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CLINICAL REPORT

Expansion of the mutational spectrum of *BMPER* leading to diaphanospondylodysostosis and description of the associated disease process

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Abstract

Background: Diaphanospondylodysostosis (DSD) is a rare congenital, lethal skeletal disorder caused by recessively inherited mutations in the *BMPER* gene, which encodes the bone morphogenetic protein-binding endothelial cell precursor-derived regulator. The most prominent features of DSD are missing ossification of the axial skeleton, rib abnormalities and thoracic hypoplasia/insufficiency, as well as intralobar nephrogenic rests within the kidneys.

Methods: We report on the case of a 22-month-old patient with DSD where trio-exome sequencing was performed.

Results: Genetic testing revealed a homozygous nonsense variant c.1577G>A (p.Trp526*) in the *BMPER* gene, leading to a premature stop in protein translation. Both parents are asymptomatic carriers for the *BMPER* variant, which has not been described in the literature before.

Conclusions: Our findings expand the genotypic and phenotypic spectrum of *BMPER* variants leading to DSD.

KEYWORDS

BMPER, diaphanospondylodysostosis, DSD, ischiospinal dysostosis, ISD, skeletal dysplasia

1 | INTRODUCTION

Diaphanospondylodysostosis is a rare congenital, lethal skeletal disorder caused by recessively inherited mutations in the *BMPER* gene (OMIM *608699), which encodes the bone morphogenetic protein-binding endothelial cell precursor-derived regulator (Funari et al., 2010). The most prominent features are missing ossification of the axial skeleton, predominantly of the lumbar spine, rib abnormalities and thoracic hypoplasia/insufficiency, as well as intralobar nephrogenic rests within the kidneys (Prefumo et al., 2003). The term "diaphanospondylodysostosis" was coined by Gonzales et al. in 2005, taking into account the diaphanous appearance of the vertebral bodies with increased radiolucency, concluding the origin to be a defect of blastogenesis (Gonzales et al., 2005). The hitherto reported cases encompass 18 different mutations of *BMPER*, including point mutations and deletions, both homozygous and heterozygous, as well as compound heterozygous cases. While heterozygous *BMPER* mutations cannot be linked to the characteristic DSD phenotype in humans with certainty, pulmonary pathology has been shown in $BMPER^{+/-}$-mice (Kelley et al., 2009).

Only few patients who survived beyond infancy are known and the oldest known patient in the literature is 9 years old. Leading causes of death are respiratory insufficiency and Wilms' tumor (Funari et al., 2010; Ben-Neriah et al., 2011; Zong et al., 2015; Kuchinskaya et al., 2016; Hofstaetter et al., 2018; Legare et al., 2017; Salian et al., 2019; Scottoline et al., 2012, Greenbaum et al., 2019). Ischiospinal dysostosis (ISD) is another congenital, polytopic dysostosis associated with mutations in the *BMPER* gene, but mostly describes a milder phenotype than DSD and may also be associated with nephroblastomatosis (Kuchinskaya et al., 2016).

Bone morphogenic proteins (BMPs) are extracellular signaling factors and members of the TGFβ-superfamily (Ben-Neriah et al., 2011; Helbing et al., 2017). Bone morphogenetic protein endothelial cell precursor-derived regulator (BMPER) is a homologue of Crossveinless (CV-2) in *Drosophila melanogaster* and part of the chordin family (Helbing et al., 2017). BMPER plays an essential role in organogenesis, osteogenesis, angiogenesis, and endothelial-barrier function (Ben-Neriah et al., 2011; Helbing et al., 2017; Ikeya et al., 2006; Kelley et al., 2009; Salian et al., 2019; Xiao et al., 2018).

Here, we provide a comprehensive report on disease progression in a 22-month-old female patient suffering from a homozygous nonsense mutation of *BMPER*, which has previously not been described in the literature, thus expanding the current molecular genetic spectrum of the disease. Comparison with cases described in the literature shows an expansion of phenotypical and clinical variability.

2 | CLINICAL REPORT/PATIENT DESCRIPTION

2.1 | Family history

Our patient is the second child of a consanguineous Lebanese Arab couple, who are first-degree cousins. The mother had undergone treatment for infertility and a boy from the couple's first pregnancy is reported to be healthy. She had been treated for androgenital syndrome and polycystic ovaries syndrome with metformin and progesterone. The maternal grandmother is reported to have a cystic kidney disease of unknown origin. The mother's kidneys presented normally in ultrasound.

