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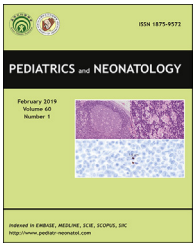

Short Communication

Next-generation sequencing identifies *TRPV4*-related skeletal dysplasia in a boy with progressive bowlegs

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1. Introduction

Angular deformities of the lower limbs are common during childhood. In children under 2 years of age, bowleg (genu varum) may represent a normal physiological process. In certain circumstances, pathologic bowlegs result from Blount disease, rickets and other metabolic bone diseases, skeletal dysplasia, asymmetric growth secondary to infection, trauma and neoplasia even in a child without a family history.[1]

Skeletal dysplasias form a large group of disorders with genetic and clinical heterogeneity.[2] Given the complex phenotypes and individual variations, identifying the precise genetic defect is laborious through traditional Sanger sequencing. Alternatively, next-generation sequencing (NGS) is a cost-effective and beneficial method to diagnose patients with skeletal dysplasia and provide data relevant to prognosis and future therapeutic intervention.[3] Here, we report the usefulness of molecular analysis with NGS for diagnosis of skeletal dysplasia in a patient with a non-classical phenotype.

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2. Case report

A six-year-old boy was referred to the genetic outpatient clinic due to progressive bowlegs since birth. His body weight, body height and head circumference were within normal range at birth. The family history was non-contributory. The parents exhibited above average height relative compared with the general population (father 183 cm, mother 172 cm). On physical examination, the boy was 115 cm (25th-50th percentile) and 25.1 kg (75th-90th percentile). He had prominent upper incisors, a thin upper lip, relatively short limbs, lumbar lordosis and bowlegs. The remainder of the examination was normal.

Laboratory examinations did not reveal vitamin D metabolism defects (intact parathyroid hormone (iPTH) 25.7 pg/dl with a reference range of 12—65 pg/dl, calcium 2.4 mmol/L with a reference range of 2.15—2.58 mmol/L, phosphorus 6.0 mg/dl with a reference range of 2.5—5 mg/dl, alkaline phosphatase 235 U/L with a reference range of 145—420 U/L, and 25-hydroxyvitamin D (25OHD) 28.2 ng/ml with a reference range of 20—50 ng/ml). X-ray of the spine revealed flattened vertebra especially at the thoracic spine (T-spine), increased spinal kyphosis at the junction of the thoracic and lumbar spine (T-L spine), wide ribs and squared bilateral iliac wings (Fig. 1(a) and (b)). Plain films of the lower extremities revealed osteopenia, scoliosis of the spine, horizontal acetabular roofs and irregular capital femoral epiphyses on both sides, metaphyseal flaring and bowing deformity of the bilateral tibial shafts (Fig. 1(c) and (d)). The lumbar spine (L1—L4) bone mineral density was within the normal range (0.464 g/cm^2; Z score −0.86). A mucopolysaccharidosis (MPS) screen for urine glycosaminoglycans (GAGs) as well as the leukocyte MPS IV enzyme assay were normal. Sanger sequencing of the *PHEX* gene, which results in X-linked dominant hypophosphatemic rickets, did not reveal pathogenic variants. The NGS panel for skeletal dysplasia, including 54 genes for collagenopathies and related skeletal dysplasias selected from OMIM,[4] revealed a *de novo* heterozygous *TRPV4* c.1781G > A (p.Arg594His) mutation (Fig. 1(e) and (f)). This mutation was not present in general population database (The Exome Aggregation Consortium; ExAC) and was predicted to be deleterious and damaging by SIFT (score = 0.0) and PolyPhen-2 (HVAR score = 0.999) for functional prediction. This variant was further confirmed by Sanger sequencing and was reported in patients with spondylometaphyseal dysplasia of the Kozlowski type.[5]

3. Discussion

TRPV4-associated disorders are a group of inherited disorders with various clinical presentations and are mainly involved in neuromuscular disorders and skeletal dysplasias. Individuals with *TRPV4* mutations may have an

