Reviewer’s report

Title: An atypical form of AOA2 with myoclonus associated with mutations in SETX and AFG3L2

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Reviewer: Giovanni STEVANIN

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The manuscript submitted by Dr Brusco reports a family in which 3 patients have a complex form of inherited ataxia. The authors used exome sequencing to explore the genetic causes and focused their analysis under a recessive inheritance and found a known homozygous mutation in SETX/AOA2, a gene responsible for ataxia with oculomotor apraxia. The patients have a compatible phenotype without oculomotor apraxia and adequate biological marker (elevated alphafoeto protein). Under a dominant model, they also found a heterozygous variant in AFG3L2 in the 3 patients and in a healthy carrier showing subtle pyramidal and myoclonic signs. The authors hypothesize that this variant, having clear functional significance in yeast complementation tests, may contribute to the phenotype and may explain some of the unusual signs observed in the patients. The lack of data from the parents is a pity.

The paper is very well written and the data support the conclusions and are convincing.

I only have minor points (Minor Essential Revisions):

- Readers would appreciate to have the full list in a supplemental file of the common heterozygous (dominant mode), common compound heterozygous and common homozygous variants (recessive mode) found in both sequenced patients in ataxia genes. The sentence “a single homozygous … topped both P1 and P2 lists” is not clear: please explain why is this variant is on the top of both (single non sense? single to be homozygous?...). In addition, it is not clear why the authors focused their attention on the AFG3L2 variant while there are probably other variants in other ataxia genes. The data are convincing, but the way they were obtained needs clarification.

- The authors could look at the Broad Institute exomes (62.000 exomes) to increase the number of “controls” for the presence of the AFG3L2 variant.

- Page 6, line 156, supplemental table 1 should be referenced instead of 2.

- Sup table 1: are all variants corresponding to heterozygous or homozygous ones; please indicate this in the legend.

- Page 7, line 180: I would replace “almost completely impaired…” by “did not compensate or restore” since the deleted strains have an impaired mitochondrial activity and the authors are trying to see if the variant is biologically active and can restore the normal mitochondrial activity.
- Page 7, line 172: figure 1A should be referenced and not 1B.
- Haplotypes are not fully visible in Figure 1A (marker D9S148).

**Level of interest:** An article of outstanding merit and interest in its field

**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