Reviewer’s report

Title: A new genetic variant of hereditary Apolipoprotein A-I amyloidosis: a case-report followed by discussion of diagnostic challenges and therapeutic options

Version: 0 Date: 28 Nov 2018

Reviewer: Dorota M. Rowczenio

Reviewer's report:

1) Throughout the manuscript (Abstract, Background) the authors' state that mutation occur in the protein, which is a false statement. Mutations or genetic variants occur in the genes (DNA sequence) and result, in this case, in the amino acid substitution of Leucine to proline at position 60 of the mature ApoA1 protein. The manuscript needs to be amended.

2) When listing the variant proteins authors should include the apolipoprotein CII, and apolipoprotein CIII and beta-2-microglobulin.

3) In the abstract conclusion needs re-writing. I don't think the current report extend the AApoAI phenotype, as the phenotype described in this patient (amyloid affecting the liver and testes) has already been reported in this type of hereditary amyloidosis.

4) In the Background the authors state: More than 50 variants in the APOA1 gene encoding apolipoprotein AI (ApoAI) are known, of which 20 have been associated with ApoAI amyloidosis (AApoAI).
   I don't think this numbers are correct; i.e. there is more than 20 mutations known to cause ApoAI amyloidosis.

5) Individuals with AApoAI present mainly manifestations due to liver, kidney, laryngeal, skin and myocardial involvement.
   Authors should change this sentence as the English is incorrect.

6) By the next generation sequencing, the proband was found to carry an heterozygous single-base substitution at the codon for residue 60 of the mature ApoAI protein from 5'-GCAAGCTGCGCGA for Leu-60 or 5'-GCAAGCCGCGCGA for Pro-60.

   Authors should re-write this paragraph
   - ...The proband was found to be a heterozygous for a single base substitution
   - Edit the paragraph in accordance with suggestions in point 1.
   - Furthermore, it should be mentioned that the DNA change is at position c.251T>C, changing the codon CTG to CCG, resulting in a change of amino acid from leucine to proline.

7) Sanger sequencing validation of all family members revealed that his siblings (two brothers) and his mother lacked the mutation, but paternal DNA was unavailable.
In this case Sanger sequencing was used for subsequent screening of the proband family members not for validation.

8) Discussion and Conclusions
In this case-report we recognized a new subtype of hereditary AApoAI for first time in a Greek patient caused by an heterozygous mutation at codon 60 from CTG to CCG in the APOA1 gene leading to an amino-acid substitution from Leu to Pro in the mature ApoAI protein.

This is not a new subtype of hereditary AApoAI, but hereditary AApoAI caused by a novel mutation in the APOA1 gene, described, for the first time, in a patient of Greek ancestry. The remaining of this paragraph needs to be edited in accordance with suggestions in point 1.

9) ……and only one with isolated liver involvement (Leu60_Phe71delinsValThr) [7] The reference (7) used here refers to (Leu60_Phe71delinsValThr)? In that case it is not correct. 10) Leu60_Phe71delinsValThr and Leu60_Phe71delins60Val_61Thr are the same variants so authors should be consistent with the nomenclature.

11) In conclusion, the identification of this new APOA1 mutation broadens the spectrum of known genetic mutations associated with hereditary ApoAI amyloidosis with liver and gonadal involvement. See point 3 and correct accordingly.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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