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Delayed Onset of Labor After Full Cervical Dilation: The Role of Proinflammatory Mediators and Genetic Variants – A Case Report

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Case Report

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Abstract

Understanding the molecular triggers that initiate labor remains essential for managing preterm birth, especially in atypical cases where cervical dilation precedes uterine contractions. Here we report a rare case of a 28-year-old with full cervical dilation who remained quiescent for 12 days before spontaneous labor onset. Longitudinal analysis of inflammatory markers revealed a "silence-then-surge" pattern: pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) decreased during the latency phase but exhibited a massive (> 10-fold) surge immediately preceding active labor, confirming that inflammation—rather than mechanical dilation alone—was the primary driver of uterine contractions. Persistently stable IL-10 suggested inadequate anti-inflammatory regulation, allowing unchecked inflammation to trigger labor onset. Whole Exome Sequencing (WES) uncovered a complex genetic architecture underlying this phenotype. We identified pathogenic variant clusters related to immune dysregulation (HLA, LILR) and compromised mucosal barriers (MUC genes), which may explain the prolonged latency and cervical weakness. Crucially, we reveal that Variants in ECM1 and SLC9B1 represent candidate genetic biomarkers for preterm birth, as they may predispose to cervical fragility and impaired uterine responsiveness. Collectively, these findings suggest that genetic defects in tissue cohesion and immune regulation predisposed the patient to cervical insufficiency, while the timing of delivery was ultimately dictated by a threshold-level inflammatory cascade.

Background:

Preterm labor and preterm birth remain major challenges in obstetric care. While uterine contractions are traditionally considered central to the initiation of labor, instances have been observed where the cervix is fully dilated without the onset of active labor. Recent evidence suggests that proinflammatory mediators play a key role in stimulating prostaglandin production, which in turn facilitates uterine contractility. Genomic analysis via Whole Exome Sequencing (WES) revealed critical loss-of-function variants in *ECM1*, *SLC9B1* alongside gene clusters associated with immune regulation and epithelial barrier function. We report a rare case of a woman with full cervical dilation in whom true labor was delayed for 12 days, in order to investigate the contribution of proinflammatory markers, including white blood cells (WBC), C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and IL-10, as well as maternal exome sequencing.

Case Presentation:

A 28-year-old primigravida was admitted with threatened preterm labor and a fully dilated cervix. After uterine contractions were suppressed with magnesium sulfate, labor did not ensue for 12 days. During this latency period, peripheral blood samples were collected at three time points: upon full cervical dilation (Day 0), five days later (Day 5), and at the onset of labor (Day 12), as well as from umbilical cord blood at birth. Whole-exome sequencing was performed on maternal blood collected at the onset of labor. The 3799 variants detected, we identified two rare variants: ECM1 (stop-gained), SLC9B1 (frameshift) with the immune LILR/HLA/KIR/SIRPA cluster and mucin genes cluster offer a plausible genetic explanation for the sustained maternal-fetal tolerance observed despite complete cervical dilation. On Day 0, IL-1β levels peaked at 14 ± 7.3 pg/mL, with elevated levels of other inflammatory markers (CRP: 5.76 mg/L; WBC: 8.6 G/L; IL-6: 18 ± 3.8 pg/mL; IL-10: 31 ± 7.6 pg/mL; TNF-α: 20 ± 2.0 pg/mL). Following antibiotic therapy, these markers decreased markedly by Day 5 (e.g., TNF-α: 16 ± 3.8 pg/mL; IL-1β: 6.9 ± 2.6U pg/mL). On Day 12, just prior to labor, WBC rose to 22.6 G/L, IL-1β: 208 ± 14 pg/mL, IL-6 reached 577 ± 174 pg/mL, and TNF-α increased to 131 ± 17 pg/mL, while CRP and IL-10 showed minimal changes.

Conclusions:

Marked fluctuations in proinflammatory markers (WBC, IL-6, TNF-α, IL-1β) during the latency period highlight their potential role in the initiation of preterm labor. Variants in ECM1 and SLC9B1 may serve as potential biomarkers for preterm birth. Furthermore, the immune (LILR/HLA genes) and mucin (MUC genes) clusters helped preserve maternal tolerance, allowing the fetus to remain in utero despite the loss of the cervical barrier. Yet, effective labor required the overriding of these protective mechanisms by a critical surge in proinflammatory mediators to initiate parturition, highlighting the combined role of genetic predisposition and inflammation in driving preterm labor onset. This case underscores the importance of integrating clinical monitoring, genetic with inflammatory biomarker profiling to guide timely interventions and improve maternal-fetal outcomes.

Introduction

Preterm birth remains one of the leading causes of neonatal mortality worldwide (1, 2). Each year, an estimated 15 million infants are born before 37 weeks of gestation. Globally, approximately 1 in 10 babies is born prematurely, and reliable data indicate that the prevalence of preterm birth is increasing in most countries (1, 3).

The diagnosis and management of preterm labor are challenging due to the complex interplay between mechanical and immunological factors, with uterine contractions considered central to labor onset. Cervical length and fetal fibronectin concentration have been identified as key predictors of preterm birth risk (4, 5). Cervical effacement and dilation cause tension on the lower uterine segment and fetal membranes,

leading to localized separation between the chorion and decidua. This separation stimulates prostaglandin synthesis—an essential hormone in initiating and amplifying uterine contractions—thus promoting early labor onset (6, 7).

One of the key mechanisms in preterm labor is the excessive activation of inflammatory responses in the decidua, fetal membranes, and myometrium. This inflammatory response can be either infectious or non-infectious in origin but leads to increased production of proinflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These mediators stimulate prostaglandin synthesis and the production of matrix-degrading enzymes, resulting in cervical ripening and myometrial activation. This inflammatory cascade ultimately contributes to the initiation of uterine contractions (7–9).

In rare instances, full cervical dilation may occur without the onset of labor for an extended period. Such cases raise critical questions regarding the role of genetic mutations, external stimuli, or local and systemic inflammatory responses in triggering uterine contractility and preterm birth.

To date, there have been few documented cases of significantly delayed labor following complete cervical dilation in the absence of effective uterine contractions. This lack of data poses challenges in clinical decision-making, including whether to pursue expectant management based on the underlying cause, or to intervene early in consideration of risks such as infection or premature rupture of membranes.

Here, we present a rare case of a pregnant woman with full cervical dilation who did not progress to active labor until 12 days later. Serial measurements of proinflammatory markers were performed using both cervical fluid and peripheral blood throughout the latency period. This report aims to contribute further evidence supporting the role of proinflammatory cytokines in the mechanisms of labor initiation and to guide future monitoring and intervention strategies in similar clinical scenarios.

Clinical Presentation

A 28-year-old primigravida woman with no significant obstetric history was admitted at 31 weeks and 4 days of gestation due to uterine contractions and vaginal mucus discharge. Initial clinical evaluation documented uterine contractions occurring twice per 10 minutes, cervical dilation of 4 cm, intact amniotic membranes, absence of infection signs, and a normal fetal ultrasound examination (Table 1).

The diagnosis of threatened preterm labor was established, and treatment with intravenous Magnesium Sulfate was initiated to inhibit contractions. After 48 hours, contractions ceased, although cervical dilation progressed to full dilation (10 cm), with membranes remaining intact and no active labor detected. This clinical status persisted for 12 consecutive days. Subsequently, spontaneous labor ensued, resulting in a vaginal delivery of a male neonate weighing 1850 g with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, without postpartum complications.

Table 1
Clinical progression and inflammatory markers at three time points during maternal follow-up.

Time point	Clinical Signs	Uterine Contractions	Cervical Status	Leukocyte Count (G/L)	CRP (mg/L)	TNF-α (pg/mL)	IL-1β (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	Treatment/ Intervention
D0	No abdominal pain, stable	None	Fully dilated, 100%	8.6	5.76	20	14	18	31	$MgSO_4$
D5	No new symptoms	None	No change	Decreased	Decreased	16	6.9	13	21	Continue monitoring
D12	Abdominal pain, labor	Regular contractions	No change	22.6	Unchanged	131	208	577	29	Labor – vaginal delivery

During follow-up, peripheral blood was analyzed for leukocyte count, C-reactive protein (CRP), and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-10) at three specific timepoints: D0 (day of full cervical dilation), D5 (post antibiotic therapy), and D12 (onset of active labor).

Serum concentrations of IL-1β, IL-6, IL-10, TNFα, CRP, and WBC–neutrophil counts measured at day 0, day 5, day 12, and cord blood. Data are presented as mean ± SD. Statistical significance is indicated as shown (*p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001; ns, not significant*).

At D0, IL-1β was elevated at 14 ± 7.3 pg/mL, TNF-α at 20 ± 2.0 pg/mL, IL-6 at 18 ± 3.8 pg/mL, IL-10 at 31 ± 7.6 pg/mL, leukocyte count at 8.6 G/L, and CRP at 5.76 mg/L. By D5, inflammatory markers significantly decreased (IL-1β At 6.9 ± 2.6 pg/mL, TNF-α at 16 ± 3.8 pg/mL), reflecting therapeutic response. At D12, immediately preceding labor, TNF-α, IL-1β and IL-6 surged markedly (131 ± 17 pg/mL, 208 ± 14 pg/mL

and 577 ± 174 pg/mL, respectively), leukocytes rose to 22.6 G/L, while IL-10 and CRP remained relatively stable. These findings indicate a pronounced increase in pro-inflammatory mediators coinciding with labor onset. Notably, IL-1β, IL-6 and TNF-α increased over 10-fold or 30-fold compared to D5, whereas IL-10 levels remained unchanged, suggesting an imbalance favoring inflammation, potentially facilitating prostaglandin activation and uterine contractions.

In addition to inflammatory markers, cervical length and Bishop score—an index predicting labor induction success—were monitored from 28 weeks 2 days until delivery. Uterine contractions were also recorded during this interval. The cervix demonstrated signs consistent with cervical insufficiency (Table 2). These observations are summarized in Table 2.

Table 2
Summarizes the cervix clinical progression

Gestational Age	**28w2**	**29w3**	**31w4**	**31w5**	**33w2**
Cervical Length	7 mm (U-shaped cervix)	5 mm	4 cm dilated	10 cm dilated	Pregnancy ended
Bishop Score	4	5	8	11	-
Uterine Contractions	Negative	Negative	Frequency 1–2	Negative	-

Tracking cervical changes showed typical cervical insufficiency with progressive cervical shortening and dilation. At 28 weeks 2 days, the U-shaped cervix with 7 mm length indicated a weak cervix incapable of sustaining pregnancy effectively. Over three weeks, cervical length shortened to full dilation, paralleled by an increase in Bishop score from 4 to 11, reflecting marked cervical softening and effacement typically observed in active labor. Despite low contraction frequency at 4 cm dilation, cervical dilation progressed, implying that inflammatory processes originating from cervical weakness may have initiated pro-inflammatory cytokine production. Once full dilation was reached and maintained without contractions for 12 days, elevated Bishop score without contractions suggested that uterine contraction triggers derived primarily from pro-inflammatory mediators rather than mechanical cervical factors.

Whole exome sequencing (WES) was performed on maternal peripheral blood to identify genetic variants potentially implicated in early labor initiation. WES covers all exons, representing 1–2% of the genome but harboring over 85% of pathogenic mutations. This method detects single nucleotide polymorphisms (SNPs), small insertions/deletions (indels), and some copy number variants (CNVs) (Fig. 2A), enabling elucidation of genetic contributions to complex disorders. The analysis of WES data identified 3799 genetic variants (Fig. 2B), with 79 variants of 70 gens predicted to have high impact on gene or protein function (Fig. 2C).

The Fig. 2(A) Copy number ratio (log2) plots revealed no large deletions or duplications exceeding clinical thresholds. Data points were evenly distributed around zero across all chromosomes, indicating the absence of significant structural genomic abnormalities at testing. The Fig. 2(B) A large protein-protein interaction (PPI) network constructed from 1982 genes identified through whole exome sequencing (WES). Each node represents a protein and each edge signifies a known protein-protein interaction. This network illustrates the intricate connectivity among affected genes, highlighting diverse biological pathways. Small, isolated red nodes may represent genes with weak or undefined interactions within the main cluster. Figure 2(C) A focused protein-protein interaction network featuring clinically significant genes, specifically selected from variants known or likely to be pathogenic based on the ClinVar database, and further analyzed using Cytoscape. Each color-coded node represents a gene, and edges denote interactions between their respective genes. This network highlights core candidate genes and their functional interactions that are likely to play a direct role in the pathophysiology of preterm birth in the studied case. In contrast to the broader network in Fig. 2(B), this focused view allows for a more targeted investigation of specific disease-causing gene candidates and their functional interplays. Among these, based on the network structure, we can identify several tightly linked gene clusters, each representing a crucial biological pathway or function:

Cluster 1: Immune Regulation and Maternal-Fetal Interface Interaction (Fig. 2c): The first gene cluster comprises LILRA-2, LILRB2, LILRB1, HLA-A, HLA-DRB5, KIR2DL4, and SIRPA (S. Table 1), representing a complex interacting network that modulates the immune response at the maternal-fetal interface. HLA-A and HLA-DRB5 genes are core components of the Major Histocompatibility Complex (MHC), essential for maternal immune tolerance towards the fetus. The receptors LILRA-2, LILRB1, LILRB2, and KIR2DL4 on immune cells (particularly uNK cells) interact with HLA molecules to regulate the balance between immune activation and inhibition (9, 10) SIRPA is involved in regulating phagocytosis and innate immunity. This cluster's pathogenic variants strongly suggest immune dysregulation at the maternal-fetal interface as a key mechanism (11, 12). LILR/HLA/KIR/SIRPA variants may hinder immune recognition, suppressing acute inflammatory responses and immediate contractions (13, 14). This could lead to prolonged immune tolerance, delaying labor and explaining the acontractile preterm phenotype.

