Author’s response to reviews

Title: A heterozygous duplication variant of the HOXD13 gene caused synpolydactyly type 1 with variable expressivity in a Chinese family

Authors:
Tahir Zaib (zaibi_hb@yahoo.com)
Wei Ji (jiwei@ems.hrbmu.edu.cn)
Komal Saleem (komalsaleem93@yahoo.com)
Guangchen Nie (surgeon626@163.com)
Chao Li (hmu0272@126.com)
Lin Cao (372321402@qq.com)
Baijun Xu (xbjmhgf@163.com)
Kexian Dong (dongkexian@hrbmu.edu.cn)
Hanfei Yu (yhf@hrbmu.edu.cn)
Xuguang Hao (haoxg123@163.com)
Yan Xue (xueyan1188@163.com)
Shuhuan Si (1820410367@qq.com)
Xueyuan Jia (jiaxueyuan@hrbmu.edu.cn)
Jie Wu (wujie@hrbmu.edu.cn)
Xuelong Zhang (zhangxuelong@hrbmu.edu.cn)
Rongwei Guan (guanrongwei@hrbmu.edu.cn)
Guohua Ji (jiguohua@hrbmu.edu.cn)
Jing Bai (baijingbj@hrbmu.edu.cn)
Feng Chen (chenfeng@hrbmu.edu.cn)
Yong Liu (uceduc@163.com)
Wenjing Sun (sunwj@ems.hrbmu.edu.cn)
Songbin Fu (fusb@ems.hrbmu.edu.cn)
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Response to reviewers

Reviewer #1:

Sajid Malik, PhD (Reviewer 1): The authors have made sufficient efforts to improve the manuscript. There are couple of minor things to consider

1. The authors write, 'Our results also widen the spectrum of HOXD13 mutation responsible for SPD1.' It would be worthwhile to mention the published 8 alanine expansion in HOXD13 in the manuscript and compare that phenotype with the present family.

--------We thank reviewer very much for the suggestion. We have added the information about the published 8 alanine expansion in HOXD13 in our manuscript i.e. Goodman et al. and Xin et al. reported families with 8 alanine expansion in HOXD13. We have compared the phenotype of our SPD1 family only with Chinese family reported by Xin et al. because much information about phenotypes were available, while Goodman et al. did not give any specific information about phenotypes of SPD family with 8 alanine expansion in HOXD13. We have added all these information accordingly in Discussion section in our revised manuscript, and highlighted in yellow.

“Goodman et al. reported the families from British and German populations with SPD having duplication of 24-base pair in exon one of HOXD13 and eight extra polyalanine expansions [5], while Xin et al. reported a family with SPD in Chinese population having eight extra polyalanine expansions in HOXD13 [2]. But the exact site of the duplication was not mentioned in both studies. Chinese family reported by Xin et al. showed SPD features that were consistent with our SPD family as most of the SPD patients had fusion of fingers 3rd and 4th and little toe polydactyly of right or left feet, but our patients have more severe features of SPD. In our SPD family, four out of six SPD patients has both hands affected with syndactyly, while in case of family reported by Xin et al. only two out of seven SPD patients had syndactyly in both hands. Furthermore, according to Xin et al. older generations were more severely affected than younger generations, while in our SPD family older and younger generations were equally effected. Two affected members II-3, III-1, III-7, IV-2 and V-1 showed severe complications of SPD1.”


--------We thank reviewer very much for the suggestion. We have compared the phenotype of our SPD1 family with another Chinese family reported by Xin et al. We also tried to compare the genotype but no details was mentioned by Xin et al. about the duplication site. We have added these information accordingly in Discussion section in our revised manuscript, and highlighted in yellow.

“Chinese family reported by Xin et al. showed SPD features that were consistent with our SPD family as most of the SPD patients had fusion of fingers 3rd and 4th and little toe polydactyly of right or left feet, but our patients have more severe features of SPD. In our SPD family, four out of six SPD patients has both hands affected with syndactyly, while in case of family reported by Xin et al. only two out of seven SPD patients had syndactyly in both hands. Furthermore, according to Xin et al. older generations were more severely affected than younger generations, while in our SPD family older and younger generations were equally effected that family members II-3, III-1, III-7, IV-2 and V-1 showed severe complications of SPD1.”
polydactyly of right or left feet, but our patients have more severe features of SPD. In our SPD family, four out of six SPD patients have both hands affected with syndactyly, while in case of family reported by Xin et al. only two out of seven SPD patients had syndactyly in both hands. Furthermore, according to Xin et al. older generations were more severely affected than younger generations, while in our SPD family older and younger generations were equally affected that family members II-3, III-1, III-7, IV-2 and V-1 showed severe complications of SPD1.”

3. Page 5, line 31. The sentence '... which has important role in limb development...' should be '...which have important role in limb development...'

--------We thank reviewer very much for the suggestion. We consider the suggestion and made modification accordingly in our revised manuscript, and highlighted in yellow.

‘‘There are many genes (Shh, GLI3, LMBR1/ZRS, GJA1, LRP4, BHLHA9, APC, etc.) which have important role in limb development.’’

Reviewer 2 (Reviewer 2):

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: Paper is getting better. As authors explained repeatedly in their answers there are many genes involved in SPD1 and thus they did WGS. But this does not explain why they used no panel - are none available? Is this kind of syndrome too rare to have a panel for that in place? Other points were answered - especially what is the clue result of that study?

--------We thank reviewer very much for the comments. Although there were some candidate genes already reported with SPD, we tried to identify the pathogenic variant for this SPD family if it existed a variant outside the known ones. So we did WGS instead of panel. Thank you for your consideration.

In this study, we successfully identified duplication mutation c.183_206dup in exon 1 of HOXD13 [NM_000523.3]. Based on clinical data, cosegregation analysis, in silico predictions and ACMG assessment, we classified the HOXD13 24-base pair duplication variant as pathogenic and the main cause of SPD1 in this family. Our results widen the genotypic spectrum of HOXD13 mutations that are responsible for SPD1 disorder. The phenomena of variable expressivity was quite obvious in this family. In comparison with previous studies it is established that the variable expressivity is the common phenomena in SPD1. More research is required in the area to find out the genetic factors behind phenotypic heterogeneity.

REQUESTED REVISIONS:

As mentioned - there is no clear a priori hypotheses; it is just a family identified in screening. But this has been mentioned and is overall ok.

--------We thank reviewer very much for the comments. As mentioned above, we classified the HOXD13 24-base pair duplication variant as pathogenic and the main cause of SPD1 in this family. Our results widen the genotypic spectrum of HOXD13 mutations that are
responsible for SPD1 disorder. The phenomena of variable expressivity was quite obvious in this family. In comparison with previous studies it is established that the variable expressivity is the common phenomena in SPD1. More research is required in the area to find out the genetic factors behind phenotypic heterogeneity.