Reviewer's report

Title: Prevalence of Genetic Polymorphisms in the Promoter Region of the Alpha-1 Antitrypsin (SERPINA1) Gene in Chronic Liver Disease: a Case Control Study

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Reviewer: Sally Chappell

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The aim of this study was to investigate the distribution of the -1973 promoter polymorphism of SerpinA1 in patients with liver disease compared to healthy controls. The results show that there is no difference in the allele frequency in the patients compared to the controls for any of the aetiologies considered.

The work in this manuscript follows on from a published study which compared alpha-1 antitrypsin deficient (AATD) individuals with liver disease against AATD patients with lung disease. This previous work aimed to identify genetic variants of alpha-1-antitrypsin that would identify which AATD individuals were at risk of developing liver disease rather than COPD, and found a significant difference in the allele frequency of SNP -1973.

Major Compulsory Revisions

1. The introduction in the current manuscript sets the scene well for the consideration of AATD-induced liver disease, but the subjects included in this study were not selected on the basis of AATD. There is little justification in the current study for where alpha-1 antitrypsin may play a role in the various aetiologies included in the liver disease group, and this is the main weakness of the investigation. There is considerable heterogeneity in the liver disease group, and there is little comment on how alpha-1 antitrypsin would be expected to play a significant role in all of these causes. As a consequence of including such a variety of conditions, the age at onset has a huge range –it is unsurprising therefore that no significant effect was seen.

2. The power calculations were also carried out assuming one group of 297 patients, whereas in fact this is really a collection of much smaller sub-groups.

3. Inclusion criteria for the controls is lacking – how were these individuals checked for the presence/absence of liver disease? Were they examined clinically or was this on the basis of self-reporting?

4. What quality control measures were in place to check the genotyping results? Were any samples done in duplicate? Were any sequenced, or analysed using an alternative technique, to check the accuracy of the PCR method?

5. The authors state that the distribution of Z allele heterozygosity is similar
across all aetiologies, but do not give any further detail. Were statistical tests done for all of these comparisons?

6. The distribution of -1973 alleles are likely to be different in MZ individuals compared to wildtype MM individuals – this is unsurprising, and the altered allele frequencies of -1973 in PiZ patients has already been documented (Ref 9 in the current manuscript). It is possible that similar results would be seen for the S allele, although why this should be different between the patients and control groups is unclear. Potentially these results, and the conflict with the results in References 13-15 as mentioned by the authors in the discussion (which are much larger studies), are likely to be caused by the small sample numbers in the current study.

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

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