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Early Childhood Presentation of Czech Dysplasia

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Abstract

Czech dysplasia, metatarsal type is an autosomal dominant skeletal disorder that is characterized by early-onset, progressive arthritis, brachydactyly of the 3rd and 4th toes, and characteristic radiographic findings in patients of normal stature. Patients with Czech dysplasia typically present in late childhood or later. In the present report, whole exome sequencing identified a mutation in *COL2A1* (c.823C>T, p.R275C) known to be associated with Czech dysplasia in a 3.5 year old female who had a family history of early-onset arthritis and who was asymptomatic except for prominent knees. The use of whole exome sequencing facilitated diagnosis of this rare disease (less than 15 families in the literature) in the presymptomatic period and thus enabled us to provide early anticipatory guidance and genetic counseling for the family.

Keywords

Czech dysplasia; skeletal dysplasia; prominent knees; early-onset osteoarthritis; Depressed nasal bridge; Brachydactyly of 3rd and 4th toes; Normal stature; Early-onset arthritis

INTRODUCTION

Czech dysplasia is a rare autosomal dominant type II collagenopathy associated with early-onset, progressive arthritis often requiring joint replacement as early as the 2nd or 3rd decade, brachydactyly of the 3rd and 4th toes, and platyspondyly with irregular endplates and Schmorl's nodes on skeletal radiographs (Bleasel *et al.*, 1995, Bleasel *et al.*, 1996, Carlson *et al.*, 2006, Hoornaert *et al.*, 2006, Hoornaert *et al.*, 2007, Kozlowski *et al.*, 2004, Lopponen *et al.*, 2004, Marik *et al.*, 2004, Matsui *et al.*, 2009, Reginato *et al.*, 1994, Tzschach *et al.*, 2008, Williams *et al.*, 1993). Other radiographic findings include: short metacarpals and metatarsals, reduced intervertebral distances, and osteochondromatosis. Patients typically present with joint pain and progressive arthritis in the setting of family history of similar presentation. Fewer than 15 families with this condition have been reported in the literature (see references above), and only two other patients less than 4 years of age has been described. These patients, an asymptomatic 2 year old with platyspondyly and a 3 year old

with only prominent knees, were diagnosed as part of large pedigrees affected by the condition (Reginato *et al.*, 1994, Tzschach *et al.*, 2008). The majority of the reported patients are in their second decade or beyond.

The present case is only the third clinical report of a child less than 4 years old diagnosed with Czech dysplasia. Like the previous toddlers, our 3.5 year old patient was asymptomatic except for prominent knees, and her family history was consistent with an autosomal dominant form of early-onset osteoarthritis. However, brachydactyly of the 3rd and 4th toes, a characteristic finding of the disorder, was not evident in the patient or her mother, and the diagnosis in the child was made by whole exome sequencing.

INVESTIGATIONS

Clinical study

Study subjects were enrolled in our skeletal dysplasia study according to the Baylor College of Medicine's Institutional Review Board. Informed consent was obtained specifically for whole exome sequencing and the publication of medical information.

Clinical report

The proband was born full term by caesarian section because of her mother's history of bilateral hip replacements. Per parental report, she had a history of gastroesophageal reflux during infancy that improved. At 2.5 years of age, she presented to the skeletal dysplasia clinic because her prominent knees were similar to other family members with early osteoarthritis. Otherwise, the proband was asymptomatic and had no joint pain or stiffness. Her development was normal and her vision and hearing were normal although she had no formal hearing evaluation. On physical exam, her weight was at the 91st percentile and height was at the 64th percentile. Apart from prominent knees bilaterally and a depressed nasal bridge, her exam was unremarkable (Figure 1). Specifically, she had no brachydactyly (Figure 1). A skeletal survey revealed flattening of the distal femoral and the proximal and distal tibial epiphyses. In addition, there was generalized shortening of the metacarpals and metatarsals with short and broad proximal phalanges of bilateral hands and feet (Figure 2). In particular, the first metatarsal and the phalanges of the great toe were quite broad. Her spine was normal (Figure 2). She presented for follow-up at 3.5 years of age. At that time, she still had no joint pain or joint stiffness, and since no clinical diagnosis was obvious, testing by whole exome sequencing was attempted. At a second follow-up visit at 4.5 years of age, her mother reported that the proband was starting to exhibit signs of joint stiffness but still had no complaints of joint pain.

The family history was remarkable for multiple maternal family members across four generations with symptoms of early-onset arthritis and who were diagnosed with a nonspecific "epiphyseal dysplasia". The proband's mother had a history of degenerative joint disease requiring hip replacements between 11 and 13 years of age. At approximately 24 years of age, she also required bilateral knee replacements. At the age of 31 years, the mother reported significant pain in her neck, shoulders, arms, elbows, hands, hips, knees, and feet that negatively impacts her activities of daily living. Multiple other maternal family members (see pedigree, Figure 1) had similar symptoms and the early onset arthritis phenotype appeared to segregate as an autosomal dominant trait in this family. There was no history of joint problems in the paternal side of the family. Mother described the maternal family ancestry as Cajun. Skeletal radiographs on the mother revealed joint space loss in the hands and feet, wide first metatarsal and phalanges in the great toe, an osteochondroma in the shoulder, and playspondyly and Schmorl's nodes in the spine (Figure 2). On exam of the proband's mother, brachydactyly was not present.

