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Case Report

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A Case Report of Suspected Achondrogenesis Type 1A with Novel TRIP11 Variant: Parental Carrier Detection and Targeted Prenatal Exclusion in a Subsequent Pregnancy

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Abstract

Background: Achondrogenesis type 1A (ACG1A) is a rare perinatally lethal skeletal dysplasia that results from biallelic loss-of-function variants in TRIP11, which encodes the Golgi microtubule-associated protein GMAP-210. A case of clinically suspected ACG1A in an unrelated couple is described after termination at 19 weeks of gestation of a severely micromorphic fetus with cloverleaf skull, sacral agenesis, vertebral flattening, and thoracic hypoplasia. Genetic testing was not done on the affected fetus.

Case Presentation: A heterozygous 13-base-pair deletion in exon 13 of TRIP11 (Chr14:g.91999349_91999361del) was discovered in the mother during a subsequent preconception genetic evaluation using whole exome sequencing (WES). In the father, Sanger sequencing confirmed the same heterozygous variant consistent with an autosomal recessive inheritance. According to the American College of Medical Genetics and Genomics (ACMG) criteria, the frameshift deletion, which is expected to cause premature termination, was deemed likely pathogenic (PVS1, PM2, PP3) and was not present in public variant databases. Although molecular confirmation in the affected fetus was unavailable, the phenotype was highly suggestive of TRIP11-related ACG1A. While molecular confirmation in the affected fetus was not possible, the phenotype strongly suggested TRIP11-related ACG1A. In the subsequent pregnancy, targeted prenatal testing with amniocentesis showed absence of the familial variant in the fetus and the pregnancy was continued.

Conclusion: This case expands the mutational spectrum of TRIP11 and underscores the clinical utility of exome sequencing for carrier detection and recurrence prevention in lethal skeletal dysplasias. It also emphasizes the importance of clinical phenotyping integration with molecular diagnostics while recognizing the limitations that arise in the absence of fetal genotyping.

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Introduction

Skeletal dysplasias are a heterogeneous group of more than 400 heritable disorders that affect cartilage and bone development, with an estimated prevalence of approximately 1 in 4,000 to 5,000 live births; however, lethal forms such as achondrogenesis occur at rates closer to

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around 1 in every 40,000 pregnancies (1). These disorders are caused due to genetic mutations that affect osteochondrogenesis, resulting in disproportionate short stature and limb malformations along with craniofacial anomalies, with implications for neonatal survival and long-term quality of life (2). Clinical manifestations display a broad range from mild and non-lethal variants to perinatally lethal forms, with inheritance patterns of dominant, recessive or sporadic de novo mutations, each associated with different re-currence risks for families (3, 4).

Achondrogenesis type 1A (ACG1A) is among the most severe lethal skeletal dysplasias, which fall under the definition of type I because of their perinatally lethal phenotype resulting from extreme micromelia, thoracic hypoplasia, and marked skeletal demineralization (5). Radiographically, ACG1A is characterized by unossified skull base, aplastic or hypoplastic vertebrae, short ribs with flared metaphysis, and poorly ossified long bones with fractures (6). Histologically, it demonstrates disorganization of chondrocytes with sparse matrix, representing defective endochondral and intramembranous ossification (7).

The thyroid hormone receptor interactor 11 (TRIP11) gene encodes Golgi microtubule-associated protein 210 (GMAP-210), which is essential for Golgi apparatus function and, in turn, chondrogenesis and osteogenesis (3). The TRIP11 mutation spectrum correlates with phenotypic severity; null alleles (nonsense, frameshift, essential splice-site disruptions) cause lethal ACG1A, while hypomorphic variants (missense, in-frame deletions) yield milder odontochondro-dysplasia (ODCD) featuring short stature, dentinogenesis imperfecta, and metaphyseal irregularities (2). Prenatal diagnosis relies on ultrasound detection of short limbs (<3rd percentile), narrow chest, and polyhydramnios from second trimester onward, confirmed by molecular testing via amniocentesis or CVS (3). Early identification enables reproductive counseling, highlighting the 25% recurrence risk in autosomal recessive cases like ACG1A (8).

Case Presentation

A couple presented to Perinatal Clinic at All India Institute of Medical Sciences, Bhubaneswar, Odisha, India in August 2023 with radiological images and photographs of previous abortus for preconception counselling. This study was performed after the approval was obtained from the Institutional Ethics Committee of All India Institute of Medical Sciences (AIIMS), Bhubaneswar, India. Written informed consent was obtained from the patient for publication of clinical details and images included in this report. All efforts have been made to maintain patient anonymity.

