Reviewer’s report

Title: Identification and characterization of a novel 43-bp deletion mutation of the ATP7B gene in a Chinese patient with Wilson's disease: a case report

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Reviewer: Prahlad Balakrishnan

Reviewer’s report:

The manuscript entitled 'Identification and characterization of a novel 43-bp deletion mutation of the ATP7B gene in a Chinese patient with Wilson's disease: a case report' is written moderately well, but, can be improved little more. The molecular genetics of Wilson's disease has been reported quite often, but the characterisation and mechanism of deletions / duplications or complex rearrangements are rarely found in literature.

This is an interesting article describing the molecular genetics part as well as the possible mechanism behind the novel deletion in ATP7B with adequate pictures. The article follows a satisfactory way of presentation, but can be modified well before the acceptance. Below mentioned are a few comments:

Few points are mentioned below, to be noticed.

1. Gene name to be changed to italics. e.g., ATP7B gene to be ATP7B gene or ATP7B.

2. ATP7B protein to be changed to ATP7B.

(HGNC Guidelines:- Appendix 1: Gene symbol use in publications -It is recommended that symbols denoting nucleic acid products (genes, alleles, mRNAs etc) are italicized in print (or underlined in manuscript); symbols denoting amino acid products (proteins)should be represented in standard fonts. Italics need not be used in gene catalogs. To distinguish between mRNA, genomic DNA and cDNA the relevant prefix should be written in parentheses (mRNA)RBP1, (gDNA)RBP1, (cDNA)RBP1.)

3. In multiple places it has been mention. Pathogenic mutations / deletion mutation etc... it can be changed to either mutations or pathogenic variants

In para 1 of Backgroud,

4. ATP7B gene mutations lead to ATP7B protein dysfunction, which in turn causes a massive accumulation of copper in the liver, brain, kidneys and corneas, with a wide range of clinical symptoms, including hepatic disorders, neuronal degeneration of the brain, and Kayser-Fleischer rings at the corneal limbus [5, 6]. ('a massive' can be removed)
5. However, mutations are identified in only one allele or none in a substantial number of WD patients. (reference to be included if possible)

In Para 1 of Case presentation

6. The proband was the first child of healthy non-consanguineous Chinese parents from Jiangsu Province. (It is not 'form', it is 'from').

7. Sanger direct sequencing of the 21 exons of the ATP7B gene revealed two heterozygous mutations in the proband, including c.3517G>A and c.532_574del. The c.3517G>A mutation in exon 16 resulted in the conversion of glutamate to lysine at amino acid position 1173 (p.Glu1173Lys), and is responsible for Wilson's disease [17]. The c.532_574del deletion covered a 43-bp region starting from nucleotide 481 to 523 in exon 2; it included CTCAGCAACCAAGAGCCGTCATCATCAGCCCTTATCTCA, and resulted in a frame shift mutation (p.Leu178PhefsX10). His parents were screened for mutations, and his mother was heterozygous for the c.3517G>A mutation, while the father was heterozygous for c.532_574del (Figure 1). Accordingly, the proband was compound heterozygous for c.3517G>A and c.532_574del mutations in both alleles inherited from his mother and father, respectively. According to previous reports and the Wilson Disease Mutation Database (http://www.wilsondisease.med.ualberta.ca/database.asp), the c.532_574del in exon2 in this WD patient was unknown so far. When these two pathogenic mutations were identified, prenatal diagnosis during a second pregnancy (testing the amniotic fluid) in the family was carried out, and the unborn sibling of the proband harbored only the heterozygous c.532_574del mutation and not c.3517G>A.

(The above paragraph is to be re-written in a more scientific way)

8. In the discussion and conclusions part, -- the deletion mutation c.532_574del (p.Leu178PhefsX10) in the ATP7B gene firstly reported in this study existed in the proband's parent, was therefore not a de novo mutation. (can be made in like, the deletion mutation c.532_574del (p.Leu178PhefsX10) in the ATP7B gene was reported for the first time in present study, and was observed in proband's parent, was therefore not a de novo mutation).

9. In the same paragraph, unable to understand the meaning of 'the severe mutation'. What is it? Please change to more attractive way like, "The variant would be considered as a pathogenic variant with more severe phenotype than the other missense pathogenic variants".

10. MMEJ is currently used to explain the possible formation of large deletions belonging to structural variations (SVs), commonly referred to as copy number variants (CNVs) which are generally defined as DNA regions of approximately 50 bp and larger in size, and not small deletions belonging to indels which are small insertions or deletions generally between 1 and 50 bp in size. (any reference).
11. The presence of DNA sequence motifs, including 2 "Deletion hotspot consensus", 2"DNA polymerase arrest site", 1 "Ig heavy chain class switch repeat 1", 1 "Ig heavy chain class switch repeat 2", 1 "Vaccinia topoisomerase I consensus", and 1 "oligo(G)n tracts" in adjacent regions of the c.532_574del mutation, is......(repeated in the same paragraph).

12. None of the supplementary files have a connection with the main article.

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.

Unable to assess

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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