Larissa, November 4, 2022

Jin-Lei Wang

Editor-in-chief

World Journal of Orthopaedics

Dear Editor,

We would like to thank you and the reviewers for the thorough review of our manuscript entitled **"Hand and foot polydactyly: clinical and molecular manifestations"** (Manuscript NO: **80416**) and for the thoughtful comments and constructive suggestions, which helped us improve the quality of our manuscript. We carefully considered all the comments and suggestions, and we revised the manuscript accordingly. All additions are marked in the manuscript with yellow colour. Please find below a point-by-point answer:

Company editor-in-chief 2022-10-21 02:48

Comment: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Orthopedics, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, the author(s) must add a table/figure to the manuscript. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Answer: Thank you for your valuable suggestions. We have added tables summarizing responsible genes for each disorder and characteristic hand and foot polydactyly photos from our own archive, illustrating the most common phenotypes (preaxial/postaxial foot/hand polydactyly). We applied the new tool, the RCA and included 19 latest highlight references (mentioned below). These offered useful and new information about the latest cutting-edge research results related to the topic, which were incorporated in the manuscript. The following references were added:

-Ullah A, Umair M, Majeed AI, Abdullah, Jan A, Ahmad W. A novel homozygous sequence variant in *GLI1* underlies first case of autosomal recessive pre-axial polydactyly. *Clin Genet* 2019; **95**:540-1. [DOI: 10.1111/cge.13495]

-Ansar M, Meitinger T, Ahmad W. Whole-exome sequencing revealed a nonsense mutation in *STKLD1* causing non-syndromic preaxial polydactyly type A affecting only upper limb. *Clin Genet* 2019; **96**:134-9. [DOI: 10.1111/cge.13547]

-**Sharma D,** Mirando AJ, Leinroth A, Long JT, Karner CM, Hilton MJ. HES1 is a novel downstream modifier of the *SHH-GLI3* Axis in the development of preaxial polydactyly. *PloSGenet*2021;**17**:e1009982.[PMID: 34928956 DOI: 10.1371/journal.pgen.1009982]

-**Xu C,** Yang X, Zhou H, Li Y, Xing C, Zhou T, Zhong D, Lian C, Yan M, Chen T, Liao Z, Gao B, Su D, Wang T, Sharma S, Mohan C, Ahituv N, Malik S, Li QZ, Su P. A novel *ZRS* variant causes preaxial polydactyly type I by increased sonic hedgehog expression in the developing limb bud. *Genet Med* 2020;**22**:189-98. [PMID: 31395945 DOI: 10.1038/s41436-019-0626-7]

-**Wang T**, Xuan Z, Dou Y, Liu Y, Fu Y, Ren J, Lu L. Identification of novel mutations in preaxial polydactyly patients through whole-exome sequencing. *Mol Genet Genomic Med* 2019;**7**:e690. [PMID: 30993914 DOI: 10.1002/mgg3.690]

-Ni F, Han G, Guo R, Cui H, Wang B, Li Q. A Novel Frameshift Mutation of *GLI3* Causes Isolated Postaxial Polydactyly. *Ann Plast Surg* 2019; **82**:570-3. [PMID: 30562203 DOI: 10.1097/SAP.0000000000001685]

-Umair M, Palander O, Bilal M, Almuzzaini B, Alam Q, Ahmad F, Younus M, Khan A, Waqas A, Rafeeq MM, Alfadhel M. Biallelic variant in *DACH1*, encoding Dachshund Homolog 1, defines a novel candidate locus for recessive postaxial polydactyly type A. *Genomics* 2021;**113**:2495-502. [PMID: 34022343 DOI: 10.1016/j.ygeno.2021.05.015]

-**Bakar A,** Ullah A, Bibi N, Khan H, Rahman AU, Ahmad W, Khan B. A novel homozygous variant in the *GLI1* underlies postaxial polydactyly in a large consanguineous family with intra familial variable phenotypes. *Eur J Med Genet* 2022;**65**:104599. [PMID: 36067927 DOI: 10.1016/j.ejmg.2022.104599]

-Ishigaki T, Akita S, Udagawa A, Suzuki H, Mitsukawa N. Central polydactyly of the foot: An experience of a treatment of 22 patients. *J Orthop Sci* 2021:S0949-2658(21)00379-1. [PMID: 34922808 DOI: 10.1016/j.jos.2021.11.013]

-Lohan S, Spielmann M, Doelken SC, Flöttmann R, Muhammad F, Baig SM, Wajid M, Hülsemann W, Habenicht R, Kjaer KW, Patil SJ, Girisha KM, Abarca-Barriga HH, Mundlos S, Klopocki E**.** Microduplications encompassing the Sonic hedgehog limb enhancer *ZRS* are associated with Haas-type polysyndactyly and Laurin-Sandrow syndrome. *Clin Genet* 2014;**86**:318-25. [PMID: 24456159 DOI: 10.1111/cge.12352]

