

GENETICS, PROTEOMICS AND METABOLOMICS

THE ROLE OF THE *FLT1* GENE ALTERNATIVE SPLICING IN THE FETAL GROWTH RETARDATION DEVELOPMENT

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RESUME

Background. Fetal growth restriction (FGR) is a major pregnancy complication often associated with placental dysfunction and angiogenic imbalance. The *FLT1* gene encodes VEGFR-1, producing both membrane receptors and soluble isoforms (sFlt-1) through alternative splicing. Soluble variants sequester VEGF/PlGF and suppress angiogenesis. While the role of sFlt-1 in preeclampsia is widely studied, its splicing regulation and contribution to FGR remain unclear.

The aim. To evaluate the alternative splicing role of the *FLT1* gene expressed in placental decidual cells in the molecular mechanisms of fetal growth retardation.

Materials and methods. The study included biopsies of the placenta maternal part of patients with physiological pregnancy (n = 8) and FGR (n = 13). RNA sequencing was performed on the Illumina NextSeq 2000 platform. Alternative splicing events were identified and quantified using the MAJIQ program.

Results. This work provides the first analysis of *FLT1* gene alternative splicing in decidual cells during FGR. Four splicing events were shared across both groups, including exon skipping, intron retention, and a complex event with two sub-events. The FGR group additionally demonstrated a unique complex event and three intron retentions absent in controls. These changes indicate a shift toward enhanced production of soluble VEGFR-1 isoforms, which act as antiangiogenic "traps", reduce uteroplacental blood flow, and contribute to growth restriction.

Conclusions. Alternative splicing of the *FLT1* gene plays an important role in the FGR pathogenesis. Excessive intron retention and exon skipping lead to increased expression of shortened antiangiogenic proteins, disrupting the balance of angiogenesis and contributing to placental dysfunction.

Key words: fetal growth retardation, placenta, decidual cells, *FLT1*, alternative splicing, VEGFR-1, sFlt-1

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РОЛЬ АЛЬТЕРНАТИВНОГО СПЛАЙСИНГА ГЕНА *FLT1* В РАЗВИТИИ ЗАДЕРЖКИ РОСТА ПЛОДА

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РЕЗЮМЕ

Обоснование. Задержка роста плода остаётся одной из значимых патологий беременности, ассоциированной с высокой перинатальной и постнатальной заболеваемостью. Несмотря на прогресс в изучении молекулярных механизмов развития патологии, роль альтернативного сплайсинга ключевых плацентарных генов, в частности *FLT1*, кодирующего рецептор фактора роста эндотелия сосудов-1 (*VEGFR-1*), изучена недостаточно. Это ограничивает понимание связи между ангиогенезом и нарушениями развития плаценты при задержке роста плода.

Цель исследования. Оценить роль альтернативного сплайсинга гена *FLT1*, экспрессируемого в децидуальных клетках плаценты, в молекулярных механизмах задержки роста плода.

Методы. В исследование включены биоптаты материнской части плаценты пациенток с физиологической беременностью ($n = 8$) и задержкой роста плода ($n = 13$). Проведено секвенирование РНК на платформе Illumina NextSeq 2000. Анализ альтернативного сплайсинга выполнен с использованием пакета MAJIQ.

Результаты. Впервые проведён анализ альтернативного сплайсинга гена *FLT1* в децидуальных клетках плаценты при задержке роста плода. Общими для физиологической беременности и задержки роста плода являются четыре события альтернативного сплайсинга, включающие пропуск экзона, удержание интрона и два события, образующих комплекс. Кроме того, только при задержке роста плода выявлены одно комплексное событие и три события удержания интрона, отсутствующие при физиологической беременности. Суммарно, эти изменения отражают активацию механизмов, приводящих к формированию укороченных изоформ рецептора *VEGFR-1*, которые действуют как антиангиогенные «ловушки» и впоследствии приводят к снижению маточно-плацентарного кровотока и развитию задержки роста плода.

Заключение. Альтернативный сплайсинг гена *FLT1* играет важную роль в патогенезе задержки роста плода. Избыточное удержание интронов и пропуск экзонов ведут к повышенной экспрессии укороченных антиангиогенных белков, нарушая баланс ангиогенеза и способствуя плацентарной дисфункции.

