Reviewer's report

Title: Identification of compound heterozygous patients with Primary Hyperoxaluria Type 1: Clinical Evaluations and In Silico Investigations

Version: 0 Date: 21 Dec 2016

Reviewer: Mohamed Atta

Reviewer's report:

Kanoun and colleagues examined the impact of compound heterozygous mutations in 4 patients from 2 non-consanguineous PH1 families on clinical phenotype. In the first family, more than one pathogenic known variants were revealed on mutation analyses. The impact of these mutations on the generated AGT protein was the introduction of new alpha helix into amino acid chain. In the second family, mutation analyses also revealed known variants (two nucleotide changes in the N-terminal region of AGT protein) introducing several changes in the overall RNA secondary structure compared to wild type. Their findings indicate that compound heterozygous sharing the same haplotype for the c.731T>C, c.32C>T, c.1020A>G and c.33_34insC presented with more severe phenotype.

These findings highlight the genotype-phenotype correlations in non-consanguineous PH1 Tunisian families with variable clinical severity at severity. Overall, the study is well executed but the authors have not clearly stated in the discussion section the relevance of those results and how would they affect future research in this area. What is their recommendations? It is generally known that there are more than 150 known mutations for AGXT, with the three most common mutations c.33_34insC, c.508G>A, and c.731T>C and that genotype phenotype variability are common like any other genetic disorder. Compound heterozygous mutations have also been identified in patient with PH. As such, I would appreciate a statement from the authors in the discussion regarding novelty and expected future applicability of their findings.

Grammatical corrections and proofreading are advised.

Other suggested revisions

Abstract:

Background: Objective should be focused in the background section with clear message. It also needs grammatical corrections
Introduction/background

Page 5, Line 25, Please delete "The" in the beginning of the paragraph

Subjects and Methods

Page 6, line 41: Suggest revising "mean clinical features" and revise to baseline clinical characteristics or main clinical characteristics

Results

Page 9, line 45: Please delete "is" before the word occurred.

Discussion

Page 12, Line 32: Please revise the first sentence "In the present study, we reported clinical and molecular analysis ....." to " In the present study, we report the clinical and molecular analysis ...."

Page 12, Line 40: Please revise "In Tunisia, one of countries" to "In Tunisia, one of the countries"

Page 12, Line 47: please delete "the" in the sentence "in exon 10 were detected in the patient P1"

Page 12, Line 52: please revise "Family F2 presented only two known" to "Family F2 presented with only two known"

Page 13, Line 34: Please revise the sentence or break up into 2 sentences for clarity "However, the coexistence of this mutation with c.32C>T (p.Pro11Leu ) substitution causes a stable interaction between the AGT protein and molecular chaperones and thus lead to aggregation and rapid degradation of this enzyme and therefore, the decrease of AGT activity to less than 5%".

Page 14, Line 44: It appears that there a missing word in "we expected that causes alterations in the protein structure". Please revise
Page 15, Line 54: Please revise "They present the disease early before 1 year of age" to "Disease was presented early before 1 year of age" and replace "under the age of 1 year and presented a" from the following line with "with".

Page 16, Line 22: Please delete "The" and "respectively" in "The patients P1 and P4 presented less severe phenotypes respectively" and add "with" before the word "less"

Page 16, Line 46: Please revise the sentence "20 to 50% of patients had advanced chronic kidney disease or even ESRD at the time of diagnosis" as appears randomly inserted and don't start the sentence with a number

Table 1, can the author change the title from "Clinical features in studied patients" to "Patients' Baseline Demographics and Key Clinical characteristics"?

References needs to be formatted to BMC nephrology style.

**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.

Yes

**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?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript
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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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