Author’s response to reviews

Title: Novel NOG (p.P42S) mutation causes proximal symphalangism in a four-generation Chinese family

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Miss. Anne Menard
Manuscript Editor, BMC Medical Genetics

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Dear Miss. Menard

My co-authors join me in expressing our sincere appreciation for your time and efforts in handling the above referenced manuscript and to the reviewers for their constructive and thoughtful comments to strengthen the manuscript. We have critically reviewed the comments from editors and reviewer, and revised the manuscript as per comments and suggestions. Our point-by-point responses to their comments are addressed below and all changes in the revised manuscript are highlighted (Blue).
RESPONSE TO EDITOR

Q1. Please reformat your Abstract to contain the following headings: Background, Methods, Results, Conclusions.

A1: According to the editor’s comment, we have reformatted the abstract in the revision manuscript.

Q2. Please have the text edited by a professional language editing service or a native English speaking colleague. There are many issues with grammar, wording, spelling, and/or punctuation that need to be addressed.

A2: Thank you for your carefully work. We have corrected this kind of mistake following your suggestion. Moreover, our manuscript has also been polished by Editage [www.editage.cn] for English language editing.

Q3. Please change the Introduction heading to Background.

A3: According to the editor’s comment, we have changed the Introduction heading to Background in the revision manuscript.

Q4. Please change the Materials and Methods heading to Methods.

A4: According to the editor’s comment, we have changed the Materials and Methods heading to Methods in the revision manuscript.

Q5. Please note that all manuscripts must contain all the following sections under the heading 'Declarations'. The Declarations should follow the Conclusions section, and be before the References.

Ethics approval and consent to participate

Consent for publication

Availability of data and material

Competing interests

Funding
Authors' contributions

Acknowledgements

Please see here for details on the information to be included in these sections:

https://bmcmedgenet.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article

If the information required is already provided in the main manuscript, please also copy the relevant statements to the Declarations.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

A5: According to the editor’s comment, we have added the Declarations section in the revision manuscript.

Q6. Please note, the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared in the Funding section.

A6: According to the editor’s comment, we have added all the Funding in the revision manuscript.

Q7. Please add a section "Additional files" (after the References/Figure legends) where you list the following information for each additional-supplementary file in the file inventory:

- File name (e.g. Additional file 1)
- Title of data
- Description of data

A7: According to the editor’s comment, we have added the "Additional files" section in the revision manuscript.
Sajid Malik, PhD (Reviewer 1): BMC Medical Genetics

Q8. It is not clear how many subjects were subjected to whole genome sequencing.

A8: Thank you very much to point out this mistake. We subjected the genomic DNA of the proband to whole genome sequencing. We have corrected this mistake in the revision manuscript.

Q9. The subjects who were blood sampled should be mentioned on the pedigree

A9: Thank you for your carefully work. We have mentioned the subjects who were blood sampled on the pedigree in the revision manuscript.

Q10. Please mention the UCSC genomic coordinates of the variant.

A10: Thank you for your carefully work. We have modified the expression in the revision manuscript.

Q11. It is not clear how the variant in NOG was detected. Please mention the filtration strategy in detail.

A11: Thank you for your carefully work. We have added the filtration strategy in detail in the Methods sections of Bioinformatics analysis in the revision manuscript.

Q12. The list of all variants observed in brachydactyly/sympalangism genes should be presented in a separate table.

A12: We apologized for the omission. We have list of all variants observed in the proband in Supplemental Table 2 in the revision manuscript.

Q13. Please mention that it is not an isolated type of symphalangism. Slight hearing loss is observed in two subjects. Therefore, the authors should not present this case as an isolated entity. The hearing loss in two subjects should be mentioned in the Abstract.

A13: Thank you for your carefully work. We have added the hearing loss in two subjects in the abstract in the revision manuscript.
Q14. The association of symphalangism and hearing loss should be discussed. Detailed differential diagnosis of a combination of symptoms (symphalangism and hearing loss) should be presented. There are several disorders which exhibit both features, like MULTIPLE SYNOSTOSES SYNDROME 1; X-LINKED DEAFNESS 2; DFNX2; TEMTAMY PREAXIAL BRACHYDACTYLY SYNDROME; etc.

A14: Thank you for your valuable suggestion. We have discussed the association of symphalangism and hearing loss in the Discussion section and added detailed differential diagnosis of a combination of symptoms (proximal symphalangism and hearing loss) in the Subjects section in the revision manuscript.


A15: Thank you for your carefully work. We have modified the expression according to the standard human sequence variant nomenclature of the Human Genome Variation Society (HGVS) in the revision manuscript.

