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CASE REPORT

Prenatal Diagnosis of Costello Syndrome: A Case Report

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ABSTRACT

Introduction: Costello Syndrome (CS) is a rare RASopathy caused by germline activating variants in the *HRAS* gene. The disorder presents with multisystem involvement and overlaps phenotypically with other RASopathies, making prenatal diagnosis challenging.

Case Report: We describe a gravida 2 woman referred for evaluation after a first-trimester scan revealed increased nuchal translucency (NT) and nasal bone hypoplasia. Subsequent ultrasound showed progressive fetal abnormalities including generalized edema, bilateral pleural effusion, redundant skin folds, tachycardia, echogenic bowel, and unilateral talipes equinovarus. Microarray analysis from chorionic villus sampling was normal. Whole exome sequencing detected a pathogenic *HRAS* variant (c.37G>T; p.Gly13Cys), confirming Costello Syndrome. Following counselling, the couple opted for medical termination. Post-termination examination correlated with ultrasound findings.

Conclusion: This case highlights the importance of integrating detailed fetal imaging with advanced genomic testing for the prenatal diagnosis of single-gene disorders such as Costello Syndrome. Early diagnosis facilitates informed decision-making and targeted counselling.

KEYWORDS

• Costello Syndrome • RASopathy • Prenatal Diagnosis • *HRAS* • Whole Exome Sequencing • Non-immune Hydrops • Talipes

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INTRODUCTION

Costello Syndrome (CS) is a rare autosomal dominant disorder within the group of RASopathies, resulting from activating mutations in the HRAS gene.[1,6] These mutations lead to abnormal functioning of the Ras/MAPK pathway, producing a wide spectrum of clinical abnormalities involving growth, craniofacial structures, the cardiovascular system, skin, and the nervous system.[2,3,4] Although most cases arise de novo, the overall incidence remains very low, with fewer than 150 molecularly confirmed cases reported worldwide.

Prenatal diagnosis is difficult because early ultrasound signs—such as increased NT, hydrops, polyhydramnios, tachyarrhythmia, or musculoskeletal abnormalities—are nonspecific and may resemble other RASopathies such as Noonan syndrome or cardio-facio-cutaneous syndrome. With the increasing availability of genomic sequencing, especially trio-based whole exome sequencing (WES), detection of pathogenic *HRAS* variants in utero has become feasible.

We report a prenatally diagnosed case of Costello Syndrome, emphasizing the role of ultrasound surveillance and WES in reaching a definitive diagnosis.

CASE REPORT

A 30-year-old gravida 2, abortus 1 woman, married for three years in a non-consanguineous relationship, presented for second-opinion evaluation following abnormal first-trimester screening. There was no family history of congenital anomalies, genetic disorders, or previous affected pregnancies. Her blood group was B Rh-positive.

First-Trimester Ultrasound

At 13 weeks 6 days, transabdominal ultrasound revealed:

- Increased nuchal translucency-3.38 mm (>95th percentile) (Figures 1)
- Normal ductus venosus A-wave and tricuspid flow
- The patient received counselling regarding further evaluation including FISH, chromosomal microarray analysis (CMA), and whole exome sequencing.

Genetic Investigations

Chorionic villus sampling with CMA revealed no clinically significant chromosomal abnormality. Due to persistent suspicion of a single-gene disorder, WES was advised.

Second-Trimester Findings

A targeted anomaly scan at 18 weeks demonstrated:

- Generalized fetal edema (anasarca)
- Bilateral mild–moderate pleural effusions (Figure 6)
- Redundant skin folds over limbs (Figure 3)
- Fetal tachycardia
- Echogenic bowel (grade 2)
- Depressed nasal bridge
- Unilateral left congenital talipes equinovarus (Figure 2)
- Thickened nuchal fold (Figure 5)

