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Fibular Agenesis and Ball-Like Toes Mimicking Preaxial Polydactyly: Prenatal Presentation of Du Pan Syndrome

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Established Facts

- Du Pan syndrome (DPS) is a rare, recessively inherited chondrodysplasia within the GDF5-BMPR1B spectrum, characterized by fibular agenesis or hypoplasia and carpotarsal fusions with deformed phalangeal bones.
- Overall, less than 30 DPS cases have been reported with the vast majority lacking molecular confirmation, and none of the affected individuals were diagnosed in the fetal period.

Novel Insights

- This is the first report of DPS diagnosis established in the fetal period, bringing the total number of families with molecularly confirmed DPS up to 5.
- The presence of bilateral fibular agenesis and a preaxial polydactyly of the feet on fetal ultrasound should alert suspicion to DPS, with the latter possibly being a sonographic pitfall representing a mimicking image for ball-shaped toes.
- A detailed clinical examination of the expectant parents is of great importance in establishing a preliminary diagnosis of DPS.

Keywords
Du Pan syndrome · GDF5 · Prenatal diagnosis · Acromesomelic dysplasia · Brachydactyly

Abstract

Introduction: GDF5-BMPR1B signaling pathway-associated chondrodysplasias are a genetically heterogeneous group of conditions with significant phenotypic and genotypic overlap, consisting of Hunter-Thompson-type acromesomelic dysplasia, Grebe dysplasia, and Du Pan syndrome. Constituting a spectrum of clinical severity, these disorders are characterized by disproportionate short stature mainly involving middle and distal segments of the extremities. Du Pan syndrome represents the mildest end of this spectrum with less marked shortened limbs, fibular agenesis or hypoplasia, absence of frequent joint dislocations, and carpotarsal fusions with deformed phalangeal bones. ***Case Presenta-***

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tion: Here, we report the first prenatal diagnosis of Du Pan syndrome based on the sonographic findings of bilateral fibular agenesis and ball-shaped toes mimicking preaxial polydactyly accompanying subtle brachydactyly in the family. *GDF5* (NM_000557.5) sequencing identified a homozygous pathogenic variant c.1322T>C, p.(Leu441Pro) in the fetus and confirmed the carrier status in the mother. ***Discussion:*** We suggest that the presence of bilateral fibular agenesis and the apparent image of preaxial polydactyly of the feet on prenatal ultrasound should alert suspicion to Du Pan syndrome, with the latter possibly being a sonographic pitfall. Alongside the fetal imaging, a detailed clinical examination of the expectant parents is also of great importance in establishing a preliminary diagnosis of Du Pan syndrome, as well as the other GDF5-BMPR1B-associated chondrodysplasias.

Introduction

Acromesomelic dysplasias (AMDs) comprise a group of inherited skeletal disorders characterized by disproportionately short stature primarily involving middle and distal segments of the appendicular skeleton [Khan et al., 2016]. According to the 2019 revision of the nosology and classification of genetic skeletal disorders, the AMD group is sorted into six diseases: AMD type Maroteaux (MIM #602875), Grebe dysplasia (AMDG, MIM #200700), Hunter-Thompson-type AMD (AMDH, MIM #201250), Du Pan syndrome (DPS, MIM #228900), Osebold-Remondini syndrome (MIM #112910), and Demirhan-type AMD (MIM #609441) [Mortier et al., 2019]. The four subtypes, namely, AMDG, AMDH, DPS, and Demirhan-type AMD, occur due to pathogenic variations in the genes involved in the GDF5-BMPR1B signaling pathway and likely represent varying clinical severity of one spectrum rather than being completely distinct entities [Khan et al., 2016].

