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A novel *MECOM* gene variant causes severe thrombocytopenia in a neonate: a case report and review of the literature

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Abstract

Background Mutations in the *MECOM* gene have been recognized as a causative factor in MECOM-associated syndrome, which encompasses a spectrum of hematologic and extra-hematologic manifestations. Hematologic features range from isolated thrombocytopenia to severe bone marrow failure, while extra-hematologic manifestations may include skeletal, cardiac, renal, and other abnormalities. Here, we present a case of a Han Chinese newborn with a previously unreported variant in the *MECOM* gene.

Case presentation We report a 0-day-old female Han Chinese neonate who presented with severe thrombocytopenia and intracranial hemorrhage, ultimately succumbing to multiple organ failure and intracranial hemorrhage on the third day after birth. Genetic sequencing identified a heterozygous frameshift variant, c.157_158del, within the *MECOM* gene. This variant led to a substitution of the 53rd amino acid from methionine to glycine, terminating at the 54th amino acid. A comprehensive review of literature indicated that *MECOM* gene mutations included missense (68.3%), deletion (8.5%), splice site (8.5%), frameshift (7.3%), and nonsense (7.3%) mutations. Patients with missense mutations frequently exhibited radioulnar synostosis, while bone marrow failure was more commonly associated with the other four types of mutations.

Conclusion This study adds a novel variant of the *MECOM* gene to the current body of knowledge. In addition, we provide a comprehensive summary of previously reported cases. This case expands the phenotypic spectrum of *MECOM* variants and underscores the potential for rapid progression to a life-threatening condition.

Keywords *MECOM* gene, Thrombocytopenia, Gene variant, Radioulnar synostosis, Case report

Background

The *MECOM* gene, a complex locus located on chromosome 3q26.2, encodes myelodysplastic syndrome 1 (MDS1), ecotropic viral integration site 1 (EVI1), and MDS1-EVI1 through selective splicing of the N-terminus extremity [1, 2]. *MECOM* is expressed in hematopoietic stem cells and plays a crucial role in hematopoiesis and bone marrow differentiation [3, 4]. Variants in the *MECOM* gene can cause MECOM-associated syndrome, which presents with a wide range of phenotypes [5]. Hematologic features include mono or multi-lineage cytopenia, progressive bone marrow failure (BMF), and leukemia, often requiring hematopoietic stem

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cell transplantation (HSCT) [6–9]. As the number of reported *MECOM* variants increases, extra-hematologic features have also been identified, including radioulnar synostosis (RUS), cardiac and renal abnormalities, hearing loss, and other limb defects [10–13]. The clinical phenotypes vary among patients, depending on the location and type of variant, as summarized in Supplementary Table 1. Herein, we report a unique case in China with a novel *MECOM* variant, c.157_158del (p.Met53Glyfs*2). In addition, we review the genotypes and phenotypes of previously reported cases to further establish the characteristics of this syndrome.

Case presentation

The patient was a 0-day-old newborn female of Han Chinese ethnicity, born at 36 weeks of gestation to a gravida 3, para 2 woman, weighing 2650 g. She was delivered by emergent cesarean section owing to fetal distress, with Apgar scores of 6 at 1 min and 5 min. Her blood type was O, and RhD was positive. At birth, she presented with pallor, scattered ecchymosis across multiple areas of the body, mucosal bleeding, and respiratory failure, with minor hemorrhagic oozing also observed at venipuncture sites. Umbilical artery blood gas analysis showed a hematocrit of 0.08 and hemoglobin of 23 g/L. The patient required endotracheal intubation and mechanical ventilation. After red blood cell suspension transfusion, initial blood counts revealed severe thrombocytopenia (platelet count of 12×10^9/L), anemia (hemoglobin of 46 g/L), and leukopenia (leukocyte count of 1.11×10^9/L).