2.2 | Neonatal period

Fetal movements in pregnancy were reported as normal while nuchal translucency was increased.

The patient was born spontaneously after 40 + 1 weeks of gestation. Cardiorespiratory adaptation was delayed and the patient was transferred to the neonatal intensive care unit with low blood oxygen saturations for oxygen therapy. Mechanical ventilation was not required, and respiratory function normalized within the first day of life.

After the initial need for a glucose-electrolyte infusion, she was fed without problems from the third day of life. In the course of the hospital stay, she developed one-sided mastitis with a small abscess that cured under intravenous antibiotic therapy.

Born with low birthweight (2720 g, 3. Pct., −1,82 z), short body length (47 cm, 2. Pct., −2,17 z), and a head circumference in the low range (33 cm, 7. Pct., −1,49 z), further striking clinical features were a short neck, short thorax, protruding abdomen, thick hair on forehead and shins, as well as a low posterior hairline. Ultrasound revealed irregularly located cysts in both kidneys with no sign of restriction of urinary flow. Ultrasound of the brain was normal, physiological delay of hip maturation on the left side was noted. Brainstem audiometry and ophthalmological examination showed normal results. X-ray led to suspicion of fusion of the cervical spine and showed an incomplete fusion of the vertebral bodies to the Procc. spinosi in the lower thoracic and the upper lumbar spine. The lumbar vertebral bodies 1–3 appeared rudimentary with lumbar vertebral bodies 4–5 and sacrum not discernible. There was strong kyphosis of the thoracic spine (Figure 1a,b). Clinically, there was no sign of affection of the appendicular skeleton.

Echocardiography at discharge showed an open foramen ovale and suspected atrial septal defect type II. An initial chromosome analysis revealed a normal female karyotype.

Having regained her birth weight after an initial weight loss, the patient was discharged to the family's home on day of life 15 without the need for mechanical ventilation.

2.3 | Infancy

Regular ultrasound examinations of the kidneys confirmed multiple medullar and cortical, partially subcapsular cysts and elevated echogenicity. Laboratory tests showed normal kidney function. The patient received nursing care at home and was supplied with cardiorespiratory monitoring and home oxygen for emergency care during acute bronchospasms after respiratory crises, RSV-associated bronchiolitis and events of cyanosis had occurred. Bronchoscopy revealed a pulsating compression of the trachea, an atypical bronchus medially of the right median lobe and an atypical configuration of the left lower lobe. Computed tomography showed a late, left paramedian origin of the truncus brachiocephalicus from the aortic arch with a semi-circular path ventrally of the trachea. In supine position, no relevant constriction of the trachea was seen and dystelectasis was found in both lower lobes. Skeletal findings at this age included hypoplasia of the