Cluster 2: Epithelial Barrier Integrity and Mucin Function (Fig. 2c): The second gene cluster comprises MUC16, MUC3A, and MUC6, which encode mucins – large glycoproteins that constitute the protective mucus layer on epithelial surfaces, including the reproductive tract (S.

Table 2). The cervical mucus plug serves as a crucial physical and immunological barrier, preventing the ascent of pathogens into the uterine cavity (15, 16). In the supplementary table 2 is shown the biological roles of some highly expressed genes suspected to be related to mucus gel barrier. Pathogenic variants within these *MUC* genes may compromise the structural integrity or functional efficacy of the cervical mucus plug. A compromised mucus barrier would facilitate the invasion of bacteria or other noxious stimuli into the uterine compartment (17). Such chronic, low-grade pathogen invasion through a weakened barrier could act as an initial trigger for the preterm labor process (18). However, in the context of immune dysregulation, as discussed in Cluster 1, the inflammatory response to this invasion might be insufficient to elicit immediate uterine contractions, leading to a prolonged latency period between the onset of preterm symptoms and active labor.

Nevertheless, an in-depth analysis of, whole-exome sequencing revealed two rare, potentially deleterious variants in ECM1, SLC9B1 (Fig. 3), each of which may contribute to the pathogenesis of preterm birth through distinct biological mechanisms.

Figure 3 illustrates the genomic organization and predicted protein consequences of the identified variants in *ECM1* and *SLC9B1* based on the GRCh38 reference genome.

In Fig. 3(A), the genomic structures of *ECM1* is depicted with exons represented as boxes. First, *ECM1* stop-gained mutation (c.841C > T), which is predicted to result in a truncated protein of 280 residues, instead of the full-length protein of 567 residues, is of particular interest. *ECM1* encodes a secreted glycoprotein essential for the structural and biochemical integrity of the extracellular matrix (ECM). ECM1 regulates tissue cohesion, remodeling, and angiogenesis through interactions with perlecan, laminin, and matrix metalloproteinases (19–23). Figure 3(C) shows the corresponding protein schematic. This substitution introduces a premature termination codon at position 281 (p.Arg281*). The nonsense mutation is predicted to result in a truncated ECM1 protein lacking the C-terminal region, which may disrupt functional domains and potentially lead to nonsense-mediated mRNA decay. Loss-of-function variants are predicted to compromise ECM stability and heighten susceptibility to inflammation (21).

Another high pathogenic variant is SLC9B1. In Fig. 3(B), the genomic structure of *SLC9B1* are depicted with exons represented as boxes. The c.1338_1339delGT variant results in a frameshift mutation, p.Leu447fs. As illustrated in Fig. 3(D), this deletion causes a frameshift beginning at codon 447 (p.Leu447fs), altering the downstream amino acid sequence. Given that SLC9B1 encodes a 515-amino-acid protein, the frameshift is expected to substantially affect the C-terminal portion of the protein, potentially impairing its structural integrity or functional activity. Given SLC9B1's role in encoding a Na+/H+ exchanger protein vital for pH regulation and ion balance, these variants could severely compromise protein function, thereby contributing to the pathophysiology of preterm birth through effects on myometrial activity, amniotic membrane integrity, or placental function (24, 25).

Taken together, these findings expand the repertoire of candidate genes implicated in preterm birth, linking ECM remodeling and ion transport to the risk of early parturition. While functional studies are needed to validate these associations, the identification of rare, loss-of-function variants in ECM1 and or SLC9B1 provides new insight for Aligning with the shift toward precision medicine in obstetrical care.

Discussion

This study employed a multi-layered approach (pro-inflammatory cytokines, CNV, WES, and PPI network analysis) to elucidate the genetic basis and mechanical factors of a preterm birth case with a distinct clinical phenotype: cervical dilation with prolonged absence of uterine contractions. This observation suggests that, in addition to mechanical factors, a sufficiently strong biological signal is required to truly activate uterine contractions (7–9). CNV analysis (Fig. 2A) revealed chromosomal stability, directing focus towards gene-level variants. The focused protein-protein interaction network of clinically significant genes (Fig. 2C) highlighted two primary pathogenic mechanisms implicated in this case: dysregulated immune regulation and impaired epithelial barrier integrity.

