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A novel de novo MECOM frameshift variant presenting with early fetal edema and cardiac anomalies: a case report with literature review

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Case Report

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Abstract

Background

Germline pathogenic variants in *MECOM* are associated with a rare multisystem disorder traditionally characterized by radioulnar synostosis, thrombocytopenia, and bone marrow failure. However, prenatal presentations remain poorly defined.

Case presentation:

We report a fetus with severe abnormalities detected at 13^{+} weeks of gestation. Ultrasound revealed increased nuchal translucency, generalized edema, micrognathia, right clubfoot, reversed a-wave in the ductus venosus, and complex cardiac anomalies. The pregnancy was terminated after counseling because of the poor prognosis. After a negative copy number variation sequencing result, trio whole-exome sequencing identified a novel de novo heterozygous frameshift variant in *MECOM*, NM_004991.4:c.2403dup (p.Gly802ArgfsTer37), classified as likely pathogenic according to ACMG/AMP criteria.

Conclusions

This case expands the prenatal phenotype of *MECOM*-associated disorders. The early gestational onset, generalized edema, and prominent cardiac abnormalities indicate that *MECOM*-related disease may manifest prenatally as a cardiovascular-dominant condition, distinct from the more familiar postnatal pattern of skeletal and hematologic disease.

Background

MECOM encodes transcription factors that play essential roles in hematopoietic stem cell maintenance and embryonic development(1–4). Germline pathogenic variants in *MECOM* have been associated with a rare autosomal dominant disorder, historically described as radioulnar synostosis with amegakaryocytic thrombocytopenia type 2, and more broadly recognized as *MECOM*-associated syndrome(2, 3, 5–12).

The phenotype is highly heterogeneous, classically involving thrombocytopenia, bone marrow failure, and radioulnar synostosis, but also including renal, auditory, immune, and cardiac abnormalities(13–15). More recently, severe perinatal presentations, including fetal hydrops and early neonatal death, have been reported(16–18). However, the prenatal phenotype remains insufficiently characterized.

Here, we describe a fetus with early-onset multisystem abnormalities detected at 13^{+} weeks of gestation. Trio whole-exome sequencing(WES) identified a novel de novo *MECOM* frameshift variant. This case highlights a severe early prenatal presentation dominated by generalized edema and complex cardiac abnormalities and contributes to the expanding phenotypic spectrum of *MECOM*-associated disorders.

Case presentation

A 25-year-old gravida 2, para 0 woman was referred at 13^{+} weeks of gestation because of fetal abnormalities detected on ultrasound. Her previous pregnancy had ended in missed miscarriage at approximately 9 weeks of gestation without genetic evaluation. The current pregnancy was naturally conceived. There was no history of consanguinity, teratogenic exposure, radiation exposure, or maternal infection during pregnancy. The family history was unremarkable for congenital anomalies, skeletal abnormalities, hematologic disease, or known genetic disorders.

Ultrasound examination at 13^{+} weeks revealed multiple fetal abnormalities. The crown-rump length was 6.85 cm, and the nuchal translucency (NT) measured 5.0 mm. Generalized subcutaneous edema was observed. Additional findings included micrognathia and right clubfoot. Doppler assessment demonstrated a reversed a-wave in the ductus venous (DV). Cardiac evaluation showed an abnormal three-vessel view, suspicious for complex congenital heart disease (CHD), including possible pulmonary atresia with coarctation of the aorta, suspected ventricular septal defect (VSD), moderate tricuspid regurgitation (TR), and mild mitral regurgitation (Figure 1).

Given the severity of the abnormalities and the expected poor prognosis, the pregnancy was terminated after counseling. Postmortem examination was declined.

After a negative copy number variation sequencing (CNV-seq) result, trio WES was performed. Sequence alignment and variant calling were conducted using standard pipelines, and variant interpretation followed the ACMG/AMP guidelines. A heterozygous duplication in *MECOM*, NM_004991.4:c.2403dup, predicted to result in a frameshift and premature termination (p.Gly802ArgfsTer37), was identified. The variant was absent in both parents, indicating a de novo event, and was not present in population databases.

The variant was classified as likely pathogenic based on ACMG/AMP criteria, including PVS1 (predicted loss-of-function), PS2 (de novo occurrence), PM2 (absence from population databases), and PP3 (supportive computational evidence). Given that loss-of-function is a known disease mechanism of *MECOM*, the frameshift variant was considered to provide strong evidence (PVS1) for pathogenicity.

