Reviewer's report

Title: Fibrinogen beta variants confer protection against coronary artery disease in a Greek case-control study

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Reviewer: Charalambos Antoniades

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In this case-control study the effect of genetic variability on fibrinogen chains’ genes on coronary artery disease (CAD) risk was investigated in a Greek population. The authors determined the genotype in a total of 13 SNPs on fibrinogen #, # and # chains genes (FGA, FGB and FGG respectively) in 305 cases and 305 controls. None of the haplotypes was associated with increased susceptibility to CAD after adjustment for risk factors. However, FGB rs1800787 and rs1800789 SNPs were associated with lower CAD risk (by about 50% in homozygotes for the minor alleles). Despite the valuable findings, the study has some major limitations regarding its design that should be addressed.

Major comments

1. A major limitation of the study is the lack of any information on the effect of genetic variability on fibrinogen levels. The adjusted OR of each haplotype / SNP should have been adjusted for fibrinogen levels.

2. Importantly, the two groups (cases-controls) are not matched for cardiovascular risk factors (Table 1). Indeed this constitutes a major limitation of the study that makes the extrapolation of the findings debatable.

3. More demographic data should have been reported. For example, the selected SNPs/haplotypes associated in bivariate analysis with increased OR for CAD, should have been adjusted not just for presence of dyslipidemia but for LDL, HDL and total cholesterol levels. Besides, all participants obviously undergone a routine laboratory screening before entry to exclude renal and/or hepatic disease and subsequently this data should exist. Please present this data in Table 1 and present the relative adjusted OR and p-value in Table 3.

4. Please provide power calculations for the study.

5. It would be interesting to present the linkage disequilibrium measurements performed by Haploview. Table 4 can be replaced by the relative Haplotype maps.

6. Furthermore, as it has been previously demonstrated (Jacquemin et al. JACC 2008) some fibrinogen SNPs exhibit high sensitivity to pro-inflammatory stimulation, inflicting greater changes on fibrinogen plasma levels under pro-inflammatory states. Therefore acute phase response status has a critical impact on the role of selected SNPs. In the present study the proinflammatory
background (e.g. determination of proinflammatory cytokines levels) or acute phase response status (e.g. determination of CRP or even fibrinogen per se) was not determined in any of the participants. Subsequently the role of each SNP/haplotype may have been over- or underestimated. A multivariate regression analysis that included an inflammatory marker (e.g. CRP, IL-6) as a possible confounder will significantly enhance study’s findings.

7. The abovementioned limitation is important since almost 2/3 of the cases were acute coronary syndromes (ACS) and only 1/3 stable coronary patients. It would be interesting to examine whether ACS-induced changes in inflammatory status have the ability to affect fibrinogen levels in this population.

Minor comments

Abstract: p=0,026 replace comma (",") with "."
The same applies for:
Page 7 last line: p=0,081
Page 8, first two lines: OR=1,51 (p=0,013) and OR=1,39 (p=0,077)
Page 10, line 6 same with r² values

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests