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ARCN1 Related Syndrome: A Rare Case Report

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ABSTRACT

Background: ARCN1-related syndrome is a rare genetic disorder with a wide phenotypic spectrum. The most commonly reported features include fetal and postnatal growth restriction, micrognathia, microcephaly, rhizomelic limb shortening, and preterm birth. The syndrome is caused by variants in the *ARCN1* gene, which encodes the delta subunit of the coatomer protein complex I (COPI), a key component involved in intracellular protein transport between the Golgi apparatus and the endoplasmic reticulum.

Case presentation: We report a prenatal case of a fetus presenting with severe fetal growth restriction, short long bones, and microcephaly, which was delivered preterm. Fetal whole-exome sequencing identified a novel de novo heterozygous variant in *ARCN1* (c.1313T>C), which has not been previously reported in the literature or population databases. The observed prenatal and early postnatal phenotype was consistent with the spectrum of features described in ARCN1-related syndrome.

Conclusion: This report represents the first case described in Greece and the first report of this specific *ARCN1* variant. Our findings expand the prenatal phenotypic and molecular spectrum of ARCN1-related syndrome and highlight the importance of early molecular diagnosis for accurate prenatal counseling and pregnancy management.

Keywords: ARCN1; Micrognathia; Microcephaly

INTRODUCTION

The first description of ARCN1-related syndrome (OMIM: 617464) was reported by Izumi *et al.* in 2016 and was based on the identification of four affected individuals. The clinical features that were common in these cases and established the phenotype of ARCN1-related syndrome, included facial dysmorphism, severe micrognathia, rhizomelic limb shortening, microcephalic dwarfism, and mild developmental delay.[1]

The etiology of the syndrome lies in pathogenic variants of the archain 1 (ARCN1) gene, which encodes the delta subunit of the coatomer protein complex I (COPI), a key component involved in intracellular vesicular

trafficking. Disruption of COPI function affects protein transport between the endoplasmic reticulum and the Golgi apparatus, leading to impaired cellular homeostasis and abnormal skeletal and craniofacial development. [1]

To date, a total of 23 cases of ARCN1-related syndrome have been described, including the present case, comprising 17 postnatal patients and 6 fetuses from four families.[2] Among the reported fetal cases, pregnancy termination was elected in three families due to severe fetal anomalies, one pregnancy resulted in spontaneous miscarriage at 14 weeks of gestation, and two cases ended in intrauterine fetal demise at 25 and 26 weeks of gestation, respectively.[3,4]

Prenatal diagnosis of ARCN1-related syndrome remains extremely limited, with only a small number of fetal cases reported in the literature. Here, we present a case of prenatal identification of a heterozygous ARCN1 variant (c.1313T>C) detected by fetal whole-exome sequencing (WES) in a fetus presenting with fetal growth restriction and skeletal abnormalities. The parents have normal phenotype. The identified variant was initially classified as a variant of uncertain clinical significance / likely pathogenic, is absent from public population and clinical databases including ClinVar and gnomAD, and has not been previously reported in the literature. Multiple in silico predictive algorithms support a pathogenic effect.

This case further expands the prenatal phenotypic and molecular spectrum of ARCN1-related syndrome and underscores the diagnostic value of fetal WES in the evaluation of severe fetal growth restriction with suspected skeletal dysplasia.

CASE REPORT

A 38-year-old primigravida woman conceived through in vitro fertilization (IVF). Her last menstrual period was on 28 March 2025, and oocyte retrieval was performed on 11 April 2025. Her medical history included two previous failed IVF attempts and was otherwise unremarkable. Family history revealed a relative with diabetes mellitus and hypercholesterolemia. Her partner was 47 years old with no significant medical history.

Early in the first trimester, the patient experienced mild uterine bleeding that did not require hospitalization.

A first-trimester ultrasound examination was performed at 12 weeks and 4 days of gestation by a Fetal Medicine Foundation–certified physician. The examination demonstrated a viable fetus with a heart rate of 155 bpm. The crown–rump length (CRL) was 63 mm, consistent with gestational age based on IVF dating. Nuchal translucency measured 1.72 mm, within normal limits. Amniotic fluid volume was normal, the placenta was anterior high, and cervical length was 39 mm.

Doppler assessment showed a ductus venosus pulsatility index (PI) of 1.0 with a positive a-wave, while the mean uterine artery PI was 1.933 MoM, corresponding to the upper 10th percentile. First-trimester biochemical screening revealed free β-hCG 0.887 MoM and PAPP-A 0.297 MoM. Due to the low PAPP-A value and increased uterine artery resistance, aspirin 160 mg daily was initiated.

The diagnosis of fetal growth restriction (FGR) was established at 22+0 weeks of gestation during the detailed anatomical scan, performed by the same physician. Ultrasound findings included rhizomelic limb shortening, with femur length (FL 30.5 mm) and humerus length (HL 28.9 mm), both below the 1st percentile **(Figure 1)**. The estimated fetal weight (EFW) was 330 g (<3rd percentile), the head circuference (HC) was 1.79cm (5th percentile), while the amniotic fluid index (AFI) was 12.4 cm. No structural abnormalities were identified in the fetal face or internal organs. External genitalia were consistent with female sex.

Color Doppler evaluation demonstrated normal resistance in the uterine arteries, umbilical artery, and middle cerebral artery, with positive end-diastolic flow in the ductus venosus. Given the combination of severe FGR and short long bones, the couple was counseled to undergo amniocentesis with fetal whole-exome sequencing (WES), with achondroplasia and hypochondroplasia as the primary differential diagnoses.

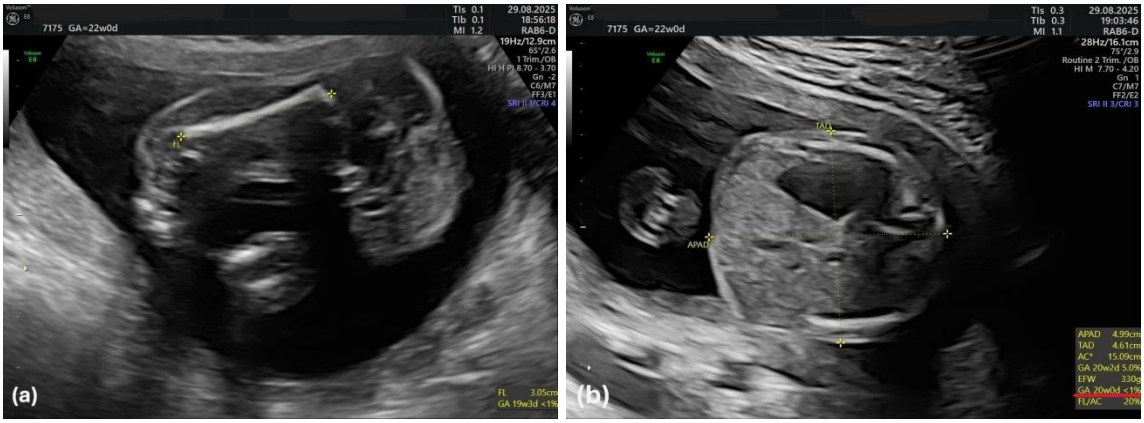

Figure 1: (a) Femur Length (FL) 3.05cm (<1st percentile), (b) Estimated Fetal Weight (EFW) 330gr (<1st percentile)

METHODS

Genomic DNA was extracted from the submitted fetal specimen. Standard library preparation kits were used to target the exon regions of the genome, and sequencing was performed on the Illumina platform using 100-bp paired-end reads. Sequencing data were aligned and analyzed against the UCSC hg38 human reference genome. After removal of low-quality and duplicate reads, variants were identified using GATK HaplotypeCaller and GermlineCNVCaller. The assay detects single-nucleotide variants (SNVs), small insertions and deletions (indels), and copy number variants (CNVs) within coding regions, flanking intronic sequences (±20 bp), and known splice sites.

The average sequencing depth was >80×, with >99.8% of the targeted exome covered. Reportable variants were confirmed by Sanger sequencing using an independent DNA sample where applicable. Variant classification followed the American College of Medical Genetics and Genomics (ACMG) guidelines and included the categories: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign.[5]

In this WES analysis, only pathogenic and likely pathogenic variants relevant to the clinical phenotype were reported. Likely benign, benign variants, and VUS were not routinely reported, except for rare CNVs of potential clinical significance.

GENETIC ANALYSIS

Genetic analysis identified pathogenic and likely pathogenic variants in the ARCN1 and POLR3A genes, as well as heterozygous variants in CFTR, VPS45, MVK, ABCA4, and RUBCN. The findings were reviewed by a clinical geneticist.

The heterozygous likely pathogenic variant in POLR3A (c.1909+22G>A) was considered unlikely to explain the phenotype, given the autosomal recessive inheritance pattern and absence of additional clinically relevant findings. The same interpretation applied to the heterozygous variants identified in CFTR, VPS45, MVK, ABCA4, and RUBCN.

A heterozygous variant c.1313T>C (p.Leu438Pro) in the ARCN1 gene (NM_001655.5) was identified and classified as variant of uncertain significance / likely pathogenic. Parental testing was negative, indicating a de novo mutation. Pathogenic variants in ARCN1 are associated with short stature–micrognathia syndrome (SSMG; OMIM #617164), a disorder characterized by significant phenotypic variability.

The c.1313T>C variant results in substitution of leucine by proline at position 438 of the ARCN1 protein. This variant is absent from Clinvar (https://www.ncbi.nlm.nih.gov/clinvar/) or gnomAD (https://gnomad.broadinstitute.org/) databases and has not been previously reported in the literature. Multiple in silico prediction tools support a deleterious effect.[5]

After detailed genetic counseling and consideration of the variable phenotypic severity associated with ARCN1-related disorders, the couple elected to continue the pregnancy.

Follow-up

Close surveillance was undertaken, with weekly follow-up examinations. Due to concern for preterm labor, antenatal corticosteroids were administered at 32+3 weeks of gestation for fetal lung maturation. Doppler studies remained normal until 34 weeks of gestation. Thereafter, recurrent absent end-diastolic flow in the umbilical artery was observed, prompting an increase in surveillance to twice-weekly assessments.

At 35+1 weeks of gestation, ultrasound examination demonstrated an estimated fetal weight (EFW) of 1281 g (<1st percentile) and a maximum vertical pocket of 3.2 cm. Doppler evaluation revealed increased umbilical artery resistance (PI 1.39), with normal middle cerebral artery (PI 1.92) and ductus venosus flow patterns.
At 35+4 weeks of gestation, the patient was admitted due to persistent absent end-diastolic flow in the umbilical artery and abnormal middle cerebral artery Doppler findings. A repeat course of antenatal corticosteroids was administered. Given the progressive deterioration of Doppler parameters and due to fetal compromise, delivery by cesarean section was undertaken at 35+5 weeks of gestation.

Following delivery, the neonate was admitted to the neonatal intensive care unit (NICU). Birth measurements were as follows: birth weight 1500 g (<3rd percentile), length 39 cm (<3rd percentile), and head circumference 27 cm (<3rd percentile). No obvious congenital anomalies were identified. The neonate remained hospitalized for 20 days. During hospitalization, chest radiography and cranial ultrasound revealed no pathological findings, and respiratory support was not required.

At discharge, the infant's measurements were weight 2030 g (<3rd percentile), length 46 cm (3rd percentile), and head circumference 31.5 cm (3rd percentile).

At the most recent follow-up, at 54 days of life, the infant demonstrates short body length and low body weight (both below the 3rd percentile), with head circumference between the 3rd and 10th percentiles. These postnatal growth findings are consistent with the growth restriction reported in ARCN1-related syndrome.

DISCUSSION

ARCN1-related syndrome was first described in 2016 by Izumi *et al.* and was initially associated with loss-of-function variants in the *ARCN1* gene.[1] The *ARCN1* gene, originally identified in 1995, is located on chromosome 11q23.3 and spans approximately 30 kb, comprising 10 exons. It encodes the delta subunit of the coatomer protein complex I (COPI), which plays a fundamental role in intracellular vesicular trafficking.[6]
In eukaryotic cells, protein transport from the rough endoplasmic reticulum is mediated by three major vesicular systems: COPI, COPII, and clathrin. COPI is a heptameric protein complex responsible primarily for retrograde transport from the Golgi apparatus to the endoplasmic reticulum, as well as intra-Golgi trafficking. Proper COPI function is essential for maintaining cellular homeostasis. Pathogenic variants in *ARCN1* disrupt COPI-mediated transport, leading to intracellular protein accumulation, activation of the endoplasmic reticulum (ER) stress response, and subsequent cellular dysfunction or apoptosis when compensatory mechanisms are exceeded.[1]

COPI-mediated transport is particularly critical for the intracellular trafficking of type I collagen, providing a mechanistic explanation for the prominent skeletal abnormalities observed in ARCN1-related syndrome. Disruption of this pathway induces ER stress in chondrocytes, resulting in impaired endochondral ossification and reduced bone growth.[7] Houck *et al.* proposed that the skeletal phenotype associated with ARCN1-related syndrome is driven primarily by ER stress–mediated cellular dysfunction rather than by a direct defect in collagen synthesis or metabolism.[8] Izumi *et al.* further emphasized the importance of COPI transport in skeletogenesis, particularly in mandibular bone formation. In addition, dysfunction of COPI has been implicated in neurodevelopmental involvement, likely through impaired vesicular transport of molecules essential for neurotransmitter release and intracellular RNA trafficking in neuronal cells.[1]

The clinical spectrum of ARCN1-related syndrome is remarkably broad, ranging from embryonically lethal presentations to milder phenotypes characterized by intrauterine growth restriction, micrognathia, and postnatal short stature, with most affected individuals having heights between −2 and −4 standard deviations for age and, in some cases, normal intellectual development.[3] Significant intrafamilial variability has been reported; Izumi

et al. described an affected mother with a relatively mild phenotype compared with her affected fetus, supporting the concept of variable expressivity.[1]

Additional features reported in ARCN1-related syndrome include developmental delay, microcephaly, preterm birth (with a mean gestational age of approximately 34 weeks), genitourinary anomalies—predominantly affecting males and commonly including hypospadias and micropenis—transient liver dysfunction, glycosylation abnormalities (particularly during intercurrent illness), hepatoblastoma, giant cell hepatitis, central precocious puberty, and cataracts. Due to the combined effects of prematurity and severe micrognathia, some affected individuals have required tracheostomy for airway compromise.[2,3,9] The wide phenotypic variability suggests that disease expression is multifactorial, and further studies are needed to refine genotype–phenotype correlations.[4]

Compared with previously reported fetal cases of ARCN1-related syndrome, the present case shares key prenatal features, including severe fetal growth restriction and rhizomelic limb shortening, while classical craniofacial anomalies were not prominent during prenatal ultrasound evaluation. This finding highlights the challenges of prenatal phenotypic recognition and underscores the limited sensitivity of ultrasound alone in identifying ARCN1-related syndrome. Consequently, comprehensive genomic testing plays a pivotal role in establishing a diagnosis when skeletal dysplasia and early-onset fetal growth restriction are identified.
The present report describes a novel heterozygous de novo variant in *ARCN1* (c.1313T>C; p.Leu438Pro), which expands the known molecular spectrum of ARCN1-related syndrome. The variant was classified as variant of uncertain significance / likely pathogenic, was absent from population and clinical databases, and was supported by multiple in silico prediction tools suggesting a deleterious effect. The fetal phenotype—characterized by severe growth restriction, microcephaly, short long bones, and preterm labor—is consistent with the reported spectrum of ARCN1-related disease. To our knowledge, this represents the first reported case from Greece and one of the few prenatally diagnosed cases described in the literature.

A limitation of the present report is the relatively short duration of postnatal follow-up. At the time of writing, the infant is 54 days old and demonstrates short body length and low body weight (both below the 3rd percentile), with head circumference between the 3rd and 10th percentiles. No additional structural anomalies or overt neurological abnormalities have been identified to date. However, given the well-documented phenotypic variability of ARCN1-related syndrome and the potential for progressive growth impairment and late-onset neurodevelopmental manifestations, long-term clinical follow-up is essential to better define the natural history associated with this novel *ARCN1* variant.

Given the de novo occurrence of the variant, the recurrence risk for future pregnancies is considered low, but not negligible, due to the possibility of parental germline mosaicism, estimated at approximately 1%. Accordingly, the couple was counseled regarding the option of invasive prenatal testing or preimplantation genetic testing for the *ARCN1* c.1313T>C (p.Leu438Pro) variant in future IVF pregnancies.[10]

CONCLUSION

In conclusion, this study represents the first reported case of ARCN1-related syndrome in Greece and identifies a novel ARCN1 variant, thereby expanding the known genotypic spectrum of this rare disorder. Although ARCN1-related syndrome is extremely uncommon, it should be considered in the differential diagnosis of fetuses presenting with severe growth restriction and micromelia. Ongoing close postnatal follow-up of the infant is planned in order to monitor growth and to detect additional clinical features that may emerge and further define the phenotype associated with this variant.

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