**Reviewer's report**

**Title:** Association of HLA Class I with Severe Acute Respiratory Syndrome Coronavirus Infection

**Authors:**

Prof Marie Lin (marilin@ms2.mmh.org.tw)
Hsiang-Kuang Tseng (drtseong@anet.net.tw)
Mr Jean A Trejaut (trejaut@ms1.mmh.org.tw)
Hui-Lin Lee (leehl@ms1.mmh.org.tw)
Jun-Hun Loo (jjunhun@ms1.mmh.org.tw)
Dr Chen-Chung Chu (chucc@ms1.mmh.org.tw)
Pei-Jan Chen (q8640@ms13.hinet.net)
Ying-Wen Su (yingwen_su@yahoo.com.tw)
Ken Hong Lim (klim@seed.net.tw)
Zen-Uong Tsai (tsaizu@ms1.mmh.org.tw)
Ruey-Yi Lin (lin-8424@mail.hoping.gov.tw)
Ruey-Shiung Lin (rueshiung@yahoo.com)
Chun-Hsiung Huang (chhuang@ms2.mmh.org.tw)

**Version:** 5  **Date:** 5 Aug 2003

**Reviewer:** satoshi horai

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

**Advice on publication:** Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

I am satisfied with the changes that the authors made in response to my comments, with the following exceptions.

**Compulsory revisions:**

1) The authors still claim the association of HLA alleles (B*4601/B46 and B*1301/B13) with SARS infection, based on statistical inferences from the uncorrected P-values. In significance testing, a type I error (a false-positive finding) is generally considered to be more serious, and therefore more important to avoid, than a type II error (missing a positive finding). When independent multiple comparisons are carried out (as done in this study), one way to avoid a type I error is to correct the bias for the number of the comparisons, thereby obtaining the corrected P-value (Pc-value). The authors do present the Pc-values in the Results of the manuscript, but not take them into consideration in the Discussion and the Abstract. My major criticisms are as follows:

I. If the authors favor the uncorrected P-values over the Pc-values, please explain the reason(s) in the Discussion; otherwise, the readers could not understand even why the two types of P-values are calculated.

II. Disease association of two other alleles (B*5401/B54 and B*3901/B39) should be fully discussed (and positively concluded) if the uncorrected P-values are used to conclude. This is because the two alleles exhibit a significant association with SARS infection in some case-control combinations with the uncorrected P-values (not with the Pc-values; Table 2), as B*1301/B13 does. To ignore B*5401/B54 and B*3901/B39 among these three alleles is somewhat arbitrary.
III. For the discussion of B*1301/B13 (p. 5), the authors describe that high frequency of occurrence throughout Asia make HLA-B13 a good contender to be considered as protecting against SARS (lines 6-7 from the bottom). This discussion is unreliable and should be revised because high frequency of B*1301/B13 is not found in every Asian population (e.g., 1.3% for mainland Japanese; Tokunaga et al. 1997, Immunogenetics, 46:199-205). Moreover, higher frequencies of HLA-B13 (over 16%) among most indigenous Taiwanese tribes (lines 10-11 from the bottom) may explain only why the tribes have had no probable SARS patients to date, although the authors prefer the above expanded discussion.

IV. On p. 5, last paragraph, the authors imply that B*1301/B13 in the Taiwan indigenous tribes is a protective factor for SARS infection. This is incompatible with the statement that the HLA makeup of the Taiwan indigenous peoples () may not contain any factor associated with SARS infection (lines 17-18 from the bottom). Please revise either (or both).

V. Generally speaking, a single retrospective association study could give no conclusion, but only lead for further investigation. The emphasis on the association of the two HLA-B alleles with SARS infection (especially in the case of B*1301/B13) should be decreased in the Conclusions of the Abstract and the Discussion, on the basis of statistical inferences from the Pc-values.

2) On pp. 6-7, some references still need to revise; De Vries RRP et al. 1976 (reference no. 10) should be De Vries RRP et al. 1979, and Imanish T, () Gojobori: The allele (), 1992, 1067-1074 (reference no. 18) should be Imanishi T, () Gojobori T: Allele (), 1992, 1065-1220. Also, one new reference (no. 17) could be revised (not appropriate).

3) Other comments on the revised parts of the manuscript
In the Results of the Abstract, the authors include additional description of the need for further independent studies as suggested. To add this to the Abstract is OK, but not a matter of the Results; please revise.
On p. 5, line 3, control A (P=01, ) should be control A (P=0.01, ).

Competing interests:

None declared.