Reviewer's report

Title: The D9N, N291S and S447X variants in the lipoprotein lipase (LPL) gene are not associated with type III hyperlipidemia.

Version: 2 Date: 22 June 2007

Reviewer: Pierre Julien

Reviewer's report:

General

The authors submitted a new version of their paper, including new data, error corrections as well as new subjects added to their data.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

In the original manuscript, three groups were studied, i.e. 200 anonymous blood donors, 100 apoE2/2 patients and 1197 lipid clinic patients. In the new version of the paper, the number of subjects in the lipid clinic group increased to 1514 for the D9N and the N291S groups and to 1308 for the S447X group, stating that biological specimens were no longer available to complete the S447X analyses in 206 of these patients. These dyslipoproteinemic patients were obtained from an outpatient clinic between 1997 and 2004. This increase in the number of dyslipoproteinemic patients suggests that patients were selected, using an undetermined procedure, from a larger pool of lipid clinic patients. A major concern is thus the selection procedure used for this study. The method section should indicate how patients were selected, including that patients taking drugs affecting lipid metabolism were excluded. Comparing frequencies in the apoE2/2 group to that of “pre-selected” outpatients is not a valid comparison if these lipid clinic patients are not representative of all dyslipoproteinemic patients.

Furthermore, the total number of subjects reported in table 4 should indicate 1408 instead of 1404, indicating that 206 patients, included in the D9N and N291S results (table 3), have been excluded from the genotypes detailed in table 4. However, table 4 gives us interesting results showing that 2 out of 3 apoE 2/2 patients heterozygote for the N allele (D9N) were combined heterozygotes, carrying a LPL gene variant expressing lower LPL activity as well as a LPL gene variant expressing higher LPL activity, probably annihilating the effect of LPL activity reduction. These findings suggest that the effect of LPL gene variant on type III expression could be affected by the presence of S447X, suggesting the importance of collecting S447X data from all subjects. Furthermore, the lower frequency of type III expression in apo E 2/2 group (D9N carriers of DN variant) could also be explained by the presence of S447X rather than the absence of effect of D9N on type III expression. Taken together, these...
findings indicate that the frequencies of these LPL variants are not increased in apoE 2/2 patients suggesting that they could not represent a major factor in type III expression in these patients. However, these data do not support the conclusion that the same LPL variants could not play a major role in type III expression when present in a apo E 2/2 patients.

Finally, characterization of type III patients is unclear. It seems that VLDL data are not available in the present study. Screening for type III patients could also be carried out using the apoB/total cholesterol (TC) ratio (Blom DJ et al Clinical chemistry 51,5: 904-907). Remnant accumulation may also occur due to the presence of metabolic defects, such as diabetes and hypothyroidism. To clearly identify type III dyslipoproteinemia another test is required such as the apoB/TC ratio lower than 0.15, easily calculated using the present data. I thus propose to report the TC/ TG and ApoB/TC ratios in apo E2/2 patients (table 2) with or without type III.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Apo AI and apoB data (genotype and protein data) are reported in table 1 but methods are not reported in the method section.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests