CASE REPORT

DOI: 10.4274/jcrpe.galenos.2021.2021.0099

J Clin Res Pediatr Endocrinol 2022;14(4):475-480

A Novel Mutation in the *TRIP11* Gene: Diagnostic Approach from Relatively Common Skeletal Dysplasias to an Extremely Rare Odontochondrodysplasia

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What is already known on this topic?

Most patients with odontochondrodysplasia (ODCD) have a compound heterozygous mutation. ODCD is a rare skeletal dysplasia that is associated with dentinogenesis imperfecta.

What this study adds?

The c.3296_3298delinsTG is a novel pathogenic variant in the *TRIP11* gene, inherited in a compound heterozygous fashion, that led to ODCD. Joint limitation and craniocervical stenosis have not been observed in patients with ODCD to date. In this respect, our patient is the first such case in the literature.

Abstract

Odontochondrodysplasia (ODCD, OMIM #184260) is a rare, non-lethal skeletal dysplasia characterized by involvement of the spine and metaphyseal regions of the long bones, pulmonary hypoplasia, short stature, joint hypermobility, and dentinogenesis imperfecta. ODCD is inherited in an autosomal recessive fashion with an unknown frequency caused by mutations of the thyroid hormone receptor interactor 11 gene (*TRIP11*; OMIM *604505). The *TRIP11* gene encodes the Golgi microtubule-associated protein 210 (GMAP-210), which is an indispensable protein for the function of the Golgi apparatus. Mutations in *TRIP11* also cause achondrogenesis type 1A (ACG1A). Null mutations of *TRIP11* lead to ACG1A, also known as a lethal skeletal dysplasia, while hypomorphic mutations cause ODCD. Here we report a male child diagnosed as ODCD with a novel compound heterozygous mutation who presented with skeletal changes, short stature, dentinogenesis imperfecta, and facial dysmorphism resembling achondroplasia and hypochondroplasia.

Keywords: Odontochondrodysplasia, *TRIP11*, skeletal dysplasia, dentinogenesis imperfecta, rare disease

Introduction

Odontochondrodysplasia (ODCD, OMIM #184260) is a rare, non-lethal skeletal dysplasia characterized by involvement of the spine and metaphyseal regions of the long bones, pulmonary hypoplasia, short stature, joint hypermobility, and dentinogenesis imperfecta (1). Spondylo-metaphyseal dysplasias (SMD) are a group of skeletal dysplasia that includes miscellaneous disorders with vertebral and metaphyseal defects. ODCD is inherited in an autosomal recessive fashion with an unknown frequency and is caused by mutations of the thyroid hormone receptor interactor 11 gene (*TRIP11*; OMIM *604505). Initially, homozygous mutations in *TRIP11* were associated with a lethal skeletal dysplasia, achondrogenesis type 1A (ACG1A, OMIM #200600) associated with severe thorax hypoplasia, hypomineralization of several bones, and short extremities (2). ODCD is towards the milder end of the spectrum of *TRIP11* gene mutations compared to ACG1A which is at the severe end. Maroteaux et al. (3) reported two cases with short limbs, and metaphyseal irregularities and dentinogenesis imperfecta; they used the term ODCD for

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Conflict of interest: None declared
Received: 14.04.2021
Accepted: 07.06.2021

this condition. ODCD is also called Goldblatt syndrome or SMD with dentinogenesis imperfecta. Short stature is one of the most common complaints referred to genetics clinics. Here we report a male child diagnosed as ODCD with a novel compound heterozygote mutation who presented with skeletal changes, short stature, dentinogenesis imperfecta, and facial dysmorphism resembling achondroplasia (ACH) and hypochondroplasia (HCH).