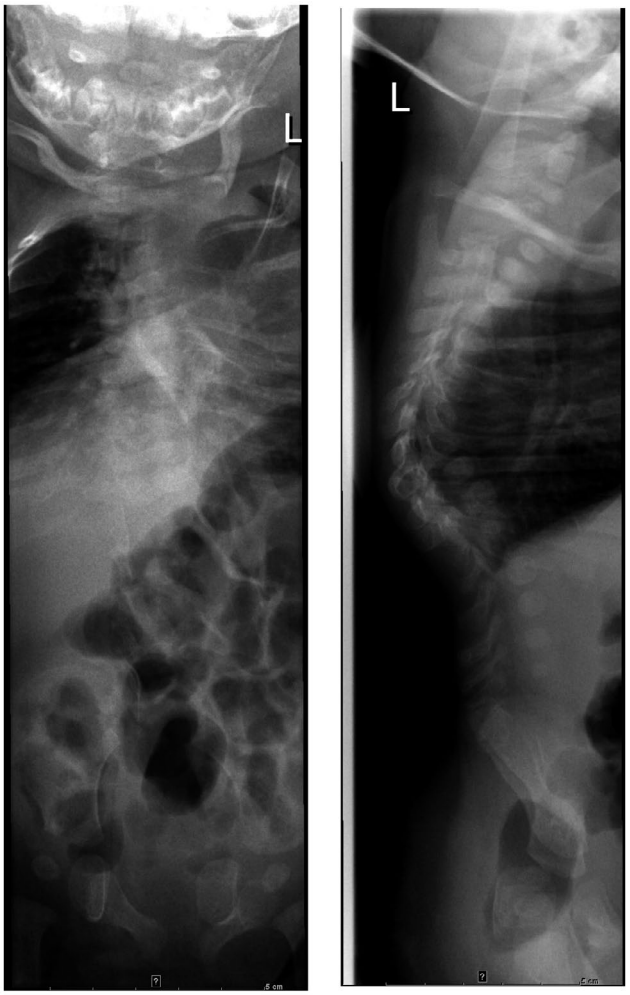

FIGURE 1 X-Ray spinal column at age 4 months, (a) a.p. view: lumbar vertebral bodies 1–3 appear rudimentary, lumbar vertebral bodies 4–5 and sacrum not discernible. (b) lateral view: fusion of the cervical spine, kyphosis of the thoracic spine, incomplete fusion of the vertebral bodies to the Procc. spinosi in the lower thoracic and the upper lumbar spine

first rib as well as bifurcation of the third rib on both sides with a whole of 11 ribs on either side. There is multisegmental, partial fusion of the vertebrae in the median and lower thoracic spine as well as lacking ossification at the ventral side of the vertebral bodies and of the pedicles. (Figure 2a–d).

Surgery to prevent tracheal compression was discussed at 11 months of age and a watchful waiting approach was taken. The patient remained hospitalized for 4 months with several episodes of agitation leading to cyanosis despite constant HighFlow-therapy (HFNC High Flow Oxygen Nasal Cannula). The agitation had to be treated with rectal diazepam. Currently, the patient is on constant HFNC with only short interruptions of several hours per day. Cardiopulmonary resuscitation was necessitated once during pulmonary infection.

2.4 | Early childhood

At 16 months of age, she presented with severe combined developmental retardation. She has a social smile and produces sound, but no syllables. She developed facial hypertrichosis with synophrys, anteverted nares, a high palate, a tented vermillion of the upper lip and has a small porus on the left earlobe (Figure 3a,b).

Upper limb function appears unimpaired and she reaches with her hand. Muscular reflexes are normal. Notably, she is not able to sit without support, but rolls from prone to supine position and can propel herself backwards in supine position, pushing with her legs. Her left foot appears as a talipes equinovarus, but is fully redressable. The appendicular skeleton is otherwise unaffected (Figure 3c).

She presents with a short neck and gibbus, hyperkyphosis of the thoracic spine, no scoliosis. In prone position, she arches upward on her arms and turns her head at will (Figure 3d).

3 | METHODS

3.1 | Ethical compliance

All data concerning our patient was extracted from her medical routine files. This approach was approved by our local ethics committee. For all diagnostic steps, written informed consent was obtained from both parents. The permission to publish clinical data and photos was obtained from the parents. The study was conducted in accordance with the principles of the Declaration of Helsinki.

3.2 | Genetic testing

After establishing our patient's regular, female karyotype (see above), molecular genetic testing with a specific fluorescent probe for the chromosomal region 22q11.2 showed no sign for a microdeletion 22q11.2. Chromosome analyses of both parents were performed and they both have a normal karyotype. Considering the family history autosomal recessive inheritance was suspected and due to the broad spectrum of differential diagnoses and relevant genes, trio-exome sequencing was performed.

Trio-exome sequencing was performed on genomic DNA from the patient and her parents. Coding genomic regions were enriched with a SureSelect Human All Exon Kit V7 (Agilent technologies, Santa Clara, California) for subsequent sequencing as 2x 101 bp paired-end reads on an NovaSeq6000 system (Illumina, San Diego, California). Generated sequences were analyzed using the megSAP pipeline (https://github.com/imgag/megSAP). In the index case, generated sequence data

