Author's response to reviews

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

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Author's response to reviews: see over
Dear Editor,

Please find attached our revised manuscript. We hope that we have now adequately replied to your questions.

Sincerely Yours,

Eirini Theodoraki

Comments from the Associate Editor

"Although both reviewers recommended to accept this manuscript without further modification, a new concern arose when reading this manuscript in depth. I will recommend acceptance of this manuscript provided that the authors answer the following point:

According to Figure 1, the rs1800787 and rs1800789 are in very strong LD (r² = 0.97). This raises two comments. First, it is not completely right to conclude, as written in the Abstract, that two SNPs seem to decrease the risk of MI as these two SNPs are in fact in nearly complete association. They should "represent" only one SNP.

We thank the Associate Editor for the important comment as we falsely referred to r² values instead of D' values in the legend of figure 1. Actually, we have constructed LD block consisting of five SNPs in FGB gene according to pairwise D' values. We agree hereby that rs1800787 and rs1800789 are in strong LD indeed, but 0.97 was actually pairwise D' value, whereas pairwise r² was 0.92. Because single SNP association signals for these SNPs were of the similar strength after correction for confounding factors, this could be the evidence of the same association signal and either of them could be the reference SNP representation of a single SNP association with disease and another SNP is a flanking marker (proxy) which is in strong LD with the reference SNP.

An appropriate sentence has been rewritten in Discussion section (p. 11 lines 4-6) as:

One could hypothesize that the effect of rs1800790, found in the previous studies, is attributed to the strong LD with SNPs rs1800787 and/or rs1800789 - these two tightly linked SNPs most likely are representing the evidence of the same signal of association with the disease and either of these SNPs might be the functional one.

Secondly, they mentioned in the method section that these SNPs were selected from HapMap to be tag SNPs to avoid redundancy between SNPs and that a threshold of 0.80 was used. The authors should discuss why many pairwise r² LD were greater than 0.90 in Figure 1."

First: according to the previously published associations with cardiovascular traits in a literature, a SNP rs1800787 was force-included to Tagger selection procedure. An appropriate sentence has been inserted in Methods section (p. 6 lines 17-18) as:

A SNP rs1800787 in FGB gene was force-included to Tagger selection.

Secondly, within FGB LD-block all pairwise D' values were above 0.90, but only 4 pairwise r² values exceeded 0.90 threshold. Other r² pairwise values were between 0.80 -0.85. The same occurs also when running Tagger for FGB region with CEU population as a reference - we can observe very similar LD data (D' and r²) in comparison with Greek population data. Therefore we consider the LD data presented in this manuscript are not exceptional to warrant further discussion in details.