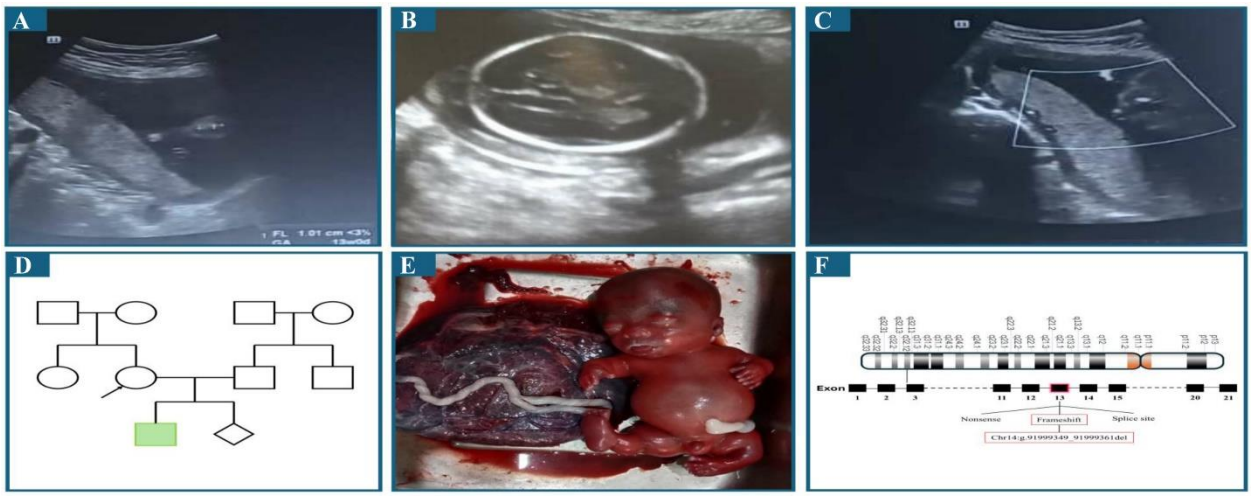
The woman was 24 years old and the husband was 29. They were married for 3 years and it was a non-consanguineous marriage. They conceived spontaneously after one year of marriage. First trimester NT scan and aneuploidy screening were not performed. The second trimester anomaly scan showed a single live fetus at 19 weeks' gestation with cloverleaf skull, sacral agenesis, flattening of the vertebrae, narrow thorax, bilateral mild renal pelviectasis, and bones of upper and lower limb were significantly small (<5 percentile). No other fetal anomalies were identified. The overall findings were suggestive of a skeletal dysplasia (Figures 1A-C). A pedigree chart was constructed (Figure 1D).

The couple opted for medical termination of pregnancy in view of suspected lethal skeletal dysplasia at a local center. The patient vaginally expelled a male abortus (Figure 1E). Neither autopsy nor genetic evaluation was performed on the abortus at the time of expulsion.

Upon review of the obstetric history, available radiological imaging, and post-abortive photographs, a clinical suspicion of a lethal skeletal dysplasia was established. Following pre-test counseling, whole exome sequencing (WES) was initiated for the female partner to identify potential carrier status. WES identified a heterozygous 13-base-pair deletion within exon 13 of the TRIP11 gene (Chr14:g.91999349_91999361 del) (Figure 1F). To determine familial segregation, subsequent targeted Sanger sequencing of the male partner's peripheral blood was performed, which confirmed the presence of the identical heterozygous TRIP11 mutation (Table 1). The identified TRIP11 exon 13 frameshift deletion (Chr14:g.91999349_ 91999361del) was not found in ClinVar, HGMD, OMIM, or gnomAD at the time of analysis and thus appears to represent a previously unreported variant.

To formally evaluate the pathogenicity of this novel variant, the American College of Medical Genetics and Genomics (ACMG) guidelines were applied. The identified TRIP11 exon 13 frameshift deletion was classified as "Likely Pathogenic" according to ACMG guidelines (PVS1,

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Figures 1. A-C) Second-trimester anomaly scan demonstrating features suggestive of lethal skeletal dysplasia. D) Pedigree chart of the family. E) Post-expulsion photograph of the fetus. F) Genomic localization of the TRIP11 variant on chromosome 14. Schematic representation of the TRIP11 gene (chromosome 14q32) showing the location of the identified 13-base-pair deletion in exon 13 (chr14:g.91999349_91999361del; c.4771_4783del). The variant is predicted to cause a frameshift leading to premature termination (p.Ser1591IlefsTer15), consistent with a loss-of-function mechanism

Table 1. Whole exome and targeted Sanger sequencing reports of proband (mother), husband (father), and their current fetus (second pregnancy)