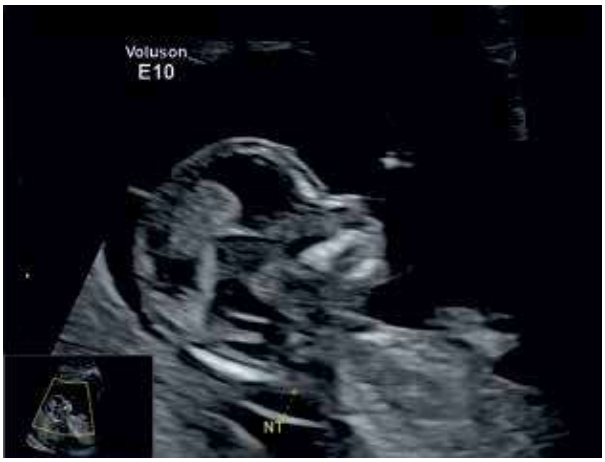


Figure 1: Sagittal scan showing increased nuchal translucency

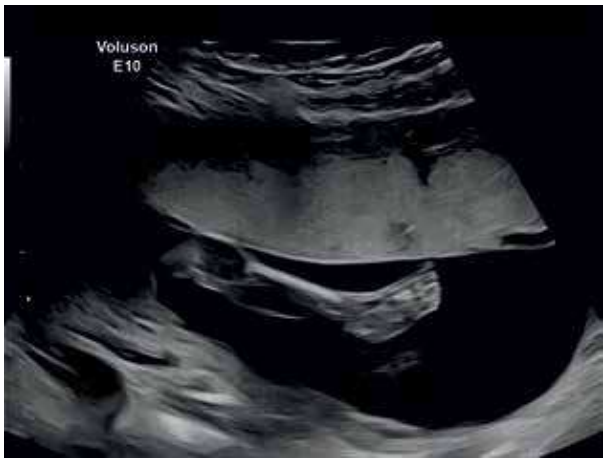


Figure 2: Unilateral congenital talipes equinovarus

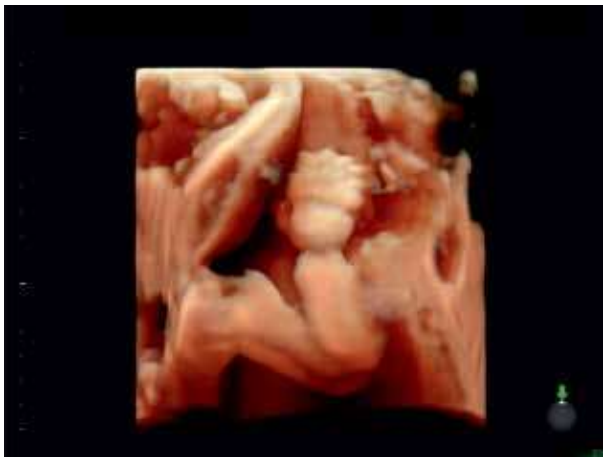


Figure 3: Redundant skin folds over fetal upper limb

