to be applauded for attempting to investigate the relationship between three promising candidate SNPs involved in oxidative stress and diabetes.

1. Is the question posed by the authors new and well defined?
   Well defined but probably not new.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
   Satisfactory. Some deficiencies (described below)

3. Are the data sound and well controlled?
   Some major concerns (details below)

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Adequate

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   Some major deficiencies (described below)

6. Do the title and abstract accurately convey what has been found?
   Adequate

7. Is the writing acceptable?
   Satisfactory.

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

1. The paper is too long, making the trend of thoughts less than succinct. It can probably be shortened by ~30%. 
2. Description of study subjects (i.e. phenotype) needs to be improved. How did the authors define type 1 & 2 diabetes (T1 & T2DM) and healthy subjects?

3. What is the statistical justification for recruiting the number of study subjects (120 T1DM, 306 T2DM and 140 healthy)? Genotyping available samples at-hand without a priori statistical planning can inadvertently lead to positive or negative association by chance. Given the relative small sample size (in comparison with current genetic epidemiological studies), the statistics is unlikely to be robust and subsequent replication (arguably one of the most important requirements for confirmation of causal inference in genetic association study) difficult. This problem is further aggravated by subgroup analysis – into diabetic subjects with and without complications (only 66 subjects with macrovascular complication available). Therefore, the conclusions drawn have to be a lot more tentative and the authors are encouraged to discuss this as part of the limitation of the study.

4. Subjects with T2DM are much older than healthy. Therefore, age could potentially confound (or attenuate) the relationship between serum SOD activity and diabetic status. Did the authors attempt statistical adjustment for the difference in age? Having said so, the substantial difference in SOD activity between diabetic and healthy subjects (>50%) is probably largely accountable by diabetes per se (not withstanding the age difference).

5. In addition, it appears somewhat surprising that the authors reported a positive association between SOD activity and SOD1 & 2 genotypes. The numeric figures in table 3 appear non-convincing and unlikely to be statistically significant (within the stratum of T1DM, T2DM or healthy), especially given the small sample size (e.g. only 5 T1DM subjects with SOD2 CC genotype). Did the authors pool all the diabetic & healthy subjects together as one group for this part of the study? This may improve the statistical power but the rationale behind pooling them together needs to be carefully justified (given the expected and unaccounted difference between these subjects e.g. disease status, treatment received, other co-morbidities, age etc.)

6. Numeric figures in table 4 are also difficult to understand. Within the group MA+, the genotype frequency adds-up to be greater than 100% (0.32+0.54+0.28=1.04). Similarly, MI+ genotype distribution adds-up to be 113%. These seem improbable.

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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. Genotyping methods – need to report genotyping failure rate, validation of genotyping results (preferably by another genotyping platform), PCR amplicon product size and size of nucleotides fragments after restriction enzyme digestion. Blinding (to the phenotype status) of investigators scoring the genotyping results.

2. Consistency of genotype distribution with Hardy-Weinberg Equilibrium among controls. For negative observation e.g. CAT SNP, the estimated power of the
study.

3. Typographical error – under the section statistical analysis, somehow the candidate gene of interest changed from SOD to PON

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 limited interest

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

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

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None