**ORIGINAL ARTICLE**

**BMPR1B gene in brachydactyly type 2–A family with de novo R486W mutation and a disease phenotype**

Marcin Bednarek¹,² | Marek Trybus¹,² | Monika Kolanowska³ | Mateusz Koziej⁴ | Beata Kiec-Wilk¹,⁵ | Artur Dobosz⁶ | Marta Kotlarek-Łysakowska³ | Anna Kubiak-Dydo⁷ | Ewelina Użarowska-Gąska³ | Julia Starega-Rosłan³ | Paweł Gaj³ | Izabela Górzynska³ | Katarzyna Serwan³ | Michał Świerniak³ | Adam Kot³ | Krystian Jażdżewski³,⁷ | Anna Wójcicka³

¹²nd Department of General Surgery, Jagiellonian University Medical College, Krakow, Poland
²University Hospital, Krakow, Poland
³Warsaw Genomics INC., Warszawa, Poland
⁴Department of Anatomy, Jagiellonian University Medical College, Kraków, Poland
⁵Department of Metabolic Diseases, Jagiellonian University Medical College, Krakow, Poland
⁶Department of Medical Genetics, Jagiellonian University Medical College, Krakow, Poland
⁷Laboratory of Human Cancer Genetics, University of Warsaw, Warsaw, Poland

**Correspondence**
Anna Wójcicka, Warsaw Genomics INC., Kiwerska 33A, 01-682 Warszawa, Poland.
Email: anna.wojcicka@warsawgenomics.pl

**Funding information**
Warsaw Genomics; Uniwersytet Jagielloński Collegium Medicum, Grant/Award Number: K/ZDS/006278

---

**Abstract**

**Background:** Brachydactylies are a group of inherited conditions, characterized mainly by the presence of shortened fingers and toes. Based on the patients’ phenotypes, brachydactylies have been subdivided into 10 subtypes. In this study, we have identified a family with two members affected by brachydactyly type A2 (BDA2). BDA2 is caused by mutations in three genes: BMPR1B, BMP2 or GDF5. So far only two studies have reported the BDA2 cases caused by mutations in the BMPR1B gene.

**Methods:** We employed next-generation sequencing to identify mutations in culpable genes.

**Results and Conclusion:** In this paper, we report a case of BDA2 resulting from the presence of a heterozygous c.1456C>T, p.Arg486Trp variant in BMPR1B, which was previously associated with BDA2. The next generation sequencing analysis of the patients’ family revealed that the mutation occurred de novo in the proband and was transmitted to his 26-month-old son. Although the same variant was confirmed in both patients, their phenotypes were different with more severe manifestation of the disease in the adult.

**KEYWORDS**
BMPR1B, brachydactyly, human genetics, mutation
1 | INTRODUCTION

Brachydactylies belong to a large group of genetically determined dysostoses (Hall, 2002), inherited in an autosomal dominant pattern. The disease symptoms encompass variable shortening of bones within the hands or feet and can exist as isolated or syndromic disorders. Isolated brachydactyly, which was subdivided into 10 distinct subtypes (listed in the OMIM database), is a rare disease, except for the relatively prevalent types A3 and D (David et al., 2015). Brachydactyly type A2 (BDA2, OMIM #112600) is characterized by hypoplasia/aplasia of the second middle phalanx of the index finger, sometimes little finger and anomalies of the second toe. Affected individuals have a triangular-shaped middle phalanx in the index fingers and second toes. The end of the index finger usually is curved. Deformity of the second toes are more consistent finding than deformity of the index finger. The big toes show malformation of the proximal phalanx resulting in fibular deviation of the distal phalanx (Su et al., 2011; Temtamy & Aglan, 2008), without other accompanying abnormalities. BDA2 is a very rare syndrome, with only few cases reported in the literature, all of which have been summarized in OMIM. Based on the Orphanet, the prevalence of the disease is less than 1 in 1,000,000. The disease is caused by pathogenic variants in one of three genes: members of the bone morphogenetic protein signaling group, BMPR1B (OMIM #603248) and BMP2 (OMIM #112261) or their corresponding ligand, GDF5 (OMIM #601146) (Dawson et al., 2006; Kjaer et al., 2006; Ploger et al., 2008; Seemann et al., 2005).