The patient was admitted to the neonatal intensive care unit at 3 hours of life for further treatment. During hospitalization, she was diagnosed with disseminated intravascular coagulation (DIC), with activated partial thromboplastin time (APTT) 73.10 seconds, prothrombin time (PT) 25.4 seconds, fibrinogen (FIB) 1.01 g/L, international normalized ratio (INR) 2.26, and D-dimer > 20 mg/L. She was supported with mechanical ventilation, correction of acidosis, and transfusion of fresh frozen plasma. Despite multiple transfusions of red blood cells and platelets, hemoglobin and platelet levels remained below normal (hemoglobin 106 g/L and platelets 11×10^9/L on day 3). She also received anti-infective treatment, cardiotonic therapy, vasopressors, and other symptomatic treatment. A peripheral smear showed enlarged pale staining areas of red blood cells, with a reticulocyte proportion of 1.5% and a negative direct Coombs test. Bone marrow aspiration was not performed owing to her severe condition. There was no clinical or laboratory evidence of neonatal sepsis, and tests for toxoplasma, rubella, cytomegalovirus, and herpes simplex virus (TORCH); hepatitis virus; and *Treponema pallidum* were negative. Physical examination on admission revealed poor mental status, decreased muscle tone in the extremities, and sluggish pupillary reflex to light. All other findings were normal. Bedside cranial ultrasound and electroencephalogram revealed severe intracranial hemorrhage and low voltage, respectively. Echocardiogram findings were suggestive of patent ductus arteriosus, patent foramen ovale, and pulmonary hypertension. Abdominal ultrasound indicated gastrointestinal hemorrhage. Despite all efforts, the patient died on the third day of life due to multiple organ failure and massive intracranial hemorrhage (detailed information can be found in the Supplementary Report).

The patient's parents were non-consanguineous and both had thalassemia. The mother, who shared the same blood type as the patient, had mild anemia during pregnancy (hemoglobin level of 97 g/L) and a history of induced abortion. Prenatal examinations showed no abnormalities, including no fetal hydrops, and she did not receive any medications during pregnancy that could lead to early-onset hemorrhagic disease in the newborn. The patient also had a 1-year-old brother who was in good health. Her grandfather had a history of mild anemia (specifics unknown).

Informed consent was obtained from the patient's parents, and Sanger sequencing was performed to discover the cause of the disease. A novel heterozygous *MECOM* frameshift mutation [NM_001105078: c.157_158del (p.Met53Glyfs*2)] was detected in the proband (Fig. 1A). This variant changed the 53rd amino acid from methionine (codon ATG) to glycine (codon GGT), followed by an early termination (Fig. 1B, C). The mutation was not found in the parents or elder brother (Fig. 1A, B). The variant was classified as pathogenic according to American College of Medical Genetics (ACMG) guidelines [14]. The "AutoPVS1" algorithm provided strong support for the PVS1 interpretation of p.Met53Glyfs*2, indicating pathogenicity [15]. The variant has not been previously reported in the Human Gene Mutation Database (HGMD) or Clinvar. Conservation analysis showed that the Met53 residue is highly conserved across mammalian species (including human, mouse, rat, chimpanzee, and bovine) using Clustal Omega [16] (Fig. 1D). Three-dimensional protein structure models of the wild type and mutant MECOM proteins were generated using SWISS-MODEL [17] (Fig. 2), indicating that the frameshift mutation caused early termination of amino acid synthesis, significantly altering the protein structure.

Discussion and conclusions

In this study, we described a rare case of MECOM-associated syndrome with a heterozygous *MECOM* pathogenic variant leading to pancytopenia at birth, severe thrombocytopenia, and massive intracranial hemorrhage.