Case Report

The patient was the second child of a nonconsanguineous couple of Turkish origin. Maternal history revealed short limbs on second-trimester ultrasonography (US) that ended with a full-term male baby born through cesarean section due to breech presentation. Fetal mobility and amniotic fluid were normal. Birth weight was 4035 g (90th percentile), the length was 47 cm (3-10th percentile) and head circumference was 38 cm (≥97th percentile). After birth, he was admitted to the neonatal intensive care unit and treated for respiratory distress for 17 days. The mother and father were 40 and 35 years old, respectively, at the time of delivery. The patient has an older healthy sister. The family history was unremarkable. The patient was referred at the age 2.5 months for evaluation for possible skeletal dysplasia. On physical examination, the patient's body weight was 4.9 kg (10th percentile), height was 55 cm (10th percentile) head circumference was 40.5 cm (50-75th percentile). Anterior fontanelle was 5x4 cm. Relative macrocephaly, midfacial hypoplasia, frontal bossing, downslanting palpebral fissures, depressed nasal root, short nose, anteverted nares, short neck, and redundant nuchal skin were noted as dysmorphic features. Narrow thorax, disproportionately short extremities, redundant skin folds on upper and lower limbs with skin dimpling over the knees, inability to extend elbow/knee fully and brachydactyly were present. No head control was observed on neurologic examination. Examination at 15 months of age revealed his body weight to be 7.2 kg [-3.2 standard deviation score (SDS)], height 67 cm (-3.9 SDS) head circumference 46 cm (25-50th percentile). At this time anterior fontanelle was 3x3 cm. and at 12 months of age, the proband had attained neck control. He could stand with support by 14 months.

The first tooth erupted at age 9 months and it was blue-gray and translucent, which was confirmed as dentinogenesis imperfecta by a pedodontist. It was learned that he was suffering from insomnia. Intellectual development was normal based on the Denver developmental screening test. Echocardiogram and abdomen US were normal. Extra cerebrospinal fluid space was at the upper limit of normal on cranial US.

Skeletal survey at the age of 2.5 months showed short long bones with irregular flaring of metaphyses, small thoracic cage, small sacroiliac notch, flat acetabular roof, enlargement of iliac wings, and short tibia in relation to fibula. Additionally, when he was 15 months old, platyspondyly, coronal clefts in the lower thoracal vertebrae, broad-cupped metacarpals, short phalanges, cone-shaped epiphyses, and mildly delayed carpal ossification were detected on roentgenogram. His radiologic examination was otherwise unchanged from the previous visit. Photographs and X-rays of the patient, who was 2.5 and 15 months old, are shown in Figures 1 and 2, respectively. Although there was no neurological abnormality, the patient was referred to neurosurgery in terms of craniocervical involvement when he was about 2 years old. His magnetic resonance imaging showed craniocervical stenosis and he was operated by neurosurgery. Metabolic screening (calcium, phosphorus, alkaline phosphatase, parathyroid hormone, 25-hydroxy vitamin D, and thyroid hormone) was normal. After obtaining written informed consent, genetic analysis was performed on blood samples from the proband and his parents. Karyotyping was normal 46, XY in standard resolution in the proband. No mutation was detected in the FGFR3 gene in the patient. Afterward, whole-exome sequencing was performed. Two heterozygous variants, c.1225G>T (p.Asp409Tyr) and c.3296_3298delinsTG (p.Lys1099Metfs*6), were identified in the *TRIP11* (NM_001321851.1) gene. The c.1225G>T variant is located in the first base of exon 9 and has previously been reported to cause missplice, resulting in ODCD (4). It was reported in the ClinVar database and submitted as a likely pathogenic variant. DANN, EIGEN, FATHMM-MKL, M-CAP, MutationAssessor, MutationTaster, and SIFT computational algorithms predicted the variant as deleterious. The novel c.3296_3298delinsTG variant causes frameshift and leads to a premature stop codon after six residues. Neither variant was found in the gnomAD exomes and genomes. Finally, both variants were considered pathogenic according to American College of Medical Genetics guideline (5). Finally, the c.1225G>T variant in the mother and the c.3296_3298delinsTG variant in the father were present in a heterozygous state, thus confirming the compound heterozygosity in the patient. Images of variants in the Integrative Genomics Viewer are shown in Figure 3. His sister had none of the variants in *TRIP11* present in her parents or sibling. As a result, our patient was diagnosed with ODCD given the evidence of the clinical, radiological, and molecular findings.