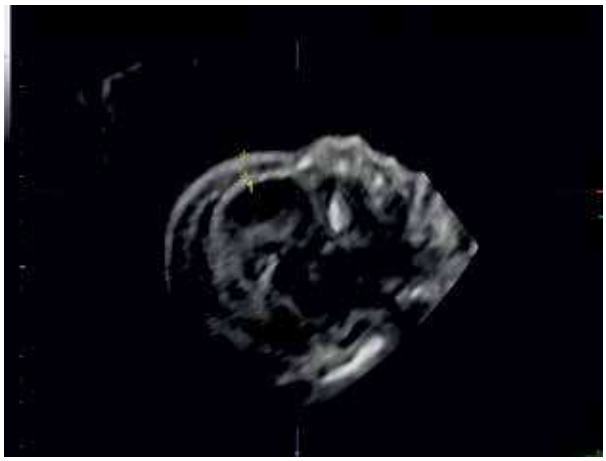


Figure 4: Scalp edema observed on anomaly scan

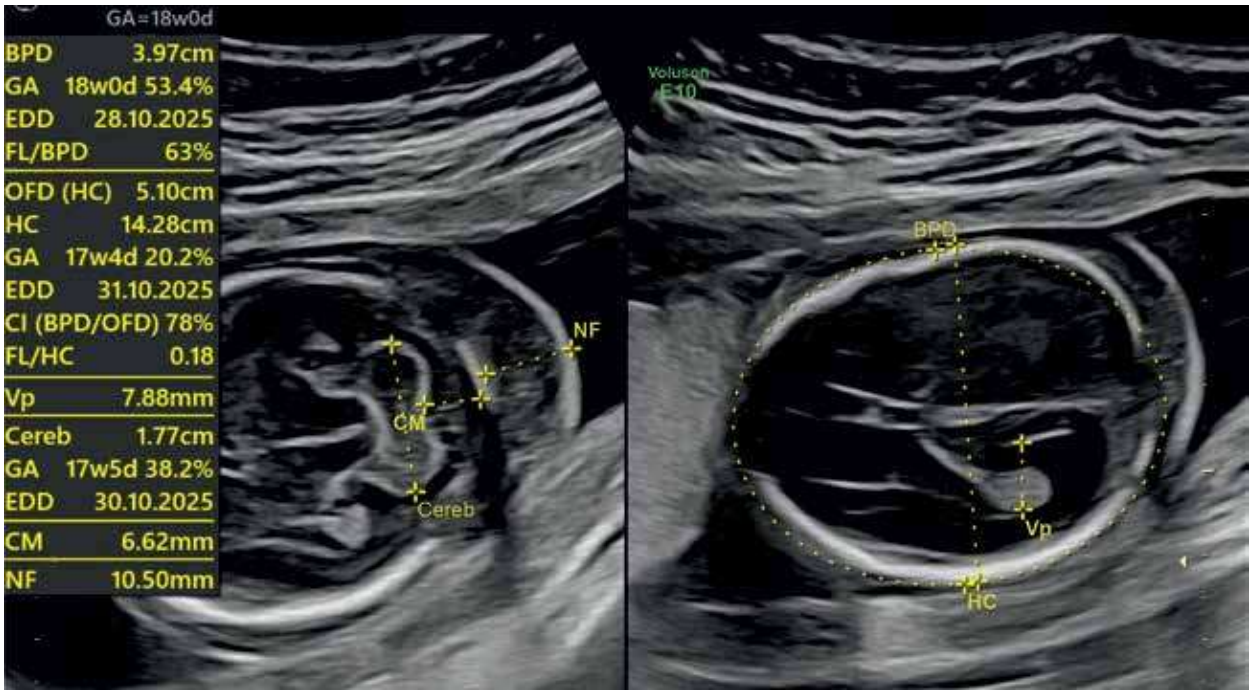


Figure 5: Thickened nuchal fold in second trimester

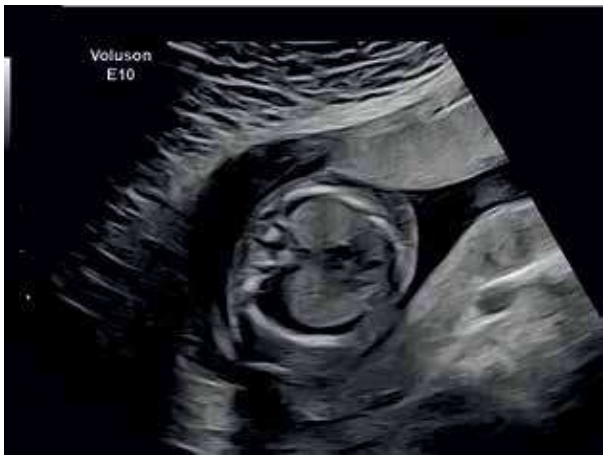
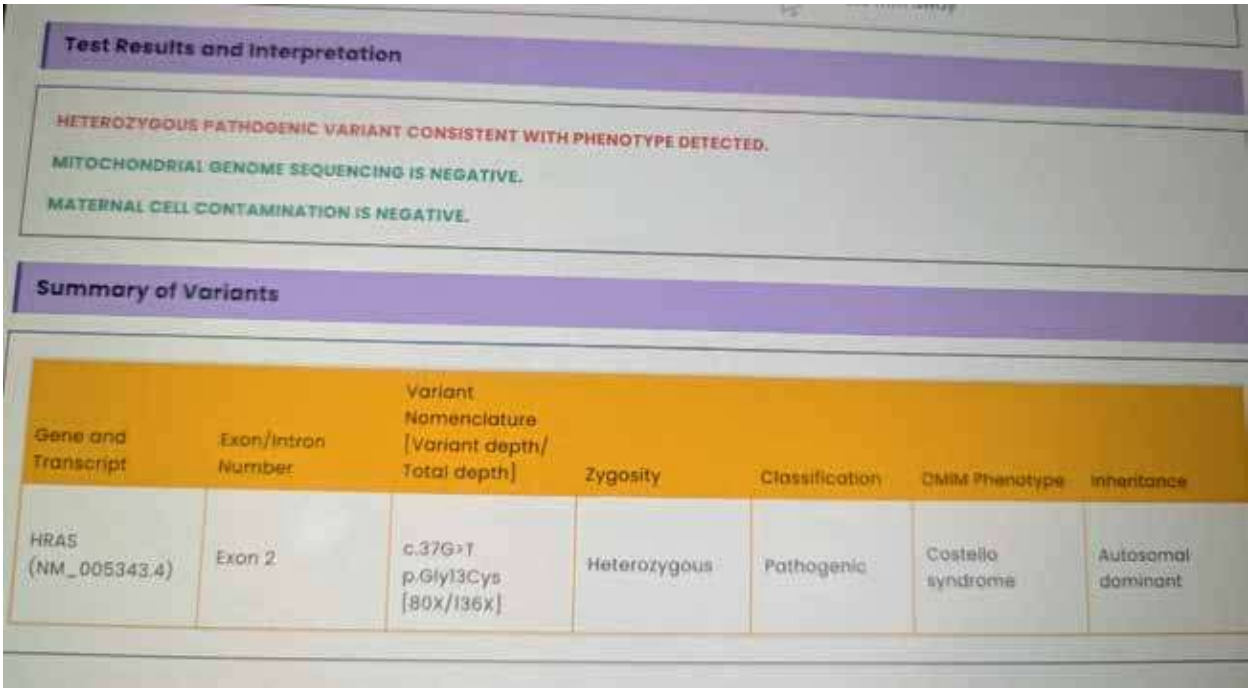


