Author’s response to reviews

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

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Version: 3
Date: 16 January 2015

Author's response to reviews: see over
Dear Editor

Thank you for considering our submission “An atypical form of AOA2 with myoclonus associated with mutations in SETX and AFG3L2” (MS: 1646497839150528) for publication in BMC Medical Genetics.

I thank reviewers for suggestions which improved our manuscript. Below, a point-by-point reply.

I hope our manuscript is suitable for publication, if you have any further comment, please feel free to contact me.

Thank you

Yours Sincerely,

Alfredo Brusco

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Reviewer #2 (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

Our answer: We thank the reviewer for highlighting this part of the manuscript which was not clear. There is only one homozygous variant shared by both sequenced patients after filtering on allele frequency and variant annotation, and the variant is the stop gain mutation c.6292C>T (p.Arg2098*) in SETX. We are attaching the full list of homozygous variants before filtering, in supplement table 3. No shared compound heterozygous mutations were found.

Thus, we looked for heterozygous variants shared by all three sequenced samples (over 4,000 before filtering). After filtering for frequency there are 76 SNVs and 5 indels, and after QC and variant annotation (nonsynonymous changes) there are only 22 SNVs left (see supplement table 4). Among these, only one mutation, in an ataxia gene AFG3L2.

- 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.

Answer: We checked the ExAc database (~62K samples) and c.346G>A variant in AFG3L2 was not found. We added the database in the text at page 7 line 175.

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

Answer: edited as requested.

- Sup table 1: are all variants corresponding to heterozygous or homozygous ones; please indicate this in the legend.
**Answer:** Variants in supplemental table 1 are either heterozygous or homozygous. A sentence was added 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.
  **Answer:** Edited accordingly.

- Page 7, line 172: figure 1A should be referenced and not 1B.
  **Answer:** Edited accordingly.

- Haplotypes are not fully visible in Figure 1A (marker D9S148).
  **Answer:** We replaced figure 1, increasing resolution.