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Case report

A novel mutation in the *TRIP11* gene: Diagnostic approach from relatively common skeletal dysplasias to an extremely rare Odontochondrodysplasia

Short Title: A novel mutation in the *TRIP11* gene with Odontochondrodysplasia

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What is already known on this topic?
Most patients with odontochondrodysplasia have a compound heterozygous mutation as in our case. Odontochondrodysplasia is a very 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 that leads to odontochondrodysplasia. Joint limitation and craniocervical stenosis were not observed in patients with odontochondrodysplasia so far. In this respect, our patient is the first case in the literature.

Abstract
Odontochondrodysplasia (ODCD, OMIM #184260) is a quite 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). TRIP11 gene encodes the Golgi microtubule-associated protein 210 (GMAP-210), which is an indispensable protein for the function of the Golgi apparatus. Mutations of the TRIP11 gene 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 heterozygote mutation who presented with skeletal changes, short stature, dentinogenesis imperfecta, and facial dysmorphism resembling Achondroplasia (ACH) and Hypochondroplasia (HCH).

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

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Introduction

Odontochondrodysplasia (ODCD, OMIM #184260) is a quite rare non-lethal skeletal dysplasia characterized by involvement of spine and metaphyseal regions of the long bones, pulmonary hypoplasia, short stature, joint hypermobility, and dentinogenesis imperfecta (1). Spondylo-metaphyseal dysplasias stand for a group of skeletal dysplasia that includes miscellaneous disorders with vertebra and metaphysis defects. 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). At first, homozygous mutations of *TRIP11* gene were defined for 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 a rather mild form compared to ACG1A that leads to a lethal spectrum of *TRIP11* gene mutations. Maroteaux et al. reported two cases with short limbs, and metaphyseal irregularities and dentinogenesis imperfecta and they used the term ODCD for this condition (3). ODCD is also called Goldblatt syndrome or spondylometaphyseal dysplasia with dentinogenesis imperfecta. Short stature is one of the most common complaint referrals 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 (90.p), the length was 47 cm (3-10p) and head circumference was 38 cm (≥97p). 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 a older healthy sister. There was no particular familial history. The patient was referred at age 2,5 months for evaluation for possible skeletal dysplasia. On physical examination, the patient's body weight was 4,9 kg (10.p),

height was 55 cm (10.p) head circumference was 40,5 cm (50-75p). Anterior fontanel was 5*4 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 knees, inability to extend elbow/knee fully and brachydactyly were defined. No head control was observed on neurologic examination. Examination at 15 months of age revealed his body weight was 7,2 kg (-3,2 SDS), height was 67 cm (-3,9 SDS) head circumference was 46 cm (25-50p). Anterior fontanel was 3*3 cm. 12 months of age, the proband attained his neck control. He could stand with support by 14 months. The first teeth erupted at age 9 months and it was blue-gray and translucent which was confirmed as dentinogenesis imperfecta by pedodontist. It was learned that he was suffering from insomnia. Intellectual development was normal according to the Denver developmental screening test. Echocardiogram and abdomen US were normal. Extra cerebrospinal fluid space was at the upper limit of normal on the cranial US. Skeletal survey by 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 at 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. Although there was no neurological finding, the patient was consulted to neurosurgery in terms of craniocervical involvement when he was about 2 years old. His magnetic resonance imaging (MRI) was detected craniocervical stenosis and he was operated by neurosurgeon. 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 *FGFR3* gene in the patient. Afterward, whole-exome sequencing was performed. Heterozygous variants c.1225G>T (p.Asp409Tyr) and c.3296_3298delinsTG (p.Lys1099Metfs*6) were determined 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 is also found 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 6 residues. Both variants were not found in the gnomAD exomes and genomes. Finally, both variants were considered as pathogenic according to American College of Medical Genetics guideline (5). Also, the c.1225G>T variant in the mother and the c.3296_3298delinsTG variant in the father were detected as heterozygous, thus confirming the compound heterozygosity in the patient. Images of variants in the Integrative Genomics Viewer are shown in Figure 3. His sister had no relevant variants mentioned above in this gene. As a result, our patient was diagnosed with ODCD with all these clinical, radiological, and molecular findings.