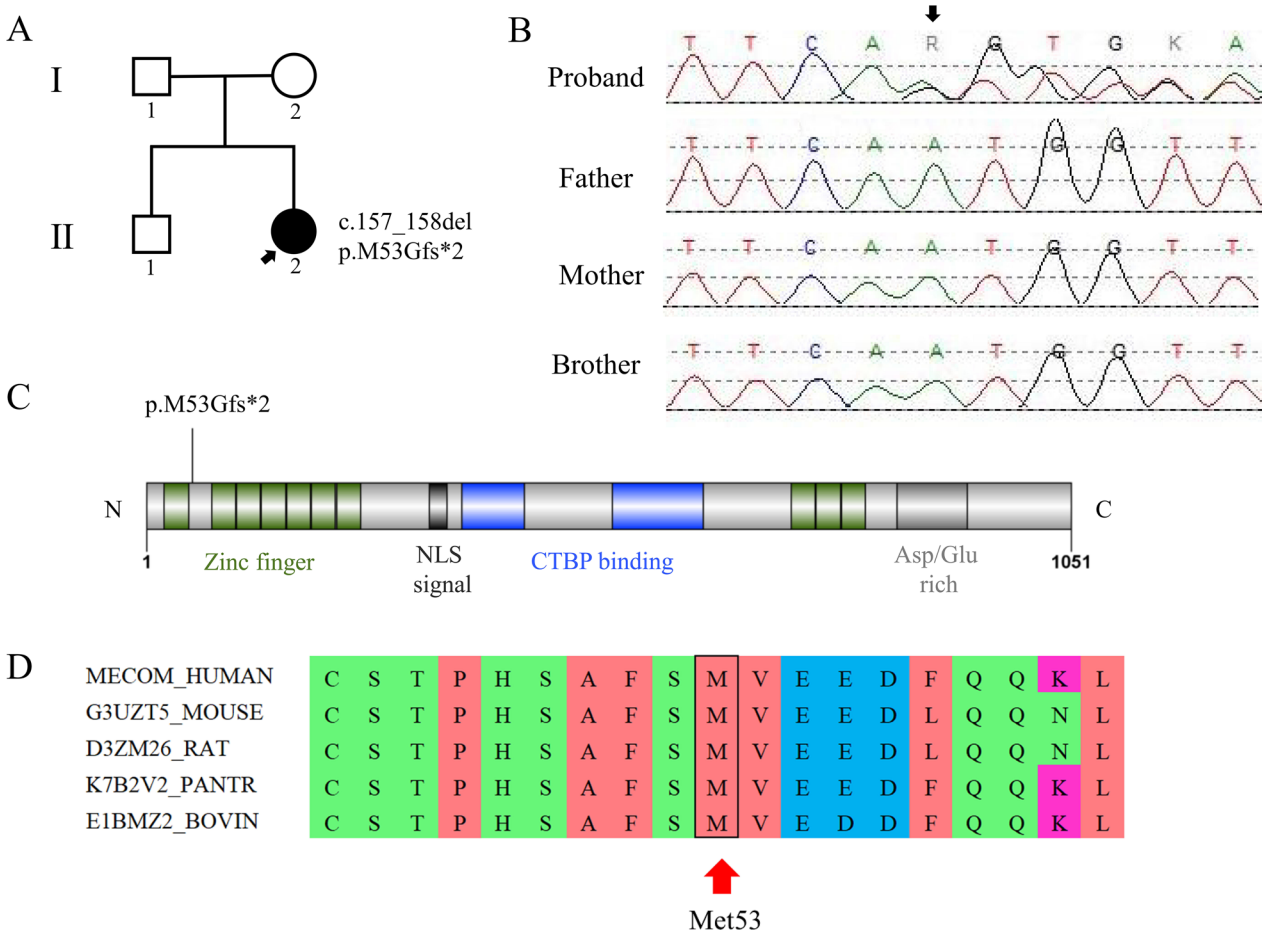

Fig. 1 Identification of a *MECOM* gene variant in the proband. **A** The family pedigree of the proband. **B** Sanger sequencing results for the family. The black arrow indicates the mutation site detected exclusively in the proband, which is absent in her parents and brother. **C** Schematic of the *MECOM* domain and the location of the novel c.157_158del (p.M53Gfs*2) variant. **D** Conservation analysis of the p.M53Gfs*2 variant, showing the conservation of the Met53 residue across different mammalian species, including human, mouse, rat, chimpanzee, and bovine. NLS, nuclear localization sequence; CTBP, C-terminal-binding protein

This case highlights the perinatal lethality of this syndrome, which may begin with abnormal intrauterine development. Dash *et al.* [12] described two infants born preterm with BMF and fetal hydrops, both of whom died. Unlike those cases, our patient did not present with BMF or hydrops. In addition, the mutation type in our case (frameshift) differed from the splice site and missense mutations described in those reports. To raise awareness of this disease, we reviewed all reported cases of *MECOM* variants. Over 80 cases have been reported worldwide (Supplementary Table 1) [5–12, 18–31].

The *MECOM* gene, which contains 24 exons, is located on chromosome 3q26.2 and encodes a transcriptional regulator and oncoprotein that plays an essential role in hematopoiesis, apoptosis, development, and cell differentiation and proliferation [32, 33]. Murine models show that *MECOM* is highly expressed in the urinary system, heart, lung, and limb buds during embryonic development, indicating its importance in multi-organ development [34]. *MECOM* variants have been reported to affect transcriptional activity by altering the folding stability of zinc finger motifs and the DNA-binding ability of the C-terminal domain of EVI1 [35, 36].