Ключевые слова: задержка роста плода, плацента, децидуальные клетки, *FLT1*, альтернативный сплайсинг, *VEGFR-1*, *sFlt-1*

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BACKGROUND

Fetal growth restriction (FGR) continues to be one of the leading causes of neonatal morbidity and mortality, and poses a significant risk of long-term health disorders in children [1]. In the pathogenesis of FGR, biological processes occurring within the placenta play a crucial role. The placenta is the organ responsible for the transport of oxygen and nutrients, as well as endocrine support and immunological tolerance during pregnancy [2]. Disruption of the balance of angiogenic factors and insufficient vascularization of the placenta lead to chronic intrauterine hypoxia, impaired uteroplacental blood flow, and reduced substrate delivery. These molecular changes in the placenta are linked to the FGR phenotype. In this context, the regulatory system of angiogenesis, based on the interaction between vascular endothelial growth factor (VEGF), placental growth factor (PlGF), and their receptors, primarily *FLT1* (VEGFR-1), draws particular attention. These molecules form a crucial signaling pathway that controls the proliferation, migration, and differentiation of endothelial cells. This process is essential for the development and maintenance of the placental vasculature [3].

The *FLT1* gene codes for vascular endothelial growth factor receptor-1 (VEGFR-1). Classically, *FLT1* is a transmembrane tyrosine kinase receptor that is involved in recognizing VEGF-A, PlGF, and some other ligands. This interaction regulates endothelial cell proliferation, vascular permeability, and angiogenesis [4]. However, in the context of the placenta, *FLT1* also produces several alternative forms of the protein, including a soluble form (sFlt-1). These alternative isoforms are generated through alternative splicing and premature transcript termination [5]. The sFlt-1 protein lacks transmembrane and cytoplasmic domains, and acts as a “trap” for VEGF and PlGF. By binding to these growth factors, sFlt-1 reduces their free concentration and inhibits angiogenic activity [6].

Alternative splicing (AS) plays a critical role in this process. AS is a fundamental post-transcriptional regulatory mechanism [7] that allows a single pre-mRNA to generate multiple mRNA transcripts and, consequently, proteins with diverse functions. This process contributes to cellular and tissue proteome diversity, and it is essential for the body’s adaptation to environmental changes [8]. For the placenta, a highly specialized and rapidly growing organ with a complex regulatory network, alternative splicing is especially significant. It provides flexibility in gene expression related to angiogenesis, immune tolerance, nutrient transport, and cellular stress response [9]. Disruption of this balance can destabilize these processes, potentially leading to pregnancy complications such as FGR.

In this context, the alternative splicing of *FLT1* pre-mRNA, which gives rise to both membrane-bound and placenta-specific soluble isoforms (for example, sFlt1-e15a, etc.) [10], is of particular interest. This mechanism can be seen as a fine regulatory switch between

pro-angiogenic and anti-angiogenic signals. Under normal conditions, moderate sFlt-1 synthesis in late pregnancy contributes to vascular stability and prevents excessive vessel growth. Under pathological conditions, its overexpression leads to an angiogenic blockade, resulting in placental dysfunction and consequently FGR.

While the role of sFlt-1 in the development of preeclampsia has been widely discussed, the mechanism linking *FLT1* pre-mRNA alternative splicing to FGR have not yet been studied. Therefore, **the aim of this study** is to evaluate the role of the alternative splicing of the *FLT1* gene expressed in placental decidual cells in the molecular mechanisms underlying fetal growth restriction.

MATERIALS AND METHODS

Biological material

Sample collection, clinical characterization (including examination, medical history, complaints, and paraclinical data), and biopsy collection from the maternal side of the placenta in women with physiological pregnancies (NP) and FGR were conducted at the Regional Perinatal Center named after I.D. Evtushenko in Tomsk. A diagnosis of O36.5, indicating insufficient fetal growth requiring maternal medical care, was made by an obstetrician-gynecologist, based on the International Classification of Diseases (ICD-10), following the criteria outlined in the clinical guidelines published by the Russian Society of Obstetricians and Gynecologists in 2022. The groups were comparable in terms of key clinical and anthropometric features (Table 1). No significant differences were observed when comparing the prevalence of concomitant medical conditions.