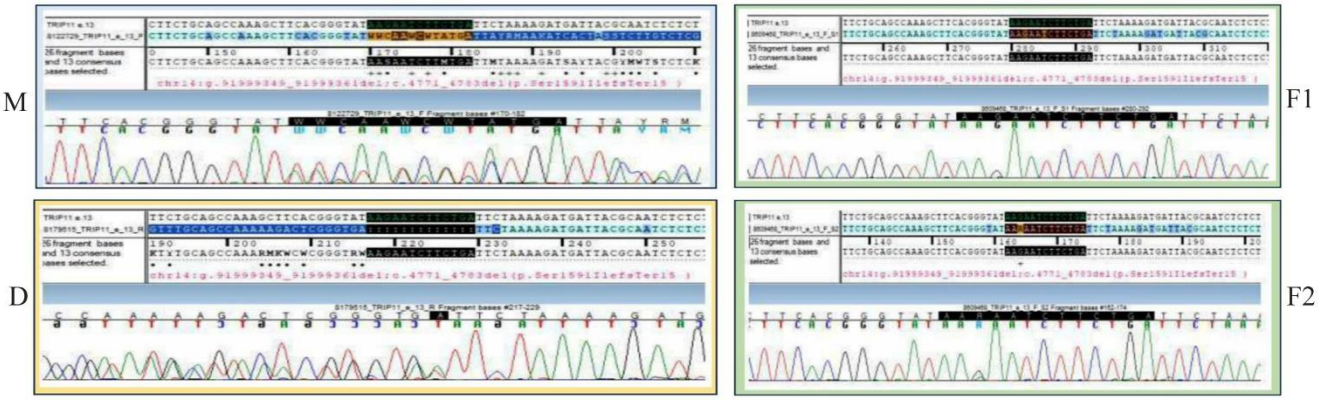
Mother: whole exome sequencing (WES)						
Gene* (transcript)	**Location**	**Variant**	**Zygosity**	**Disease (OMIM)**	**Inheritance**	**Classifications**
TRIP11 (-) (ENST00000267622.8)	Exon 13	c.4771_4783del (p.Ser1591IlefsTer15)	Heterozygous	Achondrogenesis, type IA (OMIM#200600)/ Odontochondrodysplasia 1 (OMIM#184260)	Autosomal recessive	Likely pathogenic (PVS1, PM2)
Father: Targeted Sanger sequencing						
Gene name	**Exon/ Intron**	**Variant reported in the proband**		**Variant detected in family member***		**Clinical condition of family member**
TRIP11	Exon 13	chr14:g.91999349_91999361del; c.4771_4783del (HET); (p.Ser1591IlefsTer15)		Present and heterozygous		Asymptomatic
Current fetus: Targeted Sanger sequencing						
Gene name	**Exon/ Intron**	**Variant reported in the proband**		**Variant detected in family member***		**Clinical condition of family member**
TRIP11	Exon 13	chr14:g.91999349_91999361del; c.4771_4783del (HET); (p.Ser1591IlefsTer15)		Absent		NA

PM2, PP3). The affected fetus was not genetically tested, but the clinical phenotype closely resembled achondrogenesis type 1A and both parents were heterozygous carriers which supported an autosomal recessive mode of inheritance.

The couple received detailed post-test genetic counseling after definitive molecular diagnosis. Autosomal recessive inheritance of the condition and the corresponding 25% risk of recurrence in future pregnancies were described. Reproductive planning was discussed in terms of targeted prenatal diagnosis through chorionic villus sampling (CVS) or amniocentesis in future pregnancies.

When they presented again with the second pregnancy, the routine antenatal care was continued, with amniocentesis planned for 16 weeks'

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Figures 2. A and B) Sanger sequencing chromatograms showing validation and segregation of the identified variant in a case of achondrogenesis. Sequences are shown for the mother (M), father (D), and fetus (second pregnancy) with two primer sets (F1 and F2)

gestation. Sanger sequencing was performed on the amniotic fluid for the reported variant. No mutations were detected in the fetus and the couple was advised to continue the pregnancy with routine antenatal care (Table 1 and figure 2).

Discussion

Achondrogenesis type 1A (ACG1A, or Houston-Harris type) represents the severe end of the TRIP11-related skeletal dysplasia spectrum, distinguished from types IB (Parenti-Fraccaro, due to SLC26A2 mutations) and II (Langer-Saldino, due to COL2A1 mutations) by its Golgi-specific pathogenesis and characteristic radiological findings (4). At the molecular level, ACG1A results from biallelic loss-of-function variants in the TRIP11 gene on chromosome 14q32, encoding Golgi microtubule-associated protein 210 (GMAP -210) (9). The cisternal-stacking protein, GMAP-210, is essential for Golgi ribbon stability, vesicular transport, and glycosylation of cartilage-specific proteins like type II collagen and aggrecan (8). Variants of TRIP11 exhibit extraordinary pleiotropy; homozygous null mutations abolish GMAP-210 function, leading to Golgi fragmentation and accumulation of developmental proteins, thereby disrupting the proper trafficking of IFT20 (intraflagellar transport 20), a motor protein essential for primary cilia function during chondrocyte differentiation (8, 10). Chondrocytes are particularly vulnerable to defective protein secretion due to their high secretory demands during skeletal growth. Studies in TRIP11-knockout mice confirm cartilage-specific defects, with intramembranous bones spared, underscoring chondrocyte hypersensitivity to Golgi stress (11).