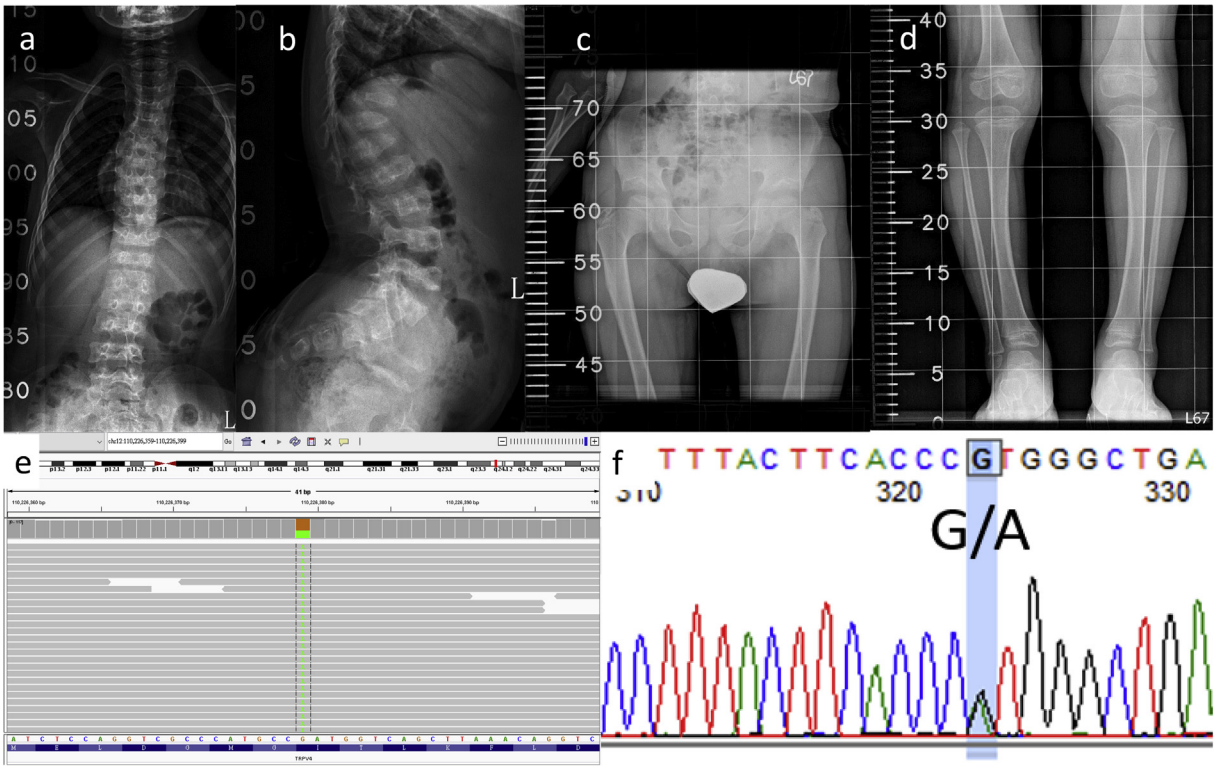

Figure 1 Radiological and molecular evaluation of the patient. Whole spine (a) PA and (b) lateral views depicting flattened vertebra, especially at the T-spine; increased spinal kyphosis at the junction of the T-L spine; widened ribs; and squared bilateral iliac wings. Plain films of the lower extremities (c) and (d) revealing osteopenia, horizontal acetabular roofs and irregular capital femoral epiphyses on both sides, metaphyseal flaring, and bowing deformity of the bilateral tibial shafts. Integrative Genomics Viewer (IGV) screen shot of the *TRPV4* gene depicting the c.1781G > A (p.Arg594His) mutation (e), as further confirmed by Sanger sequencing (f).

affected parent with autosomal dominant transmission or exhibit a *de novo* pathogenic variant. The diagnoses are based on clinical and neurophysiological findings, radiographic findings, and the identification of a heterozygous *TRPV4* pathogenic variant. *TRPV4*-associated skeletal dysplasias form a phenocontinuum of overlapping disorders ranging from mild to severe, each with the characteristics of short stature, progressive spinal deformity, and at least one additional distinctive feature (e.g., brachydactyly, metaphyseal changes, genu varum, or irregular acetabulae).[6] Our case fits the clinical diagnosis of spondylometaphyseal dysplasia of the Kozlowski type, an intermediate form of *TRPV4*-associated skeletal dysplasia.[5] The condition is characterized by short trunk and short stature, although the chest is broader than in some more severe forms. Birth length is average. Clinicians typically identify affected children in early childhood when poor growth with disproportionate stature and a waddling gait with genu varum become evident. Premature osteoarthritis is common. Management includes physical therapy, exercise, possible orthopedic intervention, and symptomatic treatment for pain and depression with a multidisciplinary team, including orthopedic surgeons, neurologist, physiatrists, and physical and occupational therapists.[7]

The phenotype of the patient was rather mild. However, the parents were very tall, and he did not meet his target height. This finding further emphasized the spectrum of the disease and indicated that the phenotype of the patient might be influenced by other modifying genes from his parents. The patient revealed no short stature, indicating that short stature may not always be apparent given the effects of parental height. Thus, if the height of a child with bowlegs is relatively short compared with the parental height, prompt assessment is still necessary.

In conclusion, bowlegs in children should always raise suspicion for pathological causes, even in the absence of short stature. In addition to clinical, biochemical and radiographic features, molecular analysis with NGS facilitates an accurate diagnosis and is beneficial for further management and care.

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