

(EP11.17) Case report: compound heterozygous variants of the COL1A1 gene and implications for prenatal diagnosis of osteogenesis imperfecta

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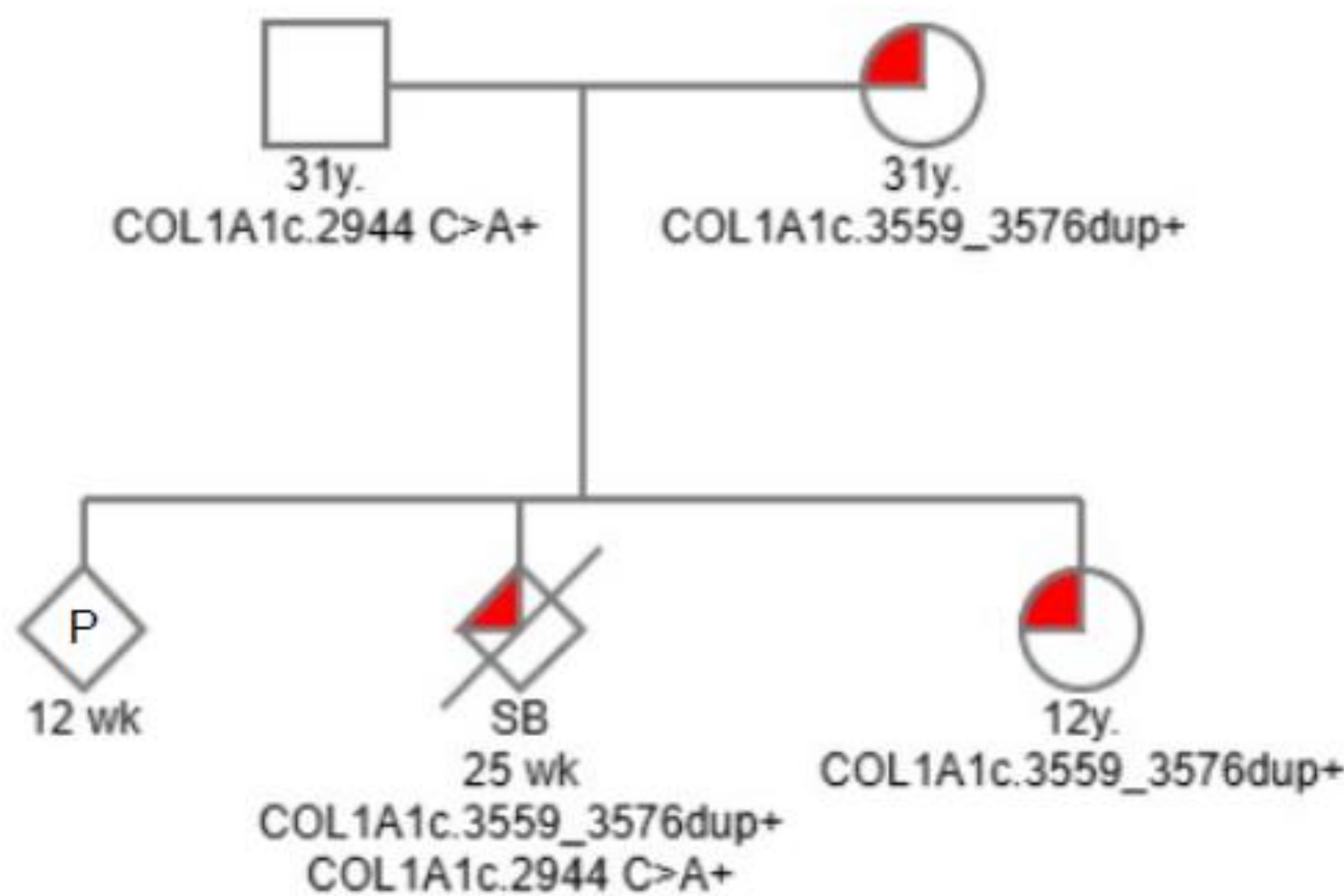
Introduction

Osteogenesis imperfect (OI) is a connective tissue disorder that can cause bone fragility, congenital bowing of long bones, and easy fractures. OI is clinically and genetically heterogeneous, with over 1,000 pathogenic variants identified inCOL1A1 alone.

De novo etiology accounts for approximately 20-30% of OI cases, dominant inheritance accounts for 60% of cases, and recessive inheritance accounts for 5-10% of cases, with complex etiology increasingly being documented.

This case report adds to a few other reports of compound heterozygosity in COL1A1-related OI.

Family Pedigree



Ultrasound Discussion

OI does not affect fertility. OI type III has not been associated with an increased risk for IUFD^[5]. Therefore, the condition may be passed down from parent to offspring. OI type III usually presents with significant prenatal ultrasound findings, including fractures, bowing of long bones, and bone demineralization, features also characteristic of perinatal lethal OI (type II)^[4].

Currently ACMG recommends an early ultrasound examination at 13-14 weeks for OI type II (perinatal lethal) vs 16-20 weeks for OI type III^[2]. However, there may be a perinatal lethal phenotype associated with other types of OI, as evidenced by cases of compound heterozygosity. This recommendation is worth reexamining.

Case Report

We present a case of a fetus affected by autosomal dominant, COL1A1-related OI. A 12 week NT / 1st trimester anatomy scan was unremarkable. 20-week anatomy scan findings of bilateral femoral bowing and shortened long bones were consistent with an OI diagnosis. An IUFD was diagnosed at 25 weeks gestation. Genetic testing on products of conception included a SNP microarray and skeletal dysplasia panel. The microarray returned normal, male results. The panel identified two heterozygous COL1A1 variants:

- COL1A1c.2944C>A(p.P982T), a variant of unknown significance(VUS) associated with OI type I and Ehlers-Danlos syndrome.
- COL1A1c.3559_3576dup(p.G1187_P1192dup), a likely pathogenic variant causative of OI type III

The VUS was identified in the healthy father of the pregnancy, and the likely pathogenic variant was identified in the affected mother.

Genotype / Phenotype Discussion

The COL1A1c.2944C>A(p.P982T)variant has been identified in at least one individual with Ehlers-Danlos syndrome^[7]. However, the mechanism of disease is questionable. The COL1A1c.3559_3576dup variant is a known cause of OI type III. Notably, there are other case reports of individuals with compound heterozygosity in COL1A1 who have an OI/EDS phenotype^[1]. It is not known what the full phenotypic spectrum of COL1A1 compound heterozygosity is.

There are biallelic lethal forms of dominant skeletal dysplasias such as achondroplasia^[6]. Theoretically, compound heterozygosity for certain COL1A1 variants could be perinatal lethal.

Current OI recurrence risk estimates factor in parental mosaicism, present in 5-8% of all cases.^{[3][8]} This may underestimate the true recurrence risk, as unidentified germline variants may also be contributory.

Conclusion

- ★ All pregnancies at risk of OI may benefit from an early detailed anatomy ultrasound.
- ★ A skeletal dysplasia panel and/or whole exome sequencing should be considered in the prenatal diagnosis of OI, even when there is a known familial variant.
- ★ Future studies should focus on the clinical outcomes of pregnancies affected by OI with compound heterozygosity, digenic inheritance, double heterozygosity, and other complex etiology.

Contact & References

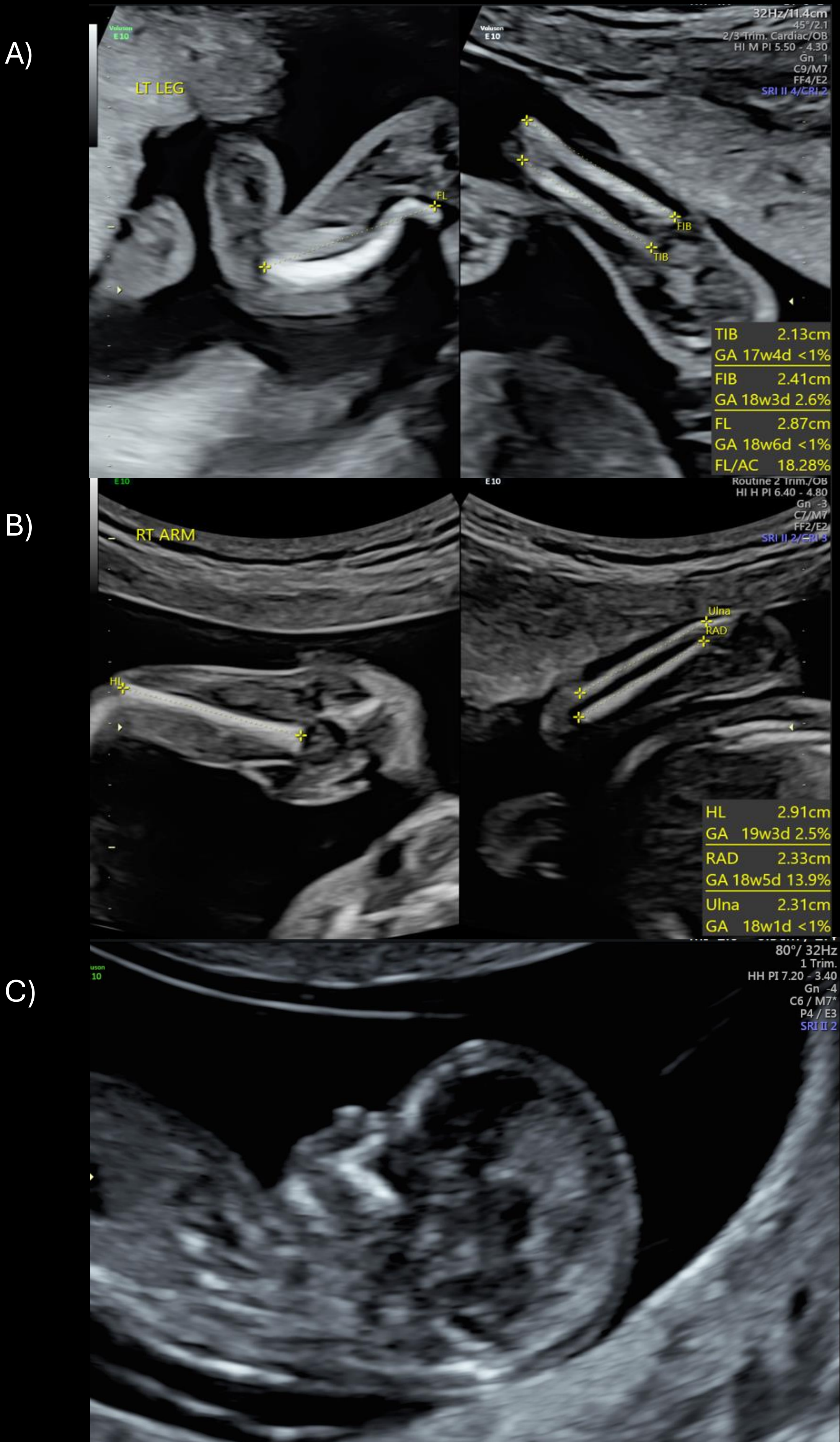


Image1: Anatomy ultrasound at 21 weeks 3 days gestational age showing A) Campomelia and shortening of the femur and tibia B) Shortening of the humerus, radius, and ulna C) Normal skull thickness and thorax.