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The role of the *HLA-G* gene and its expression in the genesis of recurrent miscarriage

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This review summarizes the results of modern foreign and domestic clinical studies that provide information on the importance of the main histocompatibility complex (HLA), in general, and the expression of non-classical HLA-G molecules on trophoblast cells, in particular, in the physiological course of early pregnancy. The *HLA-G* gene has central functions in the processing and presentation of antigen and inhibits the receptor of NK cells, which leads to a decrease in the immune response at the fetal-maternal interface and provides immune tolerance to the fetus from the maternal body. *HLA-G* expression is dependent on combinations of transcription factors, miRNAs, and environmental factors. Based on this, more than a hundred studies have been put into clarifying how *HLA-G* expression influences the development of pregnancy complications, such as recurrent pregnancy losses, in which immunological factors are believed to play a crucial role.

Keywords: *HLA-G*; pregnancy; miscarriage; recurrent pregnancy loss; reproductive loss.

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Роль гена *HLA-G* и его экспрессии в генезе привычного невынашивания беременности

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Обобщены результаты современных клинических исследований зарубежных и отечественных работ, в которых представлена информация о значении молекулы главного комплекса гистосовместимости (HLA) и экспрессии неклассических молекул HLA-G на клетках трофобласта, в частности, при физиологическом течении беременности на ранних сроках. Ген *HLA-G* выполняет центральные функции при процессинге и представлении антигена, ингибирует рецептор клеток естественных киллеров, что приводит к снижению иммунного ответа на границе мать – плод и обеспечивает иммунную толерантность к плоду со стороны материнского организма. Его экспрессия зависит от комбинаций факторов транскрипции, микроРНК и факторов окружающей среды. Исходя из этого, проведено более 100 экспериментальных исследований с целью изучения экспрессии гена *HLA-G* и продемонстрировано его влияние на развитие осложнений беременности, таких как привычная потеря плода на ранних сроках, когда иммунологические факторы, как считается, играют решающую роль.

Ключевые слова: *HLA-G*; беременность; самопроизвольный выкидыш; привычное невынашивание беременности; репродуктивные потери.

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ЭКО•ВЕКТОР

An increased number of infertile couples with a history of miscarriage, including repeated fetal loss, is an unfavorable background in the demographic Russian Federation presentation. Immunological factors in 50%–80% of cases were the main causes of early reproductive losses. Regardless of the gestational age, a unique combination of human leucocyte antigen (HLA) expression on extravillous trophoblast (EVT) cells and maternal leukocytes in decidual tissue at the border of the mother–placenta–fetus system is observed. Cells of the EVT express polymorphic nonclassical class I human major histocompatibility complex antigens HLA-E, HLA-F, HLA-G, and HLA-C (Fig. 1). HLA-G represents a molecule that protects the fetus from destruction by its mother's immune system, thus greatly contributing to the tolerance of the two organisms.

HLA-G functions as an immune escape mechanism from tumors through shield-like direct interaction with immune effectors [2]. In 2001, when the word "shield" was used to define the function of HLA-G molecules to protect against foreign or unwanted tissues and cells, the immunologically programmed destruction was due to its structural content. However, over time, these intercellular ligand to receptor interactions that block immune responses have been given a new name, the immune checkpoints [3]. Immune checkpoints are not molecules, but pathways for implementing a response; therefore, HLA-G is no longer a shield, and the HLA-G/immunoglobulin-like transcript (ILT) interaction is an immune checkpoint.

DEVELOPMENT OF REPRODUCTIVE IMMUNOLOGY AND RESEARCH OF THE MAIN HISTOCOMPATIBILITY COMPLEX

In 1953, P. Medawar, posing the question "why is a semiallogeneic fetus protected from rejection by the maternal immune system?", laid the foundation for reproductive