Bone morphogenetic proteins (BMPs) belong to the TNF-β family and play important roles in morphogenesis. BMPs are active during early development and their function is important in the neurological, cardiovascular, gastrointestinal, urinary, adipo, and musculoskeletal systems; thus these proteins were proposed to be called body morphogenetic proteins (Gomez-Puerto et al., 2018; Wagner et al., 2010). BMPs signal might be transduced either through the canonical or non-canonical pathways. In the canonical pathway, BMPs bind to the serine/threonine kinase type receptors on the cell surface, what leads to the formation of active complexes and phosphorylation of the downstream proteins (Horbelt et al., 2012). The BMP receptors (BMPRs) have been classified in two groups: type I, containing the activin receptor-like kinases, and type II, containing three distinct receptors: BMPR-II, ActR-II, and ACTR-IIB. The type I receptors are subdivided into three sub-groups: the BMPR1 and ALK1 groups, activating Smad1/5/8 proteins and the TjR-I group, which interacts with SMAD2/3 (Miyazono et al., 2010). The BMPR1 group comprises the BMPR-IA and BMPR-IB receptors; though other receptors are expressed in various cell types, the expression of BMPR-IB, encoded by BMPRIB gene, is significant in the adrenal, brain, endometrial, ovarian and prostate tissue (NCBI Gene database (OLeary et al., 2016). Aberrances in the BMPRIB gene have been associated with brachydactyly type A, as well as with pulmonary arterial hypertension and autosomal recessive acromesomelic dysplasia. Current research shows that BMPRIB is also indispensable for genetic control of the reproductive performance (Zhang et al., 2017). Due to rarity of the disease, the association of BMPRIB with brachydactyly type A2 has been shown in only two studies (Lehmann et al., 2003, 2006) and no broader epidemiologic data are available.

In this study, we describe a family with the c.1456C>T, R486W variant in BMPRIB, presenting with the brachydactyly type A2 phenotype and lacking other systemic abnormalities that could potentially result from aberrant BMPRIB signaling in other tissues and organs. The disease symptoms differ from the previously described, indicating variable spectrum of the disease and its different expression depending on the developmental status of the patient.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

All the participants or their parents signed an informed consent form before entering the study.

2.2 | Patient samples

The proband and other family members were examined at the Department of Surgery, Orthopedics, Rescue Medicine and Polytrauma at the University Hospital in Cracow and at the Department of Medical Genetics, Jagiellonian University Medical College.

2.3 | Genetic testing

Total genomic DNA was isolated from the peripheral blood leucocytes according to Miller et al (Miller et al., 1988). The complete coding sequence of the genes associated with brachydactyly and syndactyly (BMPRIB; ESCO2; GDF5; GNAS; HOXA13; HOXD13; IHH; NOG; RECQL4; ROR2; SOX9; TP63) was analyzed in next-generation sequencing (NGS) on the NextSeq500 instrument (Illumina), according to the standard protocol. The mean depth coverage was 95.4x and the quality threshold 100%. The identified genetic variants were classified following the guidelines on NGS variant interpretation (Richards et al., 2015).

3 | RESULTS AND DISCUSSION

The proband, a 31-year-old male, was admitted to the Department of Surgery, Orthopedics, Rescue Medicine and Polytrauma of the University Hospital in Cracow due to a post-traumatic fracture of the left tibia. The physical
examination revealed the presence of shortened middle phalanx of index fingers in both hands and abnormal position of the thumbs, with a slight cutaneous syndactyly. In the feet, physical examination revealed bilateral shortening and dorso-lateral deviation of the first toe and elongated second toe. All toes and fingernails were present, but the nail plates of the thumbs showed abnormal shape. Subsequent hands radiographs showed bilateral underdevelopment of the distal part of the metacarpal bone in the thumb and bilateral absence of the middle phalanx in the index fingers (Figure 1).

