Mid-trimester ultrasound findings in tricho-hepato-enteric syndrome: A case report

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Abstract. Tricho-hepato-enteric (THES) syndrome is a severe congenital diarrheal disorder. It is caused by homozygous or compound heterozygous mutations in the *SKIC3* (THES1) or *SKIC2* (THES2) gene. Primary manifestations include nine clinical signs: Intractable diarrhea, hair abnormalities, facial dysmorphism, IUGR, immunodeficiency, skin abnormalities, liver disease, congenital cardiac defects and platelet anomalies in the 96 cases reported to date. A case of early, isolated severe fetal growth restriction with a non-placental etiology is presented, consistent with postnatal findings reported in the literature. Furthermore, this case introduces two novel prenatal ultrasound findings: Severe echogenic bowel, and dolichocephaly in contribution to the limited body of knowledge. Trio-whole exome sequencing (WES) analysis revealed that the embryo was compound heterozygous for two mutations in *SKIC2*, both of which were of parental origin. The report also discusses potential mechanisms underlying the observed ultrasound signs, highlighting that the expanded application of WES in prenatal settings will add more cases of sporadic disorder

Introduction

Tricho-hepato-enteric (THES) syndrome is a rare and severe congenital diarrheal disorder, also known as syndromic diarrhea (1). With a prevalence of ~1 in 1,000,000 births, only 96 neonatal cases have been reported to date (2). Currently, there is only one single incidental reference regarding its prenatal diagnosis (3). The present case report seeks to expand the knowledge base by offering novel insights into the prenatal ultrasound findings associated with THES syndrome.

Historically, Stankler *et al* (4) first described this condition in 1982, followed in 1994 by Girault *et al* (5) THES is classified into two types, THES1 and THES2, which are caused by homozygous or compound heterozygous mutations in the SKI3 subunit of superkiller complex (*SKIC3*, formerly *TTC37*) and SKI2 subunit of superkiller complex (*SKIC2*, formerly *SKIV2L*) genes, respectively (6). Intractable diarrhea (100% of cases) that persists even with bowel rest is the hallmark symptom and typically manifests within the first days of life but can be delayed up to 8 months (2). Other phenotypic findings include hair abnormalities (90%) such as thin, sparse, wooly (trichorrexis nodosa) and brittle hair, significant facial abnormalities (84%) such as a prominent forehead and cheeks, broad nose, long philtrum and hypertelorism. IUGR/SGA is frequent, observed in 70% of the *SKIC3*-mutated and 86% of the *SKIC2*-mutated patients clinically explored (2). Most affected children fall below the 10th percentile (30 cases) in growth charts or even below the 3rd centile (27 cases) (1). A defective immune system is frequently diagnosed (50%) with low immunoglobulin levels and platelet disorders are present in 73% of cases (2). Skin abnormalities, such as 'café-au-lait' spots, are observed in 39-53% of patients (2). Liver disorders, including cholestatic jaundice, cirrhosis, or siderosis, are more prevalent in *SKIC2*-mutated patients (88%) compared with those with *SKIC3-mutations* (51%) (2). Rare cardiac defects (20%), such as aortic insufficiency, septal defects, peripheral pulmonary stenosis, and Tetralogy of Fallot, have also been documented (1,2).

THES syndrome is part of a broader family of congenital diarrheal disorders, which also includes microvillous inclusion disease (MVID) and congenital tufting enteropathy (7). These conditions share the life-threatening intractable diarrhea requiring parenteral nutrition and intestinal transplantation (6,7). Despite differing histological and genetic profiles, their pathogenic mechanisms appear similar. Specifically, intestinal biopsies from patients with THES revealed mild

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Abbreviations: THES, tricho-hepato-enteric syndrome; WES, whole exome sequencing; FGR, fetal growth restriction; EB, echogenic bowel

Key words: severe EB, severe dolichocephaly, isolated severe early FGR, THES, WES, prenatal diagnosis

to severe villous atrophy in the intestinal brush border (6,8). The primary function of the microvillous brush border is the formation of a surface responsible for absorption and digestion. Notably, villi begin to develop in the fetus around the ninth week of gestation (9).

