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

**Version:** 2  **Date:** 23 October 2009

**Reviewer:** pascal pineau

**Reviewer's report:**

In their report Karin Kok and coworkers analyse a series a 297 patients with liver disease for the presence of three polymorphisms in the SERPINA1 gene responsible of a1-antitrypsin deficiency (A1AT). Patients are compared with a series of 297 controls matched for age and sex.

The major aim of the study was to determine the potential role played by a recently discovered polymorphism (c.-1973T>C) suspected to be preferentially involved in the liver manifestations of A1AT.

The novel c.-1973T>C polymorphism was found in the same proportions in patients and controls. It was found independent of any risk factors and did not influence the age at disease onset.

The authors found, however, a significant association of S allele (p.G264V) with drug induced liver injury.

Given the number of cases with adverse effects involving the liver recorded in each year, this latter aspect of the work is potentially of great medical importance although it is barely commented by the authors.

**Major Compulsary revision**

**Discussion :** Were the drugs involved in the 11 patients with DILI identified ?

The power of the study is a key issue of this work as the authors recognized it honestly. They suggest that future research should include patients homozygous for PiZZ, absent from the present study.

I consider, therefore, that the authors should somewhat attenuate their conclusion claiming that they « demonstrate that c.-1973T>C polymorphism is not associated with liver disease ».

Finally, the reader will find a great interest in a more detailed development of the relationships between SERPINA1 and drug-induced liver disease. To my knowledge, very few reports exist on this topic. I suggest to cite at least the work of Mindikoglu and coworkers (Hepatogastroenterology. 2003 Sep-Oct;50(53):1338-40).

**Minor essential revisions**
Abstract:

« these divergent expressions » is a bit misleading for geneticists. Using « divergent disease expressions » will be more appropriate.

c.-1973T>C polymorphism... is increased: should be replaced by « more frequent » or by « the proportion/rate of c.-1973T>C polymorphism... is increased ».

« In addition, S allele... »: This « addition » comes after a minimal explanation and without any explicative context. I think that it deserve to be more developed in the conclusions inasmuch it is the only results associated with a significant P value.

Results:

« Contrary, in healthy control ... » : « contrary » does not seem appropriate in this instance. "Similarly", "symetrically", "on the other hand" might be preferred.

Discussion:

« COPD »: should developed at least once.

« Z and S allele heterozygosity »: in the context, I suspect that « homozygosity » is more appropriate.

« pR25P is associated with advanced hepatic fibrosis... but not in patients with chronic liver disease »: this sentence is far to be clear. « other chronic liver disease » will maybe clarify this point.

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.