Larissa, October 8, 2022

To Mr. 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 **"Genetics in congenital anomalies of the hand"** (Manuscript NO: **79620**) 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 2022-09-26 10:34

Comment: I have reviewed the Peer-Review Report, 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, 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 suggestion. We have 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.

Reviewer 1 (Anonymous 2022-09-09 01:42):

Comment: The manuscript needs improvement with respect to English language usage.

Answer: The corresponding author of the manuscript, who is a proficiency level user of the English Language and has lived and worked in the USA for several years, has repeated the English language quality check and made several corrections.

Reviewer 2 (Anonymous 2022-09-03 04:20):

Comment: This is an interesting article on a timely topic. However, of the 23 references, only 2 are from the last 5 years. It is recommended to add references to modern sources of literature.

Answer: The authors would like to thank the reviewer for his valuable suggestion. The following 19 references, which have been published in the period 2017-2022, were added and both in the text and in the references list:

-Wessel LE, Daluiski A, Trehan SK. Polydactyly a review and update of a common congenital hand difference. Curr Opin Pediatr 2020; 32: 120-4.
[PMID: 31851054 DOI: 10.1097/MOP.0000000000000871]

-Zeng L, Jin J, Luo F, Sheng Y, Wu P, Xiang R. ZPA Regulatory Sequence Variants in Chinese Patients With Preaxial Polydactyly: Genetic and Clinical Characteristics. Front Pediatr 2022; 10: 797978 [DOI: 10.3389/fped.2022.797978]

-Nguyen JL, Ho CA. Congenital Disorders of the Pediatric Thumb. JBJS Rev 2022; 10
[PMID: 35230999 DOI: 10.2106/JBJS.RVW.21.00147]

-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. *PLoS Genet* 2021; **17**: e1009982.
[PMID: 34928956 DOI: 10.1371/journal.pgen.1009982]

-Ahmad Z, Liaqat R, Palander O, Bilal M, Zeb S, Ahmad F, Jawad Khan M, Umair M. Genetic Overview of Postaxial Polydactyly (PAP): Updated Classification. Clin Genet 2022.
[PMID: 36071556 DOI: 10.1111/cge.14224]

-Ullah I, Kakar N, Schrauwen I, Hussain S, Chakchouk I, Liaqat K, Acharya A, Wasif N, Santos-Cortez RLP, Khan S, Aziz A, Lee K, Couthouis J, Horn D, Kragesteen BK, Spielmann M, Thiele H, Nickerson DA, Bamshad MJ, Gitler AD, Ahmad J, Ansar M, Borck G, Ahmad W, Leal SM. Variants in KIAA0825 underlie autosomal recessive postaxial polydactyly. Hum Genet 2019; 138: 593-600.
[PMID: 30982135 DOI: 10.1007/s00439-019-02000-0]

-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]

-Qiu L, Li C, Zheng G, Yang T, Yang F. Microduplication of BTRC detected in a Chinese family with split hand/foot malformation type 3. Clin Genet 2022.
[PMID: 35908152 DOI: 10.1111/cge.14204]

-Caylor R, Fee T, Lay A, Skinner C, Everman D, Blue E, Bamshad M, Schwartz C, Friez M, Stevenson R. eP326: Genome sequencing reveals BHLHA9 gene duplication as cause of multi-generational split-hand/foot malformation with long bone deficiency. Genet Med 2022; 24: S204. [DOI: 10.1016/j.gim.2022.01.361]

-Peng Y, Yang S, Xi H, Hu J, Jia Z, Pang J, Liu J, Yu W, Tang C, Wang H. Whole genome sequencing reveals translocation breakpoints disrupting TP63 gene underlying split hand/foot malformation in a Chinese family. Mol Genet Genomic Med 2021; 9: e1604.
[PMID: 33471964 DOI: 10.1002/mgg3.1604]

-Papasozomenou P, Papoulidis I, Mikos T, Zafrakas M. Split Hand Foot Malformation Syndrome: A Novel Heterozygous FGFR1 Mutation Detected by Next Generation Sequencing. Curr Genomics 2019; 20:226-30.
[PMID: 31929729 DOI: 10.2174/1389202920666190530092856]

-Yamoto K, Saitsu H, Nishimura G, Kosaki R, Takayama S, Haga N, Tonoki H, Okumura A, Horii E, Okamoto N, Suzumura H, Ikegawa S, Kato F, Fujisawa Y, Nagata E, Takada S, Fukami M, Ogata T. Comprehensive clinical and molecular studies in split-hand/foot malformation: identification of two plausible candidate genes (LRP6 and UBA2). Eur J Hum Genet 2019; 27: 1845-57. [PMID: 31332306DOI: 10.1038/s41431-019-0473-7]

-Kantaputra PN, Kapoor S, Verma P, Intachai W, Ketudat Cairns JR. Split hand-foot malformation and a novel WNT10B mutation. Eur J Med Genet 2018; 61: 372-5.
[PMID: 29427788 DOI: 10.1016/j.ejmg.2018.02.001]

-Lindelöf H, Horemuzova E, Voss U, Nordgren A, Grigelioniene G, Hammarsjö A. Case Report: Inversion of LMX1B - A Novel Cause of Nail-Patella Syndrome in a Swedish Family and a Longtime Follow-Up. Front Endocrinol (Lausanne) 2022; 13: 862908.
[DOI: 10.3389/fendo.2022.862908]

-Jones MC, Topol SE, Rueda M, Oliveira G, Phillips T, Spencer EG, Torkamani A. Mutation of WIF1: a potential novel cause of a Nail-Patella-like disorder. Genet Med 2017; 19: 1179-83. [PMID: 28383544 DOI: 10.1038/gim.2017.20]

-Shao J, Liu Y, Zhao S, Sun W, Zhan J, Cao L. A novel variant in the ROR2 gene underlying brachydactyly type B: a case report. BMC Pediatr 2022; 22: 528.
[PMID: 36064339 DOI: 10.1186/s12887-022-03564-z]

- Zeng F, Liu H, Xia X, Shu Y, Cheng W, Xu H, Yin G, Xie Q. Case Report: Brachydactyly Type A1 Induced by a Novel Variant of in-Frame Insertion in the IHH Gene. Front Genet 2022; 13: 814786. [DOI: 10.3389/fgene.2022.814786]

-Cassim A, Hettiarachchi D, Dissanayake VHW. Genetic determinants of syndactyly: perspectives on pathogenesis and diagnosis. Orphanet J Rare Dis 2022; 17: 198.
[PMID: 35549993 DOI: 10.1186/s13023-022-02339-0]

-Patel R, Singh SK, Bhattacharya V, Ali A. Novel HOXD13 variants in syndactyly type 1b and type 1c, and a new spectrum of TP63-related disorders. J Hum Genet 2021. [PMID: 34321610 DOI: 10.1038/s10038-021-00963-5]