Author’s response to reviews

Title: Genetic variants in FBLIM1 gene do not contribute to SAPHO syndrome and chronic recurrent multifocal osteomyelitis in typical patient groups

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Author’s response to reviews:

Dear Editor,

Thank you for sending out our manuscript for review! The comments of the two reviewers have been very helpful. We changed the manuscript accordingly and include a point-to-point response to their comments (below).
We hope that the manuscript is now acceptable for publication and look forward to hearing from you!

Yours sincerely

Ulrike Hüffmeier

Reviewer reports:

Hermann Girschick (Reviewer 1): the authors have picked up recent genetic findings in only a few families affected by CRMO where FBLIM1 gene mutations with significance had been demonstrated.
Now in a reasonably large regional cohort from southern Germany no general mutations could be identified. Presence of polymorphisms was compared to a representative european control- NO instructive mutations were defined.
Even though negative as a finding, it is of significant relevance, a puzzle piece in understanding CRMO and SAPHO syndrome.

We thank the reviewer for these comments.

Sigrun Ruth Hofmann, M.D. (Reviewer 2): MGTC-D-19-00527

Genetic variants in FBLIM1 gene do not contribute to SAPHO syndrome and chronic recurrent multifocal osteomyelitis in typical patient groups

The authors analyzed SAPHO and CRMO patients for the frequency of FBLIM1 mutations. The study does not support FBLIM1 as a disease-modifying gene. The patient population is very small (which authors mentioned). There is no control group in this study. CRMO/SAPHO patients are compared to a database (FBLIM1 allele frequencies in the largest group of European control individuals (gnomAD)). The allele frequency of FBLIM1 was identical between SAPHO/CRMO patients and healthy controls from the database.

There are not many data in this study, however, it adds to the current knowledge that the allele frequency of FBLIM1 variants in SAPHO/CRMO patients was identical to healthy controls. Therefore, these variants do not seem to contribute to the disease. However, "mice null for FBLIM1 have severe osteopenia and increased osteoclast differentiation marked by increased RANKL expression in bone marrow stromal cells" (Cox et al.). "…functional validation of the regulatory mutation rs41310367 suggests that there may be other non-coding mutations in linkage disequilibrium with rs114077715 contributing to CRMO disease." Cox et al.

Please extend the discussion to the data of Cox et al. PLOSOne 2017. Comment on the functional assays and the observations mad in FBLIM1-null mice...

We rephrased some sentences that indicate the relevance of the two variants rs41310367 and rs114077715 in the discussion in the 2nd paragraph on p.8/ beginning p.9. We comment on the murine model that provide some evidence that FBLIM1 is an interesting candidate for CRMO in the last but not least paragraph of the discussion also by including the relevant citation (p.9).

There are some minor corrections:

Abstract: …patient group of patients…. - please correct
Thank the reviewer for this suggested correction.

Page7/Lane 8: Eight CRMO patients had multifocal osteomyelitis… CRMO is defined as multifocal…. CNO is the common sentence for milder forms (also unifocal)
We understand the reviewer’s concern. We used the term CRMO, as it is much wider used in the literature. We discuss CNO and CRMO and the use of both names in the background section (end of p. 3, beginning of p. 4) including an additional citation. We describe the results by including the term CNO also, but use CRMO in most passages of the manuscript.

Page8/Lane 17: ….variants was comparable… a large group…. - missing comparable to…
We included a “to” at the end of p.7.
Suppl Table 2B: CRMO patients number 10? Should be 8 and 1 patient with unifocal CNO
Thank you for this attentive observation. As assumed, we have 9 CRMO patients, but
erroneously presented 10 patients in the one row of Supplementary Table 2B in the
submitted, but not the current version of the manuscript.