Author’s response to reviews

Title: Association between mutation of the NF2 gene and monosomy 22 in menopausal women with sporadic meningiomas.

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Author’s response to reviews: see over
Dear Prof Maurizio Genuardi (or Mr Ervin Cenzon),

Please find enclosed a revised version of the manuscript # MS: 2115712779102704 “Association between mutation of the NF2 gene and monosomy 22 in menopausal women with sporadic meningiomas” by Taberner et al, which has been modified according to the comments and suggestions of the reviewers and the editor. Attached you will also find a point-by-point list of the answer to the comments of the reviewers and the editor, indicating the specific changes introduced in the new revised version of the paper.

We hope in its present format, the manuscript is now acceptable for publication in BMC Medical Genetics.

Looking forward to hearing from you soon at your earliest convenience.

Yours sincerely

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Point-by-point description of the changes

Editor’s comments:

Comment 1.
"The manuscript is of potential interest, but is not acceptable in the present form. The authors should address the comments raised by the reviewers and make changes accordingly."

Answer to comment 1.- The manuscript has been carefully revised and modified according to the editor’s and the reviewers’ comments. More detailed information about the specific changes introduced are also described below in the answer to the comments of the reviewers.

Comment 2.
"In addition, kindly include these changes (Editorial Requirements) when you submit your revised manuscript: *Competing interests: manuscripts should include a 'Competing interests' section. This should be placed after the Conclusions/Abbreviations. Please consider the following questions and include a declaration of competing interests in your manuscript..."

Answer to comment 2.- The 'Competing interests' section has been included in the manuscript and placed after the Conclusions/Abbreviations.

Reviewers:

Reviewer 1:

Comment 1.- “a. The sentence “leading to a p.Leu163Cys mutated NF2 protein with a stop codon at position 46” is wrong; it should be changed in: “leading to a p.Leu163Cys mutated NF2 protein with a stop after 46 codons”

Answer to comment 1.- The suggested sentence has been included in the results section of the revised version of the manuscript in page 7.

Comment 2.- “b. The sentence “leading to a truncated p.Phe119del protein” should be changed in “leading to an in frame deletion of Phe119”

Answer to comment 2.- The sentence indicated by the reviewer has been modified as suggested.

Comment 3.- “c. The sentence “showed no NF2 mutations in none of them.” should be changed in “showed no NF2 mutations.”
Answer to comment 3.- The suggested change is now included in the results section of the manuscript (page 7).

Reviewer 2:

Comment 1.- “Abstract, Results: “…involved five different exons and they all leaded to a truncated …” # “…involved five different exons and they all led to a truncated …”

Answer to comment 1.- The sentence has been modified in line with the reviewer’s suggestion (abstract section of the manuscript in page 2).

Comment 2. - “-Introduction, p.3, 1st paragraph: “…has rapidly lead to the identification of the NF2 gene coded…” # “…has rapidly led to the identification of the NF2 gene located…”

Answer to comment 2.- The sentence has been changed in the background section of the revised manuscript (page 3) following the suggestion of the reviewer.

Comment 3.- “-Methods, p. 5-6: “DNA from the 20 meningioma samples as well as PB DNA from two of these patients (M13 and M20 tumors) who had mutations which have been previously reported in neurofibromatosis type 2 patients [20, 31], was amplified by conventional PCR for further assessment of the presence of the NF2 mutations identified in the corresponding tumor sample from the same patient.” # “DNA from the 20 meningioma samples was amplified by conventional PCR; in addition, PB DNA from two of these patients (M13 and M20 tumors) who had mutations previously reported in neurofibromatosis type 2 patients [20, 31] was analyzed for further assessment of the presence of the NF2 mutations identified in the corresponding tumor sample from the same patient.” Also, why were constitutional DNA samples investigated only in these 2 cases?

Answer to comment 3.- The sentence highlighted by the reviewer has been modified as indicated by him. In addition, a new sentence has been included in the subsection on “Identification of NF2 mutations” of the Methods section (page 6) in which the reason to investigate constitutive DNA only in 2 cases is explained. The mutations found in these 2 cases have been reported in neurofibromatosis Type II and our purpose was to rule out that these patients has a germinal mutation.

Comment 4.- -Results, p. 7: Mutation description is too detailed in the text, there is no need to explain each single mutation, Fig. 1 is sufficient to this purpose. “The remaining deletion identified involved three consecutive bp (“CTT”) at exon 3 (c.357_359del), also leading to a truncated p.Phe119del protein”; this is a single aminoacid in frame deletion, not a truncating mutation.

Answer to comment 4.- The mutation description has been shortened and modified in the first part of the results section as suggested by the reviewer.
Comment 5.- “Results, p. 8, 2nd paragraph: “Consequently, NF2-mutated meningiomas accounted for most (6/9; 67%), including cases with isolated monosomy 22 (4/6; 67%) or monosomy 22 and other chromosomal alterations (2/3, 67%); ...” # “Consequently, NF2-mutated meningiomas accounted for most cases associated with monosomy 22 (6/9; 67%), including cases with isolated monosomy 22 (4/6; 67%) or with monosomy 22 combined with other chromosomal alterations (2/3, 67%);... ”

Answer to comment 5.- Following the indication of the reviewer, the sentence in page 8 has been modified as suggested.

Comment 6.- “Discussion, p. 11: “monosomy 22 is typically found at higher frequencies than NF2 mutations”; the frequency of NF2 mutations could be higher depending on the detection methods used (the authors later mention the possibility of epigenetic changes, but more frequent than these are gene rearrangements identifiable by MLPA or other techniques; mutations in promoter and other non coding regions are also possible”.

Answer to comment 6.- A new sentence about additional genetic mechanism potentially involved in silencing NF2 expression in meningiomas with monosomy 22 has been added in page 10 of the discussion section of the revised manuscript.

Comment 7.- “Discussion: The authors mention the possible involvement of a second gene on chromosome 22: SMARCB1 should mentioned in this regard”.

Answer to comment 7.- The potential involvement of other genes on chromosome 22 like SMARCB1 is now mentioned in the discussion section of the new revised manuscript (page 11).

Comment 8.- “Discussion, p. 11, last paragraph: the inclusion of the transitional histotype among the features of NF2 mutated meningiomas with monosomy 22 is questionable, since the difference with the other meningiomas was not significant.”

Answer to comment 8.- Following the comment of the reviewer, a new sentence has been added in the text of the discussion section of the revised manuscript to highlight the controversial association between monosomy 22 and NF2 mutation with the transitional histopathological subtype.

Comment 9.- “Discussion, p. 12, 1st paragraph: “...each NF2-mutated meningioma case, they all leaded to a truncated...” # “...each NF2-mutated meningioma case, they all led to a truncated...”

Answer to comment 9.- The sentence has been changed in page 12 line 2.

Comment 10.- “In addition, as mentioned above, one mutation is a small in frame deletion, so this sentence has to be modified.”
Answer to comment 10.- The sentence in page 12 has been modified in the new revised version of the manuscript.

Comment 11.- “Finally, the authors could discuss the LOH results in table 2 and the significance of lack of LOH in 2 cases with complete or partial monosomy 22.”

Answer to comment 11.- A new sentence has been added in the text of the discussion section (page 10) in which the LOH results from table 2 are discussed.