Written informed consent was obtained from the patient for publication of this case and any accompanying images.

Discussion and Conclusions

This case highlights a previously underrecognized aspect of *MECOM*-associated disease: severe fetal edema may arise in the absence of overt hematologic dysfunction and instead be driven by cardiovascular abnormalities. Notably, our case represents the earliest gestational presentation reported to date, with abnormalities detected as early as 13+ weeks of gestation, and is associated with a novel de novo frameshift variant. Beyond this, our findings raise the possibility that *MECOM*-associated disease may manifest along a continuum of developmental severity, with distinct phenotypic features emerging at different stages of fetal and postnatal development.

In our fetus, there was no direct evidence of hematologic dysfunction during gestation. Instead, the presence of significant structural cardiac abnormalities together with abnormal venous Doppler findings indicates that cardiovascular dysfunction and impaired fetal hemodynamics likely played a major role in the development of edema. This observation challenges the conventional view that fetal hydrops in *MECOM*-associated disease is primarily secondary to severe anemia or bone marrow failure(17).

Mechanistically, *MECOM* should not be regarded solely as a hematopoietic regulator. Accumulating evidence indicates that *MECOM* functions as a central transcriptional regulator integrating multiple developmental signaling pathways, including Notch and Wnt signaling, as well as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β) pathways, which are essential for cell fate determination, angiogenesis, and cardiovascular morphogenesis(19). Disruption of these pathways may therefore lead to primary abnormalities in vascular and cardiac development, providing an alternative explanation for fetal hydrops independent of hematologic failure.

This concept is further supported by epigenetic(20) and single-cell transcriptomic(21) studies demonstrating that *MECOM* plays a critical role in endothelial lineage specification and is actively expressed in cardiac endothelial cells, where it regulates arteriovenous gene expression during early heart development. These findings position *MECOM* as a regulator of developmental timing and lineage balance rather than a gene restricted to hematopoiesis.

In this context, the predominantly cardiac phenotype observed in our fetus may reflect an early developmental perturbation affecting cardiovascular lineages, whereas the classical skeletal and hematologic features reported in postnatal cases may represent later or system-specific manifestations. This developmental stage–dependent expression of phenotype may partly explain the discrepancy between prenatal and postnatal presentations in *MECOM*-associated disorders.

Current evidence suggests that both variant type and variant location contribute to phenotypic variability in *MECOM*-associated disorders. Recurrent missense variants clustered within the C-terminal zinc finger domains, particularly around the ZF8/ZF9 region, are consistently associated with classical skeletal and hematologic manifestations(2,5,9). In contrast, loss-of-function variants, especially those occurring outside these hotspot regions, appear more frequently associated with severe early-onset phenotypes, including fetal hydrops and adverse perinatal outcomes(17,18). The frameshift variant identified in our fetus lies outside this recurrent hotspot and may preferentially disrupt developmental pathways critical for cardiovascular formation, thereby contributing to the observed phenotype.

Importantly, phenotypic heterogeneity is not solely determined by variant location but may also reflect differential sensitivity of distinct developmental systems to *MECOM* dysfunction. For example, certain variants have been reported to cause isolated skeletal phenotypes without hematologic abnormalities(22), while others present with broader multisystem involvement(13). These observations support the concept that *MECOM* variants may differentially affect specific developmental lineages.

Most reported cases of *MECOM*-associated disorders are identified postnatally, typically presenting with thrombocytopenia or bleeding manifestations shortly after birth. In contrast, prenatal manifestations remain poorly characterized. To better delineate fetal presentations, we focused on cases with prenatal or perinatal onset (Table 1), rather than those diagnosed solely based on postnatal hematologic abnormalities. Among these cases, early manifestations are predominantly characterized by structural and hemodynamic abnormalities, including fetal hydrops and cardiac defects, whereas classical skeletal or hematologic features are often absent or not yet clinically apparent. This pattern suggests that prenatal *MECOM*-associated disease represents a stage-specific developmental presentation rather than simply an earlier detection of postnatal phenotypes(23).