Prenatal diagnosis of THES remains limited due to its rarity. By contrast, conditions such as MVID frequently present with detectable prenatal ultrasonographic abnormalities, particularly in the third trimester. According to Sun *et al* (10), among 47 cases of MVID, ultrasound findings revealed echogenic bowel, bowel dilation, and polyhydramnios. The sole prenatal case of the THES was incidentally reported by Zhou *et al* (3), involving a patient with a homozygous mutation in *SKIC2*. In the present case, additional ultrasonographic findings were included, and the prenatal association will be further explored.

Case presentation

The present study was a case report of a 34-year-old healthy pregnant woman G2P2 who was referred for a mid-trimester fetal anomaly ultrasound scan due to fetal growth retardation of the fetus. The pregnancy and delivery of the first child was uneventful. The couple did not report consanguinity and the family history was not significant. The patient denied any teratogenic exposure or bleeding during the pregnancy. The gestational age was 22 weeks and 4 days based on the crown rump length of the first-trimester scan. The measurements of detailed fetal biometry were performed and noted below. The INTERGROWTH-21st charts and their measurement techniques for all parameters were used.

Biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and Estimated Fetal Weight-fell below the 3rd centile for the gestational age. The only exception was the occipital-frontal diameter (OFD), evaluated at the 43.9th centile. The ratio BPD/OFD corresponded to the cephalic index of 0.67 (CI normal range: 0.74-0.83) which is indicative of dolichocephaly (Fig. 1). Concerning the long bones, both extremities were underdeveloped below the 3rd centile. No structural anomalies were detected in the fetal organs, the fetal sex was male, and the amniotic fluid was normal by the measurement of the deepest pocket. Doppler parameters for the median uterine artery (PI 25.7th percentile) and umbilical artery (PI 37.8th percentile) were within normal limits. The bowel appeared echogenic according to the criteria developed by Slotnick and Abuhamad (11), with a grade 3 based on echogenicity relative to the surrounding bone, such as the fetal iliac crest (12) (Fig. 2).

Based on the International Society of Ultrasound in Obstetrics and Gynecology guidelines (13), the diagnosis indicates an early onset of apparently isolated fetal growth restriction (FGR) accompanied by dolichocephaly and a severe form of echogenic bowel (EB). Given these findings, the authors proceeded with an amniocentesis to obtain a sample of amniotic fluid for the purpose of prenatal testing and a molecular analysis to determine the underlying causes of the FGR.

Due to the superior diagnostic yield of Whole Exome Sequencing (WES), which ranges from 4-12% in cases of isolated FGR (14,15), compared with chromosomal microarray analysis (CMA) (16,17) it was decided to proceed with WES. Additionally, WES was performed on both parents, implementing a Trio-WES approach. DNA was isolated from the amniotic fluid sample and parental peripheral blood. Following exome amplification, sequencing by next generation sequencing was performed using the NovaSeq 600 Sequencing System (Illumina, Inc.). The samples were prepared for sequencing using Nonacus Cell3 Target Nexome (cat. no. NGS_C3T_NEX_FR; Nonacus) and NovaSeq 6000 SP Reagent Kit v1.5 (300 cycles) (cat. no. 20028400). The final library concentration was calculated by Qubit dsDNA BR assay kit (Invitrogen; Thermo Fisher Scientific, Inc.) and 0,9 nM of loading concentration was used. Short Reads Pair End sequencing of 150 bp was performed using the NovaSeq 6000 Sequencing System (Illumina, Inc.). Quality and integrity of processed samples was assessed using the log file generated by DRAGEN, which provides the exact depth and metadata of the index case. Demultiplexing of the sequencing data was performed with Binary Base Call BCL Convert (Illumina, Inc.) and Alignment and Variant Calling with DRAGEN Bio-IT platform (Illumina, Inc.). Fastq files were uploaded and all variants in genes, associated with known genetic disorders and syndromes (according to the OMIM database), were analyzed using Varsome Clinical (Saphetor) and the bioinformatics databases.