Growth and differentiation factor 5 (GDF5), also known as cartilage-derived bone morphogenetic protein-1 (CDMP1), is known to be essential for joint development and appendicular bone patterning during the embryonic period [Genovesi et al., 2021]. GDF5 is a member of the bone morphogenetic protein (BMP) family and acts as a ligand to BMP receptors, most favorably to BMPR1B. Upon ligand-receptor binding, BMPR1B becomes activated by transphosphorylation through BMPR2, which in turn activates p38 MAP kinase and/or SMAD-dependent signaling pathways to modulate the expression of the genes involved in cartilage and bone formation [Khan et al., 2016].

Alterations in the *GDF5* gene (NM_000557.5) have been associated with a broad range of skeletal disorders comprising developmental bone defects or exaggerated cartilage induction, depending on their functional effect on the protein product. Loss-of-function *GDF5* variants in heterozygous state result in brachydactyly types A1 (MIM #112500), A2 (MIM #112600), and C (MIM #113100), while activating mutations lead to proximal symphalangism type 1B (MIM #615298) and multiple synostoses syndrome 2 (MIM #610017). Biallelic loss-of-function variants, on the other hand, result in "GDF5-BMPR1B-associated AMDs" [Seemann et al., 2009]. Owing to the shared pathway, mutations in *BMPR1B* also lead to BMP signaling dysregulation, disrupt limb morphogenesis, and consequently result in similar phenotypes, as previous clinical reports have disclosed the association of *BMPR1B* variants with DPS, AMDH, AMDG, and brachydactyly subtypes [Graul-Neumann et al., 2014; Stange et al., 2015; Ullah et al., 2018].

The spectrum of GDF5-BMPR1B-associated AMDs ranges from AMDG on the severe end to AMDH on the moderate middle, and DPS on the mild end. Limb abnormalities are likely to be restricted to distal regions or mildly involved in DPS, whereas middle segments are always affected in AMDH and AMDG. Although DPS has less severe features overall, the characteristic ball-like toes usually cannot be distinguished from AMDG; however, carpal and carpotarsal fusions are comparatively consistent with DPS. Frequent joint dislocations are in favor of AMDH on clinical grounds, but lower limb and radioulnar dislocations have also been described in DPS and AMDG, respectively. Being the most severe type, AMDG is easily recognized with markedly shortened tubular bones and severe short hands with missing phalanges, occasionally accompanied by polydactyly [Faiyaz-Ul-Haque et al., 2002].

Overall, less than 30 DPS cases have been reported, and none of the affected individuals were diagnosed in the fetal period [Du Pan, 1924; Grebe, 1955; Hunter and Thompson, 1976; Kohn et al., 1989; Ahmad et al., 1990; Lees et al., 1998; Faiyaz-Ul-Haque et al., 2002; Szczaluba et al., 2005; Douzgou et al., 2008; Kaissi et al., 2009; Stange et al., 2015]. Here, we report the first prenatal case of DPS diagnosed at 20^{+} weeks of gestation (GWs) based on the subtle familial brachydactyly and ultrasonographic features which could have been easily misinterpreted.