During the collection of biological materials for this study, strict inclusion and exclusion criteria were applied. The control group consisted of women of Russian ethnicity who had a physiological singleton pregnancy, an operative delivery, an uncomplicated obstetrical history, and were aged between 18 and 45 years. These women signed informed consent to participate in the study. The FGR group included women with a singleton pregnancy who met the FGR criteria. These women also had an operative delivery and were aged 18 to 45. They also signed informed consent for participation in the study.

Exclusion criteria included: refusal to provide informed voluntary consent, age under 18 or over 45, the presence of chromosomal abnormalities in either the woman or the fetus, severe chronic gynecological or endocrine disorders, autoimmune diseases, disseminated intravascular coagulation, harmful habits or occupational hazards, the use of fetotoxic medications during pregnancy, or infectious diseases during pregnancy.

Experimental procedures

Decidual cells (DCs) were obtained from frozen placental tissue using laser microdissection with a PALM

TABLE 1
CHARACTERISTICS OF THE STUDIED GROUPS

Parameter	NP (n=8), Me [Q1;Q3]	NP (n=13), Me [Q1;Q3]	p
Maternal age, years	33.5 [25.5;35.5]	29 [23.5;34.5]	0.547
Gestational age at delivery, weeks	39.1 [38.2;39.6]	37.6 [37.1;39.1]	0.037*
Number of deliveries	2 [1;3]	1 [1;2]	0.140
BMI before pregnancy, kg/m ²	22.6 [18.3;27.9]	22.7 [21.6;26.0]	0.734
Child sex (male : female)	4 : 4	6 : 7	0.916
Child height, cm	54 [52;55]	47 [47;49]	< 0.001*
Child weight, g	3565 [3502;3775]	2290 [2065;2500]	< 0.001*
Anemia, n (%)	4(50)	5(38.5)	0.697
CVD, n (%)	2(25)	3(23.1)	0.972
Endocrine diseases, n (%)	3(37.5)	3(23.1)	0.595
GUS diseases, n (%)	0(0)	4(30.1)	0.161
Obesity, n (%)	2(25)	4(30.1)	0.750

Note. * – indicated criteria are statistically significant at $p < 0.05$; the Mann – Whitney test was used for comparisons. BMI – body mass index, CVD – cardiovascular diseases, GUS – genitourinary system diseases.

MicroBeam UV instrument (Carl Zeiss). The cells were isolated from approximately 1,000 to 2,000 DCs per sample [11]. Total RNA was then extracted using the Single Cell RNA Purification Kit (Norgen Biotek), following the manufacturer's protocol. For library preparation for whole-transcriptome analysis, SMARTer Stranded Total RNA-Seq Kit v2 (Takara BIO) was employed. The libraries were pooled, and paired-end sequencing was conducted on an Illumina NextSeq 2000 system, with an estimated read depth of at least 60 million reads per sample. The experiments were conducted at the Medical Genomics Shared Facility of the Research Institute of Medical Genetics at Tomsk National Research Medical Center.

Data analysis

The data obtained from whole-transcriptome sequencing was aligned to the reference genome (hg38) using the STAR software. Analysis of alternative splicing events was performed using the MAJIQ software package on the Linux operating system [12]. Quantitative assessment of alternative splicing under specific conditions is based on the Percent Spliced Index (PSI, Ψ) for each event junction. This program identifies and quantifies both complex (complex Local Splicing Variations, LSVs) and binary ("classical" events or simple LSVs) alternative splicing events, including exon skipping, alternative 5' and 3' splice sites, alternative first and last exons, intron retention, and mutually exclusive

exons, both annotated and novel. Complex LSVs are visualized as multiple edges in a splicing graph, representing multiple classical AS events entering or exiting one exon.

Statistical analysis

A comparative statistical analysis of clinical parameters was conducted using IBM Statistics 26.0 (SPSS, Inc., Chicago, IL, USA). To compare parameters between study groups, the Mann – Whitney U-test was employed. Differences were considered statistically significant at $p < 0.05$.

Ethical approval

This study was approved by the Committee on Bio-medical Ethics of the Research Institute of Medical Genetics at Tomsk National Research Medical Center (Protocol No. 13 dated November 15, 2021). Informed consent was obtained from all participants included in the study on a voluntary basis.