All genes that are associated with known genetic disorders and syndromes (according to the OMIM database) were analyzed using Varsome Clinical (Saphetor) and other bioinformatic tools, including Splice AI (https://spliceailookup.broadinstitute.org/), Primate AI (https://github.com/Illumina/PrimateAI), CADD (https://cadd.gs.washington.edu/), REVEL (https://sites.google.com/site/revelgenomics/) and SIFT (https://sift.bii.a-star.edu.sg/).

All findings were evaluated according to the international literature and the American College of Medical Genetics and Genomics (ACMG) guidelines (18). The reference genome was GRCh37/hg19.

Bioinformatic analysis of the Trio-WES results revealed that the embryo was compound heterozygous for two nonsense mutations in the *SKIC2* gene. The embryo carried the c.3187C>T (p. Arg1063Ter) and the c.1528C>T (p. Arg510Ter) mutations in *SKIC2*, inherited from its mother and father, respectively. Mutation c.3187C>T (Variation ID: 1323596) causes a premature stop codon in exon 26 (of 28) while mutation c.1528C>T (Variation ID: 2152010) causes a premature stop codon in exon 14. Both mutations are expected to disrupt the form and function of the produced protein and are categorized as pathogenic based on the ACMG/AMP guidelines (18).

Moreover, bioinformatic analysis of the Trio-WES results revealed that the embryo was also compound heterozygous for two missense mutations in the *SERPINA1* gene. The embryo carried the c.1177C>T (p.Pro393Ser) and the c.839A>T (p.Asp280Val) mutations in SERPINA1, inherited from its father and mother, respectively. Both c.1177C>T (Variation ID: 289135) and c.839A>T (Variation ID: 17975) are categorized as pathogenic based on the ACMG/AMP guidelines (18).

Simultaneously, quantitative fluorescence (QF) PCR, conventional karyotype, and CMA (a-CGH) were performed