**FIGURE 1** Images of the hands and feet of the proband reveal shortening of the second finger and overgrowth of the second toe. X-ray imaging of hands and feet shows bilateral loss in medial phalanx of index finger, bilateral anomaly of distal part of proximal phalanx in the toe, with the lack of inter-phalangeal joint, and a bilateral overgrowth of proximal phalanx of the second finger with underdeveloped medium phalanx.
Additionally, the image showed symphalangism between the proximal and middle phalanx in the right hand. The bones of first, fourth, and fifth fingers, metacarpals and carpals appeared to be normal. Overall, the hand phenotype resembled BDC (Brachydactyly type C, OMIM #113100) with additional features of SYM1A (Symphalangism, proximal, OMIM #185800). In the feet, the radiograph showed bilateral shortening of the distal part of proximal phalanx in the first toe.
toe, with the lack of inter-phalangeal joint and a resulting dorso-lateral deviation (Figure 1). It also revealed the presence of a bilateral elongation of the proximal phalanx with an absence of the middle phalanx. The body proportions, height, weight as well as head and thorax circumferences were normal.

The observed phenotype had no negative effect on the patient’s every day functioning. Due to the suspicion of brachydactyly, the patient was referred for genetic testing. Next-generation sequencing analysis of the **BMPR1B; ESCO2; GDF5; GNAS; HOXA13; HOXD13; IHH; NOG; RECQL4; ROR2; SOX9; TP63** genes; revealed a heterozygous, pathogenic, variant in the **BMPR1B** gene (NM_001203.3: c.1456C>T, p.Arg486Trp, rs121434418). The variant is very rare, with a MAF <0.00001 in the PAGE and ALFA Project studies.

Further interview revealed that the patient’s 26-month-old son (patient 2) presented with similar symptoms. The child’s examination and radiological imaging revealed presence of a similar phenotype to observed in his father (Figure 2). The hand radiographs confirmed malformations of the index fingers, including absence of the middle phalanx in the left hand

### Table 1: The comparison of phenotypic features of the proband (Patient 1) and Patient 2 comparing the observed hands and feet malformations

| Observation          | Proband (age at diagnosis 31 years)                                                                 | Patient 2 (age at diagnosis 26 months)                                                                 |
|----------------------|------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| **Hands**            |                                                                                                      |                                                                                                        |
| Morphological malformation | Thumb:                                                                                               | Thumb:                                                                                                   |
|                      | • bilateral deformation of the distal phalanx, more expressed in the left hand with abnormal nail plate development | • bilateral deformation of the distal phalanx, more expressed in the left hand with abnormal nail plate development |
|                      | • abnormal position of the digit with ulnar deviation at carpometacarpal (CMC) joint                | • abnormal position of the digit with ulnar deviation at CMC                                              |
|                      | **Index fingers:**                                                                                   | **Index fingers:**                                                                                        |
|                      | • shortened; single interphalangeal joint                                                            | • shortened; bilateral ulnar subluxation in CMC                                                          |
| Radiological malformation | Thumb:                                                                                               | Thumb:                                                                                                   |
|                      | • bilateral underdevelopment of the distal part of the metatarsal bone                               | • bilateral deformation of the distal phalanx                                                            |
|                      | **Index finger:**                                                                                   | **Index finger:**                                                                                        |
|                      | • bilateral absence of the middle phalanx                                                            | • bilateral absence of the middle phalanx                                                               |
|                      | **Feet**                                                                                             |                                                                                                        |
| Morphological malformation | Toe I:                                                                                                | Toe I:                                                                                                   |
|                      | • bilateral shortening of the toe and setting in the dorso-lateral position                          | • underdevelopment of the PIP/DIP and MTP                                                               |
|                      | • bilateral absence of the MTP, deviating the toe in the dorso-lateral side                           | • shortened in the right foot, set in the medial position, more expressed on the left side               |
|                      | **2nd toe:**                                                                                        | 2nd toe: underdevelopment of MTP, setting in the medial position, more expressed on the left side         |
|                      | • elongated                                                                                         | 3rd toe: underdevelopment of MTP, setting in the medial position, more expressed on the left side         |
| Radiological malformation | Toe I:                                                                                                | Toe I:                                                                                                   |
|                      | • bilateral underdevelopment of the distal phalanx and its shortening                               | • bilateral underdevelopment and shortening of the distal phalanx                                        |
|                      | **2nd toe:**                                                                                        |                                                                                                        |
|                      | • bilateral elongation of the proximal phalanx, absence of the middle phalanx                        |                                                                                                        |
| **Body proportion**  |                                                                                                      |                                                                                                        |
| **Body proportion**  | Normal                                                                                                | Normal                                                                                                   |

**Note:** Table 1 includes a comparison of the phenotypic features observed in the proband (Patient 1) and Patient 2, focusing on the hands and feet malformations.
and a very small middle phalanx in the right hand together with bilateral deformation of the distal phalanx in the thumb. Compared to the father, the child presented with additional bilateral ulnar subluxation of index fingers, which may, however, result from developmental stage of the skeletal system. A summary of phenotypic changes in both patients is presented in Table 1.