Phenotypic variability is dependent on variant type and zygosity. The deep intronic variant c.5457+81T >A in TRIP11 is an exon trapper, causing 90% mRNA downregulation as well as Golgi stack compaction, as seen antenatally in ACG1A fetuses presenting with hydrops and shortened ribs (9). Similarly, frameshift deletions such as c.1795_1818del in exon 13 (as noted in this case) may also result in nonsense-mediated decay, produce undetectable protein, and manifest with classic features of cloverleaf skull, sacral agenesis, and vertebral aplasia (2). Milder odontochondrodysplasia (ODCD) due to com-pound heterozygous missense/splice variants retains residual GMAP-210, permitting survival with dental and skeletal phenotypes without lethality (12).

Comparative analysis demonstrates stable hallmarks between cohorts. Molz and Spycher described thin calvaria and bowed ribs in ACG1A autopsy specimens, findings that reflect the hypoplastic thorax and micromelia evident in the present case (7). Aigner et al. highlighted hydrops and unmineralized vertebrae, with a focus on phenotypic homogeneity despite genetic heterogeneity within TRIP11 (5). Most lethal skeletal dysplasias are suspected on ultrasonography around 18–20 weeks' gestation with severe micromelia and thoracic hypoplasia, although there is significant phenotypic overlap with thanatophoric dysplasia or hypophosphatasia, requiring molecular confirmation (13). Although WES offers high analytical sensitivity, its clinical diagnostic yield for prenatally identified skeletal dysplasias is 40–60%. Sanger sequencing is used after WES for segregation analysis, as demonstrated here to identify carrier status and inform decisions re-

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garding amniocentesis (14).

The identification of the same novel TRIP11 frameshift variant in two apparently unrelated carrier parents raises the possibility of an unrecognized distant common ancestry or a regional founder effect, despite the absence of a reported familial relationship. In populations where endogamy is practiced, pathogenic alleles may persist within geographically or culturally defined groups without an obvious pedigree connection. Although recurrent mutational events cannot be entirely excluded, they are less likely for this frameshift variant. Further population-based studies, haplotype analysis, and screening of additional affected families will be necessary to determine whether this variant represents a founder mutation or an independently occurring rare pathogenic allele. Diagnostic delays are common, largely due to the rarity of TRIP11 variants and the phenomenon of autosomal recessivity being masked in non-consanguineous families, which often complicates preconception counseling. This case highlights the utility of WES in evaluating suspected lethal skeletal dysplasias and guiding reproductive counseling. Identification of a novel frameshift deletion in TRIP11, predicted to result in loss of function, enabled carrier detection and targeted prenatal testing in the subsequent pregnancy. The variant is predicted to result in a premature termination codon with a high deleteriousness score (CADD PHRED >20), supporting its classification as likely pathogenic. However, in the absence of molecular testing of the affected fetus, genotype–phenotype correlation in this family remains inferential. Post-diagnosis, preimplantation genetic testing for monogenic disorders (PGT-M) and non-invasive prenatal testing (NIPT) offer future reproductive options; however, technical limitations of NIPT for recessive traits, combined with the stringent medico-legal frameworks governing prenatal diagnostics in India, firmly position targeted invasive testing as the clinical gold standard for subsequent pregnancies (15).

Currently, achondrogenesis type IA remains a perinatally lethal disorder with no disease-modifying treatment available. Management is therefore focused on accurate prenatal diagnosis, genetic counseling, and informed reproductive planning. A multidisciplinary approach involving clinical geneticists, radiologists, and maternal–fetal medicine specialists is essential to ensure timely diagnosis and appropriate counseling. In the current case, targeted molecular analysis performed after anomaly detection facilitated precise carrier diagnosis and guided subsequent prenatal testing through amniocentesis, thereby enabling prevention of recurrence in current pregnancy.

Conclusion

Achondrogenesis type 1A, mediated by TRIP11 gene mutations, is a lethal skeletal dysplasia requiring sensitive prenatal surveillance and molecular diagnostic intervention. Ultrasound integrated with WES and targeted sequencing significantly improves reproductive counseling by identifying preconception and antenatal options to address the 25% recurrence risk. Future research into Golgi-targeted therapies may expand the spectrum beyond lethality, improving outcomes for TRIP11-related disorders.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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