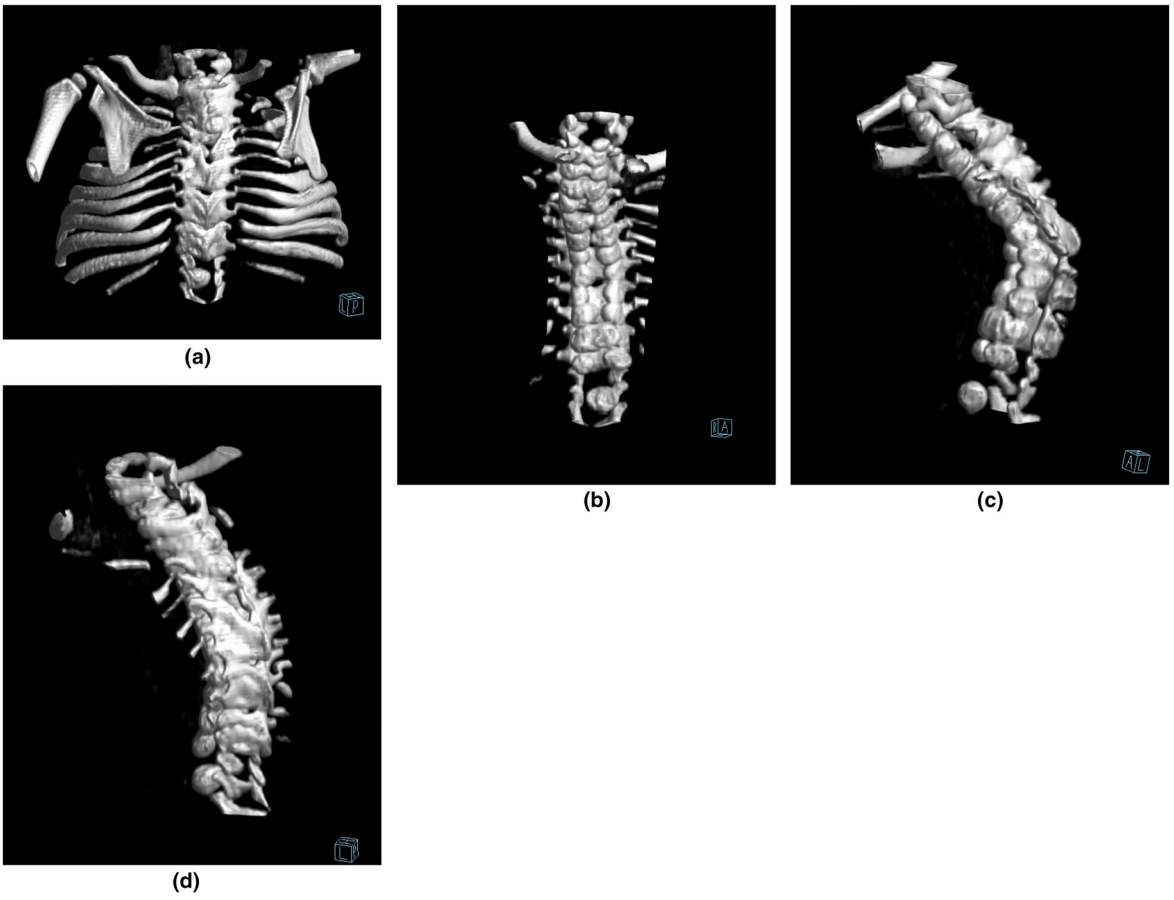

FIGURE 2 CT-scan 3D-reconstruction of thoracic skeleton at age 11 months, (a) hypoplasia of the first rib, bifurcation of the third rib on both sides with a whole of 11 ribs on either side. (b) Lacking ossification at the ventral side of the vertebral bodies. (c) Lacking ossification of the pedicles. (d) Multisegmental, partial fusion of the vertebrae in the median and lower thoracic spine

resulted in an average 120-fold coverage of the target with 96.2% being covered at least 20X. Clinical variant prioritization included different filtering steps (e.g., MAF <0.1% in 1000 g, ExAC or gnomAD, in-house database) and was conducted independently by two analysts according to an in-house standard operating procedure. This filtering step prioritized a homozygous nonsense variant in *BMPER* (ENST00000297161.2, NM_133468.4, OMIM *608699). Both parents are carriers for the *BMPER* variant and reportedly healthy.

This variant c.1577G>A (p.Trp526*) is neither present in gnomAD nor an in-house database and predicts to result in a loss of protein function either by nonsense-mediated decay of the mutant RNA or an early truncation of protein translation. According to ACMG guidelines, this variant was classified as pathogenic (Richards et al., 2015).

4 | RESULTS OF LITERATURE REVIEW

After a review of the literature and to the best of our knowledge, the following table is an exhaustive list of the mutations in the *BMPER* gene found in patients with DSD and ISD. Resulting changes on the protein level are not always clearly examined and association with a clinical diagnosis remains debatable in some cases. Of note, patients suffering from *BMPE*R associated phenotypes are from various ethnic origins (e.g., British-European, Swedish, Korean, Mexican, Jewish Balkan, Israeli Arab population; references see table) (Table 1).