Discussion

ODCD was first described by Goldblatt et al. in a 3,5-year-old male patient based upon spondylometaphyseal dysplasia, joint hypermobility, and dentinogenesis imperfecta in 1991(6). Until Wehrle et al. found *TRIP11* gene mutations leading to ODCD in 2019, the diagnosis of ODCD was made with clinical and radiologic features. *TRIP11* gene is located at 14q32.12 containing 21 exons. *TRIP11* gene encodes the Golgi

microtubule-associated protein 210 (GMAP-210), which is an indispensable protein for the function of the Golgi apparatus (7). In 2010, Smith et al. revealed in his study about lethal skeletal dysplasia that the GMAP-210 protein is essential for glycosylation and cellular transport of proteins (8). In the absence of GMAP210 protein, endochondral and intramembranous ossification is dramatically decreased (9). *TRIP11* is the only known gene associated with ODCD. Mutations of *TRIP11* gene also causes ACG1A. Null mutations of *TRIP11* lead to ACG1A, also known as a lethal skeletal dysplasia, while hypomorphic mutations cause ODCD (4). Loss of function mutations in the *TRIP11* gene lead to ACG1A which is characterized by short limbs, small thorax, domed skulls, lacked several bone ossifications, decreased alveolar formation in the lungs in mice and humans (8). ODCD is classified in group 12 Spondylometaphyseal dysplasias (SMD) because of involvement 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). Only one patient in the literature had a consanguineous marriage who had a homozygous mutation as expected (11). In 2019, Wehrle et al. suggested an autosomal recessive pattern in this disorder (4). Almost all patients diagnosed with ODCD have had a compound heterozygous mutation. The compound heterozygote appearance of this mutation in our patient stood in agreement with the autosomal recessive trait of ODCD, too. The mutations of ODCD can be listed in order of frequency: 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. published a case series which consist of 6 patients that were diagnosed with clinical and radiographic findings in 2008 (1). In that article, 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) were been ascertained. Wehrle et al. confirmed this skeletal dysplasia by studying the molecular diagnosis of these patients (4). The comparison between common abnormalities of our, Unger et al and Medina et al's patients are summarized in Table I.

Cystic renal disease, pulmonary dysplasia, and non-obstructive hydrocephaly were seen in few cases with ODCD (4). While generalized joint hypermobility is observed in ODCD, in our patient had limitation of extension at joints. Joint limitations in our case is not a typical finding observed in ODCD patients. In this respect, it was the first case in the literature. There was no joint hypermobility or limitation in one of the six patients in the publication of Unger et al. 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 like ODCD. In this respect, ODCD can be confused with these genetic skeletal disorders. Nevertheless, lumbar lordosis, 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. Dentinogenesis imperfecta is only seen in ODCD among them. Even though his phenotype overlapped significantly with achondroplasia and hypochondroplasia, as we expected, the known causal gene for these was not found in the 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 accompanied by short extremities with brachydactyly like ODCD. Whereas short stature is less conspicuous than ODCD and, skull and spine are unaffected in JATD. Poly-syndactyly 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 there is no dentinogenesis imperfecta in most genetic skeletal diseases. Dentinogenesis imperfecta is a genetic disorder caused by impaired dentin development that results in discolored and fragile teeth. Dentin is formed by odontoblasts that secrets an extracellular matrix after mineralization and this matrix is comprised of 90% of type I 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 for osteogenesis imperfecta. However, osteogenesis imperfecta has rather different clinical and radiological features than patients with ODCD such as 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 and, 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 mimic enchondroma, and mesomelic shortening occurs more apparent (1). The most characteristic clinical features are macrocephaly, short stature, pulmonary hypoplasia, dentinogenesis imperfecta. Likewise, our 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 suspected 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. proposed significantly clinical variability within the same families in this skeletal dysplasia owing to mild and severe phenotypes (for example infant death) in the same family (4).

Conclusion

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

Statement of Ethics

All experimental procedures were conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from the patient's parents.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Authorship Contributions

Ayça Dilruba Aslanger and Gözde Yeşil performed WES analysis of the patient and parents'. Nursel H. Elçioğlu reviewed the manuscript. Additionally, this case report was evaluated and approved by all of the authors.

