Reviewer's report

Title: CT60 genotype does not affect CTLA-4 isoform expression despite association to autoimmune disease in northern Sweden

Version: 2 Date: 20 September 2006

Reviewer: Koen Vandenbergroeck

Reviewer's report:

The work by Mayans is a well-written, concise account of a genetic and functional analysis of three SNPs in the CTLA4 gene in susceptibility to T1D and AITD. A functional analysis of CTLA4 isoforms and protein expression levels is performed in a competent manner. Though the paper is potentially of interest to those involved in unraveling the genetics of autoimmunity, there are some unclarities, most of these relating to the genetic association analysis, that need to be addressed.

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

1. The authors use logistic regression for association analysis. This is unusual as a regular chi-square analysis of counts in contingency tables is more commonly used for single-marker analysis. With contingency/chisquare analysis the findings seem less significant. The risk therefore exists that the logistic regression analysis has inflated the significance. The authors claim that heterozygous individuals have a greater risk compared to non-carriers. This is not at all obvious from Table 1 where the percentage of heterozygosity is very close to 47% for the three SNPs in both cases and controls. GG homozygous genotypes are consistently increased in cases with around 7 to 9%. This seems to conflict with the statement that there is no increased risk for homozygous compared to heterozygous.
2. Table 1 is a bit confusing as it is unclear to what precisely the OR’s and P value relate.
3. The genotype percentages, when calculated from the counts on the basis of the full number of controls (n=865) and cases (n=253) are incorrect. This suggests that not all controls and cases yielded suitable genotype information. It is therefore important that the genotyping success rate is given for each SNP in cases and controls separately. This should be inserted as an extra column in Table 1. For MH30, for instance, 777 controls gave genotype information out of a total 865 used. This implicates a genotyping success rate of 89.9%.
4. Since the authors have not implemented any correction method for multiple comparisons, they should clearly state the single-hypothesis replication analysis they aim to perform on the basis of the previously published work by Ueda and others.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The title and the abstract of the manuscript should be changed to reflect that the analysis refers to AITD and T1D only. The current title is a bit misleading as there are many more autoimmune diseases than only AITD and T1D.

Discretionary Revisions (which the author can choose to ignore)

The authors have pooled AITD And T1D patients. It might be interesting to evaluate the association in the separate patient cohorts as well as in the pooled one.

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

Declaration of competing interests:

I declare that I have no competing interests