Reviewer's report

Title: APOA5 Q97X mutation identified through homozygosity mapping causes severe hypertriglyceridemia in a consanguineous family.

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Reviewer: sybil charriere

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The article by Dussaillant et al. deals with the genetic of severe hypertriglyceridemia and the discovery of a new large family with APOA5 Q97X mutation using a homozygosity mapping strategy. They describe two homozygotes with major phenotypes (TG > 100 g/l and acute pancreatitis) and four heterozygotes with moderate to severe hypertriglyceridemia.

Only a few APOA5 mutations have been described in literature and two previous studies reported the same mutation:
- in a French study, one homozygote and four heterozygotes (only two related)
- in a Italian study, a family with on homozygote and three heterozygotes.

The interest of the study results in
1/ the originality of the genetic study used to discover the mutation
2/the description of cases to analyze factors that influence phenotypic variability of severe HTG

Major compulsory revisions

1/ The homozygosity mapping strategy used to identify potential mutation is particularly interesting to use when classical mutations involved in a pathology have been exclude. Up to date, LPL, APOC2 and APOA5 mutations are classically involved in severe HTG, and more recently GPIHBP1 and LMF1 mutations. Why the authors did not used first a direct sequencing of these major genes involved in severe HTG?

Was direct sequencing not easily accessible? Is this method really less expensive and faster?

The limits of the method are not clearly explained. Does it need to have large families? Would it have identified compound heterozygotes?

2/ LPL activity

The method used for LPL activity is not indicated. Moreover, the results of LPL activity are not given in Figure 1 as said in the text.

Was it a post-heparin LPL activity? LPL activity is a critical and difficult assay. The authors say in results that the “LPL activity was normal in 2006“ and in
discussion that “in 2006, even the proband had normal TG”. Normal LPL activity is probably explained by the fact that LPL activity was done when TG were normalized. The method, the results of LPL activity compared to normotriglyceridemic controls should be added and TG values at the time of LPL activity should be mentioned.

3/ In discussion, the phenotypic variability of patients compared to previous reported cases should be more detailed.

The probands exhibited very severe phenotypes (TG > 100 g/l) with several episodes of acute pancreatitis compared with Q97X reported by Priore Oliva and Charriere et al. Could you discuss this point and indicate if additional genetic variants have been studied to explain the severity of their phenotypes? (for exemple, APOE2 or E4 variants, LPL or apoC3 polymorphisms ..).

In discussion, the authors say “affected cases (HTG > 5,000 mg/l) only showed wild type S19W and -1131T>C genotypes of APOA5”. The authors referred to homozygotes. The influences of these polymorphisms are probably minor in homozygotes with non sense mutations. Moreover in the French and Italian study, no truncated peptide was identified.

On the contrary, as discussed by Charriere et al. in Atherosclerosis in 2009, the influence of the polymorphisms may be crucial in heterozygotes. The authors should analyze the influence of these polymorphisms in their heterozygous cases.

Minor essential revisions

1/ Are apoAV plasma values available in this family?

2/ In table S4, for charriere et al (2009), “clinical manifestations not described “ is wrong. It is written in the original article “None of the patients with Q97X or L242P mutation suffered from acute pancreatitis or cardiovascular diseases”.

3/ International units should be used for biological values (TG in mmol/l for example).

Discretionary revisions

1/ The authors could explain why proband 1 was treated by ezetimibe and nicotinic acid in addition to fibrates. It is an unusual treatment for hypertriglyceridemia. These treatments are usually used to treat hypercholesterolemia.

2/ The authors could comment the fact that subject 8 (Q97X heterozygote) died of coronary heart disease, and if he had additional cardiovascular risk factor.

3/ The exact name of Oliva in reference n°47 is Priore OLiva.

4/ In figure 1, the author should precise if all rs number referred to APOA5.
Level of interest: An article whose findings are important to those with closely related research interests

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' below