Reviewer’s report

Title: The interferon gamma gene polymorphism +874 A/T is associated with severe acute respiratory syndrome

Version: 1 Date: 2 March 2006

Reviewer: Maria R. R Capobianchi

Reviewer’s report:

The paper by Chong et al. shows that the allele A at position +874 of IFN gamma, involved in binding of the transcription factor NF-kB, is more frequent in SARS patients, as compared to healthy controls from Red Cross. Furthermore, in patients, the OR for the heterozygous AT and for homozygous AA genotypes is 2.57 and 5.19, respectively, versus TT individuals, suggesting an allele dosage effect. They could not demonstrate a similar effect of SNP at this position on the severity of the disease, and this failure was attributed to unbalance between survivors and succumbed patients. In addition, no significant correlation of SNP for IL-10 and TNF alpha was observed.

General comments

The manuscript provides interesting information about the relationship between host genetics and infection. The methods are appropriate and well described, and the whole paper is straightforward and clearly written. However, experimental and statistical data presented do not sufficiently support the conclusion that the allele A at position +874 of IFN gamma is protective against SARS, and additional analyses are requested.

-----------------------------------------------------------------------------------

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

The main limitation of the study is the fact that controls and patients are not matched groups for likelihood of contracting the infection, as, by definition, healthy blood donors are inherently different for many characteristics from the cases. So, it is well possible that controls are protected from many infections, possibly thanks to a specific genetic background, and the protective effect is not specific for SARS. So it is not appropriate to conclude, in this context, that a particular SNP is protective against SARS. A more appropriate control group would be SARS-CoV-exposed but uninfected people. We understand the difficulties to recruit a proper control population of sufficient size to match the case population, but, in the absence of such control, the protective role of the A allele against SARS is not demonstrated, and the conclusions should adequately stress this strong limitation. Otherwise, the Authors should base their conclusion on a more convincing evidence. Another possible explanation for the different frequency of alleles at position +874 of IFN gamma of cases and controls could be a different ethnic composition of the two groups. In fact, the nationality of individuals could influence the allele distribution, and it is not clear if the patients match the controls for ethnic characteristics. The Authors should also address this issue.

On the whole, the aid of an expert epidemiologist/statistician would be beneficial to improve the study design and analysis.

-----------------------------------------------------------------------------------

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

-----------------------------------------------------------------------------------
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 importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes

**Declaration of competing interests:**

I declare that I have no competing interests