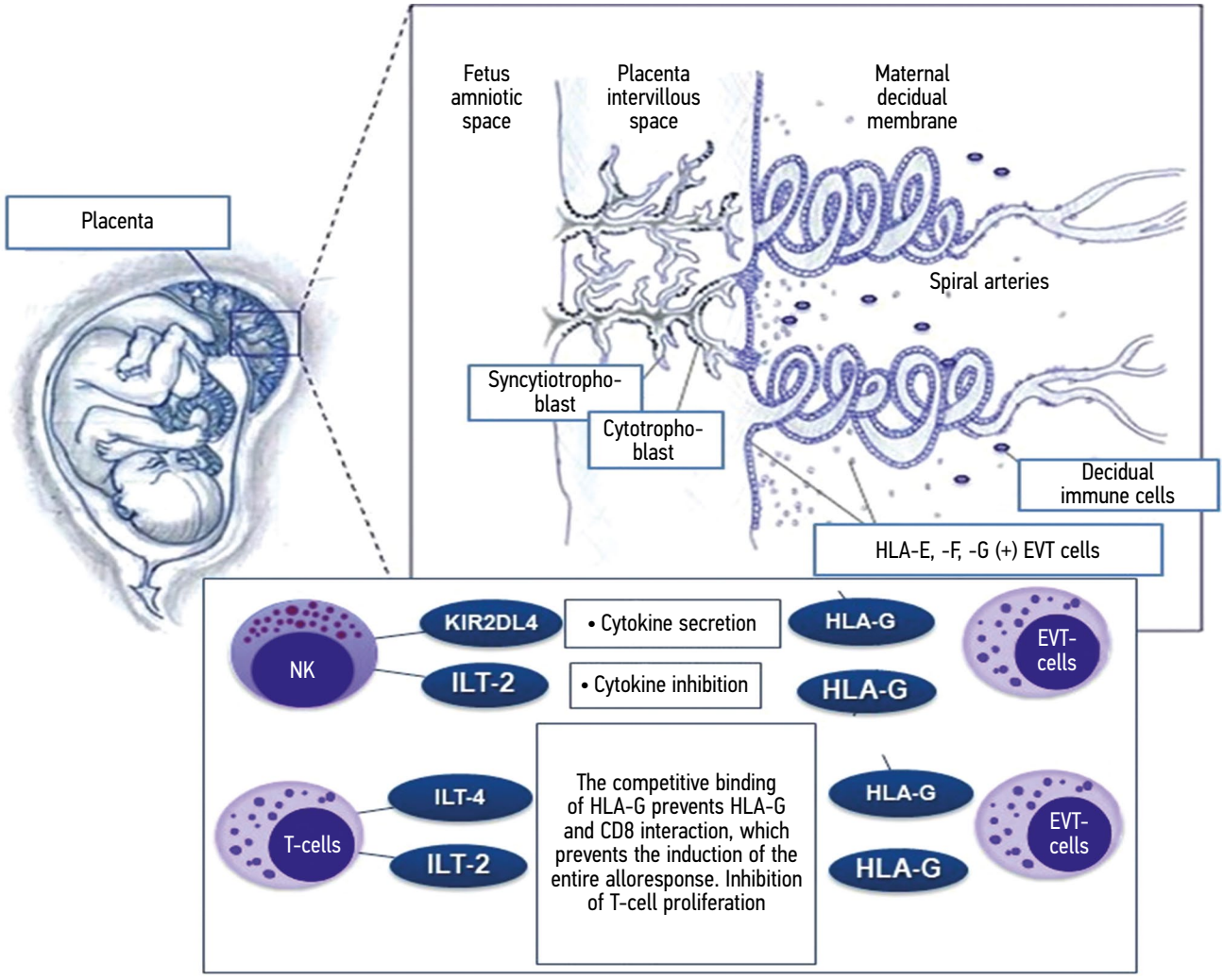

Fig. 1. Schematic representation of the fetus, placenta, decidual tissue, and the functional significance of protein molecules of HLA-G expression. The rectangular inset indicates an enlarged view of the maternal-fetal interface showing the localization of trophoblast cell populations. Cytotrophoblast cells are precursors of differentiated trophoblast cell populations; extravillous trophoblast (EVT) cells express HLA-E, HLA-G, and possibly HLA-F on their surface; syncytiotrophoblast cells can express the soluble form of HLA-G protein molecules together with villous trophoblast cells. The arrows on the round inset indicate the interactions of HLA-G with various receptors on the cell surface, namely natural killer (NK) cells of the uterus, $CD8^+$ T cells. ILT — immunoglobulin-like transcript [1]

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immunology. If the classical rules of transplantation immunity are applied to pregnancy, the fetus as a "transplant" must be rejected by the mother's body, which is the "host."

Contrarily, immunological confirmation of pregnancy by the woman's body is necessary for successful implantation and subsequent pregnancy development. Immune system activation appears to be essential for a normal outcome [4].

The French scientist-professor, Jean-Baptiste-Gabriel-Joachim Dausset, became famous worldwide due to his research in the field of immunology; first of all, his discovery in 1952 of human leukocyte antigens, which was included in the major histocompatibility complex, made by him together with the American immunologist of the Venezuelan origin, Baruj Benacerraf, and the American transplantologist-immunologist, George Davis Snell. Thanks to this discovery, scientists were able to predict the probability of a rejection reaction during organ and tissue transplantation, which made the development of modern transplantology possible [5, 6].

Subsequent studies by J. Dausset were focused on the genetic causes of several chronic diseases. In 1980, J. Dausset, B. Benacerraf, and G. Snell were awarded the Nobel Prize in Medicine and Physiology "for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions." With the money received from the Nobel Prize and a grant from French television, the Human Polymorphism Study Center (Centre d'Etude du Polymorphisme Humain [CEPH]) was founded in 1984, which was later renamed the J. Dausset-CEPH Foundation.