Discussion

ODCD was first described by Goldblatt et al. (6) in a 3.5-year-old male patient characterized by SMD, joint hypermobility,

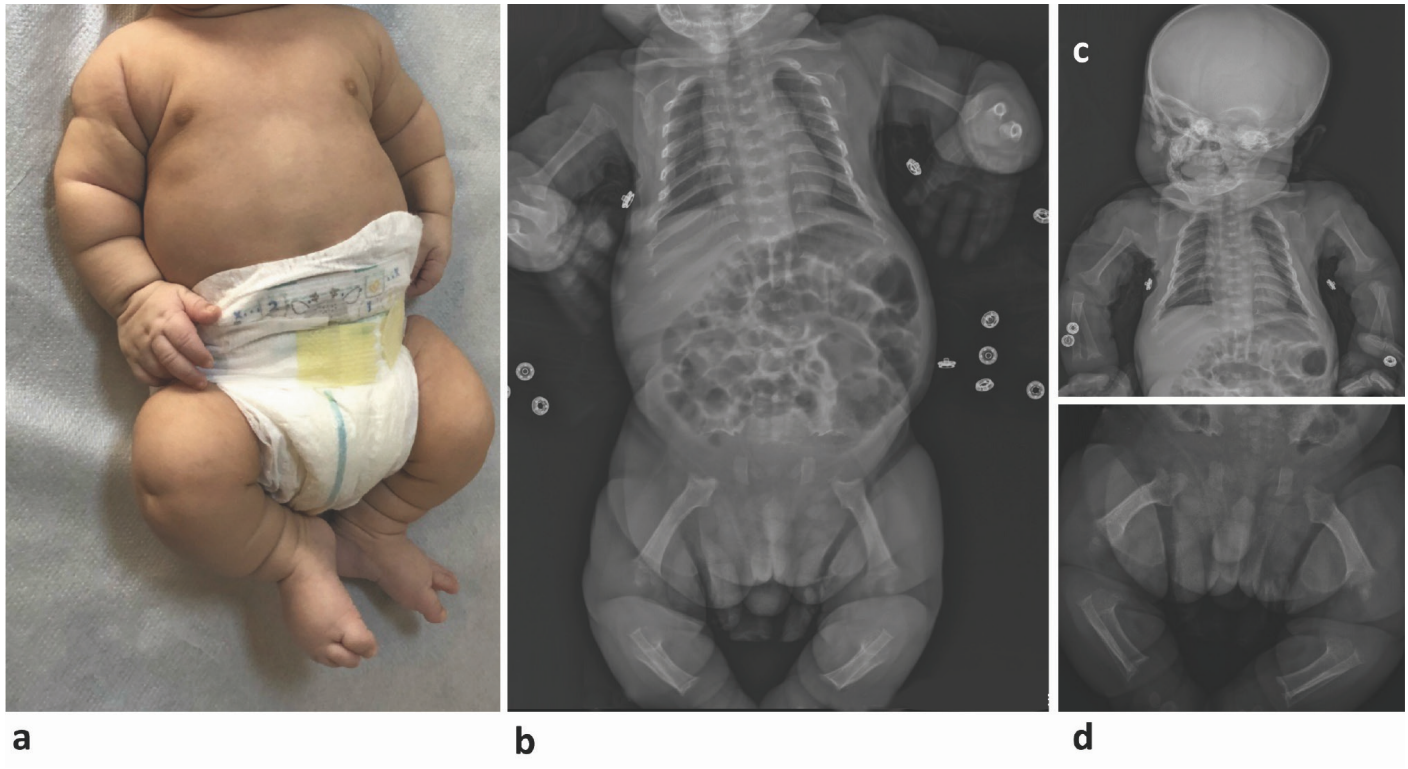

Figure 1. Clinical and radiologic findings of the proband at the age of 2.5 months. **a)** Narrow thorax, short extremities, and redundant skin folds on upper and lower limbs with skin dimpling over knees. **b, c, d)** Short long bones with irregular flaring of metaphyses, small thoracic cage, small sacroiliac notch, flat acetabular roof, enlargement of iliac wings, and short tibia in relation to the fibula