Further genetic diagnostics performed in the patient's family members confirmed that the mutation occurred \textit{de novo} in the proband and was further transmitted to his son (Figure 3). Neither of the probands' parents or siblings carried the p.Arg486Trp variant nor present with the disease phenotype. All the presented family members were genotyped for the NM_001203.3: c.1456C>T variant.

Presence of the variant within the receptor inhibits chondrogenesis (Lehmann et al., 2003), and this mechanism is responsible for most of the observed phenotypic aberrances. Interestingly, other aberrances in the \textit{BMPR1B} have been associated with brachydactyly type A (Lys325Asn) (Racacho et al., 2015), as well as with childhood pulmonary arterial hypertension (Chida et al., 2012), suggesting its important role in development and pathogenesis of human diseases.

Other studies revealed a family carrying a germline mutation at the same amino acid. The c.1456C>T missense mutation leads to an arginine to glutamine substitution (R486Q), resulting in additional features of SYM1 (Lehmann et al., 2006), which are not present in the members of the family analyzed within this study. Interestingly, the BMP signaling is also involved in the heterotopic ossification (Ranganathan et al., 2015). However, the long-term follow-up of patient 1, performed 12 months, after the surgery showed normal bone fusion without ossification. The knee flexion was 90°, instead of 100–110°, the knee extension was in normal range. No instability of the knee was noticed. Comparison of the features of both patients revealed that malformations presented in hands and feet of father and son are similar.

In contrast to previous studies, the patients described in this study did not present with clinodactyly (Ploger et al., 2008), and syndactyly was only cutaneous. In contrast to previously described patients, no hypoplasia within fifth fingers was observed (Lehmann et al., 2003). The previously described patients revealed deviation of first and second toe, with a broadening of the first toe and medial deviation of second toe. In our study, patient 1 had bilateral underdevelopment of first toe and shortening of second, while patient 2 did not show any malformation in the length of the second toe. This information indicates that \textit{BMPR1B} gene could have variable expression among family members. Moreover, the patients described within this study did not present with a triangular shaped middle phalanx of the second finger, as described in other BDA2 patients (Lehmann et al., 2006). Underdevelopment of metacarpal bones is also not typical feature for brachydactyly type A2 which indicate overlapping with brachydactyly type B. Interestingly, other authors indicated no family specific or sex correlated phenotypes in diagnosed patients. The exact mechanism leading to aberrances in chondrogenic differentiation, caused by this specific mutation remains unknown. Still, as indicated by the observed phenotypic differences, the disease outcome has to be influenced by other, yet unknown factors.

**ACKNOWLEDGMENTS**

This research was supported by Warsaw Genomics, Uniwersytet Jagielloński Collegium Medicum research grant no K/ZDS/006278. Members of Warsaw Genomics are supported by the POIR.04.04.00-00-41DB/17-00,
TEAM TECH 4/2017 grant awarded by the Foundation for Polish Science.

**CONFLICT OF INTEREST**
The authors have nothing to disclose.

**AUTHOR CONTRIBUTIONS**
MB, MT, MK, BK-W, AD: collection and analysis of clinical data. MK, MK-L, AK-D, EU-G, JS-R, PG, IG, MS, KS, AK, KJ: sequencing and genetic analysis. AW: study design, analysis of genetic data, and preparation of the manuscript.

**DATA AVAILABILITY STATEMENT**
The data that support the findings of this study are available from the corresponding author upon request.

