Author's response to reviews

Title: A novel CCM1 mutation associated with multiple cerebral and vertebral cavernous malformations.

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Version: 2
Date: 16 July 2014

Author's response to reviews: see over
Milan, July 15th 2014

To Chantal Depondt
To the Editorial Board of BMC Neurology

Dear Madame,

Re: MS: 1078284928124419
Title: “A novel CCM1 mutation associated with multiple cerebral and vertebral cavernous malformations”

Dear Editor:

Thank you very much for considering our manuscript, which we have now revised. The revision has been completed in accordance with the useful reviewer comments, resulting in improvements and clarifications. In particular we have discussed the relevance of the vertebral hemangiomas in our proband.

In the present correspondence, we have included our point-by-point responses to all of the reviewer comments. The specific changes and responses related to each point the reviewers raised are highlighted in red.

We hope that you will find the revised version of this manuscript suitable for publication in BMC Neurology.

Yours sincerely,

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Referee 1:
The authors insist of the presence of vertebral hemangiomas in this family but they don’t discuss about the eventual importance. Why has a spinal MRI been done in the proband and in his relatives? What is the interest of doing it? What are the consequences of the presence of vertebral hemangioma, is there a special follow-up for the patients? What is the frequency of vertebral cavernoma in the general population?

Spinal MRI was performed because spinal angiomas were reported in CCM cases even if their frequency is currently unknown. Spinal MRI should be included in neuroradiological assessment, since spinal angiomas may be symptomatic and may require follow up over time. In our proband, we did not observe spinal angiomas but we noticed the presence of vertebral angiomas, a finding previously disclosed in very few CCM cases. The incidence of vertebral angiomas is higher than 10% in autopsy studies with an increasing frequency with age. Vertebral angiomas are usually asymptomatic and do not require special follow-up. However, they can rarely cause back pain, myelopathy or radiculopathy or result in pathological vertebral fractures. The relative reference has been added in the revised version of the manuscript (Ropper et al, Neurosurgery 2011).

1. The numbering of the exons is not concordant with the reference sequence used by the authors (the reported mutation is located in intron 5 close to exon 6 in ref seq NM_194454)
   We only considered the coding exons in the original manuscript. The numbering of the exons is now concordant with the reference sequence NM_194454. Figure 3 and the relative legend were modified accordingly.

2. The presence or absence of the variant in polymorphisms databases should be given.
   We added a sentence listing the consulted polymorphisms databases in the Results section.

3. How do you look for the conservation of intronic regions?
   We performed a nucleotide BLAST (BLASTn) analysis to check the conservation of the intronic regions upstream exon 6.

4. There is no comment about the hepatic hemangioma. Is there an impact in the follow up?
   Retinal and cutaneous CCM lesions are the most common extra neurological manifestations, but occasionally other organs, such as liver, may be affected. They are usually asymptomatic and do not require special follow-up.

5. There are some words to be corrected: “subjesct” page 2, “widespreas” page 5, “malfrmations”, “inleft”, “retrotrascibed” page 6.
   Typos were corrected.

Referee 2

1. none of the healthy relatives has been tested for the c.263-10A>G variant. At least one of the healthy (clinically and radiologically) should be.
   Sons of Patient III-1 refused their consent for neurological examination and molecular analysis. The son of Patient III-2 (Subject IV-4) underwent clinical and radiological examination. His parents refused the consent for molecular testing for him and her underage sister.

2. vertebral hemangiomas are relatively common benign dysplasias or vascular tumors affecting the vertebral column, with an estimated incidence of 10% to 12% in the population [Acosta FL Jr, et al. Comprehensive management of symptomatic and aggressive vertebral hemangiomas. Neurosurg Clin N Am. 2008;19:17-29]. Therefore, unless authors will find at least an other affected members with vertebral hemangiomas, they should not conclude that their findings expand the spectrum of genetic defects associated with the pathogenesis of vertebral hemangiomas and cerebral cavernous
malformations.
The presence of vertebral angiomas has been already reported to be associated with CCM1 mutations in two reports (Clatterbuck et al, 2002 and Toldo et al, 2009). In a familial cases they were detected in 3 out of 8 subjects undergoing spinal MRI and in one of them microscopic examination following laminectomy confirmed the diagnosis of cavernous angiomas. We modified the Abstract and the Discussion. A new reference, citing the article indicated by Referee 2, was added in the revised version of the manuscript.