-**Wieczorek D,** Pawlik B, Li Y, Akarsu NA, Caliebe A, May KJ, Schweiger B, Vargas FR, Balci S, Gillessen-Kaesbach G, Wollnik B. A specific mutation in the distant sonic hedgehog (*SHH*) cis-regulator (*ZRS*) causes Werner mesomelic syndrome (WMS) while

complete *ZRS* duplications underlie Haas type polysyndactyly and preaxial polydactyly (PPD) with or without triphalangeal thumb. *Hum Mutat*. 2010;**31**:81-89. [PMID: 19847792 DOI: 10.1002/humu.21142]

-Dehghan R, Behnam M, Salehi M, Kelishadi R**.** Novel Mutations in the *MKKS*, *BBS7*, and *ALMS1* Genes in Iranian Children with Clinically Suspected Bardet–Biedl Syndrome. *Case Rep* Ophthalmol Med2022;**2022**:1-6. [DOI: 10.1155/2022/6110775]

-Khairat R, Elhossini R, Sobreira N, Wohler E, Otaify G, Mohamed AM, Abdel Raouf ER, Sayed I, Aglan M, Ismail S, Temtamy SA. Expansion of the phenotypic and mutational spectrum of Carpenter syndrome. *Eur J Med Genet* 2021;**65**:104377. [PMID: 34748996 DOI: 10.1016/j.ejmg.2021.104377]

-**Ouyang L,** Yang F. Cole-Carpenter syndrome-1 with a de novo heterozygous deletion in the *P4HB* gene in a Chinese girl: A case report. *Medicine (Baltimore)* 2017;**96**:e9504. [PMID: 29384951 DOI: 10.1097/MD.0000000000009504]

-**Alawneh RJ,** Johnson AL, Hoover-Fong JE, Jackson EM, Steinberg JP, MacCarrick G. Postnatal Progressive Craniosynostosis in Syndromic Conditions: Two Patients With Saethre-Chotzen Due to *TWIST1* Gene Deletions and Review of the Literature. *Cleft Palate Craniofac J*2022;:10556656221090844. [PMID: 35354337 DOI: 10.1177/10556656221090844]

-Patel R, Singh SK, Bhattacharya V, Ali A. Novel *GLI3* pathogenic variants in complex pre- and postaxial *polysyndactyly* and Greig cephalopolysyndactyly syndrome. *Am J Med Genet A* 2021;**185**:97-104. [PMID: 33058447 DOI: 10.1002/ajmg.a.61919]

-**Tanteles GA,** Michaelidou S, Loukianou E, Christophidou-Anastasiadou V, Kleopa KA. Novel *GLI3* mutation in a Greek-Cypriot patient with Greig cephalopolysyndactyly *syndrome*. *Clin Dysmorphol*2015;**24**:102-5. [PMID: 25714367 DOI: 10.1097/MCD.0000000000000074]

-Xia CL, Xiao SQ, Yang X, Liu CX, Qiu H, Jiang HK, Li-Ling J, Lyu Y. Radiological and *histopathological* features of short rib-polydactyly syndrome type III and identification of two novel *DYNC2H1* variants. *Mol Med Rep* 2021;**23**:426. [PMID: 33846808 DOI: 10.3892/mmr.2021.12065]

-**Duran I,** Taylor SP, Zhang W, Martin J, Forlenza KN, Spiro RP, Nickerson DA, Bamshad M, Cohn DH, *Krakow* D. Destabilization of the IFT-B cilia core complex due to mutations in *IFT81* causes a Spectrum of Short-Rib Polydactyly Syndrome. *Sci Rep* 2016;**6**:34232. [PMID: 27666822 DOI: 10.1038/srep34232]

Reviewer 1 (John J. Faillace 2022-10-17 02:02):

Comment: Postaxial Polydactyly A3 is related to mycobacterium TB but it is not said how. Is it maternal infection prior to pregnancy or during? Intra-uterine infection in the individual? The last sentence of that section should read "There is not AN identified gene responsible for the disorder." The study is limited mostly in that there are no images representative of the different types of polydactyly.

Answer: The authors would like to thank the reviewer for the valuable corrections. The correlation with TB is a clerical error during gene database searching, so we have deleted the relative part of the sentence. We have added characteristic hand and foot polydactyly photos from our own archive, illustrating the most common phenotypes (preaxial/postaxial foot/hand polydactyly). We have corrected the last sentence of the section as suggested.

Reviewer 2 (Anonymous 2022-09-29 13:42):

Comment: Suggested changes in the manuscript word file.

Answer: The authors would like to thank the reviewer for the suggestions. The suggested changes have been applied in the manuscript.