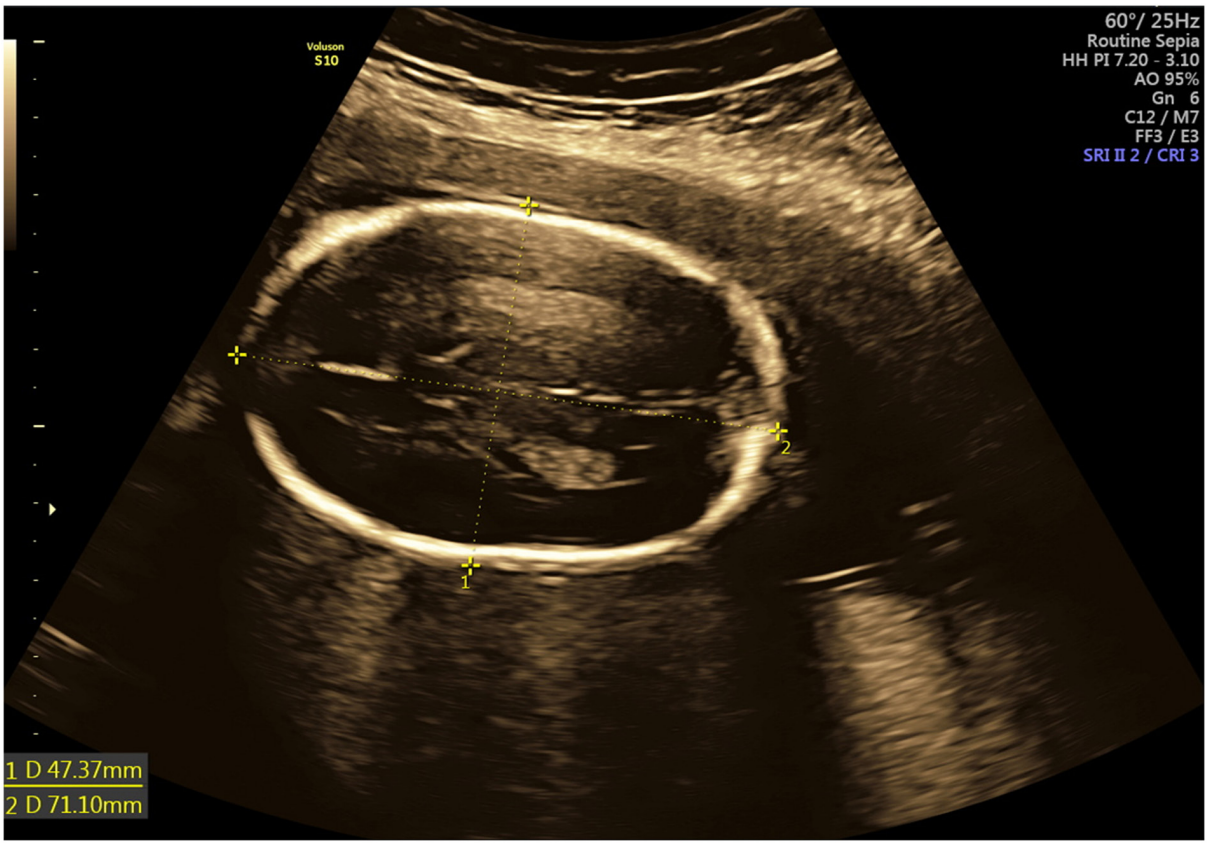

Figure 1. Severe dolichocephaly of the fetal head. Low cephalic index (ratio biparietal diameter/occipital-frontal diameter).

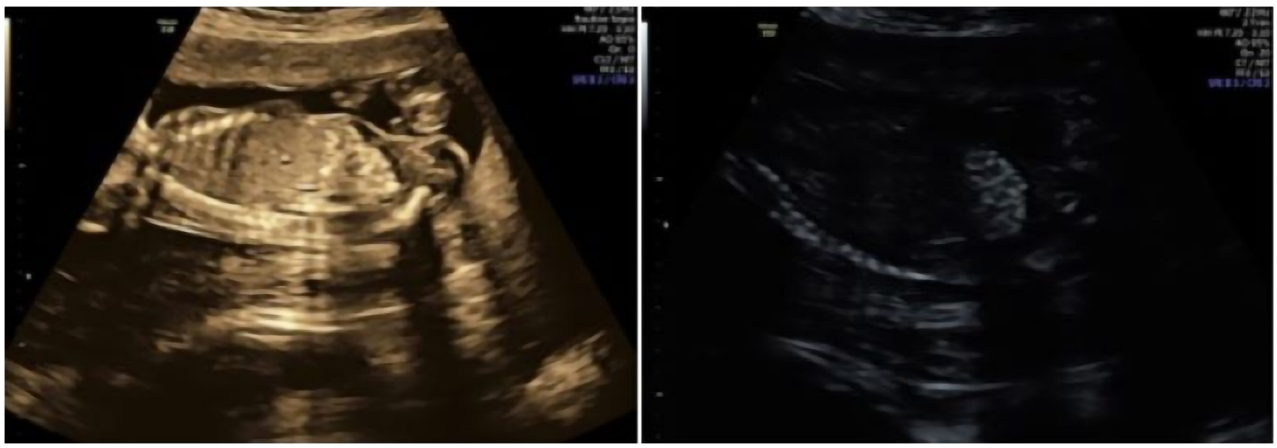

Figure 2. Right: Severe form of echogenic bowel. Left: By lowering the gain setting, the iliac crest is almost lost before bowel imaging (Grade 3).

to reduce turnaround time. An extensive molecular analysis of the CF transmembrane regulator (*CFTR*) gene to establish the *CFTR* mutation spectrum was also performed. The results were normal.