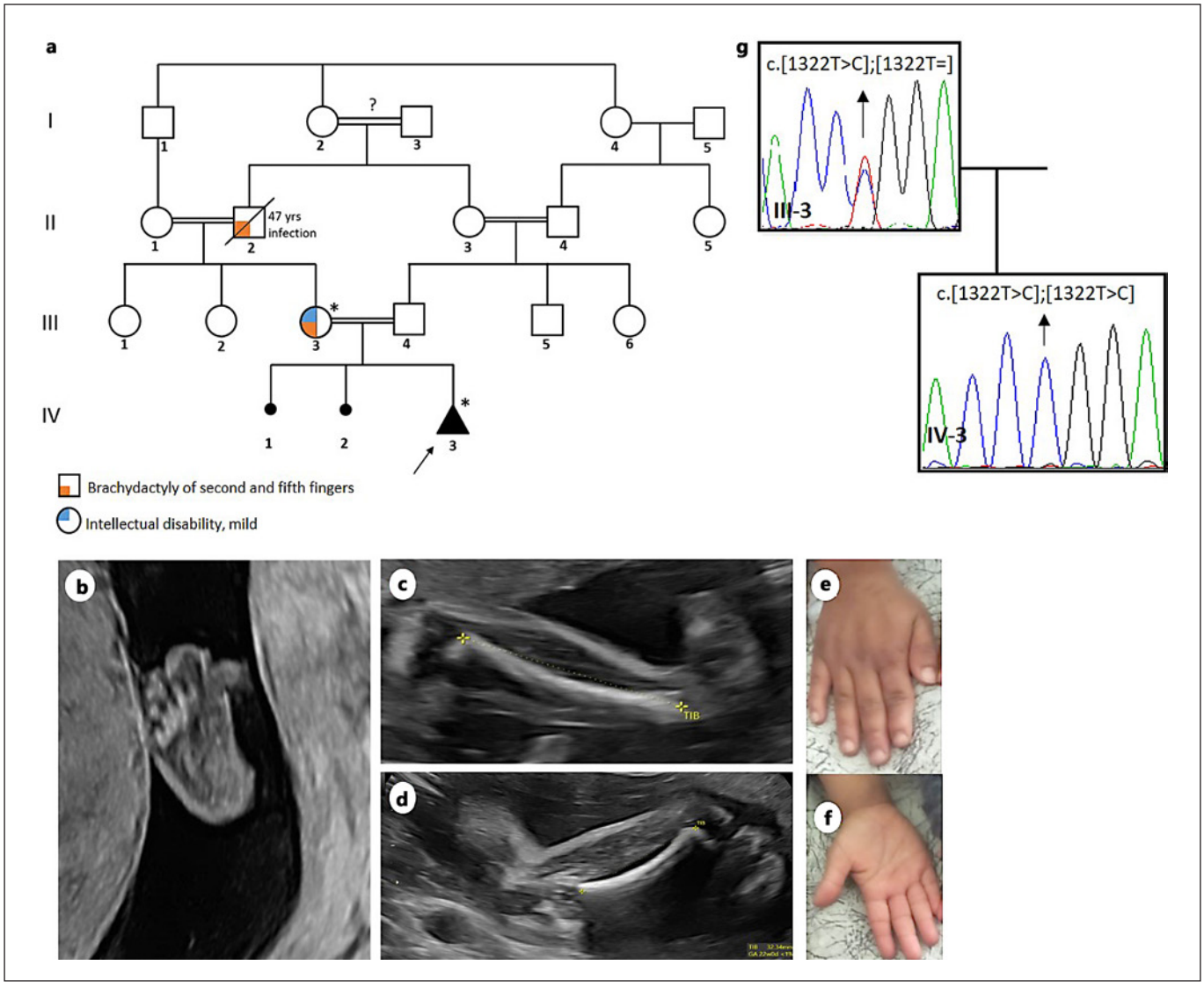

Fig. 1. a Pedigree of the family. Asterisks indicate individuals who have been clinically and molecularly examined. **b–d** Ultrasound images of the proband showing suspected preaxial polydactyly and bilateral fibular agenesis. **e**, **f** Right hand photographs of the mother from dorsal and ventral aspects, showing mild brachydactyly of the second and fifth finger. **g** Sequencing data of the family revealed the variant (c.1322T>C) of the *GDF5* gene that was heterozygous in the mother (III-3) and homozygous in the fetus (IV-3).

Materials and Methods

Informed written consent was obtained for genetic testing and the use of photographs from the family members and the parents for the fetus. Chromosomes were harvested from amniocytes and peripheral blood leukocytes of the mother and were analyzed according to standard high-resolution G-banding techniques. Fetal and maternal DNA isolation for the sequencing of the *GDF5* gene (NM_000557.5) was extracted using a commercial kit according to the instructions of the manufacturer (Qiagen, USA). Coding exons of *GDF5* together with flanking intronic regions were amplified with PCR and sequenced with the Sanger technique (ABI 3500). The human genome assembly GRCh38/hg38 was used as a reference genome. Exon 2 of *GDF5* was sequenced for familial segregation analysis.