Q16. It would be worthwhile to present hand photographs of a couple of subjects, in order to observe dermatoglyphics.

A16: Thank you for your valuable suggestion. We have added the hand photographs in Fig. 1C in the revision manuscript.

Q17. Genotypic assignment of the analyzed subjects should be mentioned on the pedigree.

A17: Thank you for your valuable advice. We have mentioned the genotypic assignment of the analyzed subjects on the pedigree in the revision manuscript.

Q18. The picture quality of Fig. 2 and 3 is poor. I am not able to assess the phenotype and chromatograms.

A18: We are sorry for the poor quality of Fig. 2 and Fig. 3. We have recheck our data and provide the uncompressed images of Fig. 2 (17.2 MB) and Fig. 3 (4.66 MB) in our revision manuscript.
Q19. There are several mutations already reported in NOG which cause symphalangism. It would be worthwhile to present a summary table showing all such known mutations in NOG.

A19: Thank you for your instructive suggestions. Following your suggestion, we have summarized the known mutations in NOG in Additional file 3 in the revision manuscript.

Jingyu Liu (Reviewer 2): In this manuscript, the authors report a novel missense NOG mutation (c.C124T:p.P42S) in a four generation Chinese family affected by proximal symphalangism (SYM1). NOG mutations have been associated with several phenotypes, including multiple synostoses syndrome-1 (SYNS1), Proximal symphalangism (SYM1), Tarsal-carpal coalition syndrome (TCC), Stapes ankylosis with broad thumbs and toes (SABTT), Brachydactyly type B2 (BDB2), and over 40 mutations has been reported. In 2008, Oxley et al. reported a family affected with SYNS1, caused by the amino acid substitution of proline to arginine at codon 42 (p.P42R) of Noggin, the same mutational position that found in this study.

Q20. This study only identified a novel mutation of NOG in a Chinese SYM1 family, which does not report new clinical findings of SYM1 or bring novel functional studies of Noggin protein.

A20: Thank you for your instructive suggestions. In our present work, we discovered patients harbouring novel mutation c.124C>T: p.(P42S) in the NOG gene only suffered from proximal symphalangism (SYM1). Of which were quite different from previous reports. Unlike mutations in other sites, the P42 amino acid residue c.124C>T: p.(P42S) did not result in conductive hearing loss, which was consistent with the previously reported mutation of c. 435C>G (P42R) by C.D. Oxley, c.125C>T (P42L) by Beom Hee Lee and c. 124 C>A (p.P42T) by H. Utkan Aydin.[1-3] Compared to the other three mutations in position 42 that caused facial dysmorphism, our newly discovered mutation c.124C>T: p.(P42S) only lead to proximal symphalangism in patients' hands and feet. In summary, we identified a novel mutation c.124C>T: p.(P42S) in the NOG gene from a four generation non-consanguineous Chinese family suffered from SYM1. We had added the above content in the Discussion section in the revision manuscript.


Minor issue:

Q21. In Page2, line 51, "Whole exome sequencing revealed a novel homozygous missense mutation in the NOG", the word "homozygous" should be "heterozygous".

A21: Thank you very much to point out this mistake. We have correct this mistake in the revision manuscript.

Tadashi Kaname (Reviewer 3): Manuscript No: MGTC-D-19-00081

Title: Identification of a novel NOG mutation (P42S) in a four generation Chinese family with proximal symphalangism. Authors: Sha et al. The authors reported a Chinese family with proximal symphalangism and no hearing loss. The patients harboured a novel missense variant in the NOG gene (c.124C>T, (p.P42S)).

Q22. This manuscript could provide additional data for molecular pathology of NOG. The manuscript, however, do not seem to be enough for publication in the BMC Medical Genetics. At least new clinical or biological findings should be needed. There are three reports of patients with variants at the same amino acid of P42 (Horm Res 69:221-6 (2008), Joint Bone Spine 81:533-6 (2013), J Plast Reconstr Aesthet Surg 66:e287-9 (2014)). The authors should compare clinical findings among them.

The text has some non-logical explanations and wrong usage of technical terms. The authors should make an effort to describe logical expression and to add more data.

A22: Thank you for your valuable advice. We have compared the clinical findings among the three reports. We have corrected the non-logical explanations and wrong usage of technical terms and added more data in the revision manuscript. Moreover, our manuscript has also been polished by Editage [www.editage.cn] for English language editing.

We again appreciate your time and efforts in handling our manuscript. We hope that the revised manuscript is satisfactory to you and the reviewer for consideration of publication in BMC Medical Genetics.
Sincerely,

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