In 2012, the first MECOM-associated patient was reported: a girl with severe thrombocytopenia at birth who subsequently developed pancytopenia [18]. Single-nucleotide polymorphism (SNP) array analysis revealed a 751.3 kb deletion in the *MECOM* locus. Three years later, Niihori *et al.* [28] identified three patients with bilateral RUS and severe pancytopenia due to different heterozygous missense mutations in *MECOM*. *MECOM* mutations are considered causes of radioulnar synostosis with amegakaryocytic thrombocytopenia (RUSAT), which overlaps phenotypically with *HOXA11*-related

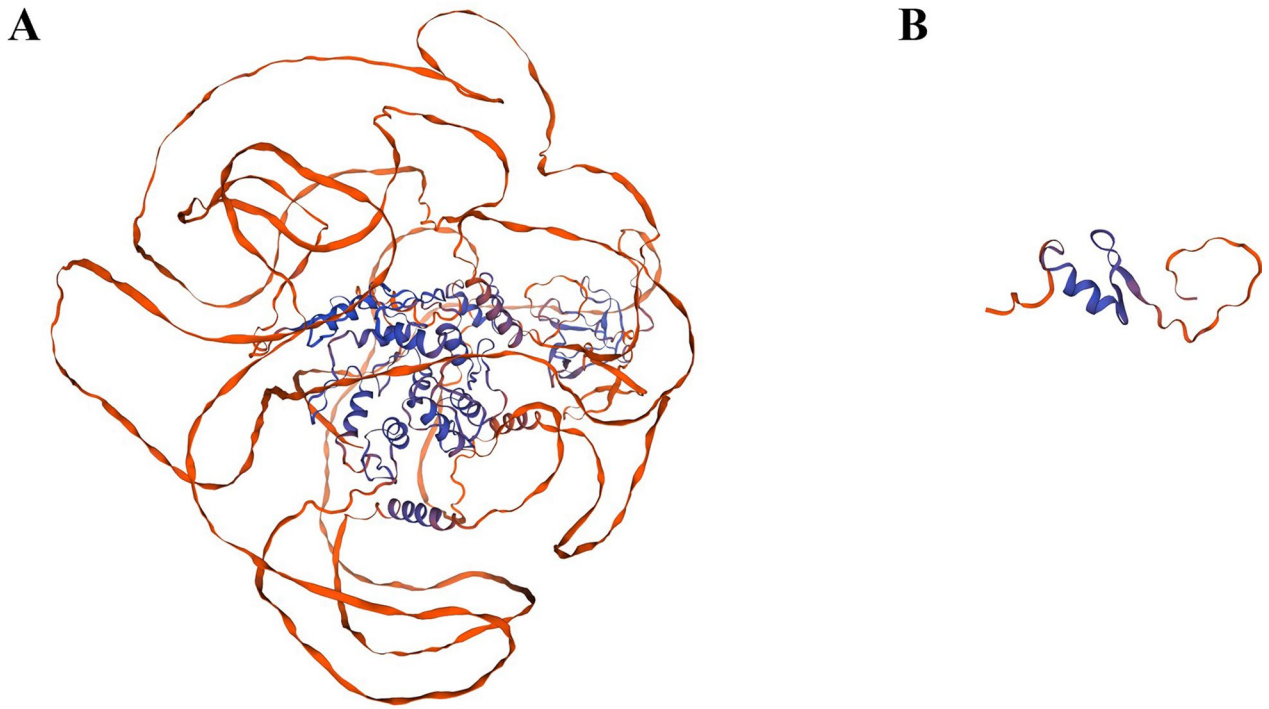

Fig. 2 Structures of the protein encoded by the *MECOM* gene. **A** Structure of the wild type MECOM protein. **B** Structure of the MECOM protein with the variant in c.157_158

RUSAT [37]. RUSAT is an autosomal dominant disorder characterized by proximal RUS and impaired pronation and supination of the forearm [38]. In the early postnatal period, bone marrow aspiration may show normal hematopoietic hyperplasia with decreased megakaryocytes, but pancytopenia may develop later. In 2018, Germeshausen *et al.* [5] identified 12 patients with *MECOM* mutations, finding that clinical phenotypes ranged from isolated RUS (with or without hematological abnormalities) to severe BMF (with or without musculoskeletal malformations). Other clinical features included clinodactyly, cardiac and renal abnormalities, hearing impairment, B-cell deficiency, and hypogammaglobulinemia. They proposed the term "MECOM-associated syndrome" to encompass the variable manifestations of this genetically heterogeneous disorder, with RUSAT as a subcategory. In 2022, Shen *et al.* [31] reported several missense variants, focusing on the ninth zinc finger motif of EVI1, and elucidated the relationship between mutation sites and phenotypic features. More recently, Voit *et al.* [32] reviewed the phenotypes and genotypes of MECOM-associated syndrome based on published data, noting that *MECOM* may regulate human hematopoietic stem cell maintenance and B-cell development [5, 11]. For patients with MECOM-associated syndrome and progressive BMF, HSCT is an effective early treatment, with most patients remaining healthy after transplantation, although some die from transplant-related complications [13].