While awaiting the results, a follow-up ultrasound was performed at 28 weeks and 4 days' gestation. The biometric measurements, including BPD, AC, and all long bone lengths, remained below the 3rd percentile, indicating no significant changes. However, the OFD had increased to the 91.8th percentile, leading to a lower cephalic index of 0.65. The amniotic fluid index was found to be within normal limits. It has been reconfirmed that there are no structural anomalies. Furthermore, Doppler assessments for the median uterine artery (PI at the 24.9th percentile) and umbilical artery (PI at the 65.8th percentile) were also normal.

In retrospect, following the diagnosis of THES and given the well-known clinical feature of a prominent forehead, the facial angle was measured and found to be within the normal range (128.12˚±10.99˚) (19) (Fig. 3).

The patient was counseled regarding the anticipated spectrum of neonatal outcomes. After considering the information, the couple opted for the termination of the pregnancy. Fetal demise was induced *via* an intra-amniotic injection of Digoxin administered 24 h before the scheduled abortion procedure.

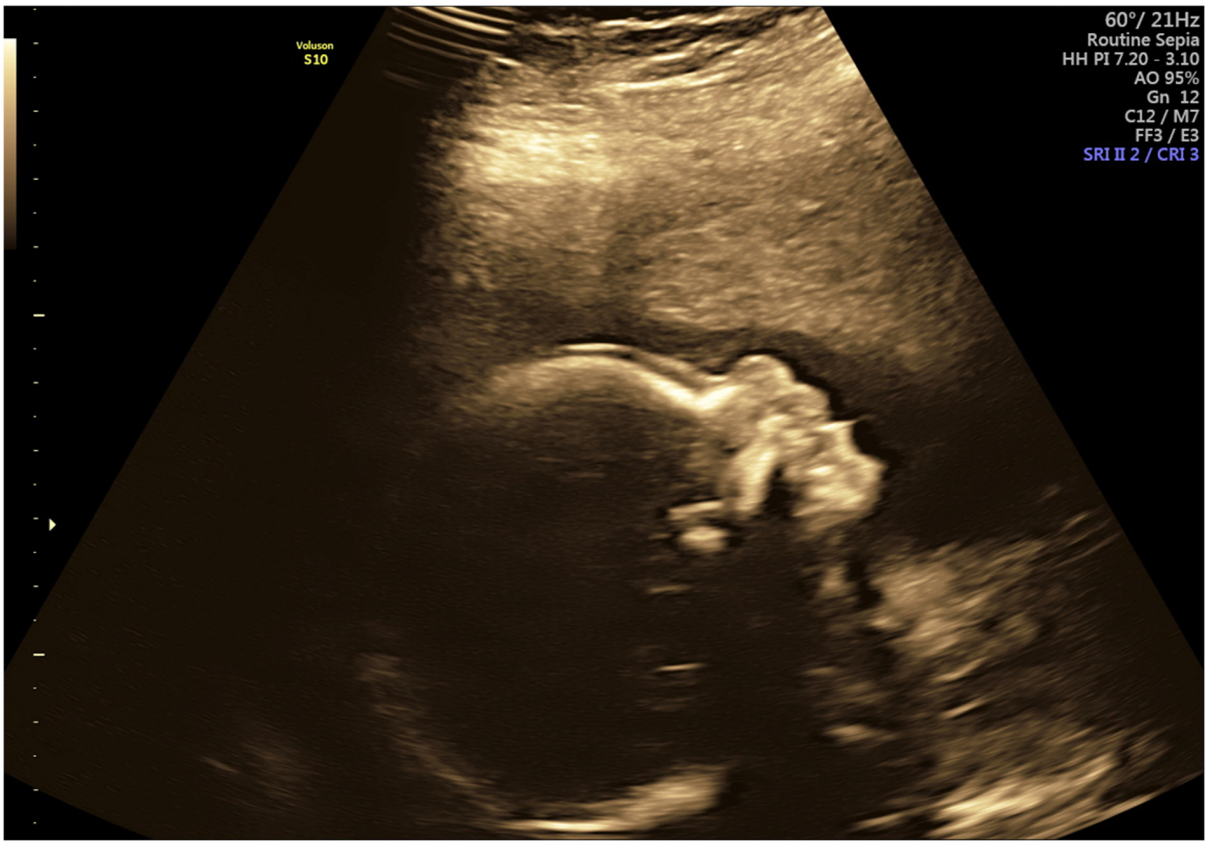

Figure 3. Fetal profile. Normal upper facial angle.

Ultimately, the couple chose not to proceed with a postmortem examination of the fetus.

Discussion

The FGR of the presented case has distinctive characteristics that prompt consideration of various potential etiologies, which can be included or excluded from the present diagnostic work-up. Firstly, the FGR was notable for the absence of any 'ultrasound apparent structural anomalies' except the EB (soft marker). Secondly, the condition is not associated with abnormal Doppler parameters, thereby allowing to exclude placental insufficiency as a primary cause (20). Thirdly, it is manifested as an early onset FGR which is symmetrical across all biometric parameters of the fetus according to the gestational age.

Given that there were no other obvious risk factors from maternal history (maternal age, exposure to toxins and substance abuse) and negative results from the mother's serological tests for TORCH infections, the focus must shift towards genetic etiologies, including chromosomal anomalies, submicroscopic and monogenic disorders (20).