The pivotal gene cluster related to immune regulation at the maternal-fetal interface includes *HLA, LILR, KIR*, and *SIRPA*. The presence of pathogenic variants within this cluster suggests a disruption of immune balance, leading to an abnormal state of immune quiescence or prolonged tolerance, rather than the typical acute inflammatory response that triggers uterine contractions (9, 10). This plausibly explains the prolonged 12-day latency period without uterine contractile activity observed in the patient. The interaction between HLA-G and inhibitory receptors (LILRB1/LILRB2) is critical for maintaining maternal tolerance (11). Additionally, variants in *KIR2DL4* and *SIRPA* may further hinder immune recognition, suppressing acute inflammatory responses (12, 13). Concurrently, the mucin gene cluster (*MUC16, MUC3A, MUC6*) indicated weakened epithelial barriers, facilitating low-grade pathogen invasion. The cervical mucus plug is a critical first line of defense against ascending genital tract infections, a leading cause of preterm birth (16). MUC16 (CA-125) not only provides a physical barrier but also inhibits NK cell-mediated immune surveillance (17). Variants compromising mucin function have been linked to increased susceptibility to infections and inflammation at other mucosal surfaces (18).

Furthermore, WES analysis identified two rare, loss-of-function variants in ECM1, SLC9B1 might have individually or cooperatively created structural or functional vulnerability of the cervix and myometrium (firgure 3). *ECM1* disruption may weaken extracellular matrix integrity and

promote inflammation, predisposing to premature rupture of membranes (19, 20). The PPeTaL study demonstrated that a panel of circulating proteins, including ECM1, could accurately stratify asymptomatic women at mid-gestation according to their risk of preterm birth, supporting its role as a novel biomarker candidate (21). SLC9B1 regulates ion transport and pH, potentially influencing uterine excitability (24). These findings highlight novel pathways in extracellular matrix remodeling, ion homeostasis that may contribute to preterm birth risk (14). However, in this patient, additional genetic effects were evident: *SLC9B1* variant could reduce *OXTR* functionality in the myometrium, suppressing intracellular Ca^{2+} signaling and thereby decreasing uterine sensitivity to oxytocin. Furthermore, the use of magnesium sulfate may have enhanced Ca^{2+} efflux from the cytoplasm, further inhibiting contractility. Altogether, ECM1 disruption may destabilize the extracellular matrix and SLC9B1 loss may disturb ionic balance and myometrial excitability. Still, these genetic predispositions alone are insufficient to convert cervical ripening into active contractions without a biological trigger. These genes expand the scope of biological pathways implicated in preterm birth. Collectively, these findings expand the repertoire of candidate genes implicated in preterm birth, linking ECM remodeling and ion transport, alongside immune regulation and barrier integrity, to the risk of early parturition.

Serial ELISA monitoring revealed that at day 0 (D0), despite full cervical dilation, pro-inflammatory cytokines were only mildly elevated, insufficient to activate the myometrium. By day 12 (D12), a marked surge in IL-6, TNF-α, and leukocytosis coincided with labor onset. This underscores that inflammation, rather than cervical status alone, is the decisive factor initiating uterine contractions. Moreover, elevated cytokine levels in umbilical cord blood indicated a fetal inflammatory response consistent with FIRS, though fetal concentrations were lower than maternal, suggesting secondary activation via placental signaling. Overall, these findings highlight the interplay between genetic predisposition and inflammatory amplification in driving preterm labor, with inflammatory activation emerging as the critical trigger for effective uterine contractions (Fig. 1).

Furthermore, elevated levels of IL-6, IL-1β, and TNF-α detected in umbilical cord blood suggest that the fetus also undergoes a systemic inflammatory response like that of the mother. This phenomenon is characteristic of Fetal Inflammatory Response Syndrome (FIRS), which is associated with preterm birth, central nervous system injury, and neonatal complications such as early-onset sepsis. However, cytokine concentrations in fetal blood were lower than maternal levels at the same time point, implying that the fetus likely reacts secondarily to the maternal inflammatory milieu via placental signaling. This also indicates that the placental barrier remains functionally intact, providing effective biological protection for the fetus. In this case, the early elevation of IL-1β suggests its role as a key upstream initiator of the inflammatory cascade, priming the maternal immune system for labor (26–28). However, the absence of immediate uterine contractions indicates that IL-1β alone is insufficient to trigger labor without subsequent amplification by downstream mediators such as IL-6 and TNF-α (29–31).

Collectively, these findings strongly support the central role of inflammation in the mechanism of labor initiation and suggest the potential application of inflammatory markers as prognostic indicators in the clinical management of preterm labor. Quantifying inflammatory mediators and targeted therapeutic interventions, aligning with the trend toward precision medicine in obstetrics (29–31).