RESULTS

In this study, 21 transcriptomes of unique placental tissue samples were obtained from women with physiological pregnancy and fetal growth retardation. After alignment with the human genome, the average read coverage per sample was 62 million. Using the MAJIQ software, alternative splicing events were

identified for 11,521 transcripts. Further analysis included AS events present in at least half of the samples in one of the studied groups (4 and 7 samples for NP and FGR, respectively). The study then focused on analyzing alternative splicing for the target gene FLT1.

In the physiological pregnancy group, four alternative splicing events were identified in the FLT1 gene (Fig. 1A). Two of these constituted a complex LSV, which included an alternative last exon with a PSI level of 0.685 and intron retention with a PSI of 0.292 (Fig. 1B). The constitutive exon-exon junction event (shown in red) had a low percentage of inclusion in the transcript at a PSI = 0.012. The third event was binary and corresponded to intron retention at a PSI = 0.068. The constitutive exon-exon event had a PSI = 0.932, making it more likely to be included in the transcript (Fig. 1C). The fourth event was also binary, corresponding to exon skipping at a PSI = 0.099. The constitutive exon-exon event had a PSI = 0.901, indicating that it was more likely to be retained in the transcript (Fig. 1D).

In the FGR group, nine alternative splicing events were identified for the FLT1 gene (Fig. 2A). Two of these events constituted a complex LSV similar to that observed in the other group. This complex included

an alternative last exon with a PSI = 0.715 and intron retention with a PSI = 0.261 (Fig. 2C). The constitutive exon-exon junction event (shown in red) had a low inclusion percentage in the transcript, with a PSI = 0.017. Another two events form another complex LSV, consisting of an exon skipping event with a PSI = 0.938 and intron retention with a PSI = 0.057. The constitutive event had a PSI = 0.005 (Fig. 2B). Of the remaining five events, four were intron retentions, with PSI values of 0.08, 0.144, 0.072, and 0.093, respectively (Fig. 2D). The last event was exon skipping, which had also been observed in other groups, with a two-fold higher splicing index (PSI = 0.207). The constitutive exon-exon event, on the other hand, had a PSI of 0.793, and was more likely to be included in the transcript (Fig. 2E).

Thus, four common alternative splicing events were observed across the study groups. Two of these events form a complex, one being intron retention and the other being exon skipping. The splicing indices for these events differ slightly, except for the exon skipping event in the FGR group, which has a PSI that approximately doubles. In the FGR group, there are also two additional events that form a complex consisting of intron retention and exon skipping as well as three instances

