Reviewer's report

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

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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

Review of article: Lin et al.; Association of HLA Class I with Severe Acute Respiratory Syndrome Coronavirus Infection

Comments for authors:

This is the first case-control study to evaluate the association of HLA type in Taiwanese with Severe Acute Respiratory Syndrome (SARS) infection. The authors examine HLA-A, -B and -DRB1 alleles in 37 Taiwanese patients diagnosed as probable SARS, 28 non-SARS patients with fever, 101 non-infected health care workers (who were possibly exposed to SARS coronavirus in hospitals), and 190 ethnically matched healthy controls. They conclude that HLA-B*4601 may be a genetic risk factor for SARS infection, and be significantly associated with susceptibility to more severe SARS in patients (such as deceased and/or intubated patients), whereas HLA-B*1301 appears to be resistant to the infectious virus.

1) A total of 190 healthy unrelated Taiwanese are used as control B (one of two control groups) in this study. They were just analyzed for HLA-A and -B loci at the serological level (Lin et al. 2001, Tissue Antigens, 57:192-199) as described in the manuscript, and hence it must be impossible to define HLA-B allele types for control B according to the previous serological data only. The authors need to explain completely how to determine individual HLA-B allele types for control B in the present study, because this case-control association study (probable SARS vs. control B) is performed at the allele type level (as shown in Table 2 and the text).
2) In the research field of HLA and disease association, it is highly possible that an observed association comes from a statistical artifact due to multiple comparisons (e.g., Svejgaard and Ryder 1994, Tissue Antigens, 43:18-27). Consequently, it is important (and necessary) to conclude HLA association with SARS on the basis of the P-values corrected for the number of comparisons (Pc-values). In the present study, only significant association of HLA-B*4601 with the severity of SARS is observed with the Pc-values (vs. control A [non-infected health care workers]). With the uncorrected P-values, on the other hand, four HLA-B alleles (B*4601, B*1301, B*5401 and B*3901/B39) may be positively or negatively relevant to SARS infection in some case-control combinations (Table 2 and 4). Taken together, therefore, the association of HLA-B*4601 with SARS is less erroneous, but the authors should mention the need for further independent studies to test this hypothesis. This is because there is no statistical significance in any comparison with control B or non-SARS patients with fever, even with the uncorrected P-values (Table 2 and 4). Next, other three alleles (B*1301, B*5401 and B*3901/B39) are unlikely associated with SARS infection. Thus, the authors should explain more fully why they conclude that HLA-B*1301 appears to be protective against SARS infection.

3) The epidemiological discussion (pp. 4-5) in this manuscript is very interesting, but additional information (such as appropriate references) is necessary for the readers to understand it more easily. For example, there is no reference about the following points: genetic characteristics of Taiwanese (p. 4, bottom line), allele frequency of HLA-B*4601 in Taiwan indigenous people (p. 5, lines 13-14), and the degree of differences in immune repertoires between Southeast Asian and Europe/African populations (p. 5, lines 19-20).

4) On p. 7, the authors should remove the SARS patient I.D. (probably initials for the patients) from Table 1, in order to keep personal genetic information confidential. Also, the patient information such as gender and age in table 3 (p. 8) is not necessary in the context of this manuscript, and can be removed.

5) Other comments
This manuscript has frequent lack of description as to which control group is used to obtain the probability and odds ratio of HLA-B allele association. This information should be mentioned explicitly. In the Abstract (p. 1), for example, there is no information about the following parts in the Results section: HLA-B*4601 (OR=2.08, P=0.05), HLA-B*5401 (OR=5.44, P=0.02) and HLA-B*1301 (OR=0.16, P=0.05).
On p. 4, line 3, the number of healthy unrelated Taiwanese examined (control B) must be 190 (not 101).
On p. 5, line 15, the cited article (reference no. 8) must be inadequate because the article contains no date on allele frequencies of HLA-B*1301 among Taiwan indigenous tribes.
In Table 2 (p. 8), why is the P-value for B*5401 (vs. control B) not available?
In Table 3 (p. 8), HLA-B alleles (B*4601, B*5601) for patient no. 1 are incompatible with those (B*4601, B*5801) presented in Table 1 (p. 7). Which is correct?
There are many mistakes in citation (pp. 5-6). Reference nos. 2, 4, 5, 8, 9, 10, 15 and 16 should be revised appropriately or updated.
While generally well written, the manuscript has several syntax errors, which make for choppy reading in some areas.

**Competing interests:**

None declared.