Limitations

As this is a single case report, the identified associations between the rare variants in *ECM1, SLC9B1* and preterm birth must be interpreted with caution. These variants are proposed as candidate biomarkers, but functional studies are required to definitively establish their impact on myometrial excitability and cervical integrity. Furthermore, while the inflammatory surge was the clear clinical trigger in this case, the specific external or internal stimuli that initiated this surge on Day 12 remain to be fully elucidated.

Abbreviations

WBC
White Blood Cells
CRP
C-reactive Protein
TNF-α
Tumor Necrosis Factor-alpha
IL
Interleukin
IL-1β
Interleukin-1 beta
IL-6
Interleukin-6
IL-10

Interleukin-10
$MgSO_4$
Magnesium Sulfate
D0
Day 0 (day of full cervical dilation)
D5
Day 5 (5 days after full dilation)
D12
Day 12 (onset of labor)
WES
Whole Exome Sequencing
SNP
Single Nucleotide Polymorphism
indels
Insertions and Deletions
CNV
Copy Number Variant
FIRS
Fetal Inflammatory Response Syndrome
PPI
Protein – protein interaction

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee in Biomedical Research of Hue University of Medicine and Pharmacy, Hue University (Approval number: H2023/461, dated September 15, 2023). All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

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

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

H.B.V., H.N.V.Q. and T.L.M. conceived and designed the study. H.B.V., and P.L.Q. collected the data. Q.T.K., T.P.V., and T.D.V. performed the data analysis. T.N.H. and L.P.T. contributed to data interpretation and literature review. H.B.V. drafted the main manuscript. D.L.V. supervised the study and critically revised the manuscript. All authors reviewed and approved the final manuscript.

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Data Availability

The datasets generated and/or analysed during the current study are available in the Zenodo repository, https://doi.org/10.5281/zenodo.18844478. The variant data have been deposited in the ClinVar database under accession number SCV007517217. The full record is available at: https://www.ncbi.nlm.nih.gov/clinvar/variation/987237/