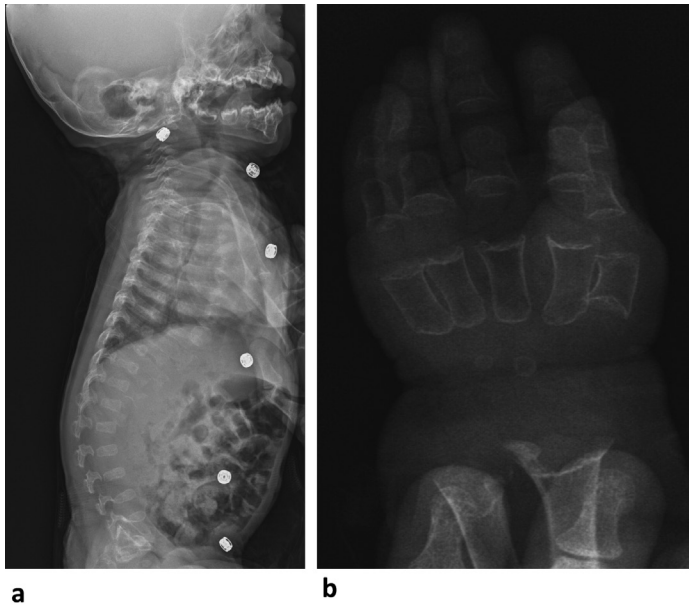

Figure 2. Radiologic findings of the proband at the age of 15 months. **a)** Platyspondyly and coronal clefts at lower thoracal vertebrae. **b)** Cupping of the metaphyses of the radius and ulna, broad-cupped metacarpals, short phalanges, cone-shaped epiphyses, and mildly delayed carpal ossification

and dentinogenesis imperfecta in 1991. Until Wehrle et al. (4) shoed *TRIP11* gene mutations leading to ODCD in 2019, the diagnosis of ODCD was based on clinical and radiologic features. The *TRIP11* gene is located at 14q32.12 and contains 21 exons. *TRIP11* encodes the Golgi microtubule-associated protein 210 (GMAP-210), which is an indispensable protein for the function of the Golgi apparatus (7). In 2010, Smits et al. (8) investigated lethal skeletal dysplasia and showed that the GMAP-210 protein was essential for glycosylation and cellular transport of proteins. In the absence of GMAP-210 protein, endochondral and intramembranous ossification is dramatically decreased (9). *TRIP11* is the only known gene associated with ODCD. Mutations of *TRIP11* also causes ACG1A. Null mutations of *TRIP11* lead to ACG1A, a lethal skeletal dysplasia, while hypomorphic mutations cause ODCD (4). Loss of function mutations in the *TRIP11* gene, leading to ACG1A, are characterized by short limbs, small thorax, domed skulls, absence of several bone ossifications, and decreased alveolar formation in the lungs in mice and humans (8). ODCD is classified in group 12 of the SMD because of involvement of vertebrae and affecting metaphyses of all tubular long bones at Nosology and classification of genetic skeletal disorders in the last revision published in 2019 (10).