**ORCID**
Marcin Bednarek https://orcid.org/0000-0003-3882-4542
Marek Trybus https://orcid.org/0000-0003-2750-8608
Monika Kolanowska https://orcid.org/0000-0003-3457-0557
Mateusz Koziej https://orcid.org/0000-0002-2635-0776
Beata Kiec-Wilk https://orcid.org/0000-0002-2526-9714
Artur Dobosz https://orcid.org/0000-0002-0279-1243
Marta Koltarek-Lysakowska https://orcid.org/0000-0002-6703-1253
Anna Kubiak-Dydo https://orcid.org/0000-0001-7613-189X
Ewelina Uzarowska-Gąska https://orcid.org/0000-0002-0443-4733
Julia Staręga-Rosłan https://orcid.org/0000-0002-6316-8922
Paweł Gaj https://orcid.org/0000-0002-5416-5412
Michał Świerniak https://orcid.org/0000-0003-0368-8077
Krzystian Jażdżewski https://orcid.org/0000-0001-5803-6397
Anna Wójcicka https://orcid.org/0000-0001-5327-6332

**REFERENCES**

Chida, A., Shintani, M., Nakayama, T., Furutani, Y., Hayama, E., Inai, K., Saji, T., Nonoyma, S., & Nakanishi, T. (2012). Missense mutations of the BMPR1B (ALK6) gene in childhood idiopathic pulmonary arterial hypertension. *Circulation Journal, 76*(6), 1501–1508. https://doi.org/10.1253/circj.cj-11-1281

Choi, Y., Sims, G. E., Murphy, S., Miller, J. R., & Chan, A. P. (2012). Predicting the functional effect of amino acid substitutions and indels. *PLoS ONE, 7*(10), e46688. https://doi.org/10.1371/journal.pone.0046688

David, A., Vincent, M., Quere, M. P., Lefrancois, T., Frampas, E., & David, A. (2015). Isolated and syndromic brachydactylies: Diagnostic value of hand X-rays. *Diagnostic and Interventional Imaging, 96*(5), 443–448. https://doi.org/10.1016/j.diii.2014.12.007

Dawson, K., Seeman, P., Sebald, E., King, L., Edwards, M., Williams, J., Mundlos, S., & Krakow, D. (2006). GDF5 is a second locus for multiple-synostosis syndrome. *American Journal of Human Genetics, 78*(4), 708–712. https://doi.org/10.1086/503204

Garamszegi, N., Dore, J. J., Jr., Penheiter, S. G., Edens, M., Yao, D., & Leof, E. B. (2001). Transforming growth factor beta receptor signaling and endocytosis are linked through a COOH terminal activation motif in the type I receptor. *Molecular Biology of the Cell, 12*(9), 2881–2893. https://doi.org/10.1091/mbc.12.9.2881

Gomez-Puerto, M. C., Iyengar, P. V., Garcia de Vinuesa, A., Ten Dijke, P., & Sanchez-Duflihues, G. (2018). Bone morphogenetic protein receptor signal transduction in human diseases. *The Journal of Pathology, 247*(1), 9–20. https://doi.org/10.1002/path.5170

Hall, C. M. (2002). International nosology and classification of constitutional disorders of bone (2001). *American Journal of Medical Genetics, 113*(1), 65–77. https://doi.org/10.1002/ajmg.10828

Horbelt, D., Denkis, A., & Knaus, P. (2012). A portrait of transforming growth factor beta superfamily signalling: Background matters. *International Journal of Biochemistry & Cell Biology, 44*(3), 469–474. https://doi.org/10.1016/j.biocel.2011.12.013

Kjaer, K. W., Eiberg, H., Hansen, L., van der Hagen, C. B., Rosendahl, K., Tommerup, N., & Mundlos, S. (2006). A mutation in the receptor binding site of GDF5 causes Mohr-Wiedt brachydactyly type A2. *Journal of Medical Genetics, 43*(3), 225–231. https://doi.org/10.1136/jmg.2005.034058

Lehmann, K., Seemann, P., Boergermann, J., Morin, G., Reif, S., Knaus, P., & Mundlos, S. (2006). A novel R486Q mutation in BMPR1B resulting in either a brachydactyly type C/sympalangism-like phenotype or brachydactyly type A2. *European Journal of Human Genetics, 14*(12), 1248–1254. https://doi.org/10.1038/sj.ejhg.5201708

Lehmann, K., Seemann, P., Stricker, S., Sammar, M., Meyer, B., Suring, K., Majewski, F., Tinschert, S., Grzeschik, K.-H., Muller, D., Knaus, P., Nurnberg, P., & Mundlos, S. (2003). Mutations in bone morphogenetic protein receptor 1B cause brachydactyly type A2. *Proceedings of the National Academy of Sciences of the United States of America, 100*(21), 12277–12282. https://doi.org/10.1073/pnas.2133476100

