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Acromesomelic Dysplasia With Homozygosity for a Likely Pathogenic *BMPR1B* Variant: Postaxial Polydactyly as a Novel Clinical Finding

Ibrahim M. Abdelrazek[1] | Alexej Knaus[2] | Behnam Javanmardi[2] | Peter M. Krawitz[2] | Denise Horn[3] | Ebtesam M. Abdalla[1] | Sheetal Kumar[4]

[1]Department of Human Genetics, Medical Research Institute, Alexandria University, Alexandria, Egypt | [2]Institute for Genomic Statistics and Bioinformatics, Medical Faculty, University of Bonn, University Hospital Bonn, Bonn, Germany | [3]Institute of Medical Genetics and Human Genetics, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität Zu Berlin, Berlin, Germany | [4]Institute of Human Genetics, Medical Faculty, University of Bonn, University Hospital Bonn, Bonn, Germany

Correspondence: Sheetal Kumar (sheetal.kumar@ukbonn.de)

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ABSTRACT

Background: Acromesomelic chondrodysplasias are a rare subgroup of the clinically and genetically heterogeneous osteochondrodysplasias that are characterised by abnormalities in the limb development and short stature. Here, we report a 2-year-old boy, offspring of consanguineous parents, with acromesomelic dysplasia and postaxial polydactyly in which exome sequencing identified a novel homozygous missense variant in *BMPR1B*. The patient showed skeletal malformation of both hands and feet that included complex brachydactyly with the thumbs most severely affected, postaxial polydactyly of both hands, shortened toes as well as a bilateral hypoplasia of the fibula.

Methods: Whole trio exome sequencing was conducted to identify potential genetic variants in the patient.

Results: The analysis identified the biallelic variant NM_001203.3:c.821A > G;p.(Gln274Arg) in *BMPR1B*, a gene encoding bone morphogenetic protein receptor 1B.

Conclusion: The skeletal phenotype can be brought in line with the phenotypes of previously reported cases of *BMPR1B*-associated chondrodysplasias. However, the postaxial polydactyly described here is a novel clinical finding in a *BMPR1B*-related case; notably, it has previously been reported in other acromesomelic dysplasia cases caused by homozygous pathogenic variants in *GDF5*—a gene which encodes for growth differentiation factor 5, a high-affinity ligand to *BMPR1B*.

1 | Introduction

Acromesomelic chondrodysplasias (ACD) are a rare subgroup of the clinically and genetically heterogeneous osteochondrodysplasias that are characterised by abnormalities in the limb development and short stature (Kornak and Mundlos 2003; Demirhan et al. 2005). The severity of limb deformations increases hereby from proximal to distal with predominantly affected hands and feet. The shortening of the mesomelic segment of the limbs, the forearm and the lower leg, results in a disproportionate shortening. To date, four disease genes and seven distinct ACD subtypes with varying severity are recognised according to the 2023 revision of the nosology and classification of genetic skeletal disorders: Pathogenic *GDF5* variants underlie

Ibrahim M. Abdelrazek and Alexej Knaus contributed equally to this work.

the severe Grebe dysplasia (including Grebe (OMIM #200700) and Hunter-Thompson (OMIM #201250) types) and the milder du Pan dysplasia (OMIM #228900), whereas pathogenic variants in *BMPR1B* can cause a Grebe dysplasia-like phenotype (OMIM #609441), as well as *BMPR1B*-related du Pan dysplasia. The remaining three ACD types encompass *NPR2*-linked Maroteaux type (OMIM #602875), the *PRKG2*-linked ACD type (OMIM #619636) and Osebold-Remondini type, which is not yet associated with a genomic locus (OMIM #112910).

Hence, loss-of-function variants in *GDF5* or *BMPR1B* show overlapping clinical features and can lead to the autosomal recessive disorders Grebe dysplasia, a Grebe dysplasia-like phenotype and du Pan dysplasia (Graul-Neumann et al. 2014; Stange et al. 2015). Both genes encode members of the same pathway: The *GDF5* ligand belongs to the bone morphogenetic protein (BMP) family and binds with a high affinity to the BMP receptor *BMPR1B* (Nishitoh et al. 1996).

Here, we present an individual with a novel biallelic missense variant in *BMPR1B* who shows du Pan dysplasia. Furthermore, we expand the phenotypical spectrum of *BMPR1B*-related ACD with postaxial polydactyly as a novel clinical finding.

2 | Case Presentation

Clinical and radiographic investigations were performed in the Department of Human Genetics, Medical Research Institute, Alexandria University, Egypt. Informed consent was obtained from the family prior to inclusion in this study in accordance with the principles of the Declaration of Helsinki.