Financial Disclosure

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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

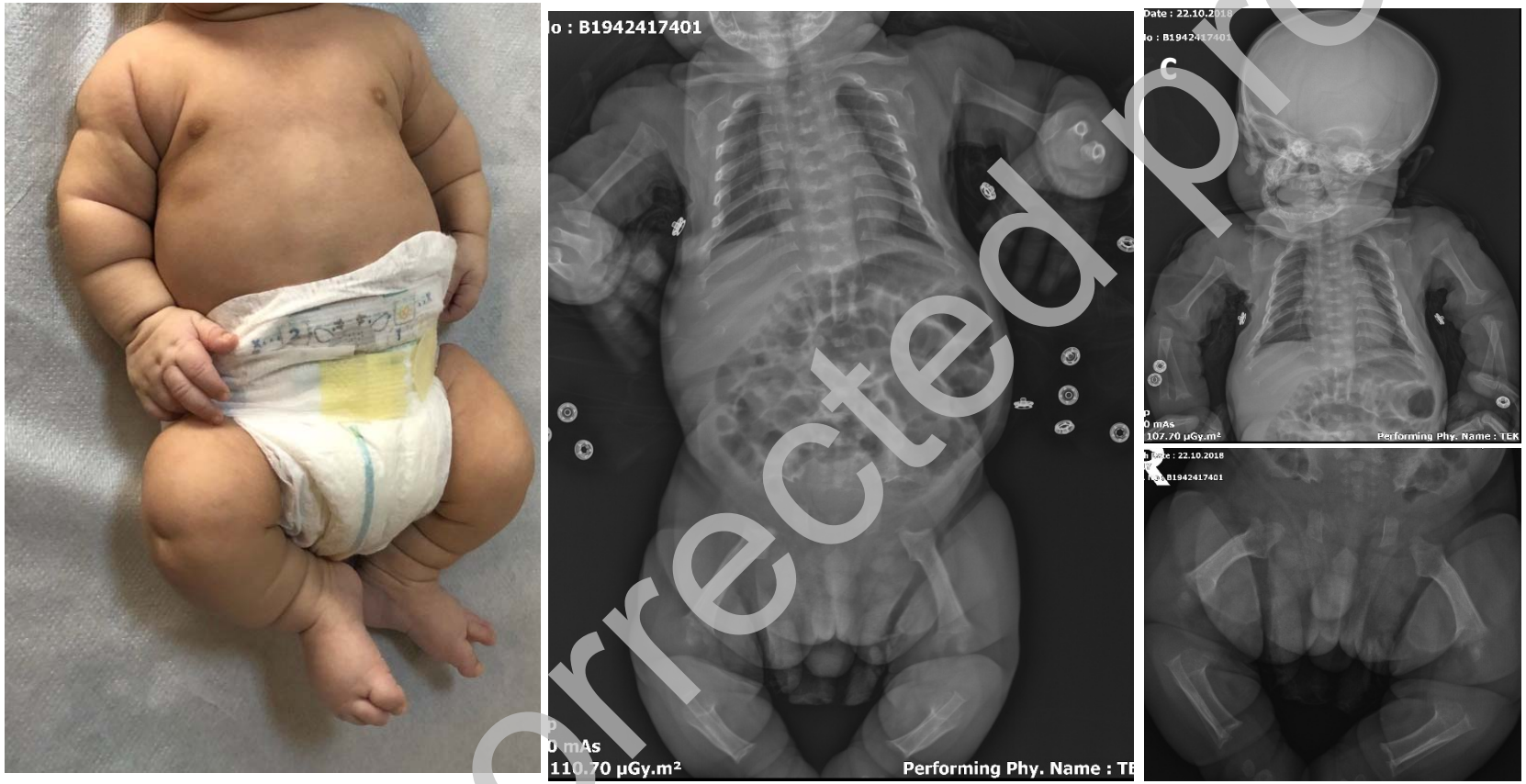
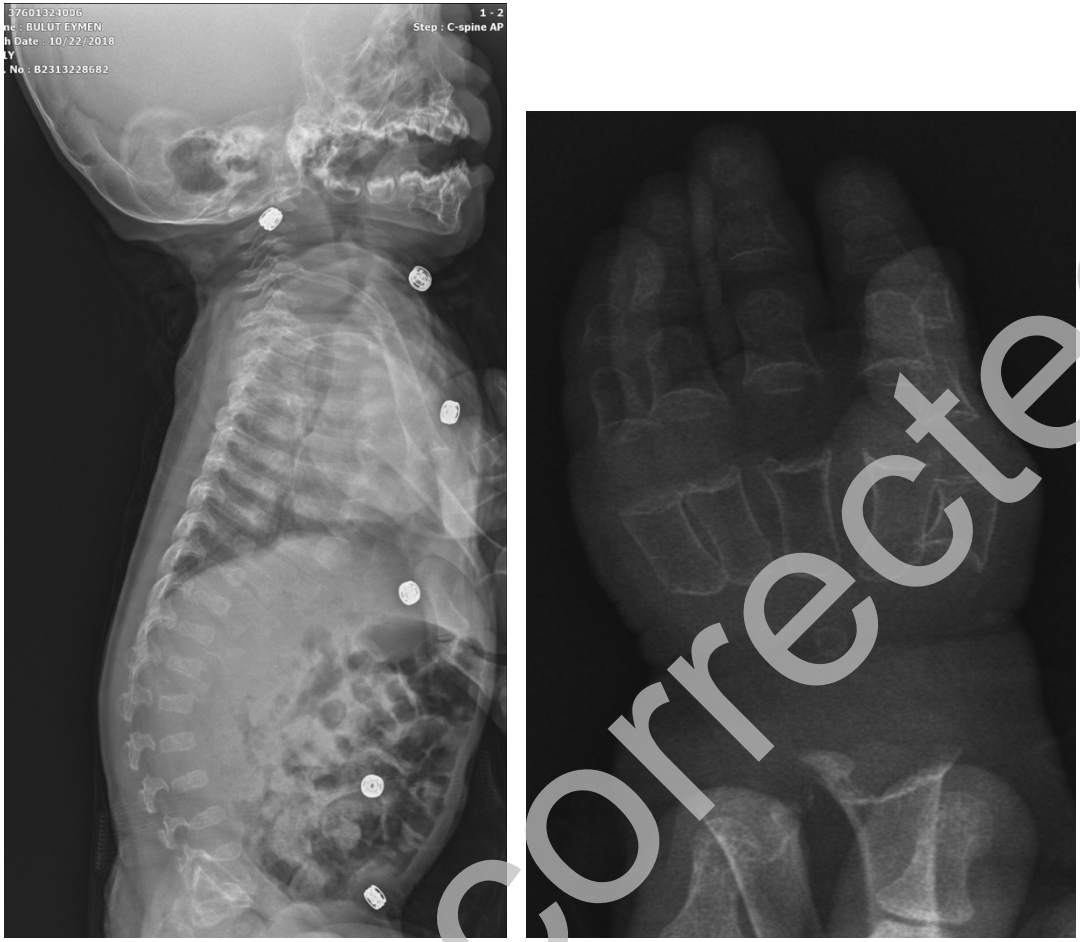