Figure 3. The Integrative Genomics Viewer visualization of the c.1225G > T and c.3296_3298delinsTG variants

Only one patient in the literature, the product of a consanguineous marriage, had a homozygous mutation as expected (11). In 2019, Wehrle et al. (4) suggested an autosomal recessive pattern in this disorder. Almost all patients diagnosed with ODCD have had compound heterozygous mutations. The compound heterozygote appearance of this mutation in our patient is in agreement with the autosomal recessive trait of ODCD. The mutation mechanisms found in ODCD can be listed in order of frequency as missense, small deletion, and splice-site mutations but for that, there were no hotspot regions in *TRIP11* gene related to ODCD (4). Unger et al. (1) published a case series of six patients that were diagnosed with clinical and radiographic findings in 2008. These authors reported mesomelic limb shortening (6/6 cases), narrow chest (5/6 cases), dentinogenesis imperfecta (5/6 cases) (1 patient could not be evaluated because he died at the age of 4 months), and scoliosis (2/6 cases). Wehrle et al. (4) confirmed this skeletal dysplasia by studying the molecular diagnosis of these patients. The comparison between common abnormalities of the present case and the patients reported by Unger et al. (1) and Medina et al. (11) are summarized in Table 1.

Cystic renal disease, pulmonary dysplasia, and non-obstructive hydrocephaly were seen in a few cases with ODCD (4). While generalized joint hypermobility is observed in ODCD, our patient had limitation of extension in some joints. These joint limitations are not a typical finding observed in ODCD patients, and thus this is the first report of such an association. There was no joint hypermobility or limitation in one of the six patients in the publication of Unger et al. (1). Short limbs on the prenatal US, large head with protruding forehead, midface hypoplasia, brachydactyly, and short tubular bones with metaphyseal flare are also observed in HCH and ACH, as in ODCD. In this respect, ODCD can be confused with these genetic skeletal disorders. Nevertheless, lumbar lordosis,

Table 1. Clinical and genetic outcomes of odontochondrodysplasia

	Case 1 (Sibling 1) Unger et. al. (1)	Case 2 (Sibling 2) Unger et. al. (1)	Case 3 Unger et. al. (1)	Case 4 Unger et. al. (1)	Case 5 Unger et. al. (1)	Case 6 Unger et. al. (1)	Case 7 Medina et. al. (1)	Case 8 Our patient
Sex	Male	Female	Female	Female	Female	Male	Female	Male
Relationship	-	-	-	-	-	-	+	-
Relative macrocephaly	-	-	-	-	-	-	+	+
Short extremities	+	+	+	+	+	+	+	+
Joint laxity	?	+	+	+	-	+	+	-
Restriction of joints	-	-	-	-	-	-	-	+
Redundant skin folds	-	-	+	-	-	+	-	+
Skin dimpling over limbs	-	-	-	-	-	-	-	+
Dentinogenesis imperfecta	?	+	+	+	+	+	+	+
Neuromotor development delay	?	+	?	+	?	+	-	+
Molecular analysis	c.(1314+5G>A); (chr14:g.(?_92.474.069)_(92.597.431_?)del	c.(1314+5G>A); (chr14:g.(?_92.474.069)_(92.597.431_?)del	c.(1228G>T); (4815_4818delAGAG)	c.(586C>T); (4534C>T)	c.(1228G>T); (2128_2129delAT)	c.(1622delA); (5416A>G)	c.1314+5G>A	c.1225G>T; c.3296_3298delinsTG

progressive narrowing, or unchanged interpedicular distance in lumbar vertebrae, short iliac bones, short femoral neck, and bowing of legs are expected in HCH and ACH (12). However, the skeletal anomalies of HCH are milder and can be detected in late childhood. Characteristic facial features are more pronounced in ACH compared with ODCD and HCH. However, dentinogenesis imperfecta is only seen in ODCD. Even though his phenotype overlapped significantly with ACH and HCH, as we expected, the known causal gene for these was not found in the presented patient. Our patient had suffered from respiratory distress in the newborn period due to pulmonary hypoplasia. Thoracic hypoplasia is observed in skeletal ciliopathies, notably in Jeune asphyxiating thoracic dysplasia (JATD). A small thoracic cage is more severe in JATD and that is accompanied by short extremities with brachydactyly, as in ODCD. Whereas short stature is less conspicuous than ODCD, the skull and spine are unaffected in JATD. Polysyndactyly is another distinctive feature seen in JATD and the other ciliopathies. Renal involvement, which is a typical feature of ciliopathies, is rarely seen in ODCD. In this respect, it has a common feature with ciliopathies besides lung hypoplasia.