Chromosomal anomalies contribute to 19% of fetal FGR cases, with isolated chromosomal anomalies accounting for 3.4-9.6%. Aneuploidy is the most common, in 5.8% of cases, with triploidy predominant 26 weeks before and trisomy 18 more prevalent after. Occasionally FGR in trisomy 21 is associated with placental deficiency and abnormal umbilical artery impedance (20). Confined placental mosaicism, particularly trisomy 16, occurs in 9-16% of cases (20,21). Submicroscopic anomalies (for example, microdeletions/duplications) account for 4% of isolated FGR cases (17), and monogenic disorders range from 4-12% (14,15), with equal postnatal prevalence at 11% (22). Meler *et al* (20) classify FGR into two groups: Symmetric FGR, affecting all fetal biometry and linked to syndromic features the present case report and asymmetric FGR, with only short long bones (below 3SD), often due to skeletal dysplasia.

The second significant finding from the fetal anomaly scan was the presence of a severe EB, a condition observed in ~0.2 to 1.8% of cases, which can occasionally be transient. A systematic review by D'Amico *et al* (23) for the incidence of isolated EB identified chromosomal anomalies (primarily trisomy 21), in 3.3%, cystic fibrosis in 2.2%, congenital infections (mostly CMV) in 2.2%, and gastrointestinal anomalies in 2.1% of cases. EB coexists with FGR in 12.6% of cases, The most likely mechanism involved the redistribution of blood flow away from the splanchnic circulation towards more vital organs such as the brain, resulting in mesenteric ischemia or edema of the intestinal wall and consequently in intestinal dysfunction. In the context of THES, this hypothesis is doubtful due to the absence of any signs of placental insufficiency or ischemia. Thus, villous atrophy remains the only plausible explanation for the intestinal dysfunction observed. Nevertheless, this hypothesis warrants further confirmation. By the authors' diagnostic work-up, all known EB etiologies were ruled out and a follow-up scan in 3rd trimester revealed no gastrointestinal anomalies. EB has also been linked to

MVID (another form of congenital diarrhea), with a 7% incidence, occasionally presenting with polyhydramnios but without postnatal bowel obstruction (10).

The severe dolichocephaly of the fetus lacks any discernible intrauterine cause, such as breech presentation or oligohydramnios and any cranial deformity indicative of sagittal craniosynostosis (24,25). This condition likely results in the prominent postnatal forehead described in most cases in the literature in the cases of THES (26). While dolichocephaly is well-explained in cases of sagittal synostosis, its occurrence in the absence of such synostosis according to a theory is attributed to a modular growth driven by gene transcription between the tissues, which can describe any level of organization, for example, the calvarium or specific areas of the cranial vault (27).

