Reviewer's report

Title: Clinical and Molecular Characterization of Ataxia with Oculomotor Apraxia (AOA) Patients in Saudi Arabia

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Reviewer: Maria-Ceu MOREIRA

Reviewer's report:

MAJOR COMPULSORY REVISIONS

Dr. Bohlega and colleagues authored the “Clinical and Molecular Characterization of Ataxia with Oculomotor Apraxia (AOA) Patients in Saudi Arabia” manuscript, which reports the clinical, biochemical and genetic characterization of nine patients from four Saudi consanguineous families. This study allowed them to identify one family (family A) with ataxia with oculomotor apraxia form 2 (AOA2) carrying a novel nonsense mutation R2287X in the Senataxin gene, and two families (families B and D) with ataxia-telangiectasia-like disease (ATLD) carrying the previously reported missense mutation W210C in the MRE11 gene. Family C remains genetically undiagnosed.

These findings are interesting and should be published; however, first, the authors must address the following issues:

1. Molecular genetic studies have allowed the characterization of a novel group of recessive ataxias defined by the association of cerebellar atrophy and peripheral sensorimotor neuropathy. This group includes ataxia with oculomotor apraxia form 1 (AOA1), ataxia with oculomotor apraxia form 2 (AOA2), ataxia-telangiectasia-like disease (ATLD) and spinocerebellar ataxia with neuropathy (SCAN1). Therefore, ataxia with oculomotor apraxia is a group of recessive ataxias and it is not a single clinical entity. Consequently, talking about AOA as a rare autosomal recessive disease is not correct.

Based, exclusively, on clinical terms is not possible to state that a patient is affected with AOA1, as the clinical features of all the diseases belonging to the group of recessive ataxias with oculomotor apraxia overlap in an extensive manner. Only genetic molecular studies can provide the doctor and the patient with accurate diagnosis for these diseases. In conclusion, a patient will be diagnosed with AOA1 if his Aprataxin gene is found mutated.

Taking this in consideration the authors must correct and/or precise the sentences/paragraphs highlighted bellow and should also avoid the use of the term “subtypes” concerning AOA1 and AOA2, but rather use “form” or “type”.

- Abstract (Objectives) line 2: “Ataxia with Oculomotor Apraxia (AOA) is a rare autosomal recessive disorder with two subtypes…”

- Abstract (Objectives) lines 8 and 9: “… from four Saudi families with either
Ataxia…

- Introduction, lines 1-3: “Ataxia with Oculomotor Apraxia (AOA) is one of the autosomal…”

- Introduction, line 33: “These findings support the genetic heterogeneity of the disorder”

- Discussion, line 16: “… with two or three patients with AOA1 were enrolled in this study…”

- Discussion, lines 20 and 21: “… comprehensive screening by direct sequencing of the APTX gene did not identify any mutations in the three Saudi families diagnosed with AOA1”

2. Ataxia-telangiectasia-like disease (ATLD) patients carry mutations in MRE11, AOA1 patients carry mutations in APTX. Even if clinically both disorders share several features they are different entities easily identified by molecular genetic studies.

Following this line of reasoning the authors must clarify the statements referred bellow:

- Abstract (Results), lines 16 and 17: “…reported missense mutation W210C in MRE11 gene was identified in two families with AOA1”

- Results (Mutations in MRE11 gene) lines 16 and 17: “…This mutation was also identified in affected individuals from family B with AOA1 phenotype”

3. New data on Aprataxin function have been recently published. The authors should add those data:

- Introduction, lines 18-20: “… it was suggested that it may play a role in the repair…”

4. The authors must take in account what was said in all the above comments and make the necessary alterations in:

- Discussion, last paragraph: “We screened nine affected…”

5. The inclusion of family C in this study should be explained/discussed, knowing that the two patients belonging to this family do not present with cerebellar atrophy.

6. The provided supplementary Table 1 does not correspond to what is stated in the text on the Materials and Methods section (Amplification and sequence …, line 44), therefore it was not evaluated.

MINOR ESSENTIAL REVISIONS

- Abstract (Methods) line 12: “Comprehensive sequencing of all coding exons of genes related to this disorder.”

Please, rephrase the sentence naming the studied genes.

- Abstract (Conclusion) line 20: “… development of this disorder …”

Please, correct the statement.
- Introduction, lines 11 and 12: “… they are genetically heterogeneous.”
  Please, rephrase the sentence.
- Materials and Methods, line 20: “derealization”
  Please, clarify the expression
- Figure 2: labels (i) and (ii) are missing
- Figure 3: labels (i), (ii) and (iii) are missing

DISCRETIONARY REVISIONS
It would be very interesting if the authors could add to Table 1 more biochemical data, such as albumin and cholesterol values as well as the mutations found and respective genes.

MINOR ISSUES NOT FOR PUBLICATION
- List of authors, line 3: see spelling of “Khalil D” and “Alkhairallah T”
- Introduction, lines 13, 21; Results, line 5; Discussion, line 26: see spelling of “missense”
- Introduction, line 23: see spelling “autosomal”
- Introduction, line 26: see spelling “arginine”
- Materials and Methods (Families and samples), line 7: see spacing “Table 1 and…”
- Materials and Methods (Amplification and sequence …), line 43: see spelling “intronic”
- Results, line 8: see spacing “Y359, H1049, …”

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

Quality of written English: Acceptable

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’.