Author’s response to reviews

Title: Leukoencephalopathy, demyelinating peripheral neuropathy and dural ectasia explained by a not formerly described de novo mutation in the SAMD9L gene, ends 27 years of investigations – A case report

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Version: 2 Date: 03 Apr 2019

Author’s response to reviews:

Technical Comments:
*23/01 -No Consent for Publication heading.
We have added a heading for Consent for Publication Page 5.
-Move Keywords section after Abstract section.
We have moved the section to the right place Page 1.

BMC Neurology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:
Hiroaki Adachi, Ph.D., M.D. (Reviewer 1): The authors reported the case of a female with de novo variant c.2686T>G, p.(Phe896Val) in SAMD9L gene. She was affected by paleness, petechiae, pancytopenia, generalized joint laxity, motor incoordination, weakened tendon reflexes, intra cerebral hemorrhage cerebellar ataxia and her brain MRI showed cerebellar atrophy, disseminated cysts in white and grey matter, dural ectasias and white matter hyperintensity. Her nerve conduction studies and electromyography suggested demyelinating neuropathy. I believe that this is an important paper describing a rare neurological disease. There are a several comments that the authors should address prior to publication:

1. The authors did not describe the origin of her gait disturbance. They should describe precisely and discuss them with the MRI findings. The authors did not describe the cerebellar atrophy.
   We think this is a valuable comment. We haveexplained better in a condensed way. Page 2 line 9.

2. The authors should add figures of the spinal cord MRI to facilitate a better understanding of the
precise patient pathology because her tendon reflexes in patella were recovered and her brain MRI shows atrophy of the spinal cord.
We added Figure 1 c. T2 weighted visualising the cervical and thoracal spine. We might have expressed ourselves unclear but the tendon reflexes have stayed lively after they appeared.

3. The authors should add the explanation of the yellow arrow in the figure legend of the figure 2.
We clearly missed the legend for the yellow arrow. We apologize for that.

Bianca Tesi (Reviewer 2): The authors report about an interesting case with a novel de novo variant in SAMD9L identified in a patient with predominant neurological symptoms, but also a history of transient cytopenia with spontaneous recovery. It is an interesting report since the neurological aspects of SAMD9L-associated syndrome are probably not yet fully described.
I have the following two comments:

1) Chen et al (PMID 27259050) and Tesi et al (PMID: 28202457) should be referenced when talking about SAMD9L mutations in ataxia-pancytopenia syndrome. At the moment only reference to the initial clinical descriptions of this syndrome are included (ref 1 and 2 in the current draft).
We clearly missed these references and apologize for that and have included them. We also found another reference, Cheah PMID 30923096 which we included.

2) It has been shown (Tesi et al 2017) that self-resolution from cytopenia is a feature of this syndrome and that it is due to revertant mosaicism in blood cells. I would like the authors to state if additional variants where found in SAMD9L gene that could represent in-cis revertant variants or if there were signs of acquired UPD of chromosome 7. I think this analysis would be a valuable addition to this case report.

Thank you, this information has now been added. No other tissue than blood was analysed, but there was no sign of mosaicism of the detected de novo variant c.2686T>G in the WES or Sanger analyses. Analysis of WES data of chromosome 7q showed no signs of acquired UPD7, SNPs were inherited from both parents and approximately equally distributed. The chromosome analysis of leukocytes of peripheral blood showed 46,XX, no sign of mosaicism.
There was one more variant detected in SAMD9L, inherited from the patients healthy father, NM_152703.4:c.1565C>T, p.( Ala522Val) with an allele frequency of 1.7% in SweGen, 1.4% in ExAC. The variant was interpreted as not disease causing due to its allele frequency and inheritance from an healthy individual. The reads was distributed 29% vs 71% in the WES analysis. We could not exclude cis with c.2686T>G by IGV.
Page 3 line 23.