Whole exome sequencing

DNA was extracted from peripheral blood monocytes and precipitated for collection. Whole exome sequencing (WES) was performed using capture reagents developed at the Baylor College of Medicine Human Genome Sequencing Center (BCM-HGSC) and made available by Nimblegen (<http://www.nimblegen.com/products/seqcap/ez/designs/index.html>). Sequencing was conducted on Illumina HiSeq2000. Alignment, filtering and analysis was performed as described previously (Campeau *et al.*, 2012). The *COL2A1* missense mutation was selected because it was known to cause a skeletal disorder with similarities to our subject and her mother's phenotype.

Sanger sequencing

Polymerase chain reaction primers were designed to amplify the *COL2A1* mutation and PCR products were generated using 1 ng/microliter of genomic DNA with TaqMan polymerase (ABI, Life Technologies, Carlsbad, CA) using the manufacturer's protocol with an annealing temperature of 50 °C and an amplification time of 1 minute. Primers used were 5'-AAGGAGGGAAGCCCTCTG-3' and 5'-GTGCTTTTCTCTCCACCAG-3'. Products were verified by agarose gel then sequenced by chain-termination (Sanger) sequencing using the same primers at Beckman Coulter Genomics.

RESULTS

Identification of mutation

Because of the unusual presentation and the lack of a clear indication of a causative gene, we opted for diagnosis by whole exome sequencing. A *COL2A1* mutation (c.823C>T, p.R275C) known to be associated with Czech dysplasia was selected as the most likely cause for the phenotype and was confirmed by Sanger sequencing in individuals IV-6 and V-1 (Figure 1).

DISCUSSION

Broad or prominent knees are the most common presenting sign or symptom of Czech dysplasia in very young children (Marik *et al.*, 2004, Matsui *et al.*, 2009, Tzschach *et al.*, 2008). A depressed nasal bridge is also a common, but non-specific, early feature of this condition (Matsui *et al.*, 2009, Tzschach *et al.*, 2008). Toddlers with Czech Dysplasia may not have joint pain or stiffness (Matsui *et al.*, 2009, Reginato *et al.*, 1994, Tzschach *et al.*, 2008) (Table 1). Thus, the diagnosis of Czech dysplasia based on history and physical examination is challenging in early childhood. However, skeletal radiographs showing platyspondyly and shortened metatarsals and metacarpals may provide clues to the diagnosis. In addition, the wide metatarsal and phalanges in the great toes, which was seen on both the proband and the mother's radiographs, has been previously reported in one other patient (Hoornaert *et al.*, 2007) and may provide another diagnostic clue.

The *COL2A1* c.823C>T mutation results in an arginine to cysteine substitution in type II collagen and appears to be recurrent since it has been observed in patients from a variety of ethnic groups (Hoornaert *et al.*, 2007, Kozlowski *et al.*, 2004). To our knowledge, this is the first Cajun patient described with this condition.

In the present case, with the atypical presentation of the mother (lack of brachydactyly of her 3rd and 4th toes) and the young age of the proband, a diagnosis was not obvious. Thus, the identification of the c.823C>T mutation in this patient by whole exome sequencing highlights the utility of whole exome sequencing in the diagnosis of rare diseases like Czech dysplasia at early stages of presentation or in the setting of an atypical presentation.

Early diagnosis allows for anticipatory guidance regarding the diagnosis (eg. avoidance of high impact sports that could accelerate joint damage), early screening (eg. hearing screen), and genetic counseling for the family.

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A**Legend**

● = Affected by early-onset arthritis

* = DNA available

E+ = Tested positive for *COL2A1* mutation **B**

C **D**

Figure 1.

A) Pedigree of the family described. B) Sanger sequencing results show that both the proband and her mother are heterozygous for the *COL2A1* c.823C>T mutation C) Photographs of the patient, demonstrating enlarged knees and unremarkable feet, as was the case for her mother's feet (D).

Figure 2.

Radiographs of the hands (A) and feet (B) of the proband show generalized shortening of the metacarpals and metatarsals. The proximal phalanges of the hands and feet are broad and short. The first metatarsal and the phalanges of the great toes are particularly wide. Frontal radiographs of lower extremities (C) demonstrate flattening of the distal femoral and the proximal and distal tibial epiphyses. Frontal and lateral spine radiographs in the proband (D) are normal. Radiographs of the hands (E) and feet (F) in the mother show no evidence of brachydactyly. There is evidence of generalized cartilage loss with joint space narrowing especially in the carpal and tarsal regions. In addition, there is widening of the metatarsal and phalanges of the great toe bilaterally. Frontal and lateral spine radiographs (G) in the mother show platyspondyly and Schmorl's nodes. Frontal radiographs of the right shoulder (H) demonstrate an osteochondroma (arrow).

Table 1
Summary of Clinical and Radiographic Features of Patients 5 Years of Age and Younger with Czech Dysplasia.

Phenotype	Reginato et al., 1994	Tzschach et al., 2008	Present Case	Tzschach et al., 2008	Matsui et al., 2009
Age (years)	2	3	3.5	5	5
Sex	M	F	F	M	M
Height	ND	Normal	Normal	Normal	Normal
Joint pain/stiffness	No	No	No*	No	Yes
Osteoarthritis	No	No	No	No	Unknown
Joint prostheses	No	No	No	No	No
Hearing loss	Unknown	Normal	Normal**	Normal	Yes
Platyspondyly	Yes	ND	No	ND	Yes
Anterior beaking	Yes	ND	No	ND	Unknown
Irregular endplates	Yes	ND	No	ND	Yes
Short metacarpals/metatarsals	Unknown	ND	Yes	ND	Yes
Short 3rd, 4th toes	No	No	No	No	Yes
Broad knees	Unknown	Yes	Yes	Yes	Yes

ND=not determined.

* Joint stiffness appeared after age 4.

** Normal by history, although formal hearing evaluation not yet performed.