5 | DISCUSSION

Diaphanospondylodysostosis and ischiospinal dysostosis are both skeletal dysplasias caused by mutations in the *BMPER* gene (Funari et al., 2010; Hofstaetter et al., 2018; Kuchinskaya et al., 2016; Legare et al., 2017). Clinical findings partially overlap and there is discussion of them being variants in severity of the same disease process in terms of a clinical continuum with DSD representing the more severe spectrum of the phenotype (Legare et al., 2017). Consequently, a classification into either one of these entities is not always clear (Kuchinskaya et al., 2016; Zong et al., 2015).

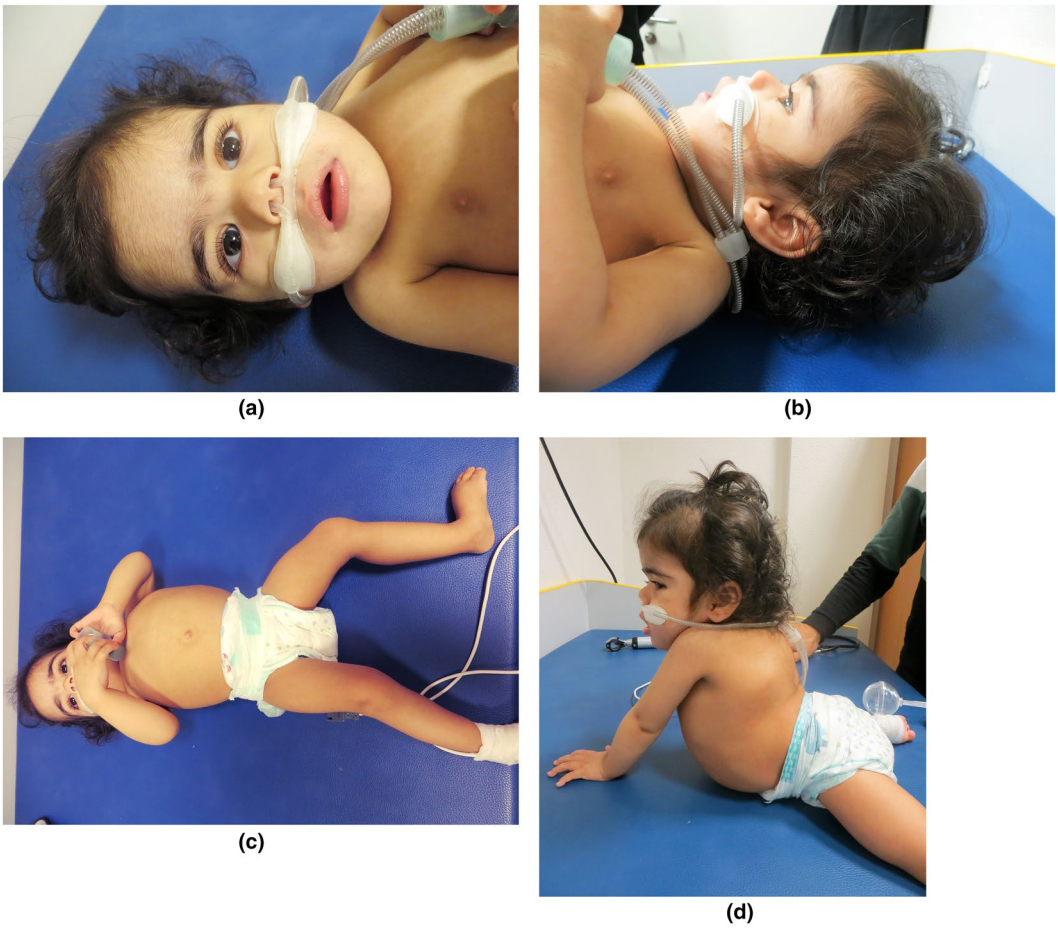

FIGURE 3 (a) Photography of patient's face, frontal view showing facial hypertrichosis, synophrys, anteverted nares, tented vermillion of the upper lip. (b) Photography of patient's face, lateral view showing facial hypertrichosis, anteverted nares, tented vermillion of the upper lip, porus on ear lobe, short neck. (c) Photography of patient in supine position showing stature and appendicular skeleton. (d) Photography of patient in prone position showing gibbus and hyperkyphosis of thoracic spine

Our patient suffering from the novel *BMPER* mutation (c.1577G>A) presents a phenotype that can be considered typical for DSD and does extend the known spectrum of genotypical and phenotypical variability.