Emerging evidence further indicates that severe *MECOM*-related phenotypes may extend to intrauterine fetal demise and pregnancy loss, suggesting that disruption of *MECOM* function during critical developmental windows may lead to non-viable phenotypes(16,23). Taken together, these findings support a developmental continuum ranging from postnatal hematologic disease to prenatal hydrops and, in more severe cases, early fetal lethality.

Importantly, the apparent discrepancy between prenatal and postnatal phenotypes may reflect both biological evolution and limitations of fetal assessment. Features such as radioulnar synostosis may be difficult to detect before ossification is complete(24,25), and hematologic abnormalities may not be clinically evident until later in gestation or after birth. Therefore, the absence of classical skeletal or hematologic findings should not preclude consideration of *MECOM*-associated disease in the prenatal setting.

Taken together, these observations support a dual-pathway model for *MECOM*-associated fetal hydrops: one driven by hematologic dysfunction due to bone marrow failure, and another mediated by primary cardiovascular and vascular developmental abnormalities. These pathways are not mutually exclusive and may predominate at different developmental stages(4,23).

From a clinical perspective, these observations suggest that in fetuses presenting with early-onset edema, abnormal venous Doppler findings, and structural cardiac anomalies, underlying genetic etiologies, including *MECOM*-related disorders, should be considered even in the absence of overt hematologic dysfunction.

This study has several limitations. First, postmortem examination was not performed, limiting detailed evaluation of skeletal and internal anomalies. Second, no direct fetal hematologic assessment was available, and subclinical dysfunction cannot be excluded. Third, no functional studies were performed to

validate the pathogenicity of the identified variant. Finally, the limited number of prenatal and perinatal cases restricts definitive conclusions regarding genotype–phenotype relationships.

In conclusion, this case expands the prenatal spectrum of *MECOM*-associated disorders and supports the concept that *MECOM*-related disease may manifest as a cardiovascular-dominant developmental disorder in early gestation. Integration of emerging molecular and developmental evidence suggests that *MECOM* dysfunction affects multiple lineage-specific pathways, providing a unifying framework for understanding the marked phenotypic heterogeneity observed across prenatal and postnatal presentations.

Abbreviations

WES
whole-exome sequencing
CNV-seq
copy number variation sequencing
LOF
loss of function
CHD
congenital heart disease
NT
nuchal translucency
DV
ductus venosus
TR
tricuspid regurgitation

Declarations

Ethics approval and consent to participate

Ethical approval was waived by the institutional ethics committee because this study is a single case report and does not constitute human subjects research.

Consent for publication

Written informed consent was obtained from the patient for publication of this case and any accompanying images.

Availability of data and materials

Datasets from this study are available upon reasonable request from the corresponding author.

Competing interests

The authors have no conflicts of interest to disclose.

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Authors' contributions

J.L. and F.L. designed the study. B.L. and W.Y. collected the clinical data. W.Y. performed the genetic analysis. J.L. drafted the manuscript. F.L. revised the manuscript. All authors read and approved the final manuscript.

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Table

Table 1. Reported prenatal and perinatal severe presentations of MECOM-associated disorders

Case ID	Stage	GA / onset	Prenatal findings	Outcome	Postnatal findings	Testing	MECOM variant	Variant class	Predominant system
Present case	Prenatal	13^{+} w	Increased NT (5.0 mm); fetal hydrops; complex CHD suspected; tricuspid and mitral regurgitation; reversed DV a-wave; micrognathia; clubfoot	TOP at 14 w	Not assessed (autopsy declined)	Trio WES	c.2403dup (p.Gly802ArgfsTer37)	Frameshift / LOF	Cardiovascu / hemodynam
Wall et al., 2023	Prenatal	20^{+4} w	Fetal hydrops; normal NT at 13 w; no prenatal skeletal anomalies detected	IUFD at 20 w	Truncus arteriosus; VSD; bilateral RUS; fetal anemia inferred	Trio WGS	c.2763T>A	Nonsense / LOF	Cardiovascu + hematolog
Dash et al., 2021 (P1)	Perinatal	29^{+6} w	Sinusoidal fetal heart tracing	Neonatal death (<12 h)	Hydrops; thrombocytopenia/bone marrow failure; gray matter heterotopia	Trio ES	c.2772-4A>G	Splice / LOF	Hematologic
Dash et al., 2021 (P2)	Perinatal	29^{+6} w	Sinusoidal fetal heart tracing	Neonatal death (>1 month)	Hydrops; thrombocytopenia/bone marrow failure; left clubfoot; no RUS reported	Trio ultra-rapid GS	c.2812C>T (p.Arg938Trp)	Missense	Hematologic
Jaspersen et al., 2024	Perinatal	33 w	Fetal hydrops; fetal bradycardia; decreased fetal movements	Neonatal death (3 d)	Hydrops; bone marrow failure; placental villous edema; no structural CHD or RUS identified	Trio WES	c.2249G>A (p.Arg750Gln)	Missense	Hematologic hydrops