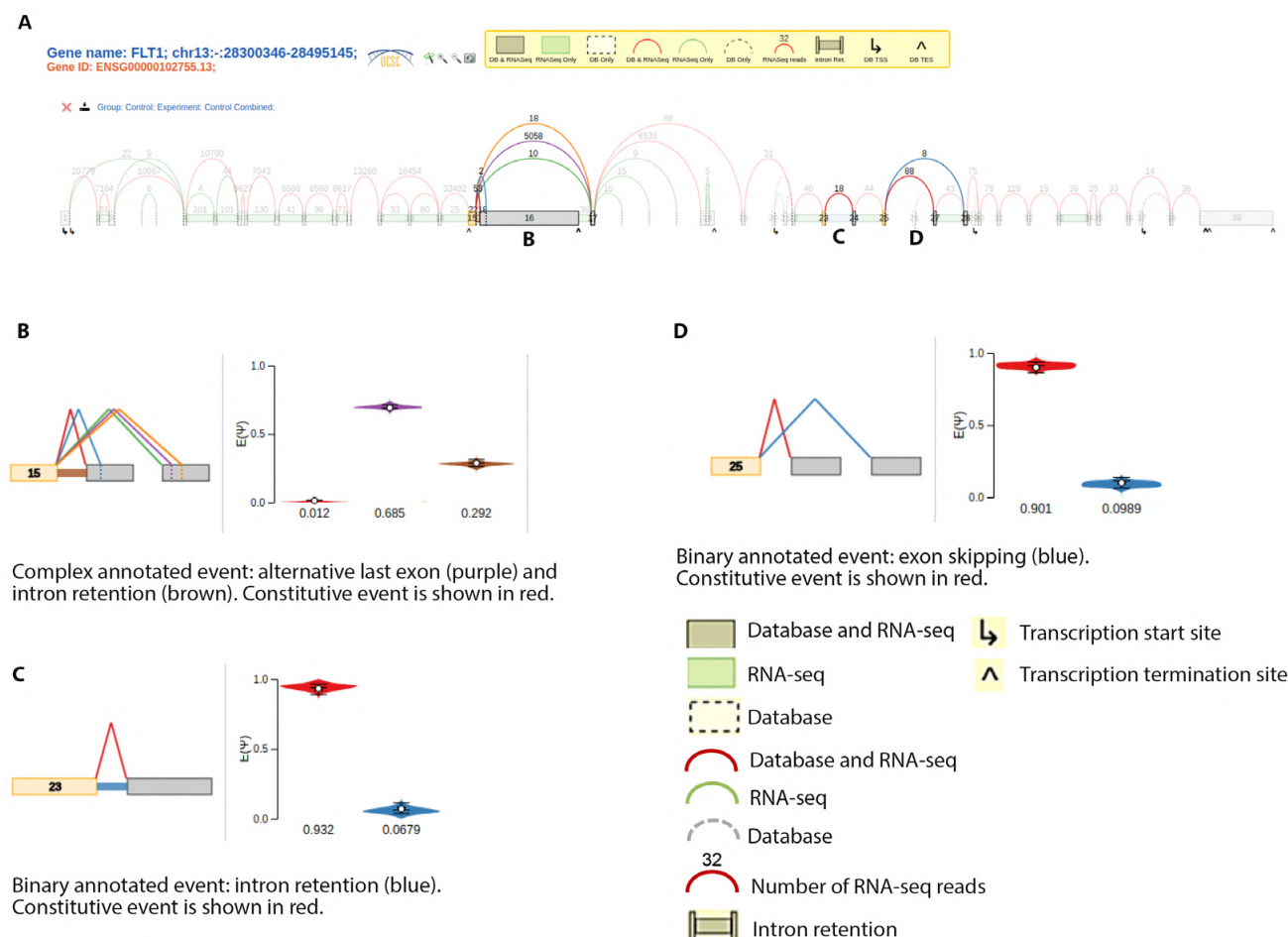


FIG. 1. Visualization of AS events in placental decidual cells for the FLT1 gene in the control group using the MAJIQ VOILA program. **A** – intron-exon structure of the FLT1 gene; **B-D** – statistically significant events in the intron-exon structure.

of intron retention that are not present in the physiological pregnancy group.

Analysis of *FLT1* transcript expression in placental tissue samples identified several variants, including the full-length variant ENST00000282397.9 (FLT1-201) and several truncated forms represented by the transcripts ENST00000615840.5 (sFLT1-i13/FLT1-207), ENST00000639477.1 (sFLT1-e15a/FLT1-209), as well as ENST00000540678.2 (FLT1-203) and ENST00000543394.2 (FLT1-205), which lack protein products. No statistically significant differences were found in the expression levels of these isoforms between physiological pregnancy and FGR groups ($p = 0.059$ for the comparison between the full-length isoform and the combined expression of the truncated transcripts). This may be due to the limited sample size, but a trend towards an increase in the expression of shorter soluble transcripts was noted in FGR, suggesting the need for further investigation with larger cohorts.

DISCUSSION

The observed differences in alternative splicing events between the physiological pregnancy group

and FGR group suggest a reconfiguration of post-transcriptional regulation in decidual cells.

Of particular interest is the near twofold increase in the PSI index for the exon skipping event in the FGR group. Exon skipping can alter protein length, leading to the loss of critical domains, or the formation of non-functional or functionally altered isoforms. Literature data indicates that skipping of exons 14–15 in the *FLT1* gene gives rise to truncated isoforms, altering the extracellular domain of the receptor and its ability to bind VEGF and PlGF [13]. We have recorded an increased likelihood of exon 26 skipping, which could affect angiogenic activity and the adaptive potential of the placenta. Moreover, a polymorphic marker, rs9554320, associated with *FLT1* regulation via interaction with long non-coding RNAs, such as those identified in this study [14], may regulate the transcription of the genes associated with. These RNAs compete for transcriptional resources and may modulate *FLT1* expression in specific target tissues. This further emphasizes the significance of the observed changes.