The results of the Trio-WES that was performed revealed that the embryo had compound heterozygous mutations in the *SKIC2* gene which it had inherited from its parents. Homozygous and compound heterozygous mutations in *SKIC2* have been associated with THES2 (OMIM#614602). Trio-WES results also revealed that the embryo was also compound heterozygous for mutations in the *SERPINA1* gene. Mutations in *SERPINA1* have been associated with Alpha-1-antitrypsin (AAT) deficiency (OMIM#613490). The most common symptom of AAT deficiency is emphysema which appears in the 3rd-4th decade and a less common symptom is liver disease which can appear in the neonatal period (28). The *SERPINA1* gene mutations were not expected to have contributed to the fetal phenotype.

From the literature, the only case of prenatal diagnosis of THES is in a study of 51 fetuses with isolated and severe FGR where Trio-WES was performed (3). One of them had a homozygous *SKIC2* mutation, causing THES. The only difference compared with the present case is the asymmetrical pattern of FGR. The fetus was preterm born at 36 weeks due to fetal distress.

The present study contributed valuable novel prenatal findings on THES, enriching the limited existing literature and building upon the few up-to-date studies in prenatal settings. Moreover, the present study highlighted a significant knowledge gap, emphasizing the need for further investigations. Finally, it potentially provided insights into diagnostic challenges faced by clinicians. In detail, it revealed the significance of the use of Trio-WES as part of the diagnostic work-up for FGR, particularly in cases without any pathognomic findings. Therefore, it has the potential to influence clinical guidelines, patient care, and future research.

The present case report has several limitations. First, it presented a single case rather than a case series due to the extreme rarity of THES. Secondly, it lacked histopathological evidence, which could have provided additional valuable insights. Furthermore, the absence of postnatal data and longitudinal follow-up, although justified by the mother's personal choice for termination-leads to an unknown clinical course of the disorder and limits the predictive value of prenatal findings for patient outcomes. Given that this is one of the first reports describing this rare genetic disorder, the present study did not allow for an investigation of causal relationships due to the lack of comparative studies and controls.

Given the extreme rarity of this disorder, the prenatal findings alone may not be immediately applicable to real-world clinical practice. However, due to the valuable novel insights provided by this case report, these findings should be considered for further research and the broader application of fetal sequencing, particularly whole-exome sequencing (WES), in prenatal settings. Expanding such investigations will help identify a larger number of cases, thereby enhancing the external validity of the results.

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Availability of data and materials

The data generated in the present study may be found in the European Nucleotide Archive (ENA), under accession number PRJEB85611 or at the following URL: https://www.ebi.ac.uk/ena/browser/text-search?query=PRJEB85611.

Authors' contributions

AlM, AnM and NZ substantially contributed to the conception and the design of the study, contributed to manuscript drafting or critical revisions on the intellectual content, approved the final manuscript version to be published, agreed to be accountable for all aspects of the work, so that any questions relating to research integrity or scientific accuracy in any part of the present study are appropriately investigated and resolved. IP performed quantitative fluorescence PCR, conventional karyotype, CMA (a-CGH) and bioinformatic analysis of the Trio-WES, contributed to manuscript drafting or critical revisions on the intellectual content, approved the final manuscript version to be published, agreed to be accountable for all aspects of the work, so that any questions relating to research integrity or scientific accuracy in any part of the study are appropriately investigated and resolved. AA agreed to be accountable for all aspects of the work and to have a major role in patient consultation for the treatment plan, so that any questions relating to research integrity or scientific accuracy in any part of the study are appropriately investigated and resolved. AlM, AnM, NZ and IP confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The parents provided written informed consent for the publication of their data (including their fetus) and the fetal images.

Competing interests

The authors declare that they have no competing interests.

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