The male proband is a 2-year-old child of healthy first cousin parents from a multiconsanguineous family originating from Egypt and was presented at the genetics department due to limb anomalies of both hands and feet. He has an elder healthy sister and no other similarly affected family members (Figure 1a). The boy showed postaxial polydactyly of both hands and a complex brachydactyly with the thumbs most severely affected. Both hands showed radial deviation of the index, the fifth and the sixth fingers, camptodactyly of the fourth fingers and ulnar deviation of the third fingers (Figure 1b). The feet presented similarly with shortened toes with fibular deviation of the big toes, tibial deviation of the fifth toes and bilateral syndactyly between the second and third toes (Figure 1c). Radiological examination of the hands revealed bilateral hypoplastic metacarpal bones, especially very hypoplastic first metacarpals and absent proximal phalanges of the thumbs, malformed proximal phalanges of the other fingers, hypoplastic or absent and malformed middle phalanges and synostosis of the proximal interphalangeal joints IV as well as postaxial polydactyly with rudimentary additional digits (Figure 2a). Radiographs of the lower limbs showed severe hypoplasia of the proximal phalanges I and V absent middle phalanx V and hypoplasia of the other middle phalanges and hypoplastic distal phalanges II–V (Figure 2b), as well as a bilateral proximal hypoplasia of the fibulas (Figure 2c,d). The height of the boy was normal (91 cm, 75th–90th centile).

No other abnormalities were present.

Portraits and X-rays of the patient were also analysed with GestaltMatcher and Deeplasia (Rassmann et al. 2024; Hsieh et al. 2022). GestaltMatcher did not yield high similarity scores to any known syndrome with facial dysmorphism represented in the GestaltMatcher database (Lesmann et al. 2024). The bone age computed with Deeplasia for the hand X-ray resulted in a mean age of 1 year and 9 months, which is only slightly above the chronological age of the patient when the X-ray was taken (1 year and 6 months) and the clinically estimated retarded bone age. Since no X-rays of molecularly confirmed cases with acromesomelic dysplasia are yet available in the GestaltMatcher database, next-generation phenotyping of the skeletal dysplasia was inconclusive.

3 | Genetic Analysis

Genomic DNA from the affected individual and his parents was extracted from peripheral blood leucocytes samples by standard methods. Trio exome sequencing was carried out at NGS core facility at the University Hospital Bonn. Enrichment of DNA libraries was performed with Twist Human Core Exome + RefSeq (Twist Bioscience, CA, USA) and sequenced on a Novaseq6000 platform (Illumina, San Diego, CA, USA). The processing and analysis of the WES raw data were conducted using an in-house developed pipeline with NVIDIA Parabricks toolkit, primarily based on the Genome Analysis Toolkit (GATK) Best

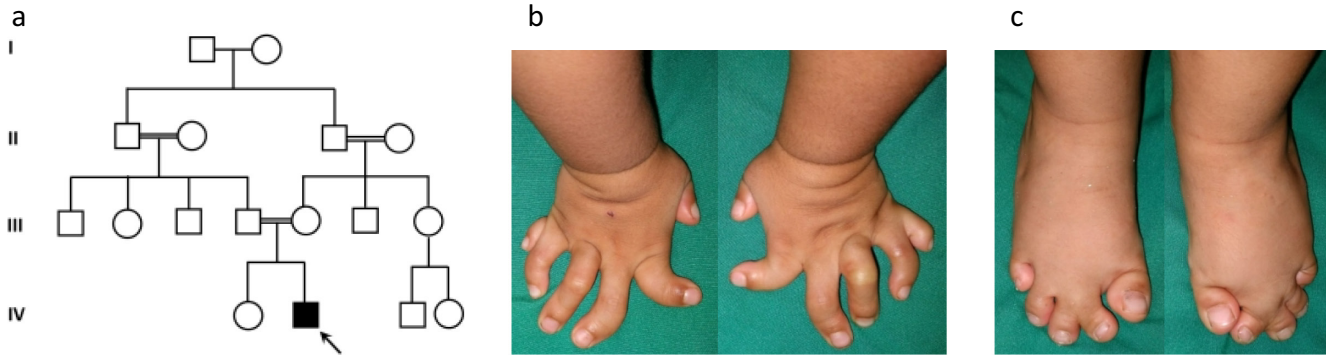

FIGURE 1 | Pedigree and phenotype of the affected individual with the homozygous *BMPR1B* variant c.821A>G;p.(Gln274Arg). (a) Pedigree of the family. The affected individual is indicated by an arrow. (b) Hands of the affected boy. Note bilateral postaxial polydactyly and complex brachydactyly. (c) Feet of the affected boy. Note shortened toes.

