Questions on ‘Sequencing of the MHC region defines HLA-DQA1 as the major genetic risk for seropositive rheumatoid arthritis in Han Chinese population’ by Guo et al

We read with great interest the paper by Guo et al addressing the HLA association with seropositive rheumatoid arthritis (RA) in Han Chinese. The authors reported that aspartic acid at position 160 of HLA-DQα1 (HLA-DQα1:160D) was the major risk factor. It was accompanied by asparagine at position 37 of HLA-DRβ1 (HLA-DRβ1:37N), which was protective. These results were obtained by targeted sequencing in 961 cases and 1812 controls distributed in discovery and validation stages. The underlying assumption is that sequencing had uncovered new susceptibility HLA alleles. Specifically, HLA-DQα1 has not previously been associated with RA, whereas the most associated HLA alleles and amino acids were those included in the shared epitope (SE) of HLA-DRβ1. These SE alleles have been associated with increased RA risk in all the ethnic groups analysed including the Han Chinese and other Asian ethnicities. The new results are, therefore, of an extraordinary novelty and need to be considered with attention.

A careful analysis shows reasons for concern due to internal inconsistencies in the Guo et al study. These inconsistencies include amino acids at DQα1:160 that do not sum up: the frequencies of the three amino acids (D, A, and S) were 0.20, 0.22 and = 0.02 in controls and 0.36, 0.37 and = 0.01 in patients with RA, respectively (table 1). The three amino acids did not add up to 1.0 as required given that they are the only amino acids at this position. Also, the OR in cases/controls of the DQα1:160 amino acids was inconsistently described: two of the amino acids were described as increased in patients with RA, DQα1:160D with OR=2.36 and DQα1:160A with OR=2.27 (table 1). These ORs are impossible considering the low frequency of the third (DQα1:160S) amino acid. None of these inconsistencies are worrisome and ask for clarification.

Cristina Regueiro, Antonio Gonzalez
Experimental and Observational Rheumatology, Instituto Investigacion Sanitaria-Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain

Correspondence to Dr Antonio Gonzalez, Experimental and Observational Rheumatology, Instituto Investigacion Sanitaria-Hospital Clinico Universitario de Santiago, Santiago de Compostela 15706, Spain; agmartinezp@ihs.es

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Competing interests
None declared.

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ORCID iD
Antonio Gonzalez http://orcid.org/0000-0002-2624-0606

REFERENCES

Table 1 Inconsistencies in the frequencies of the top associated amino acids from Guo et al

<table>
<thead>
<tr>
<th>Amino acids</th>
<th>Frequency†</th>
<th>OR‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guo et al</strong></td>
<td>Controls</td>
<td>Patients with RA</td>
</tr>
<tr>
<td>DQα1:160D</td>
<td>0.20</td>
<td>0.36</td>
</tr>
<tr>
<td>DQα1:160A</td>
<td>0.22</td>
<td>0.37</td>
</tr>
<tr>
<td>DQα1:160S</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>DRβ1:37N</td>
<td>0.23</td>
<td>0.23</td>
</tr>
</tbody>
</table>

*Taken from the Allele Frequencies Net Database (http://allelefrequencies.net).
†Frequencies taken from Guo et al. Figure 3 and supplementary tables 3, 5 and 8 for DQα1 amino acids and from supplementary tables 4, 6 and 8 for DRβ1:37N.
‡OR reported in pages 775 and 776 of Guo et al for DQα1 and DRβ1:37N, respectively.
§Results for Koreans were combined from four studies.

RA, rheumatoid arthritis.