Miller, S. A., Dykes, D. D., & Polesky, H. F. (1988). A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Research, 16*(3), 1215. https://doi.org/10.1093/nar/16.3.1215

Miyazono, K., Kamiya, Y., & Morikawa, M. (2010). Bone morphogenetic protein receptors and signal transduction. *Journal of Biochemistry, 147*(1), 35–51. https://doi.org/10.1093/jb/mvp148

O’Leary, N. A., Wright, M. W., Brister, J. R., Ciufo, S., Haddad, D., McVeigh, R., Rajput, B., Robbertse, B., Smith-White, B., Akodej, D., Astashyn, A., Badredtin, A., Bao, Y., Blinkova, O., Brover, V., Chetverinina, V., Choi, J., Cox, E., Ermolaeva, O., … Pruitt, K. D. (2016). Reference sequence (RefSeq) database at NCBI: Current status, taxonomic expansion, and functional annotation. *Nucleic Acids Research, 44*(D1), D733–D745. https://doi.org/10.1093/nar/gkv1189

Plöger, F., Seemann, P., Schmidt-von Kegler, M., Lehmann, K., Seidel, J., Kjaer, K. W., Pohl, J., & Mundlos, S. (2008). Brachydactyly type A2 associated with a defect in proGDF5 processing. *Human Molecular Genetics, 17*(9), 1222–1233. https://doi.org/10.1093/hmg/ddn012

Racacho, L., Byrnes, A. M., MacDonald, H., Dranse, H. J., Nikkel, S. M., Allanson, J., Rossier, E., Underhill, T. M., & Bulman, D. E. (2015). Two novel disease-causing variants in BMPR1B are associated with brachydactyly type A1. *European Journal of Human Genetics, 23*(12), 1640–1645. https://doi.org/10.1038/ejhg.2015.38
Ranganathan, K., Loder, S., Agarwal, S., Wong, V. W., Forsberg, J., Davis, T. A., Wang, S., James, A. W., & Levi, B. (2015). Current concepts review heterotopic ossification: Basic-science principles and clinical correlates. *Journal of Bone and Joint Surgery-American, 97*(13), 1101–1111. https://doi.org/10.2106/Jbjs.N.01056

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., & Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine, 17*(5), 405–424. https://doi.org/10.1038/gim.2015.30

Seemann, P., Schwappacher, R., Kjaer, K. W., Krakow, D., Lehmann, K., Dawson, K., & Mundlos, S. (2005). Activating and deactivating mutations in the receptor interaction site of GDF5 cause symphalangism or brachydactyly type A2. *Journal of Clinical Investigation, 115*(9), 2373–2381. https://doi.org/10.1172/JCI25118

Su, P., Ding, H., Huang, D., Zhou, Y., Huang, W., Zhong, L., Vyse, T. J., & Wang, Y. (2011). A 4.6 kb genomic duplication on 20p12.2-12.3 is associated with brachydactyly type A2 in a Chinese family. *Journal of Medical Genetics, 48*(5), 312–316. https://doi.org/10.1136/jmg.2010.084814

Temtamy, S. A., & Aglan, M. S. (2008). Brachydactyly. *Orphanet Journal of Rare Diseases, 3*, 15. https://doi.org/10.1186/1750-1172-3-15

Wagner, D. O., Sieber, C., Bhushan, R., Borgermann, J. H., Graf, D., & Knaus, P. (2010). BMPs: From bone to body morphogenetic proteins. *Science Signalling, 3*(107), mr1. https://doi.org/10.1126/scisignal.3107mr1

Zhang, X., Li, W., Wu, Y., Peng, X., Lou, B., Wang, L., & Liu, M. (2017). Disruption of the sheep BMPR-IB gene by CRISPR/Cas9 in in vitro-produced embryos. *Theriogenology, 91*, 163–172.e162. https://doi.org/10.1016/j.theriogenology.2016.10.025

**How to cite this article:** Bednarek M, Trybus M, Kolanowska M, et al. *BMPR1B* gene in brachydactyly type 2–A family with *de novo* R486W mutation and a disease phenotype. *Mol Genet Genomic Med.* 2021;9:e1594. [https://doi.org/10.1002/mgg3.1594](https://doi.org/10.1002/mgg3.1594)