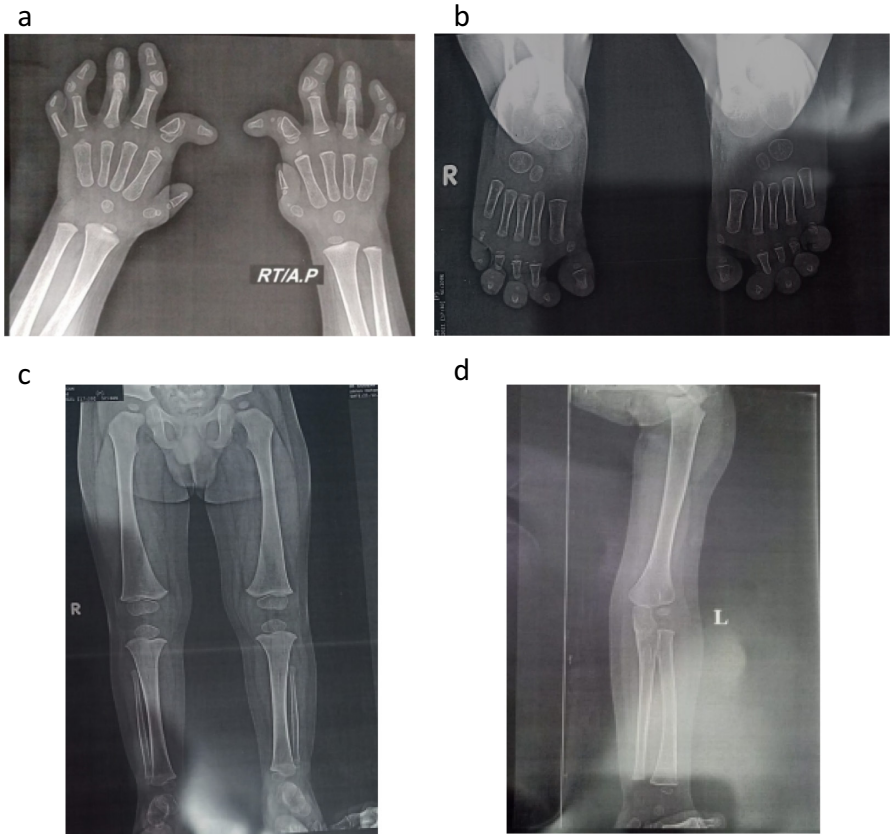

FIGURE 2 | Radiographs of the affected individual. (a) Hands: Abnormalities of metacarpals and phalangeal bones. (b) Feet: Abnormalities of phalangeal bones. (c, d) Lower limbs: Bilateral proximal fibular hypoplasia.

Practices (Van der Auwera et al. 2013). For read alignment, the reference used was the University of California Santa Cruz (UCSC) Genome Reference Consortium Human genome, build 37 (GRCh37)/Human Genome, version 19 (hg19). This was executed using the Burrows-Wheeler Aligner-Maximal Exact Match (BWA-MEM) (Li 2013), and variant calling was performed with HaplotypeCaller (Poplin et al. 2017). For the identification of potential structural variants (SVs) and copy number variations (CNVs), GATK-gCNV (Babadi et al. 2023) and Manta (Chen et al. 2016) were used. Automated variant analysis was performed using the PEDIA approach (Hsieh et al. 2019). Further variant interpretation and evaluation was carried out in VarFish (Holtgrewe et al. 2020).

4 | Results

From trio exome sequencing data the homozygous missense variant c.821A>G;p.(Gln274Arg) in exon 10 of *BMPR1B* (NM_001203.3) was prioritised as the top candidate using the PEDIA approach in the affected individual. The read coverage for the alternate allele in the index was 62 out of 62 reads (allelic balance 1), while both parents were heterozygous for the variant with an allelic balance of 0.50 (29/58 reads) in the mother and 0.49 (27/57 reads) in the father (Figure S1a). Sanger sequencing confirmed heterozygosity of the variant in both parents and homozygosity in the proband. Additionally, the unaffected sister (IV.1) was found to be heterozygous for the variant (IV.1) (Figure S1b).