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Figures

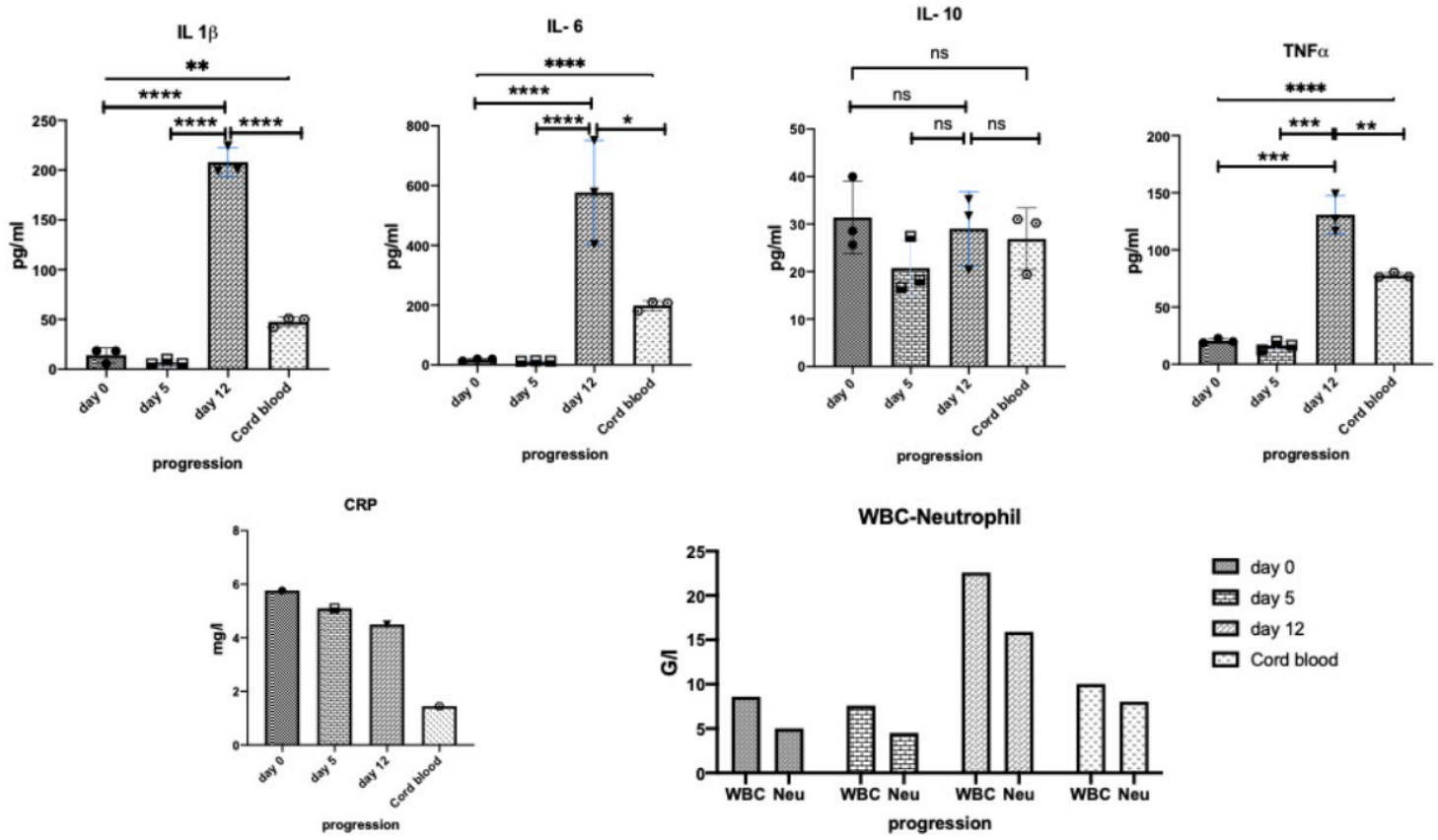


Figure 1

Cytokine concentrations and inflammatory markers during disease progression.
Serum concentrations of IL-1β, IL-6, IL-10, TNFα, CRP, and WBC–neutrophil counts measured at day 0, day 5, day 12, and cord blood. Data are presented as mean ± SD. Statistical significance is indicated as shown (*p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001; ns, not significant*).