Studies in the 1960s have proven the influence of HLA antigens on fetal development and the course and outcome of pregnancy. Studies in the 1970s have established a large number of coincidences of HLA antigens in couples with recurrent miscarriages (RM). According to L.D. Serova, if spouses are compatible with 3 or more HLA antigens, the risk of miscarriage and infertility increases to 100% [7].

C. Ober et al. revealed a high frequency of HLA-DQ matches in spouses with RM, using the polymerase chain reaction method (PCR-SSOP, sequence-specific oligonucleotide probe hybridization) [8–11].

In the 1990s, a relationship was established between recurrent fetal loss and the HLA-DR antigen (DR1 and DR3). Spouses with failed outcomes of pregnancy more often have matched HLA-DR antigens, and the HLA-B44/DR5 haplotype was much more often detected in couples with miscarriage [12].

HLA-G GENE

The *HLA-G* gene was first described as a structural homolog of the mouse Qa gene in 1987 (D.E. Geraghty, B. Koller, H.T. Orr). Among all class I major histocompatibility complex expression products, HLA-G is the most prominent representative of class Ib nonclassical proteins that are expressed on trophoblast cells. The main differences of HLA-G include the limited tissue distribution, the low polymorphism level, and the presence of 7 different isoform structures that are generated due to alternative splicing, as well as the ability to exert a suppressive effect on immunocompetent cells. The *HLA-G* gene is located on the short arm of chromosome 6 at 6p21.3 in class I major histocompatibility complex gene cluster.

The unique alternative splicing of *HLA-G* leads to the formation of 7 isoforms, which include 4 membrane-bound (HLA-G1-G4) and 3 soluble forms (HLA-G5-G7) [13]. Dimers of the soluble sHLA-G molecule increase its functional capacity. During pregnancy, HLA-G1 and HLA-G5 have the greatest influence on its development and prolongation since several studies have shown that cells of the EVT express both membrane-bound HLA-G1 molecules and its soluble forms HLA-G5/sHLA-G1 at the border of the functional interface of the mother and fetus. Information about the expression of HLA-G isoforms in the villous cytotrophoblast and syncytiotrophoblast remains controversial. Additionally, according to the latest data, the soluble form of sHLA-G is detected in the blood plasma of pregnant and non-pregnant women in the follicular fluid and oocyte supernatants. Interestingly, sHLA-G is present in plasma and seminal fluid in men [14]. The HLA-G protein molecule interacts with various immune receptors, including ILT 2 and 4 and KIR2DL4, which contributes to immunological processes that include the inhibition of T-cell proliferation and function, natural killer (NK) cell proliferation and cytotoxicity, induction of regulatory T-cells, and suppression of antigen-presenting cell differentiation, which ultimately leads to a change in cytokine secretion.

The protein products of the *HLA-G* gene expression are complex in structure and can be present as monomers, homo-, and heteromultimers, ubiquitinated proteins located in a free state in biological fluids, or being a component of exosomes [15].

HLA-G GENE EXPRESSION AND REGULATION

HLA-G expression is dependent on combinations of transcription factors, microRNAs (miRNAs), and environmental factors. *HLA-G* regulation is unique and distinct from the expression of other HLA class I molecules. Thus, HLA-G is expressed on extravillous cells of the cytotrophoblast, which is unique and depends on a 250 bp DNA fragment located at 1.1 kb before the *HLA-G* translation start codon. This DNA sequence is absent in classical HLA class I and may act as an assumed locus control region. The promoter region of the *HLA-G* gene differs from classical class I promoters mainly because (1) it lacks regulatory sensing elements for interferon-gamma (IFNγ) and transcription factor NF-κB, (2) the proximal region of the promoter (within 250 bp from

the first translated ATG codon) does not mediate transactivation via the major mechanisms of HLA class I transactivation, and (3) there are identified alternative regulatory (heat shock proteins, progesterone, and elements responsible for hypoxia) and unidentified elements responsible for interleukin (IL) 10, glucocorticoids, and other transcriptional elements.

Ikeno et al. identified a potentially negative regulator that overlaps a long insertion element (LINE1) located at a distance of 4 kb in the 3'-5' direction from the ATG start codon in the *HLA-G* gene. This silent element may explain the limited *HLA-G* expression compared to other class I genes [16]. The following three alternative regulatory factors have been identified: 1) interferon regulatory factor 1 (IRF-1), which binds stimulatory response elements to interferon; 2) heat shock proteins 1; and 3) progesterone, which activates the *HLA-G* promoter *in vitro* after attaching to a response element located between -52 and -38.