Figure 6: Bilateral pleural effusion suggesting non-immune hydrops

Figure 7: Post-termination photograph confirming prenatal findings

MOLECULAR DIAGNOSIS

Trio-based WES identified a pathogenic heterozygous *HRAS* variant: **c.37G>T (p.Gly13Cys), exon 2**, confirming Costello Syndrome. Figure 8 shows genetic report of Costello syndrome.



Test Results and Interpretation

HETEROZYGOUS PATHOGENIC VARIANT CONSISTENT WITH PHENOTYPE DETECTED.

MITOCHONDRIAL GENOME SEQUENCING IS NEGATIVE.

MATERNAL CELL CONTAMINATION IS NEGATIVE.

Summary of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygosity	Classification	OMIM Phenotype	Inheritance
HRAS (NM_005343.4)	Exon 2	c.37G>T p.Gly13Cys [80X/136X]	Heterozygous	Pathogenic	Costello syndrome	Autosomal dominant

Figure 8: WES report of Costello syndrome

After genetic counselling regarding prognosis and high risk of perinatal morbidity, the couple opted for medical termination.

Post-Termination Examination

- Physical examination of the fetus showed:
- Generalized edema
- Low-set ears
- Redundant skin on limbs
- Prominent heel pads
- Talipes equinovarus

These findings were concordant with prenatal imaging (Figure 7).

DISCUSSION

Costello Syndrome was first described in 1977 and is among the least common RASopathies.[5] The majority of affected individuals carry de novo activating mutations in exon 2 of *HRAS*, most commonly substitutions affecting codons 12 and 13. The p.Gly13Cys variant identified in our case has been previously associated with severe prenatal phenotypes.

Prenatal manifestations of CS are heterogeneous. Reported ultrasound findings include increased NT, polyhydramnios, hydrops fetalis, fetal arrhythmia, large head size, and redundant skin folds. However, these features overlap with other syndromes, making targeted genetic testing essential.

With increasing availability, WES has emerged as a powerful tool for diagnosing unexplained fetal anomalies, especially when CMA is normal and ultrasound suggests a syndromic pattern. In this case, WES provided a definitive diagnosis, enabling appropriate counselling regarding prognosis and recurrence.

Early and accurate identification of CS is clinically important, as severe cases may result in perinatal demise, while survivors require long-term multidisciplinary care.

CONCLUSION

Costello Syndrome should be considered in fetuses presenting with increased NT, hydrops, redundant skin, and musculoskeletal abnormalities. Integration of high-resolution ultrasound with molecular testing—

particularly WES—significantly improves diagnostic accuracy. This case underscores the role of genomic technology in prenatal care and highlights the value of early diagnosis for informed parental decision-making.

Ethical Considerations

Written informed consent was obtained from the parents for publication of clinical details and images. Institutional guidelines for case reporting were followed.

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