Reviewer's report

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

Version: 1 Date: 12 March 2007

Reviewer: Robert Hegele

Reviewer's report:

General

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

Summary

The authors studied 102 subjects with type 3 hyperlipidemia, 200 normolipidemic blood donors and ~1200 subjects who were ascertained through a hypelipidemia clinic and who did not carry the E2/2 genotype. They studied 3 common polymorphisms of the LPL gene: D9N, S291S and S447X. They found no association between these markers and HLP type 3. However, they observed that the S447X allele frequency was reduced in the hypertriglyceridemic patients from the hyperlipidemia clinic. They conclude that common SNPs of LPL are unlikely to contribute to HLP type III.

Comments

The study poses a very focused hypothesis but is ultimately a negative study. There are several concerns.

1. The definition or phenotype of the study subjects. There are very cursory data presented regarding the patients. Were the type III subjects defined based on the E2/E2 genotype solely, or were there additional criteria? What is the importance of type III hyperlipidemia anyway? Is it a particularly bad form of hyperlipoproteinemia? Did the non-E2/E2 subjects contain some individuals with known forms of primary hyperlipoproteinemia, such as familial hypercholesterolemia or familial chylomicronemia. If such patients were known to be included, was this appropriate? When patients were divided by triglyceride concentration, was there any attempt to further stratify according to TC (i.e. ‘familial combined hyperlipidemia’) or low HDL cholesterol?

2. A table of demographic data for all subjects should be presented. There should be a more careful discussion of biochemical methods. On page 4, the authors discuss measurement of LDL cholesterol – but how was this performed – was it through the Friedewald calculation or was it directly determined?

3. Controls. The normolipidemic subjects represented one type of appropriate controls. But what about the lipid clinic subjects with TG<200 mg/dl. These seem like very normal TGs? Why were these subjects classified as “hyperlipidemic”? Did they have elevated total cholesterol and/or depressed HDL cholesterol?

4. Did observed genotype frequencies follow the predictions of the Hardy-Weinberg equation?

5. What were the linkage disequilibrium relationships between the LPL markers? Could maximal likelihood haplotypes be formed? Could these be studied for association with the qualitative phenotypes or the lipoprotein traits?

6. Did the study have sufficient statistical power to detect clinically relevant differences in frequencies between genotype classes?

7. Did the authors considering an independent variable that would include carriage of any one of the LPL SNP rare alleles?

8. Are any of these SNPs known to have functional consequences – if so what are they and how do they relate to the findings?
9. How do the findings of the current study relate to the results of reference 4 (Zhang et al)? Why did that study seem to show such a positive finding for the N291S genotype whereas the current study shows no such relationship? Was it simply differences in the control and study samples, as mentioned, or does it go deeper than that.

10. Was there enough information to comment on vascular disease risk or diabetes in these study samples?

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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)

Throughout: Please use capitalized italics when referring to gene names in the cases of LPL and APOE.

Page 2, line 4: remove possessive from “its”
Page 4, line 11: replace “incidence” with “prevalence”
Page 4, line 20: spelling “HDL” not “HDH”
Page 5, line 9: replace “mooted” with “debated”

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Discretionary Revisions (which the author can choose to ignore)

Consider changing the title to indicate the absence of associations.

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 have no competing interests.