Reviewer's report

Title: Familial hypercholesterolemia mutations in Petrozavodsk: no similarity to St. Petersburg mutation spectrum

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Reviewer: Mathilde Varret

Reviewer's report:

The strengths of this article are the identification of new mutations in the LDLR gene in patients with familial hypercholesterolemia and the allelic heterogeneity of the Russian population indicating that, like in other populations worldwide, the best screening strategie is the systematic direct sequencing of all the exons of the gene.

Weaknesses are an English writing often difficult to understand and a poor structuring of the data set: the results section includes aspects that should go in the methodes, the discussion includes aspects that should go to the results section.

The manuscript must be reviewed by a native English speaker.

Specific issues to review:

1 - Mutations should be designated according to the Human Genome Variation Society recommendations (http://www.hgvs.org/mutnomen/).

2 - More detailed informations concerning the newly identified mutations should be given in the text of the article, as well as comments concerning their possible causative effect. Their potential clinical impact must be assessed not only with SIFT, be also using other algorithms on pathogenicity predictive web-sites such as PolyPhen and Mutation-t@ster.

3 - The p.Gly20Arg is a good exemple of a missense mutation reported in FH subjects from different countries but never with a demonstrated co-segregation. The three prediction algorithms do not suggest this change to be pathogenic, and this article gives the first exemple of non co-segregation with FH that confort the non-pathogenicity of this variation given by the in silico prediction.

This should be used in exemple to discuss the possible pathogenicity of the p.Ser447Cys and p.Leu646Ile missence variants. Are these two varaiations pathogenic ? If yes, why patient number 19 (coumpound heterozygote) only present an heterozygous phenotype of FH ?

And what about the p.Asn640= found in subject number 20 and in subject 23 as well as the p.Ser447Cys?

Since it is well known that the SSCP method do not allow the identification of all DNA variations, the sequencing of the whole LDLR gene is necessary, at least for the 4 carriers of a new missense mutation (subjects number 19, 23, 72 and
4 – In the first sentence of the results section it is stated that 19 sequence variations were found and only 18 are presented in table 1. And there is some differences between table 1 and table 2 (additional file) concerning the number of carrier of c.925-931del7 and c.2191delG.

5 – It is stated that the p.Leu511Ser has been classified as a pathogenic variant, this must be detailed, what were the arguments?

6 – The p.Pro539= variant is found at a frequency of 5% (12 of 232 chromosomes) in the Petrozavodsk FH sample that unclude 80 subjects (160 chromosomes). This point in unclear.

7 – The authors shoud comment on the specific allelic heterogeneity of this sample of FH patients and why it is surprinsing to fin dit different from the St. Petersburg mutation spectrum. It is there historical, demographic, arguments for this difference?

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

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests