CLINICAL REPORT

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A Compound Heterozygote *SLC26A2* Mutation Resulting in Robin Sequence, Mild Limbs Shortness, Accelerated Carpal Ossification, and Multiple Epiphysial Dysplasia in Two Brazilian Sisters. A New Intermediate Phenotype Between Diastrophic Dysplasia and Recessive Multiple Epiphyseal Dysplasia

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Mutations in solute carrier family 26 (sulfate transporter), member 2 (*SLC26A2*) gene result in a spectrum of autosomal recessive chondrodysplasias that range from the mildest recessive form of multiple epiphysial dysplasia (rMED) through the most common diastrophic dysplasia (DTD) to lethal atelosteogenesis type II and achondrogenesis IB. The clinical variability has been ascribed to quantitative effect of mutations of the sulfate transporter activity. Here we describe two Brazilian sisters, born to healthy and non consanguineous parents, with Robin sequence, mild shortening of upper and lower limbs, brachymetacarpalia/tarsalia, additional and accelerated carpal ossification, marked *genu valgum*, and multiple epiphysial dysplasia. This phenotype was intermediate between DTD and rMED, and both girls have a compound heterozygous mutations for the *SLC26A2*, a Finnish founder mutation (c.−26 + 2T>C), and R279W. This combination of mutations has been observed in individuals with different phenotypes, including DTD, DTD variant, and rMED. The distinct phenotype of our cases reinforces the hypothesis that other factors may be influencing the phenotype as previously suggested.

Key words: *SLC26A2* gene; diastrophic dysplasia; recessive multiple epiphyseal dysplasia; Robin sequence

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INTRODUCTION

Mutations in *SLC26A2* gene result in a continuum clinical spectrum of autosomal recessive chondrodysplasias that include, in increasing order of severity, the lethal achondrogenesis type IB (ACG-1B; OMIM 600972) and atelosteogenesis type II (AO-II; OMIM 256050); the diastrophic dysplasia (DTD; OMIM 222600) and the recessive multiple epiphyseal dysplasia (rMED; OMIM 226900). Affected individuals with a more mildly DTD phenotype

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have been described and they have been classified as DTD variant or as intermediate phenotype between DTD and rMED [Horton et al., 1978; Czarny-Ratajczak et al., 2010; Dwyer et al., 2010; Barbosa et al., 2011]. Other cases with phenotypic DTD variant, secondary to mutations in *SLC26A2*, overlapping to Desbuquois dysplasia [OMIM 251450], were described and suggested a locus heterogeneity for Desbuquois dysplasia [Miyake et al., 2008; Panzer et al., 2008].

The severity of the phenotypes related to *SLC26A2* mutation has been correlated with the residual activity of sulfate transporter resulting of the different types of mutations [Hästbacka et al., 1996; Karniski, 2001; Rossi and Superti-Furga, 2001]. Literature data have shown that homozygous for null mutation lead to phenotype of ACG-1B [Karniski, 2001; Rossi and Superti-Furga, 2001]; that compound heterozygous to a null mutation and to a mutation with some residual activity can result in AO-II, DTD or DTD variant [Hästbacka et al., 1996, 1999; Karniski, 2001; Rossi and Superti-Furga, 2001; Maeda et al., 2006; Czarny-Ratajczak et al., 2010; Dwyer et al., 2010; Barbosa et al., 2011], and that homozygous or compound heterozygous mutations with significant residual activity ("mild" mutations) result in rMED [Superti-Furga et al., 1999; Karniski, 2001; Ballhausen et al., 2003; Mäkitie et al., 2003; Cho et al., 2010; Hinrichs et al., 2010; Barbosa et al., 2011]. It has also been showed that the "Finnish founder mutation" (c.−26 + 2T>C) acts by severely reduced mRNA levels, but not abolish gene function completely [Hästbacka et al., 1999] and, that the homozygosis or compound heterozygosity for this mutation can result in variable phenotypes that include AO-II, DTD, DTD variant or rMED [Hästbacka et al., 1999; Ballhausen et al., 2003; Dwyer et al., 2010]. Here we describe two Brazilian sisters with a compound heterozygous mutation for Finnish founder mutation and for R279W, resulting in a phenotype intermediate between DTD and rMED. Clinical and molecular aspects were discussed.

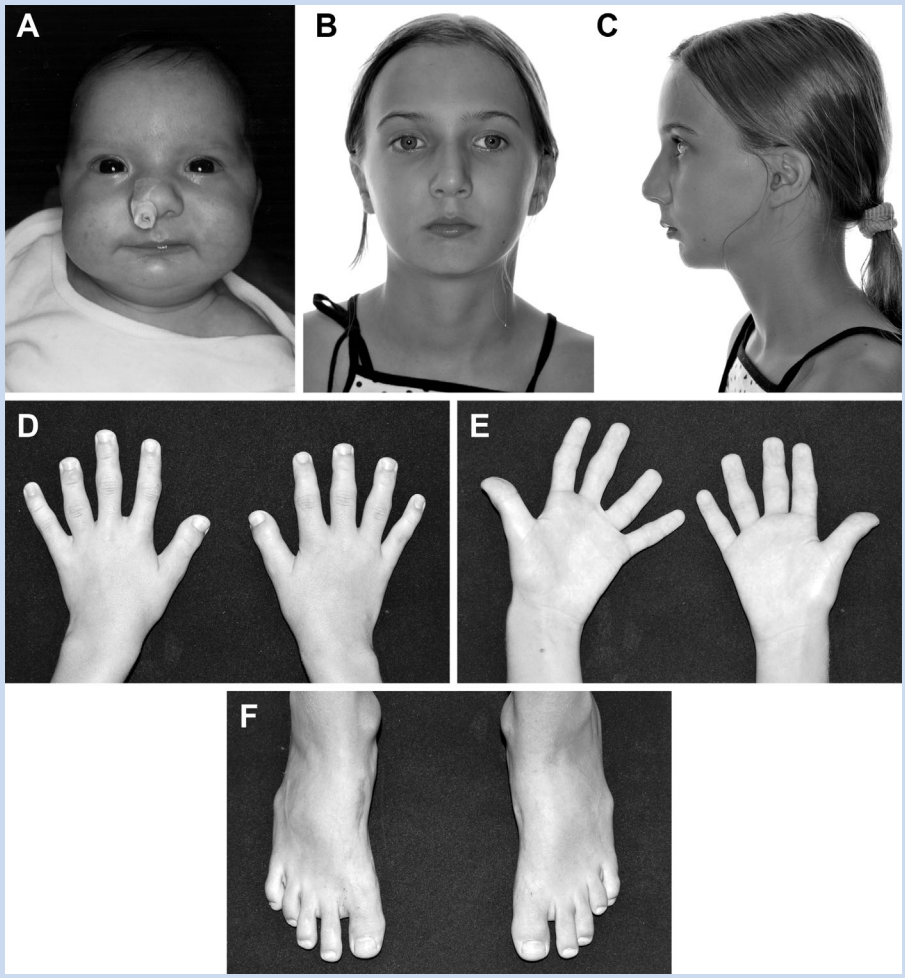

FIG. 1. Clinical features of the Patient 1. A: Frontal view at age 46 days. Note broad nasal root. B–C: Frontal and lateral view of the face at age 10 years. Note Robin facial appearance with mild micrognathia. D–E: Hands of the Patient 1 at age 10 years. Note: Brachydactyly, prominent interphalangeal joints, and poor hypothenar musculature. F: Feet of the Patient 1 at age 10 years. Note broad forefeet with abnormal position and marked brachydactyly of 4th and 5th toes.

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Patient 1

Patient 1 (Fig. 1A–F), a female, born in 1999, was the first child of healthy and nonconsanguineous Brazilian parents. The mother's and father's age at conception were 26 and 25 years, respectively. The unrelated parents were from different regions from Brazil; however both had German ancestors. The pregnancy was uncomplicated and without exposure to teratogenic factors. She was born at pre-term (8 months) with weight of 2,550 g (25th centile) and length of 46 cm (3rd centile). Cleft palate and respiratory difficulties were noted at birth. A second child, a boy, was referred as having an imperforate anus and neurogenic bladder. Unfortunately, this boy was not seen at the Hospital for Rehabilitation of Craniofacial Anomalies (HRCA-USP) and there were no additional data. A third child of the couple, a girl (Patient 2), presented the same picture of her oldest sister.

Patient 1 was first seen at Genetics Clinic of HRCA-USP when she was 46 days. At this time her length was 4,100 g (25th centile); weight was 51 cm (3rd centile), and head circumference was 36 cm (25th–50th centile). She presented with mild shortening of the upper and lower limbs, a relatively long trunk, short palpebral fissures, broad nasal root, Robin sequence (mild micrognathia, U-shaped cleft palate, and glossoptosis), mild posteriorly rotated ears, broad left helix, and mildly proximally placed thumbs. Development was normal. Respiratory and feeding difficulties were observed. The nasopharyngoscopy performed showed upper airway obstruction type 1, which was relieved after nasopharyngeal intubation. Ophthalmologic evaluation was normal. The follow-up showed worsening of the skeletal phenotype. From the 2 years she began to have difficulty in walking due to progressive Achilles tendon shortening and bilateral forefoot adduction. Despite surgical repair of the feet, the outcome was poor.

In the re-evaluation at 10 years her height was 135 cm (25th–50th centile), weight was 28.2 kg (25th centile), head circumference was 52.5 cm (50th centile), span was 121 cm, and upper/lower segment ratio was 1.08. There were some changes in the facial phenotype with high nasal bridge, mild flattened midface, and mild micrognathia. Cystic change of external ears was not observed. She was an intelligent and a very well adjusted girl. The skeletal phenotype worsened with the enlargement of elbow, wrist, digits, and knee joints. Brachydactyly is remarkable in the left 4th finger, with prominent interphalangeal joints and small nails. The palmar creases were decreased and there was a poor hypothenar musculature. Marked *genu valgum* was observed. The feet were large and abnormally positioned with marked brachydactyly of 4th and 5th toes. She had severe joint pain that worsened at night.

Radiological assessment at ages 10 and 12 years showed apparently shortness of the arm bones, dysplasic proximal and distal metaphyses of the humerus, subluxation of the radial head, dys-

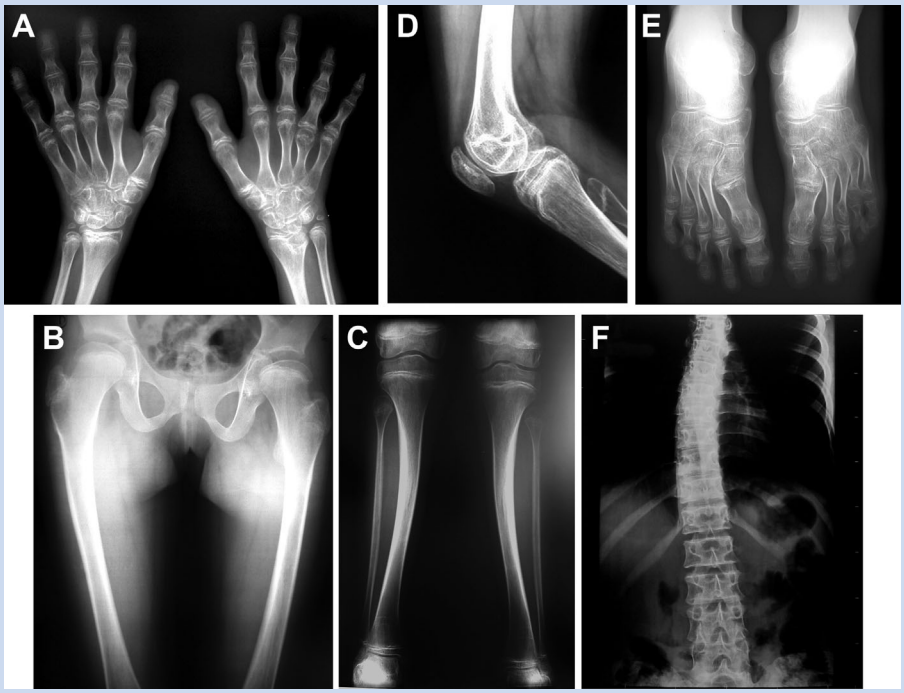

FIG. 2. Radiograph of the Patient 1 at ages 10 and 12 years. A: Hands at age 10 years: extra carpal bones with an accelerated ossification and marked shortening of the 4th metacarpal at left. B: Pelvis at age 12 years: irregularly and flatness of femoral capital epiphyses; short and broad femoral neck. C: Lower limbs at age 10 years: *genu valgum*; moderated tibial diaphyseal bowing; short proximal and end of fibulae. D: Lateral view of the knees: absence of double layered patella. E: Spine at age 12 years: scoliosis. F: Feet at age 10 years: dysplasic tarsal bones with irregular contours; short metatarsal bones; short and flattened phalanges.

plasic distal metaphyses and epiphysis of the radius and ulna, dysplastic irregularities of contour of all carpal bones, and an extra carpal bone with accelerated ossification over the distal ulnar epiphysis. Metacarpals were short (mainly the 4th at left) with distal flattened epiphyses. The phalanges were short and flattened. The epiphyses of the phalanges were markedly flattened and there were an irregular contour of the proximal epiphyses. The epiphyses of the middle phalanges were absent and the growth centers of phalangeal epiphysis were not visualized (Fig. 2A). Radiographic of pelvis and lower limbs (Fig. 2B–C) showed *genu valgum* with irregularly and flatness of femoral capital epiphyses, short and broad femoral neck, mild irregular acetabula bilaterally, mild flat and dysplastic distal femoral and proximal tibial epiphyses, moderated tibial diaphyseal bowing, and short proximal and end terminal fibulae. A lateral X-ray of the knees did not showed double-layers patellae (Fig. 2D). Tarsal bones were dysplastic with irregular contours. The metatarsal bones were short (mainly the left 4th) with tibial deviation, the phalanges were short, flattened and there were a premature closure of growth centers in all phalanges (Fig. 2E). Vertebral bones mainly in the thoracic region showed scoliosis (Fig. 2F).

Cytogenetic study was normal. Due to the clinical and radiological findings similarity with the unrelated patients reported by Lowry et al. [1996], the diagnosis of multiple epiphyseal dysplasia with rhizomelic shortness, cleft palate, and micrognathia was initially done. Subsequently, the birth of a sister with similar phenotype, who also presented cyst in the ear, led us to reconsider the diagnosis. Molecular analysis of *SLC26A2* gene was performed.

Patient 2

Patient 2 (Fig. 3A–E), a female, born in 2010, was the younger sister of the Patient 1. The mother's and father's age at conception were 36 and 35 years, respectively. The pregnancy was uncomplicated,

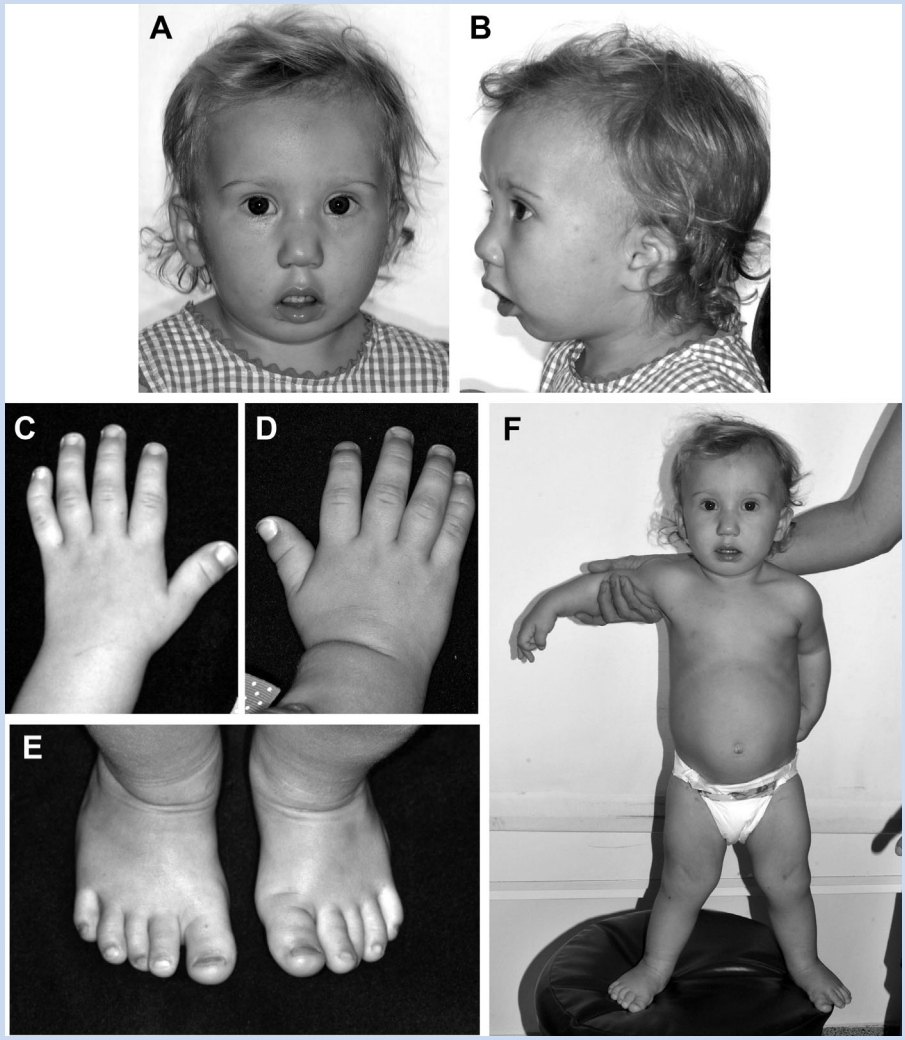

FIG. 3. Clinical features of the Patient 2 at age 15 months. A–B: frontal and lateral view of the face. C: Hands. D: Feet. E: Anterior view showing long trunk and short upper and lower limbs.

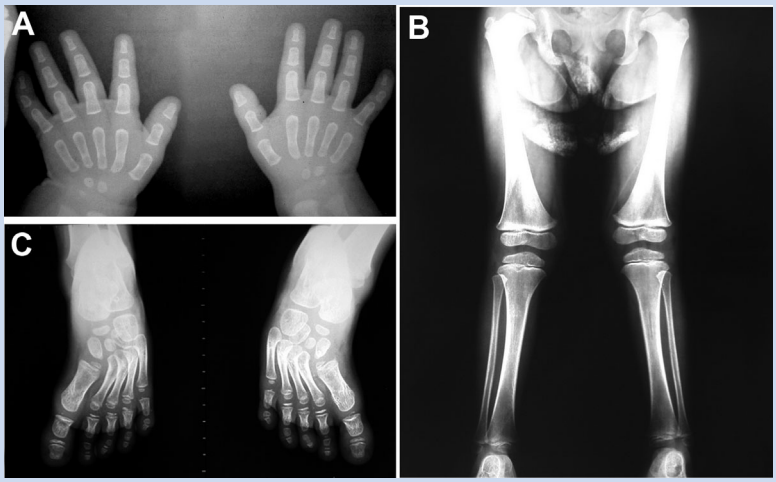

FIG. 4. Radiograph of the Patient 2 at ages 15 months and $2\frac{5}{12}$ years. A: Hands at age 15 months: advanced carpal ossification and hypoplasia of the middle phalanges of 5th fingers. B: Pelvis and lower limbs at age $2\frac{5}{12}$ years: short femur with hypoplasia of femoral capital epiphyses, broad distal metaphyses, and flattened of distal epiphyses; shortness of tibia with wide proximal and distal metaphyses and flattened proximal epiphyses; and short fibulae. C: Feet at age $2\frac{5}{12}$ years: metatarsals with tibial deviation and short phalanges.

without exposure to teratogenic factors. She was born at term with birth weight of 3,850 g (>75th centile). Birth length and head circumference was not recorded. Cleft palate and mild feeding difficulties were present at birth. Cystic swelling in the left ears was noted after the first month of life.

She was first seen at the Clinical Genetics of HRCA-USP when she was 3 months. She had length of 4,600 g (10th centile); weight of 55 cm (3rd centile), and head circumference of 40 cm (50th centile). The clinical features were very similar of those observed in her oldest sister, including mild shortening of the upper and lower limbs, a relatively long trunk, short palpebral fissures, broad nasal base, Robin sequence (mild micrognathia, U-shaped cleft palate, and glossoptosis), mild posteriorly rotated ears, broad helices, short hands with ulnar deviation, and mildly proximally placed thumbs. In addition, she had a mild cystic swelling on the left external ear. Cytogenetic study was normal.

Re-evaluation at $2\frac{5}{12}$ years showed height of 88.5 cm (25th centiles) and weight of 11.9 kg (10th centile). The development was normal. Radiographic evaluation at ages 15 months and $2\frac{5}{12}$ years showed dysplasic proximal metaphyses of the humerus; absence/hypoplasia of the distal and proximal ossification center of the radium; dysplastic irregularities of the contour of all carpal bones with accelerated ossification; mild shortness of metacarpals; hypoplasia and clinodactyly of middle phalanges of 5th finger, absence of the ossification center of the proximal and medial phalanges of the fingers (Fig. 4A); short femur with hypoplasia of femoral capital epiphyses, broad distal metaphyses and flattened of distal epiphyses; shortness of tibia with wide proximal and distal metaphyses and flattened of proximal epiphyses; short fibulae (Fig. 4B); metatarsals with tibial deviation and short phalanges (Fig. 4C).

Molecular Studies

Screening of mutation in *SLC26A2* gene was performed. Direct sequencing of the all three exons of the *SLC26A2* gene and the corresponding exon/intron boundaries showed mutations in two copies of *SLC26A2* gene in both patients. One mutation was the common "founder Finnish mutation" c.−26 + 2T>C and the other was previously reported mutation c.862C>T (R279W). Analysis of the *SLC26A2* gene in patient's mother showed that she was heterozygote to c.−26 + 2T>C. The father's and brother's DNAs were not available.

DISCUSSION

The sisters here described had a compound heterozygous *SLC26A2* mutation, c.−26 + 2T>C and R279W, resulting in a distinct phenotype characterized by Robin sequence, mild upper and lower limb shortness, brachydactyly, accelerated carpal ossification, metaepiphyseal dysplasia, *genu valgum*, and feet anomalies. Homozigous or compound heterozygous mutations in *SLC26A2* gene cause a continuum spectrum of phenotypes that ranges to the most severe and lethal ACG-1B and AO-II [Hästbacka et al., 1996; Superti-Furga et al., 1996; Dwyer et al., 2010] through the most common DTD [Hästbacka et al., 1994, 1999; Barbosa et al., 2011] to mildest rMED phenotype [Ballhausen et al., 2003; Mäkitie et al., 2003; Hinrichs et al., 2010; Barbosa et al., 2011]. The classical DTD phenotype is characterized by short-limbed dwarfism at birth, cleft palate, cystic ear swellings, small chest, large joint contractures, hitchhiker thumbs, methaphyseal widening, progressive epiphyseal abnormalities (mainly flattening and fragmentation), radius dislocation, deformed tarsal and carpal bones, advanced carpal ossifica-

tion centers, progressive scoliosis, and clubfeet [Rossi and Superti-Furga, 2001; Castriota-Scanderbeg and Dellapiccola, 2005; Barbosa et al., 2011]. rMED phenotype included normal or mild short stature, mild brachydactyly, club foot, epiphyseal dysplasia, flattening of proximal femoral epiphyses, double layered patella, and joint pain [Superti-Furga et al., 1999; Ballhausen et al., 2003; Mäkitie et al., 2003; Cho et al., 2010; Hinrichs et al., 2010; Barbosa et al., 2011]. Typical signs of both conditions were present in these patients. As observed in rMED cases, the stature of the patients was within normal average range (25–50th centile) while DTD's patient were very short (<3rd centile). Concerning the skeletal anomalies, the patients reported here were less severe when compared with DTD's patients, and more severe than those with rMED. Double layered patella, a specific diagnostic indicator for rMED [Mäkitie et al., 2003; Lachman et al., 2005], was not observed in Patient 1. In Patient 2, the patella ossification had not yet occurred. The cleft palate, present in both sisters, occur in about 35-37% of DTD patients [Horton et al., 1978; Barbosa et al., 2011] and in few cases with rMED [Ballhausen et al., 2003; Barbosa et al., 2011]. The cleft palate as part of Robin sequence, like here has also been described in DTD [revised by Cohen, 1999]. The phenotype of our patients fit between DTD and rMED; however, the whole picture clearly differs from the others observed in previously published cases as having intermediary phenotypes between these conditions, including the continuous spectrum of *SLC26A2*-related dysplasia [Horton et al., 1978; Miyake et al., 2008; Czarny-Ratajczak et al., 2010; Dwyer et al., 2010; Barbosa et al., 2011]. The present patients have a compound heterozygous mutation in *SLC26A2* gene that includes the two most common mutations: the "Finnish mutation" (c.−26 + 2T>C) and the missense mutation R279W (c.862C>T). Residual sulfate transport function studies show that the R279W allele produces ∼50% activity of the wild-type *SLC26A2*, resulting in phenotype of rMed, when in homozygosis, and in DTD or DTD variant, when in compound heterozygosis [Superti-Furga et al., 1999; Rossi and Superti-Furga, 2001; Barbosa et al., 2011]. The c.−26 + 2T>C mutation produce low levels of correct spliced mRNA and result in DTD when homozygous [Karniski, 2001; Rossi and Superti-Furga, 2001]. The combination of c.−26 + 2T>C and R279W mutations, as observed, has been previously reported in individuals with DTD, rMED, and DTD variant phenotypes. Hästbacka et al. [1999] observed the same combination of mutations in seven patients with typical clinical and radiological findings of DTD while Ballhausen et al. [2003] observed in one patient with typical rMed. On the other hand Dwyer et al. [2010] described two siblings with both mutations which had a DTD variant phenotype, consisting of short stature, typical DTD facial aspects, moderate shortening of upper and lower limbs, brachydactyly, and clubfeet. In the patients herein, findings such as normal stature, absence of typical DTD facial aspects, and skeletal phenotype worsening clearly differentiate them from those described by Dwyer et al. [2010]. According to some authors the phenotypic variability related to the same mutation indicates that factors other than sulfatase transport activity can influence disease severity [Karniski, 2001; Dwyer et al., 2010]. The distinct phenotype of *SLC26A2*-related conditions and the combination of the Finnish and R279W mutations in the patients herein suggest that other factors could also be modifying the phenotype.

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