Case Report

A 22-year-old, gravida 3 para 0 woman was referred to our tertiary prenatal diagnosis center at 20 GWs due to pathological skeletal phenotype on fetal ultrasound. It was the third pregnancy of the first-degree cousin parents, with two earlier pregnancies having ended in spontaneous abortions (Fig. 1). Detailed fetal ultraso-

nography at 20^{+5} GWs revealed bilateral fibular agenesis, short and bowed tibia on the right, extended-abducted and short thumbs, pes equinovalgus deformity on the left, bilaterally small feet, and a suspected image of preaxial polydactyly of the feet (Fig. 1). Fetal facial profile, vertebral, and bone mineralization were evaluated as normal. Thoracic circumference was within normal limits, chest-to-abdominal circumference ratio was 0.8, and femur length-to-abdominal circumference ratio was 0.19, ruling out lethality [Yoshimura et al., 1996].

Following the fetal ultrasound, we performed a physical examination of the prospective mother. She was 157 cm tall, demonstrated mildly shortened second and fifth digits in both hands, and had seemingly low-average mental performance (Fig. 1). It was later stated that her father also had short second fingers bilaterally. Chromosomal investigation of the mother due to below-average intelligence and bad obstetric history showed a balanced translocation, 46,XX,t(1;11)(q23;p15). The expectant father could not be physically assessed or genetically tested due to residential situations.

According to the ultrasound findings of bilateral fibular agenesis, the absence of severe intrauterine growth retardation, suspected polydactyly, and a family history of shortened second and fifth fingers, a differential diagnosis of DPS was established. Our assumption was based on the possibility of preaxial polydactyly appearance being falsely interpreted for the characteristic acral abnormality of DPS, "ball-shaped" toes. The genetic analysis of the *GDF5* gene was planned and performed on the mother (III-3). This study disclosed that the mother was carrying the c.1322T>C, p.(Leu441Pro) variant that was previously shown to be inactivating in DPS [Faiyaz-Ul-Haque et al., 2002]. Amniocentesis was performed concurrently at 21 GWs, and chromosomal analysis yielded a normal female karyotype. *GDF5* sequencing on a DNA sample from the cultured amniotic cells revealed that the fetus was homozygous for the c.1322T>C variant, confirming our diagnosis (Fig. 1).

Following the definitive diagnosis of DPS, the family was provided prenatal counseling about likely anticipated outcomes including the nonlethal nature of the disease, sequential surgery requirements, and the small risk of atlantoaxial dislocation due to odontoid hypoplasia in addition to counseling regarding the reciprocal balanced translocation identified in the mother for future pregnancies [Lees et al., 1998; Kaissi et al., 2009]. Due to the lack of paternal molecular analysis, it is not possible to determine the true genetic recurrence rate, given also the slight risk of uniparental disomy.

Discussion

To the best of our knowledge, this is the first report of DPS diagnosis established in the fetal period, bringing the total number of families with molecularly confirmed DPS up to 5 [Faiyaz-Ul-Haque et al., 2002; Szczaluba et al., 2005; Douzgou et al., 2008; Stange et al., 2015]. Prenatal signs of DPS are not unequivocal, making the diagnosis based on sonography challenging. This case herein highlights a collection of prenatal findings which should suggest the diagnosis of DPS, together with a detailed family assessment.

DPS is inherited in an autosomal recessive manner, and only four *GDF5* variants have been reported in biallelic form, associated with this phenotype. Exceptionally, three heterozygous variants on the same allele were identified in an affected mother and daughter, suggestively through a *cis*-acting synergistic effect [Szczaluba et al., 2005]. The pathogenic variant reported herein, c.1322T>C, p.(Leu441Pro), has been previously shown to result in a selective loss of GDF5 signaling through BMPR1B, causing brachydactyly in the heterozygous state and DPS in the homozygous state [Faiyaz-Ul-Haque et al., 2002; Kjaer et al., 2006]. To date, including our report, this variant was identified in several non-consanguineous families of Norwegian, Danish, Pakistani, and Turkish descent [Faiyaz-Ul-Haque et al., 2002; Kjaer et al., 2006]. Of note, we have also encountered this alteration in another individual with DPS originating from a different part of Turkey (unpublished data). Although p.(Leu441Pro) was previously suggested to reflect a founder effect, mutational hotspot at this nucleotide position may also be accounted for, considering no apparent ancestral connections [Kjaer et al., 2006].