Clinical phenotypes and associated genotypes of previously reported cases of MECOM-associated syndrome are summarized in Supplementary Table 1. *MECOM* variants have a wide range of mutation types, including missense (56 [68.3%] cases), deletion (7 [8.5%] cases), splice site (7 [8.5%] cases), frameshift (6 [7.3%] cases), and nonsense (6 [7.3%] cases) mutations. Among the 56 individuals with missense variants, 30.4% had BMF and 66.1% had RUS. Skeletal deformities (clinodactyly, overlapping fingers, short fingers, and clubfoot), cardiac malformations (atrial septal defect, aortic root dilation, tetralogy of fallot, patent foramen ovale, and myocardial atrophy), and renal and auricular abnormalities were also observed. RUS was predominantly found in patients with missense mutations, and Germeshausen *et al.* [5] suggested that partial loss of function of the C-terminal zinc finger domain may be the cause of this phenotype [39]. Other skeletal anomalies may involve the carboxy-terminal part of the EVI1 protein. For patients with deletion, splice site, and nonsense mutations, BMF (16 [80.0%] cases) and cardiac malformations were common, while RUS (3 [15.0%] cases) was rare, indicating the substantial impact of these mutations on hematopoietic and circulatory

systems. There have been six reported cases of patients with frameshift mutations: four deletion, one insertion, and one duplication [5, 20, 25, 26]. BMF was detected in five patients, all of whom underwent HSCT before the age of 2 years. Only one patient had RUS, while other extra-hematologic features included bilateral toe malposition, hip dysplasia, impaired hearing, and renal abnormalities. Overall, even patients with the same *MECOM* mutation type and site may present with diverse phenotypes, evolutions, and outcomes. The underlying mechanisms and genotype–phenotype relationships require further investigation.

In our study, we reported a Han Chinese newborn with a novel heterozygous frameshift mutation in the *MECOM* gene. The proband had pancytopenia at birth and persistent thrombocytopenia, with scattered skin ecchymosis, and intracranial and gastrointestinal hemorrhages. Cardiac abnormalities, including patent ductus arteriosus and patent foramen ovale, were also noted. Despite multiple transfusions and symptomatic treatment, her condition did not improve, and she died of multiple organ failure and intracranial hemorrhage. The clinical manifestations in this case were partially consistent with those reported in literature. The occurrence of DIC in this case may be linked to severe hematopoietic abnormalities caused by the *MECOM* gene mutation. *MECOM* is crucial for hematopoietic stem cell differentiation, and its mutation can result in thrombocytopenia and other deficiencies, predisposing the patient to coagulopathy. The prolonged PT and APTT also suggest possible liver involvement. Although MECOM-associated disorders mainly affect the hematopoietic system, bone marrow suppression and thrombocytopenia may indirectly impair liver function, exacerbating coagulopathy and accelerating progression to DIC. Owing to the patient's severe condition, bone marrow aspiration, skeletal X-rays, and hearing screening were not performed. Compared with other cases with frameshift mutations, it is unclear whether the proband had BMF. We acknowledge the difficulty in evaluating abnormalities in various organs and systems in this case involving premature death. In the future, clustered regularly interspaced short palindromic repeats (CRISPR)-base editors could provide an efficient pathway to enable functional screening of clinical variants, allowing for further exploration of MECOM-associated syndrome [40].

In conclusion, we reported a case of MECOM-associated syndrome with severe thrombocytopenia and intracranial hemorrhage, resulting in death on the third day of life due to rapid disease progression. Early genetic testing and clinical counseling are crucial when patients present with early-onset thrombocytopenia and skeletal deformities.

Abbreviations

MDS1	Myelodysplastic syndrome 1
EVI1	Ecotropic viral integration site 1
BMF	Bone marrow failure
HSCT	Hematopoietic stem cell transplantation
RUS	Radioulnar synostosis
RUSAT	Radioulnar synostosis with amegakaryocytic thrombocytopenia
DIC	Disseminated intravascular coagulation

Supplementary Information

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Additional file 1.

Additional file 2. Supplementary Table 1. Clinical characteristics and genotypes of patients with MECOM-associated syndrome.

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Author contributions
JL and TP collected the data and wrote the manuscript; GC participated in design of study and revised the manuscript; LY diagnosed the disease and revised the manuscript; JZ and RZ supervised data collection and analyzed the data; and PZ critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Children's Hospital of Fudan University (no. 2023–203). Informed consent was obtained from the patient's parents.

Consent for publication
Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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