Author's response to reviews

Title: The E670G SNP in the PCSK9 gene is associated with polygenic hypercholesterolemia in men but not in women

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Response to A.J. Marian

Major Revisions

1. Power to detect difference between polygenic hypercholesterolemia and LDL<50\textsuperscript{th} percentile is 0.22. Calculated using the programme from Dupont WD and Plummer WD. PS Power and sample size programme available free on the Internet. Controlled Clin Trials 1997. 18:274.

2. There are no potential confounding effects of lipid lowering therapy since only patients who were not taking lipid lowering drugs were included in the study. See Materials and Methods from line 6 “Existing therapy was, where possible, discontinued and at a second visit approximately 6 weeks later biochemical and biometric values were again determined to provide data under diet/absence of drug therapy. Only patients from whom lipid values obtained at this second visit, i.e. after the diet advice and in the absence of lipid lowering therapy were included in the study and it is this lipid value we use in our analysis.”

3 and 4. Table 1 has been modified.

5. Fig. 1 has been modified.

6. We present this sex difference as an observation. As we state in the Discussion line 7, “since the mechanism by which variation in the PCSK9 gene affects LDL levels is unknown (4, 5) we have no explanation for the different effect of such variation between men and women”

Minor Revisions

1. We are not clear what the referee means by analyzing baseline LDL levels. Assuming that the referee means value at first visit as baseline we consider this less satisfactory since probands have presumably received varying levels and non-standard advice on diet and lifestyle from their referring clinician whereas by analysing LDL levels obtained at the patients second visit after a their first session with the physician and a 30-60 minute discussion with a dietician confounding non-genetic effects are reduced. This we consider to be the appropriate baseline value, Secondly a proportion of these patients will have been taking lipid lowering medication at baseline thus giving rise to the difficulty the referee discusses in point 2 of Major Revisions.

2. Genotyping was validated by random, blind repeat genotyping.

3. Has been modified.

Discretionary Revisions

The PCSK9 E670G SNP was chosen since in the comprehensive haplotype analysis reported by Chen et al it was the marker for the haplotype associated with LDL levels.
Response to A.L. Beaudet

1. Table has been modified.
2. Reference has been completed.
3. This point has been addressed in the discussion, line 7
4. Has been corrected