Reviewer's report

Title: TNFA -863 polymorphism is associated with a reduced risk of Chronic Obstructive Pulmonary Disease: A replication study

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Reviewer: Noor Kalsheker

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This study reports on the role of TNF # genetic variation in a group of 202 COPD patients, 90 smokers and 432 healthy controls. The most significant observation relates to the protective effect of TNF # – 863 polymorphism which also correlate with severity of disease and longitudinal measures. These data are interesting but there are major limitations of the study.

1) The sample size is small for a replication study and could generate false positives – stratification is an issue and tests for stratification should be considered or discussed as this is potentially a major confounder.

2) The absolute numbers in each category of COPD e.g. GOLD and BODE index should be shown in a Table, together with the number of subjects in each group. The reported SNP occurs at an allele frequency of 16% in COPD. The final analysis included 199 patients. At best the sample numbers with severity relating to the - 863 SNP will be about 30 and to split these into groups to explore the association with severity will result in very small numbers-the studies are likely to be under powered to detect meaningful differences. This needs to be discussed.

3) A list of all studies of TNF # with COPD genetic variation should be included in a Table with the sample numbers as there are conflicting data and these need to be considered. There is at least one large study not cited in the manuscript (Chappell S. et al. Eur Resp J. 2007, 30: 1-2) where TNF # genetic variation has been investigated with a negative report.

4) There are significant differences in the age of the cases and controls with the latter being younger. It is conceivable that TNF # polymorphisms are related to survival and some discussion based on the age difference is warranted.

5) Although there was good concordance in the genotyping of samples, an independent method for validation is warranted e.g. sequencing of a small number of samples. Genotyping errors could result in false associations.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a
statistician.

Declaration of competing interests:

I declare that I have no competing interests.