Phenotypical manifestations of *BMPER* mutations are discussed sorted by respective organ manifestations and are compared with clinical findings of our case as well as highlighted in the context of functional studies:

5.1 | Age

Considering other patients described, survival to the age of 22 months at present accords with the diagnosis of DSD (Ben-Neriah et al., 2011; Legare et al., 2017; Scottoline et al., 2012). In this context, Legare et al., (2017) discussed that survival by its very nature strongly depends on early and intensive medical care and long-term survival cannot be a diagnostic criterion in itself. Still, out of the around 20 cases reported thus far, the 9-year-old patient described by Legare et al., (2017) remains the oldest known patient with DSD in the literature.

5.2 | Skeleton

Skeletal findings, including incomplete fusion of multiple vertebral bodies and rudimentary development of the lumbar spine, as well as anomalies in the number and configuration of the ribs found in our patient, are in line with already described cases and the phenotypical characteristics linked to defects in *BMPER* (Ben-Neriah et al., 2011; Kuchinskaya et al., 2016; Legare et al., 2017; Scottoline et al., 2012). Thus, the association of the skeletal malformations and the novel homozygous nonsense mutation (p.Trp526*) within the *BMPER* gene, supports the hypothesis that DSD is caused by loss of BMPER function (Ben-Neriah et al., 2011; Ikeya et al., 2006; Zong et al., 2015; Funari, et al., 2010; Xiao et al., 2018). In this context, it is important to note that Xiao et al. showed how BMPER positively regulates osteogenic differentiation

TABLE 1 List of mutations in the *BMPER* gene found in patients with DSD and ISD

Mutation in *BMPER* cDNA	Protein	Diagnosis	Reference
c.925C>T	p.Gln309*	DSD	Funari et al. (2010)
c.26_35del10ins14	p.Ala9Glufs*4	DSD	Funari et al. (2010)
c.1031+5G>A	unknown	DSD	Funari et al. (2010)
c.514C>T	p.Gln172*	DSD	Funari et al. (2010)
c.1109C>T	p.Pro370Leu	DSD	Funari et al. (2010)
c.1638T>A	p.Cys546*	DSD	Funari et al. (2010)
c.310C>T	p.Gln104*	DSD	Ben-Neriah et al., (2011)
c.251G>T	p.Cys84Phe	Attenuated DSD (ISD Kuchinskaya et al., 2016)	Zong et al., (2015)
c.1078+5G>A	Unknown	Attenuated DSD (ISD Kuchinskaya et al., 2016)	Zong et al., (2015)
c.416C>G	p.Thr139Arg	ISD	Kuchinskaya et al., (2016)
c.942G>A	p.Trp314*	ISD	Kuchinskaya et al., (2016)
c.1672C>T	p.Arg558*	ISD	Kuchinskaya et al., (2016)
c.1988G>A	p.Cys663Tyr	Unknown clinical significance	Kuchinskaya et al., (2016)
c.[496T>A; 501_502delGT];	p.[Cys166Ser; Phe168*]	DSD	Hofstaetter et al., (2018)
c.322T>C; Del (7p14.3p14.2) encompassing 9 genes, incl. *BMPER*, *RP9*, *BBS9*	p.C108R	ISD/DSD	Legare et al., (2017)
c.314G>A	p.Cys105Tyr	ISD	Salian et al., (2019)
c.26_35delCTCTGGCTGAinsAGACCAG AGCGGCG plus c.1031+5G>A	p.Ala9GlufsX44	DSD	Scottoline et al., (2012)
c.410T>A	p.Val137Asp	DSD	Greenbaum et al. (2019)
c.1577G>A	p.Trp526*	DSD	Current study

in human bone marrow stromal cells (hBMSC) and promotes osteogenesis via BMP-2/Smad signaling as well as angiogenesis and increases bone formation *in vivo* (Xiao et al., 2018), thus providing functional evidence for the phenotypical manifestation upon loss of the protein.

5.3 | Kidney

The multiple medullar and cortical, partially subcapsular cysts and elevated echogenicity of both kidneys found in our patient are in line with previously reported cases. As described previously, the absence of kidney abnormalities is a positive outcome predictor, whereas some patients developing nephroblastoma or Wilms' tumor are at significant risk (Gonzales et al., 2005; Kuchinskaya et al., 2016; Legare et al., 2017; Tasian et al., 2012). Tasian et al. postulated DSD to be a Wilms' tumor predisposition syndrome and serial monitoring for nephroblastomatosis has already been recommended (Scottoline et al., 2012; Tasian et al., 2012). In the crossveinless 2 $(Cv2)^{-/-}$ knock-out mice, Ikeya and colleagues showed essential pro-BMP roles of Cv2 in murine organogenesis with substantial defects in BMP-dependent processes of internal organ formation, particularly nephron generation in the kidney (Ikeya et al., 2006). However, Scottoline and co-workers highlighted a discrepancy between the hypoplastic kidneys with a paucity of nephrogenic precursors found in *BMPER* null mice and the frequently diagnosed nephroblastomatosis with extensive cysts in DSD patients (Scottoline et al., 2012). Ultimately, further investigations of the relationship between the Notch or Wnt pathways and the Bmper/BMPER protein are still needed to draw final conclusions.