Brachydactyly history on the maternal side of the family had a critical role in the basis of the diagnosis in our case, as certain monoallelic *GDF5* variants are known to be associated with brachydactyly subtypes. Interestingly, heterozygous individuals for DPS were occasionally reported as phenotypically normal in the previous reports. This discrepancy has been suggested to be linked to the underlying molecular mechanism of *GDF5*, and the phenotypic outcome varies depending on the mutation type, affected protein domain, or the variant's impact on GDF5 function [Genovesi et al., 2021]. Moreover, significant intrafamilial variability among the carriers implies the influence of yet unlinked modifier genes. Functional studies demonstrated that the p.(Leu441Pro) variant we report here affected the type 1 receptor-binding site and results in a selective loss of function [Seemann et al., 2005]. This variant was also described in another multiplex DPS family, and the carriers were defined as clinically normal [Faiyaz-Ul-Haque et al., 2002]. On the contrary, a further study held in an autosomal dominant brachydactyly type A2 family carrying the same mutation showed only three of the 37 affected subjects had normal acral findings, while a broad phenotypic spectrum was observed among the manifesting individuals [Kjaer et al., 2006]. Various other variants in heterozygous form were reported to have no clinical impact. Douzgou et al. [2008]

reported a mild DPS phenotype in a 20-month-old boy with two *GDF5* changes in compound heterozygous form, c.1133G>A, p.(Arg378Gln) and c.1306C>A, p.(Pro436Thr) [Douzgou et al., 2008]. Clinical examination showed the father, carrying c.1133G>A, had mild brachymesophalangy of all digits, whereas the mother with c.1306C>A displayed no radiological changes. The only reported case of BMPR1B-associated DPS carrying the homozygous c.91C>T, p.(Arg31Cys) variant was also stated to have clinically unaffected parents [Stange et al., 2015]. These observations indicate that defining the accurate genotype-phenotype correlations by identifying the modifier elements is exceedingly important to presume an accurate phenotypic outcome, especially for specified prenatal genetic counseling.

Overall, it should be noted that "ball-shaped toes," the hallmark feature of DPS, could be mistaken as preaxial polydactyly on the fetal ultrasound, yet the presence of fibular agenesis should promptly raise the suspicion of DPS. A detailed clinical examination of the prospective parents is also of great importance in establishing the diagnosis. We believe that in this case of prenatal diagnosis, the family had the opportunity of receiving comprehensive genetic counseling and arranging the medical management plan to be well prepared after birth, as well as averting the psychological tragedy in the family.

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We are grateful to the family for their participation in the study.

Statement of Ethics

Written informed consent for performing genetic tests and publication of this case report, including any accompanying images, was obtained from the patient's guardians. Genetic tests performed in this family were a part of the diagnostic investigation in search of the cause of the disease. Ethical approval was not required for this study in accordance with local/national guidelines.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

All authors helped advance and then approved the manuscript. Gozde Tutku Turgut collected clinical information, drafted the figures, and wrote the paper. Tugba Kalayci evaluated the patients and made the clinical diagnosis. Ibrahim Halil Kalelioglu and Tugba Sarac Sivrikoz performed antenatal ultrasonographic evaluations and managed the pregnancy with Tugba Kalayci. Birsen Karaman performed cytogenetic investigations. Volkan Karaman performed molecular analysis. Zehra Oya Uyguner helped Gozde Tutku Turgut finalize the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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