Reviewer's report

Title: Common variants in the lipoprotein lipase (LPL) gene and type III hyperlipidemia.

Version: 1 Date: 27 February 2007

Reviewer: Pierre Julien

Reviewer's report:

General

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

Authors are proposing to investigate the role of LPL variants in the development of type III HLP. We note that data reported are strictly frequencies of genetic data. The major concern arising from this manuscript is the assertion that these LPL gene variants are not significant co-factors for the expression of type III HLP whereas type III phenotypic expression has not been evaluated and/or is not reported.

Knowing that not all apoE2/2 patients expressed type III HLP, this paper does not discard the possibility that apoE2/2 patients, also carriers of a LPL gene variant reducing the LPL activity, might have a higher propensity to phenotypically expressed a type III HLP than apoE2/2 patients without LPL gene variants.

These data suggest that studied LPL gene variants are uniformly distributed among the three groups of subject, apoE2/2 carriers, blood donors and lipid clinic patients without apoE2/2, these genetic mutations being, presumably, independently inherited in the general population. The assumption of allele independence between apo E2 and LPL variant 447 and between LPL variants 9 and 447 in a French-Canadian population has been questioned in a recent paper by (Garenc et al J Hum Genet 2004, 49: 691-700). These data suggest that co-transmission of variants 9 (LPL deficiency) and 447 (LPL over expression) could prevent the expression of dyslipidemia. Is there combined heterozygocity for LPL gene variants among these subjects? Are there relatives among any of these groups? Are the 102 apo E2/2 subjects originating from different families?

It is thus imperative to describe the phenotypic expression of type III HLP in each group, using known criteria for type III characterization (total chol/ Tg typically 2:1, instead of 1:1, VLDL-C/Tg > 0.3 (mg) or 0.7 (mol) and presence of beta-VLDL) as previously published by Blom DJ et al in S Afr Med J 2002, 92: 892-897. Is there type III HLP in Lipid Clinic patients with Tg > 200 mg/dl? How many apoE2/2 subjects express type III HLP? The methodology section indicates that lipid determinations have been carried out but no data are included within this manuscript. Effects of polymorphisms on plasma lipids have been statistically studied (statistic section). Complete data should be reported in a table format. Not all the variables studied, such as apoAI (statistics section), are described in the biochemical analysis section! Are the lipid analyses carried out in fasting individuals not receiving medication affecting lipid metabolism? Are patients receiving medication affecting type III expression excluded from the study?

The blood donor group does not bring any significant information on type III expression because clinical data, including the frequency of apoE2/2, of type III and lipid values, seems to be unknown in blood donors. Detailed information on lipid data and on co-factors affecting the expression of type III, such as apoA5 and apoE2 (Arg145 > Cys), should be reported.

What is the ethnic composition of the study groups, are the groups similar? It has been reported that expression of type III due to apoE2 (Arg145 > Cys) is frequent in black population (Blom et al). Apo E2 and LPL frequencies have also been shown to vary, even in specific local Caucasian populations (Garenc C, et al J Hum Genet 2004, 49: 691-700), indicating the importance of ethnic characterization showing that studied groups are from the same population.

It is hazardous to generalize the observations reported in the present study to all common variants in the LPL gene as indicated in the last sentence of the abstract and in the discussion section. The present paper examine two LPL gene variants leading to partial LPL activity deficiency in homozygotes whereas some
other LPL gene variant, such as LPL 207, also frequent (common) in French-Canadian population, leads to complete LPL deficiency. Could interaction between carriers of apoE2/2 and a LPL variant leading to complete deficiency induce higher frequency and severity in type III genotypic expression than interaction between carriers of apoE2/2 and LPL variant leading to partial deficiency?

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

One subject (101 versus 102 subjects) seems to be missing in the apoE2/2 and S447X group.

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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 of limited interest

**Quality of written English:** Needs some language corrections before being published

**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