Particularly at a young age, regular nephrological controls in patients with DSD are crucial, given that Wilms tumor accounts for more than 90% of all malignant kidney neoplasms in children and median incidence is highest in the age group 0–4 years (Cunningham et al., 2020).

5.4 | Nervous system

Ikeya and co-workers described the expression profile of Cv2 in the central nervous system and showed that a loss of Cv2 prevents further differentiation of the sclerotome-derived precursor cells (Ikeya et al., 2006). Additionally, a reduction of the *Bmp4* gene dose led to an elevated frequency of the microphthalmic phenotype in $Cv2^{-/-}$-mice, ranging from actual microphthalmia to the complete absence of eyes (Ikeya et al., 2006). The spinal cord abnormality described by Scottoline et al. with ending at the junction of the thoracic and lumbar spine and the concomitant peripheral neuropathy is otherwise unreported (Scottoline et al., 2012). However, polymicrogyria involving the entire cerebral cortex has been described postmortem in a patient, who did not survive past one month of age (Vatanavicharn et al., 2007). Of note, both microcephalic and macrocephalic *BMPER*-cases have been described (Scottoline et al., 2012; Vatanavicharn et al., 2007). Nevertheless, as in our patient, there is restriction in establishing the diagnosis of microcephaly in patients with an overall short stature, where growth restriction is rather harmonious. Considering skeletal dysplasias as a whole, Krakow describes that most patients with nonlethal skeletal dysplasias are cognitively normal and have a good quality of life (Krakow, 2015). Despite the combined developmental delay of our patient, including motor function and speech, her cognitive status appears normal. In the three *BMPER*-patients described by Zong et al. as mild cases, cognitive development was normal with academic performances being above average (Zong et al., 2015). Cranial nerve involvement is shown in a patient with congenital bilateral hearing loss (Scottoline et al., 2012). Although we report no abnormal findings on brainstem audiometry, a porus on the left earlobe of our patient hints toward a possible auricular involvement. In this context, it is worth noting that audiological screening is advised in children with DSD (Legare et al., 2017). Conductive hearing loss from persistent serous otitis media was described in one patient with DSD (Legare et al., 2017).

5.5 | Lung and pulmonary function

Considering the current clinical knowledge of reported *BMPER*-cases, some of the major factors contributing to the lethality in patients with skeletal dysplasias are pulmonary problems usually resulting from small chest and thorax insufficiency, pulmonary hypoplasia, and respiratory compromise (Krakow, 2015). Measurement of lung volume by ultrasound or MRI can help to establish the diagnosis of a skeletal dysplasia antenatally, serving as a predictive outcome measure often predicting lethality rather accurately (Milks et al., 2017).

A direct link between a respiratory phenotype and protein function can be drawn from functional studies as Bmper notoriously functions as a tissue-specific Bmp inhibitor in the developing lung as shown in distal lung areas of Bmper-deficient mice (Kelley et al., 2009). Opposed to the proximal lung areas, in distal areas Bmper is expressed in the mesenchyme (Kelley et al., 2009). Moreover, the expression of Cv2 was also shown in pharyngeal and tracheal cartilage, as well as in the developing alveoli (Ikeya et al., 2006) and postmortem examination of a patient who died at one month of age due to respiratory insufficiency showed absence of cartilage in the large bronchi (Vatanavicharn et al., 2007). Taking into consideration the seemingly high susceptibility to airway infections (especially of the lower airways) as also present in our patient, it is interesting to note that studies of Helbing and co-workers on a murine model demonstrated how BMPER-modulated BMP pathway activity influences vascular barrier function through vascular endothelial (VE)-cadherin expression whereby heterozygous deficiency of BMPER was shown to enhance vascular leak in the lungs (Helbing et al., 2017).