Dentinogenesis imperfecta is one of the most characteristic features of ODCD. Nearly all patients with ODCD have dentinogenesis imperfecta although dentinogenesis imperfecta is extremely rare in other genetic skeletal diseases, with the exception of osteogenesis imperfecta. Dentinogenesis imperfecta is a genetic disorder caused by impaired dentine development that results in discolored and fragile teeth. Dentine is formed by odontoblasts that secrets an extracellular matrix after mineralization and this matrix is comprised of 90% of type 1 collagen and 10% of non-collagenous proteins and lipids (13). This entity influences both deciduous and permanent teeth. The incidence is estimated to be 1 in 7000 in the USA, according to the last published study in 1975 (14). The coexistence of dentinogenesis imperfecta and skeletal dysplasia is rare except in osteogenesis imperfecta. However, osteogenesis imperfecta has rather different clinical and radiological features compared with ODCD, including blue sclera, hearing loss, and increased frequency of fracture.

The most characteristic radiologic features of ODCD include small thorax, platyspondyly with coronal clefts, broadened iliac wings with horizontal acetabulum, cupping of metaphyses and shortening of all long bones (1). All of these radiologic findings were found in

our patient. With advancing ages, metaphyseal alterations in metacarpals deteriorate, which mimics enchondroma, and mesomelic shortening becomes more apparent (1). The most characteristic clinical features are macrocephaly, short stature, pulmonary hypoplasia, and dentinogenesis imperfecta. The presented patient had all of these findings. There is no intellectual disability, hearing loss, and ophthalmologic involvement in this skeletal dysplasia (1).

The diagnosis of ODCD is based on clinical and radiologic keystones of prenatal onset of short stature, pulmonary hypoplasia with a narrow thorax, short long bones, and dentinogenesis imperfecta and confirmed by molecular analysis. Wehrle et al. (4) reported significant clinical variability within affected families with this skeletal dysplasia.

Conclusion

In summary, ODCD is a very rare skeletal dysplasia. We describe a male affected with ODCD who had facial dysmorphism, dentinogenesis imperfecta, short stature, and joint hypermobility, due to a novel compound heterozygote mutation in the *TRIP11* gene. It is predicted that this mutation has a pathogenic and damaging influence on the protein product of *TRIP11*. More than 20 parients have been reported to date but to the best of our knowledge, this is only the third published Turkish case with a clinical, radiographic, and molecular diagnosis of ODCD. Furthermore, reporting of novel mutations, as found in this case, are crucial to extend the molecular spectrum of ODCD and to clearly understand the genotype-phenotype correlation in a larger number of patients. In skeletal dysplasias accompanied by dentinogenesis imperfecta, ODCD should be included in the differential diagnosis, unless the diagnosis is clearly osteogenesis imperfecta. We suggest that the presence of dentinogenesis imperfecta may make the diagnosis easier.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Burcu Yeter, Ayça Dilruba Aslanger, Nursel H. Elçioğlu, Concept: Gözde Yeşil, Design: Gözde Yeşil, Data Collection or Processing: Burcu Yeter, Ayça Dilruba Aslanger, Nursel H. Elçioğlu, Analysis or Interpretation: Burcu Yeter, Ayça Dilruba Aslanger, Literature Search: Burcu Yeter, Gözde Yeşil, Nursel H. Elçioğlu, Writing: Burcu Yeter, Nursel H. Elçioğlu.

Financial Disclosure: The authors declared that this study received no financial support.

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