Particular attention is paid to the fact that intron retention occurs predominantly in the FGR group. Increased frequency of intron retention may be associated with impaired function of splicing factors that

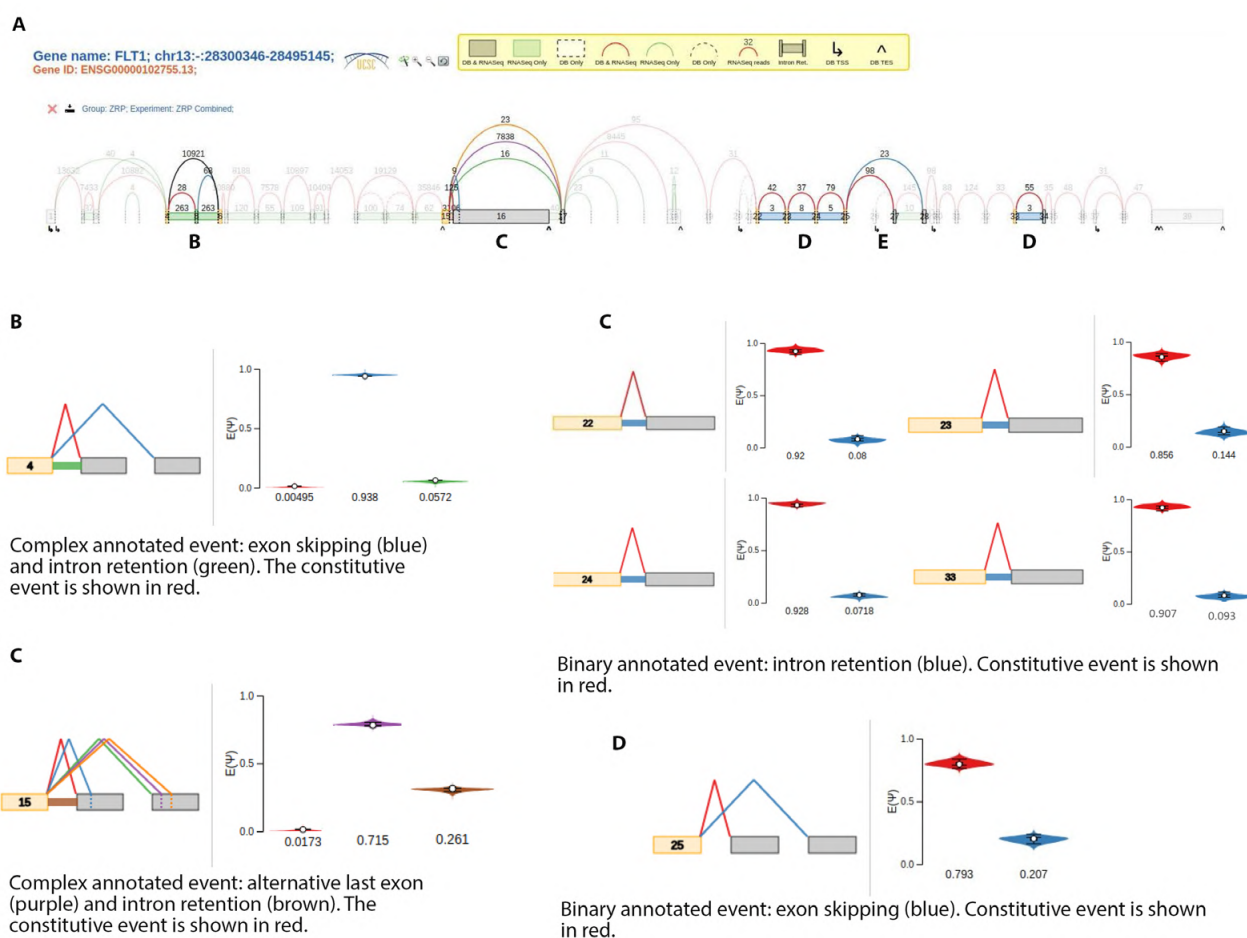


FIG. 2.