Of note, the anomalies in organogenesis observed in our patient including the atypical bronchus medially of the right median lobe and an atypical configuration of the left lower lobe, as well as the anomaly of the truncus brachiocephalicus, leading to a pulsating compression of the trachea, have not been described before thus expanding the spectrum of clinical features associated with bi-allelic *BMPER* mutations.

5.6 | Diagnosis

Prenatally, the diagnosis of skeletal dysplasia can often be made combined with the most sensitive and specific predictors of the sonographic parameters, namely the degree of femoral shortening, femur length to abdominal circumference ratio, as well as chest circumference to abdominal circumference ratio. Elevated neck translucency on fetal ultrasound was reported repeatedly (Hofstaetter et al., 2018; Prefumo et al., 2003). Early prenatal detection of skeletal dysplasia can be an advantage to preparation on anticipating severity and agreeing on the aggressiveness of measures that are to be taken, particularly assisted ventilation or resuscitation (Krakow, 2015). Especially perinatal lethality is high in the group of more than 450 skeletal dysplasias described thus far (Milks et al., 2017). As exemplified by our case presented here, antenatal history is often unremarkable, leading to a delay in the establishment of a molecular genetic diagnosis and consequently to a delay in the application of potential clinical care strategies. Considering the need for a multidisciplinary approach, Krakow devises a scheme of management in newborns with

skeletal dysplasia, discerning between cases with a positive family history and those where suspicion first arises in the prenatal or immediate newborn period (Krakow, 2015). Having performed a full skeletal survey with a genetic focus in these latter cases, *BMPER* mutations leading to DSD should be part of the differential diagnoses, even if not included in many laboratories' skeletal dysplasia panels. As in our case, whole exome sequencing can be a helpful diagnostic step especially given that clinical phenotypes of DSD are various, resulting in implications for care and genetic counseling of affected families. Predictions on survival and quality of life are hard to make due to the differing clinical courses and the rarity of cases.

Our overall clinical findings support the combination of clinical features already linked to bi-allelic *BMPER* mutations leading to DSD and moreover add atypical configuration of the bronchi and the Truncus brachiocephalicus (leading to compression of the trachea) and porus of the ear lobe to the list of clinical symptoms, thus extending the current phenotypical spectrum of this disease. In our case, a homozygous nonsense mutation results in a high severity of disease manifestation. A review of the literature, encompassing cases with both DSD and ISD, indicates that there is no clear genotype-phenotype-correlation: for instance the stop codon mutation c.925C>T (p.Gln309*) leads to DSD, while the closely located stop codon mutation c.942G>A (p.Trp314*) leads to ISD. One might speculate that in one case a loss of protein function by nonsense-mediated decay of the mutant RNA occurs, while an early truncation of protein translation leads to a reduction of protein function in the other. However, functional studies on patient derived material would be needed to prove this hypothesis. In addition, the already broad spectrum of ethnic origin of *BMPER*-patients is now expanded by a case of Lebanese Arab origin, further hinting toward a worldwide prevalence of bi-allelic *BMPER* mutations. Due to the low prevalence and limited data, a prognosis on life expectancy is difficult to make, but areas of interest for close care and regular attention, as respiratory support, nephrologic surveillance and orthopedic consultation, can be identified.

6 | CONCLUSIONS

- Our case extends the mutational spectrum of *BMPER* leading to DSD.
- Our case adds further symptoms to the list of clinical findings associated with bi-allelic mutations of this gene.
- The phenotypical characteristics described in our case further support the differentiation between DSD and ISD and add characteristics that help to exclude other differential diagnoses of skeletal dysplasias.
- A comparison with cases already described in the literature suggests that a clear genotype-phenotype-correlation does not exist and that *BMPER* mutations have a worldwide prevalence, although they are extremely rare.
- To further deepen the understanding of selective organ vulnerability in *BMPER*-patients further functional studies are needed.

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The patient´s parents kindly consented to the publication of the given data along with photographs of their child, which might make it identifiable, but would help portray phenotypical characteristics.

DISCLOSURE

The authors declare that there are no conflicts of interest.

AUTHOR'S CONTRIBUTIONS

FB, AR, and US conceptualized and designed the study; FB drafted the original manuscript; PS and TBH performed the genetic testing, interpreted the genetic data, contributed to and substantially revised the manuscript; FB and BS collected and interpreted clinical data, prepared visualizations; AR and US supervised the study. FB, AG, PS, TBH, BS, AR, and US reviewed the data, commented on and critically revised the manuscript. All authors approved the final version of the manuscript to be published and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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