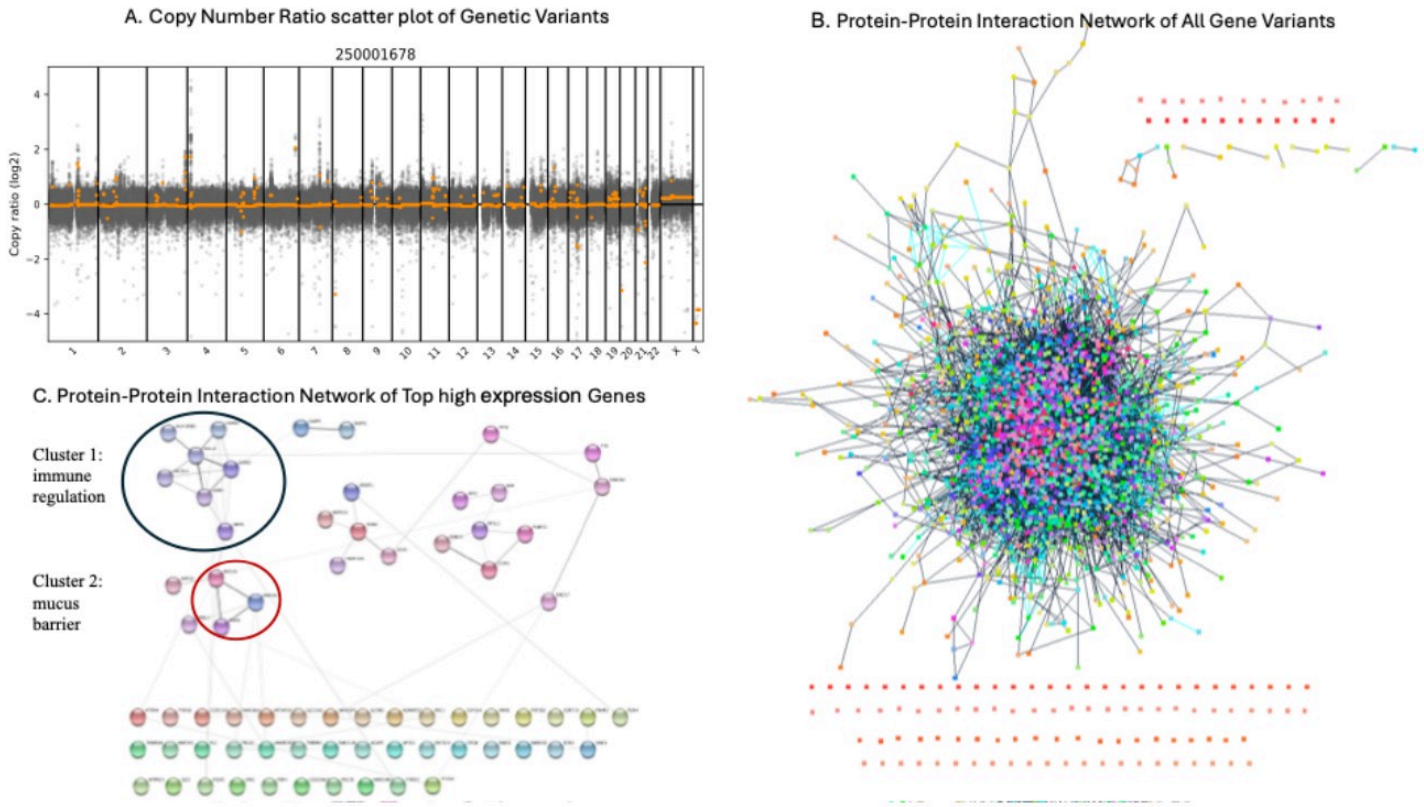


Figure 2

Genetic Analysis and Protein-Protein Interaction Network of Preterm Birth-Associated Gene Variants.

(A) Copy Number Ratio Plot of Genetic Variants Across the Genome.

(B) Protein-Protein Interaction Network of All Gene Variants Captured by Exome Sequencing.

(C) Protein-Protein Interaction Network of Top high expression Pathogenic Genes

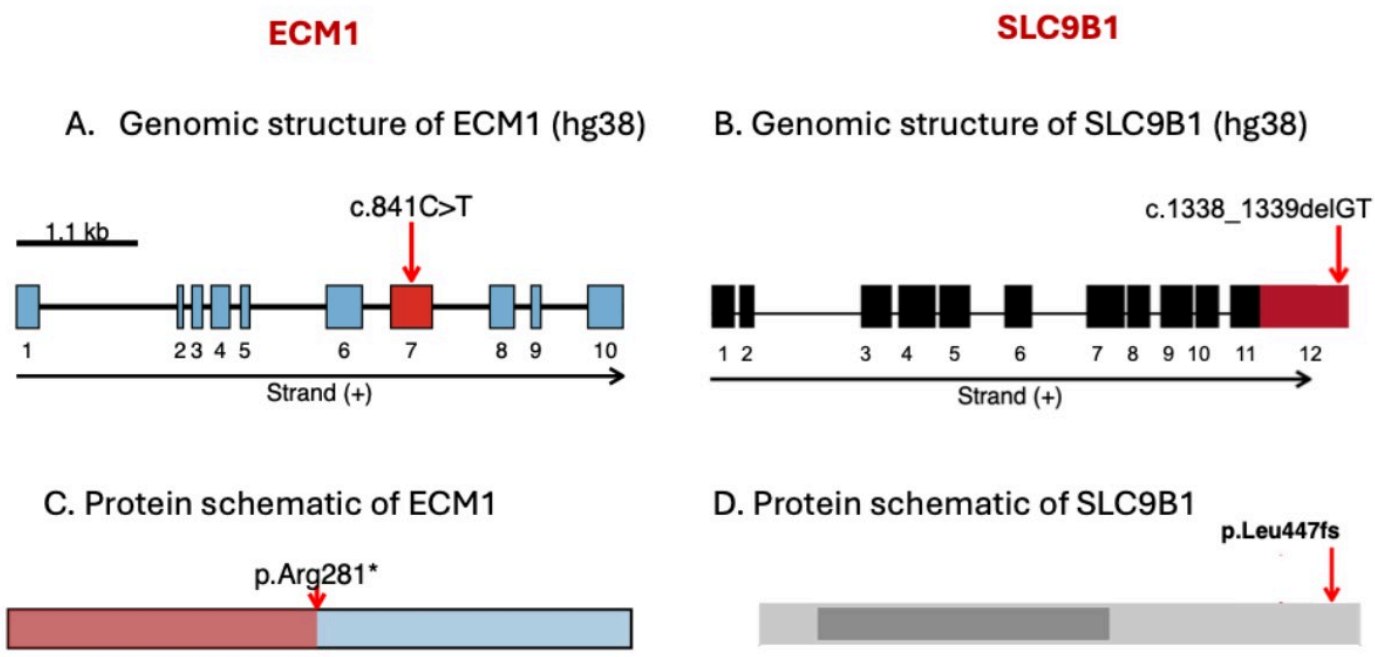


Figure 3

Gene and protein schematics of ECM1 and SLC9B1 variants.

(A) Genomic structures of *ECM1*(hg38) with exons shown as boxes. The identified variant is highlighted in red: *ECM1*c.841C>T (exon 7).

(B) Genomic structures of *SLC9B1*(hg38) with exons shown as boxes. The identified variant is highlighted in red: *SLC9B1*c.1338_1339delGT (exon 12).

(C) Protein schematic showing ECM1 p.Arg281* (premature stop) variant.

(D) Protein schematic showing SLC9B1 p.Leu447fs (frameshift) variant.

Supplementary Files

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- Supplementarydata.docx