Visualization of AS events in placental decidual cells for the *FLT1* gene in the fetal growth retardation using the MAJIQ VOILA program. **A** – intron-exon structure of the *FLT1* gene; **B–E** – statistically significant events in the intron-exon structure.

regulate splice site recognition and spliceosome assembly. It is known that hypoxia, characteristic of placental insufficiency, can alter the expression and activity of key regulators, including SRSF (serine/arginine-rich splicing factor) and hnRNP (heterogeneous nuclear ribonucleoprotein), leading to shifts in pre-mRNA processing [15, 16]. Furthermore, hypoxia induces the expression of HIF-dependent genes involved in post-transcriptional regulation, and may also affect phosphorylation of splicing factors, altering their affinity for targets [17]. Collectively, these factors create conditions for aberrant intron retention, which may reflect an adaptive or pathological response of placental cells to chronic stress. Introns contain numerous regulatory elements, as well as stop codons, which trigger mRNA degradation through nonsense-mediated decay (NMD) [18]. This leads to an increased probability of producing non-functional or unstable mRNA transcripts, resulting in reduced levels of functional, full-length protein. For *FLT1*, this can lead to a decrease in the number of full-length functional receptors and an imbalance towards soluble forms. The retention of other introns has also been described. The classic placental variant, sFlt1-i13, is formed through the retention of intron 13 and early polyadenylation [19, 20]. This results in a protein with the extracellular ligand-binding domain, but lacking the transmembrane and tyrosine kinase domains. Retention of intron 14 has also been observed in some cases, creating another soluble isoform [21].

Additionally, it is worth noting the high number of alternative splicing events in the exon 15 region. The sFlt1-e15a variant arises through the inclusion of alternative exon 15a, which is located after the standard exon 15, and premature termination of transcription, as has been well documented in preeclampsia [22]. Our data suggest that a similar process may also be significant for FGR (Fig. 3).

The figure shows a diagram of the intron-exon structure of the *FLT1* gene, highlighting alternative splicing events identified based on our data and literature sources. lncRNA refers to long non-coding RNA.

The figure illustrates the key pathophysiological mechanisms that link *FLT1* pre-mRNA alternative splicing with the development of FGR. The upper part of the diagram represents molecular events at the decidual cell transcriptome level. At the transcriptional level in decidual cells, events of intron retention, exon skipping, and cryptic exon inclusion are recorded. These events generate premature stop codons, leading to nonsense-mediated mRNA decay and early transcript termination. According to our data and literature, these events are localized in exons 13–15 and 26, forming a “hot spot” for alternative splicing. Minor differences in the frequency of alternative splicing can lead to significant changes in the functional organization of the placenta.

The next level reveals that these changes prevent the formation of full-length transmembrane *FLT1*