Figure 2. Radiologic findings of the proband at the age of 15 months. **a.** Platyspondyly and coronal clefts at lower thoracal vertebrae. **b.** Cupping of the metaphyses of the radius and ulna, broad-cupped metacarpals, short phalanges, cone-shaped epiphyses, and mildly delayed carpal ossification.



a **b**

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

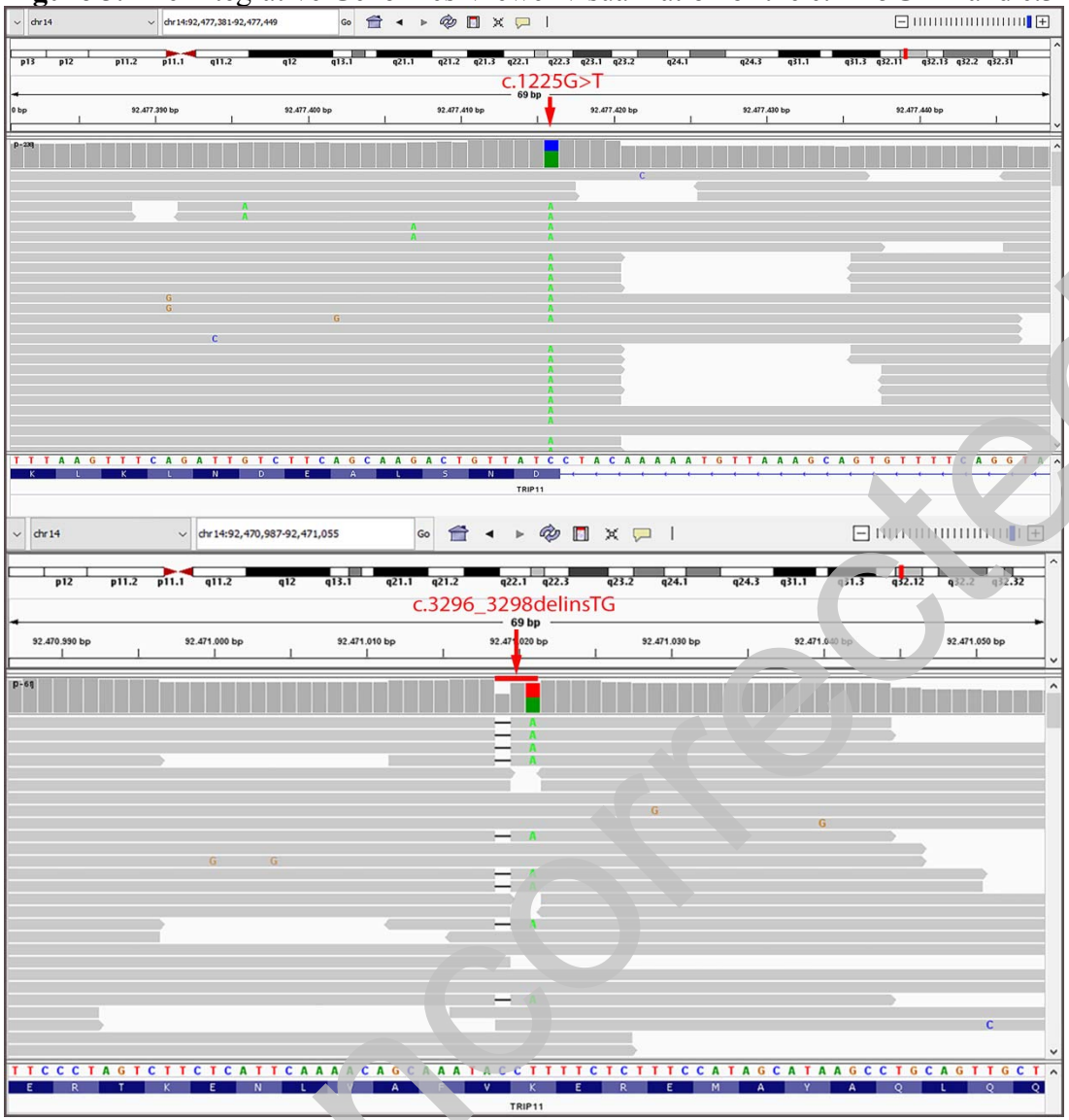


Table1: Clinical and Genetic outcomes of Odontochondrodysplasia								
	Case 1 (Sibling 1) Unger et. al	**Case 2 (Sibling 2) Unger et. al**	**Case 3 Unger et. al**	**Case 4 Unger et. al**	**Case 5 Unger et. al**	**Case 6 Unger et. al**	**Case 7 Medina et. al**	**Case 8 Our patient**
Sex	Male	Female	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	c.(1314+5G>A);	c.(1314+5G>A);	c.(1228G>T);	c.(586C	c.(1228G>T);	c.(1622de	c.1314+5	c.1225G>T;

analysis	(chr14:g.(?_92.474.069)_(92.597.431_?)del	(chr14:g.(?_92.474.069)_(92.597.431_?)del	(4815_4818delAGAG)	>T); (4534C>T)	(2128_2129delAT)	lA); (5416A>G)	G>A	c.3296_3298delinsTG