Clinical, prenatal, and genetic findings of reported severe fetal-onset and perinatal MECOM-associated disorders. Cases primarily diagnosed postnatally on the basis of thrombocytopenia or bleeding manifestations without significant prenatal or perinatal complications were not included.

Abbreviations: NT, nuchal translucency; TOP, termination of pregnancy; IUFD, intrauterine fetal demise; VSD, ventricular septal defect; CHD, congenital heart disease; RUS, radioulnar synostosis; WES, whole-exome sequencing; WGS, whole-genome sequencing; ES, exome sequencing; GS, genome sequencing; LOF, loss-of-function.

Figures

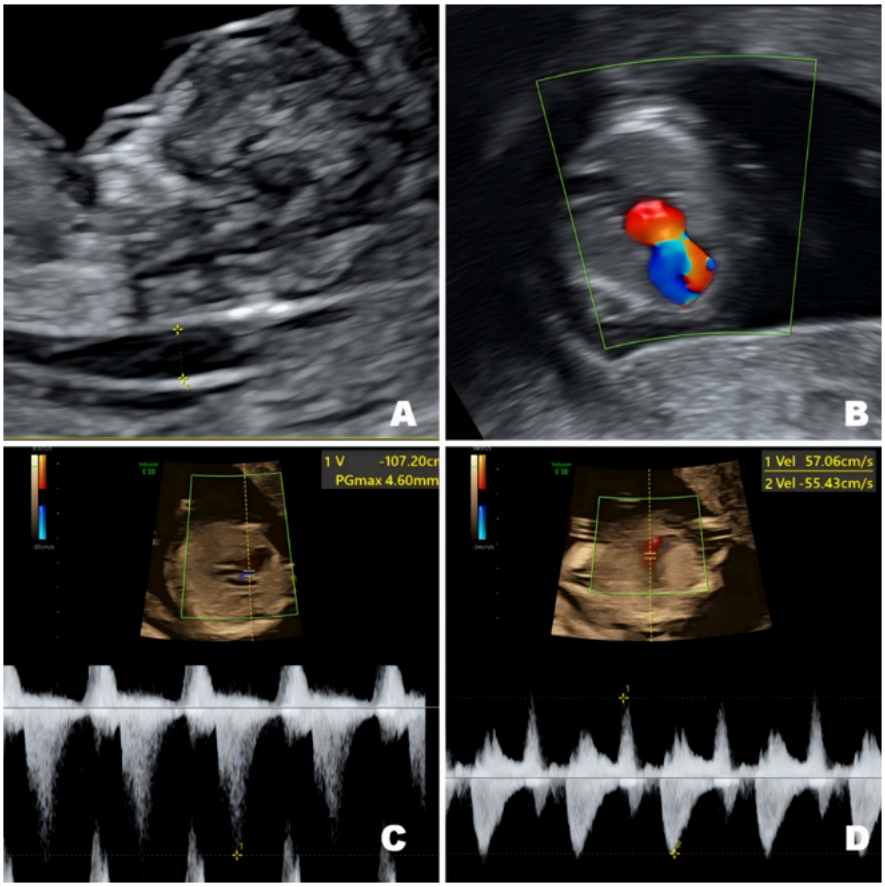


Figure 1

Prenatal ultrasound findings in a fetus carrying a novel *MECOM* frameshift variant.

(A) Increased nuchal translucency and early fetal edema identified at 13+ weeks of gestation.

(B) Abnormal cardiovascular flow pattern detected during first-trimester fetal cardiac assessment.

(C) Severe tricuspid regurgitation demonstrated on Doppler examination.

(D) Abnormal ductus venosus Doppler waveform showing reversed a-wave flow.

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