The variant has only been reported once in a heterozygous state in the gnomAD database. The exchange at chr4:96.052.408 A>G lies in a constrained coding region in *BMPR1B* (Havrilla et al. 2019) and results in an exchange of the glutamine (Gln) at position 274 to arginine (Arg) that is highly conserved over multiple species (Figure S1c) and located at the N-terminus of a buried beta sheet within the protein kinase domain. This amino acid exchange introduces a positive charge and increases polarity into the domain, which may disrupt local hydrogen bonding networks and create steric clashes. This alteration likely results in significant structural and functional perturbations of the kinase domain. A majority of pathogenic and likely pathogenic variants in *BMPR1B* reported in ClinVar are likewise located in the protein kinase domain. The CADD score (27.1) and MutationTaster suggest a deleterious effect on the gene. AlphaMissense predicts a likely pathogenic effect of the variant. Based on the guidelines from the American College of Medical Genetics and Genomics (ACMG), the *BMPR1B* variant c.821A>G was classified as likely pathogenic (PP4_strong, PP3, PM2_supporting) and is the likely underlying cause of our patient's abnormalities. No other likely pathogenic or pathogenic variant in any other known disease gene was identified.

5 | Discussion

Here, we present a 2-year-old boy with acromesomelic chrondrodysplasia with a novel likely pathogenic biallelic missense variant in *BMPR1B*. A possible genotype–phenotype

correlation according to which pathogenic *BMPR1B* variants with a strong functional effect cause the severe Grebe-like phenotype, while milder pathogenic *BMPR1B* variants result in the clinically and radiologically milder du Pan dysplasia has been postulated in the literature (Stange et al. 2015). Our patient shows du Pan dysplasia with a mild phenotype. He has a normal height as well as no short femur, tibia, humerus, ulna or radius. The brachydactyly and shortened toes as well as a bilateral hypoplasia of the fibula in the patient reported here are common findings previously reported in patients with du Pan acromesomelic dyplasia.

However, this patient additionally shows a bilateral postaxial polydactyly of the hands—a novel clinical feature that has to date not been reported in *BMPR1B*-associated dysplasia patients in general. Interestingly, polydactyly is a known finding in Grebe dysplasia caused by biallelic variants in *GDF5* (Al-Yahyaee et al. 2003; Basit et al. 2008; Faiyaz-Ul-Haque et al. 2008; Umair et al. 2017).

GDF5 is a high affinity ligand to the BMPR1B receptor and plays an essential role in skeletal morphogenesis. In mice, mutations in *GDF5* result in brachypodism, a phenotype similar to the observed phenotype in patients with pathogenic *GDF5* variants (Storm et al. 1994). In humans and in mice, the interaction between GDF5 and BMPR1B is a critical aspect of bone development by regulating the differentiation and maturation of cells involved in bone formation, from chondrogenesis to osteogenesis (Yi et al. 2000; Baur, Mai, and Dymecki 2000; Francis-West et al. 1999). Hence, it can be expected that pathogenic variants in the genes *GDF5* and *BMPR1RB* may result in clinical overlapping phenotypes as in the case described here. Thus, our finding broadens the known clinical overlap of du Pan and Grebe acromesomelic dysplasia.

Interestingly, the variant identified in this patient is located within the protein kinase domain of *BMPR1B*, a region previously associated with pathogenic variants in patients with ACD. However, no cases involving variants near c.821A > G;p.(Gln274Arg) have been reported to date. It remains elusive whether the postaxial polydactyly observed in our case is a rare phenotypic feature of the disorder in general, not yet described due to the limited number of patients published to date, or whether the specific localisation of the variant within the protein kinase domain plays a direct role in this phenotype.

6 | Conclusion

In conclusion, we present a novel likely pathogenic biallelic missense *BMPR1B* variant underlying du Pan dysplasia with additional postaxial polydactyly, a finding previously only reported in *GDF5*-associated Grebe dysplasia. Our case expands the phenotypical overlap between the different ACD types, du Pan and Grebe. This discovery also clearly affects molecular diagnostic approaches, since individuals with du Pan acromesomelic dysplasia and polydactyly who do not carry pathogenic variants in *GDF5*, should be taken into account for *BMPR1B* sequencing. Finally, the full extent of the phenotypic spectrum has not yet been fully elucidated, and patients with pathogenic variants in the vicinity of the described p.Gln274Arg variant may contribute to a deeper understanding of the genotype–phenotype correlation.

Author Contributions

Ibrahim M. Abdelrazek: conceptualization, investigation, data curation. **Alexej Knaus:** conceptualization, investigation, visualization, writing – review and editing. **Behnam Javanmardi:** investigation. **Peter M. Krawitz:** conceptualization, investigation, writing – review and editing, resources. **Denise Horn:** writing – review and editing. **Ebtesam M. Abdalla:** resources, data curation. **Sheetal Kumar:** conceptualization, investigation, writing – original draft, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.