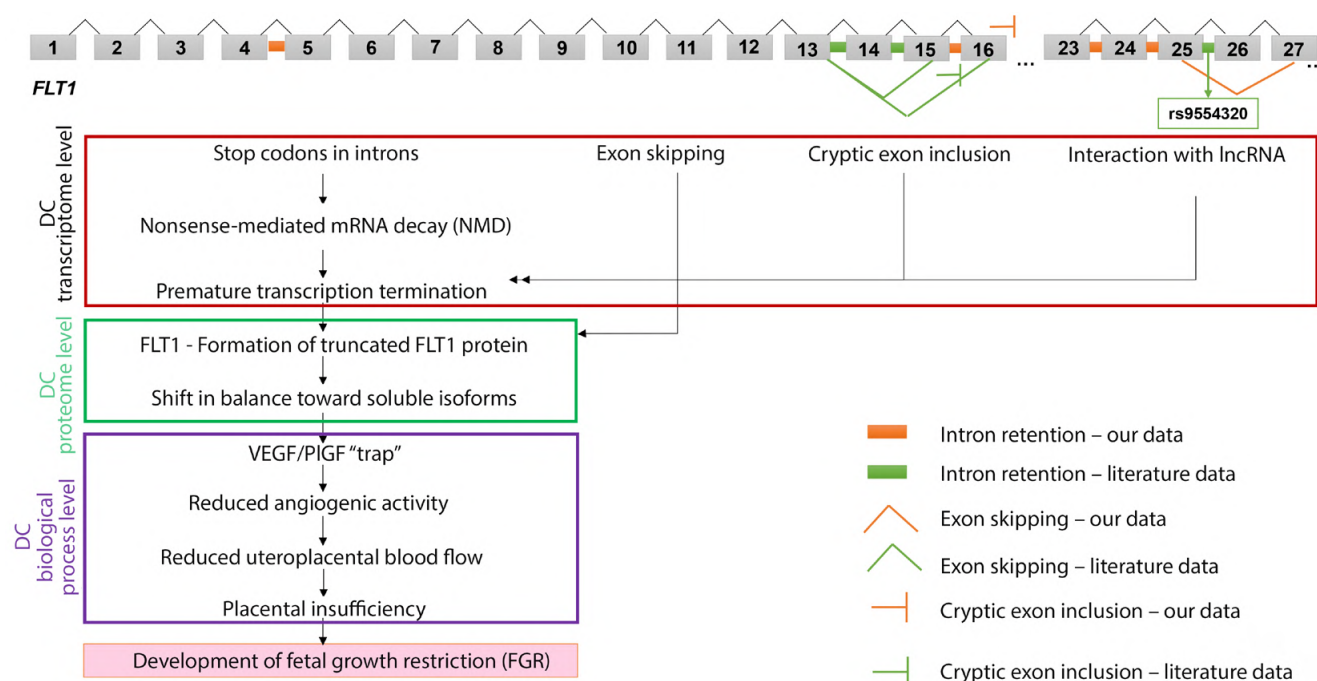


FIG. 3.

Mechanisms of the *FLT1* gene alternative splicing and their relation to the pathophysiological links of fetal growth retardation. The figure shows a diagram of the intron-exon structure of the *FLT1* gene with alternative splicing events identified from our and literature data. lncRNA is a long non-coding RNA.

receptors, shifting the balance towards the production of their soluble isoforms (sFlt-1). These latter act as molecular “traps” for VEGF and PlGF, binding them and preventing their interaction with full-length receptors on endothelial cell surfaces. As a consequence, the availability of these key vascular growth factors is significantly reduced, weakening the stimulation of endothelial cell proliferation, migration, and survival. This decreases angiogenic activity, limiting not only the formation of new blood vessels but also the stability of existing capillaries.

From a pathophysiological standpoint, this implies reduced angiogenic activity, reduced density and branching of the vascular tree of the villi, and impaired angiogenesis during early gestation and vasculogenesis during subsequent stages of pregnancy. Clinically, these alterations manifest as reduced uterine-placental blood flow, leading to conditions of chronic placental hypoperfusion. Against this backdrop, placental insufficiency arises: oxygen and nutrient supply to the fetus become inadequate to meet its requirements. At the systemic level, these disturbances manifest as chronic hypoxia and energy deficit in the fetus, resulting in the development of FGR and an increased risk of perinatal complications. Therefore, the diagram illustrates the pathogenic chain: from molecular events involving *FLT1* pre-mRNA alternative splicing, to impaired placental function, and clinical manifestations of FGR.

The appearance of additional complex events in the FGR group warrants further investigation. Their occurrence may indicate that, under pathological conditions, placental cells have been forced to utilize more variable but less efficient methods of generating protein isoforms. This could be considered a sign of transcriptome instability occurring as a result of chronic hypoxia, oxidative stress, and inflammation. This leads to cellular adaptation at the expense of stability and functional integrity. The observed pattern confirms that alternative splicing is not merely a secondary consequence of the pathological process, but an active participant in pathogenesis, influencing the balance between adaptation and decompensation in the FGR condition.

CONCLUSION

For the first time, an analysis of alternative splicing events of *FLT1* pre-mRNA in the context of FGR pathogenesis has been conducted. The findings indicate that in FGR, there is a shift in the AS landscape of placental decidual cells, characterized by an increase in intron retention and exon skipping events, particularly in key regions of exons 13–15 and 26. These alterations in AS lead to a change in the balance between the full-length and soluble forms of the vascular endothelial growth factor (VEGFR)-1 receptor, resulting in the production of anti-angiogenic factors that inhibit VEGFR/platelet-derived growth factor (PlGF)-mediated signaling and limit angiogenesis. Additionally, the emergence

of novel complex AS events in FGR reflect transcriptome instability in response to chronic hypoxia, oxidative stress, and inflammation. The data in this study emphasize the importance of *FLT1* pre-mRNA alternative splicing in placental insufficiency development and open up possibilities for its use as a potential molecular marker for studying the pathophysiological mechanisms of FGR. Analysis of specific splicing patterns in circulating maternal RNA has the potential to be used for risk stratification in FGR. However, further research with larger sample sizes and confirmation of results at the protein level is necessary to determine the diagnostic and predictive significance of these events.

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Conflicts of interest

The authors declare no conflicts of interest.

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