Peer Review File
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Reviewer A

Authors described 5 cases with MMRd. Four CMMRD patients had delayed diagnosis due to CALMs since birth without following up or clinical surveillance until their tumors developed. Authors summarized several CALM-related syndromes with the aim of reducing delays in CMMRD diagnosis by differentiating different types of CALM-associated hereditary syndromes.

The manuscript was well-written and easy to follow.

One specific comment. Is it possible for authors to generate a flow chart on diagnosis starting from CALM diagnosis at birth or very young age based on current knowledge authors presented in the manuscript? This will make readers who are not in the field easy to understand different syndromes and the diagnosis can be followed up early without delay in case of CMMRD.

Reply: We created a differential diagnosis flow chart.
Changes in the text: we added a figure(see Page 8, line 253; Page 14, line 405; Page 15, line 406-409)

Reviewer B

This study performed an important investigation regarding inherited tumour syndromes, highlighting that if there is phenotypic evidence for a hereditary cancer predisposition, genetic testing of the genes indicated should be performed, as not all cases present with a positive familial cancer history and that clinicians should be aware of the possibility of a differential diagnosis for these types of cases.

Table 1: Please change "Gender" to "Sex".
Reply1: Done.
Changes in the text: we have modified our text as advised(see Page 12, line 383)

Table 1: is the fifth row for patient 5 in Table 1 supposed to be empty? Or can you add "Not done" similar to patient 4? Just think it's better to have something written there than to have an empty cell as this could indicate that data was just not entered.
Reply2: The fifth row for patient 5 should not be empty, we made a slight adjustment to the content.

Changes in the text: we added “CTNNB1 T41A” from the fifth row and deleted “CTNNB1 T41A” from the fourth row for patient 5(see Page 12, line 383)

Table 1: I would recommend to be consistent on whether using the one-letter or three-letter amino acid writing style for all patients for the germline mutation category. For example, p.Phe1088Serfs*2 instead of p.F1088Sfs*2.
Reply3: Done.
Changes in the text: we have modified our text as advised(see Page 12, line 383, the seventh and eighth row for patient 1 and 5)

Table 1: Same with either writing out the bases that were deleted for the mutation c.1457_1460delATGA (germline mutation) or to only leave it at "c.1457_1460del", though the latter format is the more current format as recommended by HGVS.
Reply4: Done.
Changes in the text: we have modified our text as advised(see Page 12, line 383, the seventh row for patient 3)

Table 1: What does "AV" stand for in patient 5 for phenotype?
Reply5: ‘AV’ stands for atrioventricular.
Changes in the text: we have replaced acronym with full words(see Page 12, line 383, the ninth row for patient 5)

Table 1: Are the father and mother of patient 2 who are carriers symptom-free in the family history section? Or did they develop a cancer?
Reply6: The parents of patient 2 are in good health.
Changes in the text: we have modified our text as advised(see Page 12, line 383, the tenth and eleventh row for patient 2)

Table 1: For patient 3, in the family history section, are the seven tumours of the LS/CMMRD spectrum?
Reply7: Yes.
Changes in the text: we have modified our text as advised(see Page 12, line 383, the tenth row for patient 3)

Line 126: Please introduce the acronym "CRC" or write it out as it is only referred to one more time in the manuscript. It is common to only introduce an acronym once it is referenced ≥3 times.
Reply8: Done.
Changes in the text: we have modified our text as advised(see Page 6, line 158, line 161)

Table 2: For the CMMRD syndrome, in the section of Adulthood and malignancies, I think this should say "older-onset.."?
Reply9: Done.
Changes in the text: we have modified our text as advised(see Page 13, line 392)

Table 3: Would there be a reference available for the 60% CALM incidence noted for the genetic syndrome MAS?
Reply10: A reference is not available now.
Changes in the text: we deleted “60%” and change words to “common”(see Page 14, line 400).

Line 238-239: The sentence starting with "Its CALM has similar..." doesn't make sense - please amend.
Reply11: Done.
Changes in the text: we have modified our text as advised(see Page 9, line 270)

In the case series checklist, the authors have indicated that since this is a "Retrospective case review...no clinical trial registration... is needed". But perhaps add a sentence in the main text indicating that the patients consent was collected?
Reply11: Done.
Changes in the text: we have modified our text as advised(see Page 10, line 314-315)