The placenta produces and locally secretes several factors that can modulate the *HLA-G* transcription and/or the expression of its protein molecules in blood mononuclear cells and trophoblast cells. Growth factors, anti-inflammatory, or pro-inflammatory cytokines, such as IL-1β, IL-10, and IFNα, -β, and –γ, in combination with granulocyte-macrophage colony-stimulating factor and/or IL-2, leukemia inhibitory factor, epidermal growth factor, and transforming growth factor β can increase the *HLA-G* gene expression. The same effect was noted for hormones, such as glucocorticoids (dexamethasone, hydrocortisone), β-estradiol, progesterone, prolactin, and leptin, which are produced by the placenta [17–19].

Transcriptional activity of the *HLA-G* gene is required for the activity of some of these modulators. This may be provided by a key physiological microenvironment during placentation. For example, *HLA-G* mRNA activation was registered in a study with chorionic cytotrophoblast in trimester 1 of gestation [20].

DNA methylation and histone modification are interrelated epigenetic mechanisms that are the most significant in the control of transcription. CpG methylation of DNA has been analyzed in human leukemia cell lines, resulting in the detection of *HLA-G* transcription activation after treatment with the demethylating agent 5-azacytidine (5-Aza-dC) in some cell lines. However, in many other cell lines, 5-Aza-dC treatment enhanced *HLA-G* transcription without expression at the protein level. In an experiment, eight different cell lines were exposed to trichostatin A, a histone deacetylase inhibitor, and *HLA-G* transcription was noted only in M8 human melanoma cells. These findings indicate a post-transcriptional mechanism for *HLA-G* expression regulation, which may be more common than previously thought [21].

Post-transcriptional regulation is associated with miRNAs, which are molecules that are capable of suppressing gene

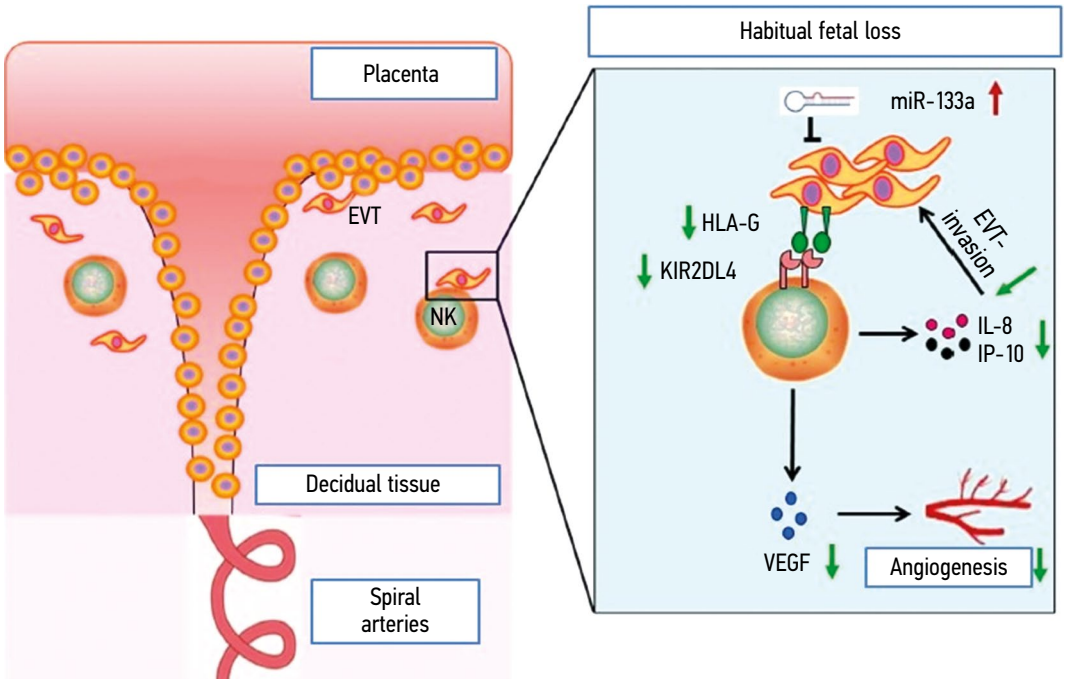

Fig. 2. Scheme illustrating the hypothesis of the relationship between a decreased *HLA-G* gene expression and dysfunction of decidual natural killer (NK) dysfunction in recurrent miscarriage (recurrent fetal loss). Lower KIR2DL4 expression in decidual NK cells in patients with recurrent miscarriage may suppress the proinvasion and secretion of pro-angiogenic cytokines in these cells. Additionally, reduced *HLA-G* gene expression by miRNA-133a in the trophoblast cell line, HTR-8/SVneo, may affect the secretion capacity of decidual NK cells when bound to KIR2DL4. Decreased levels of cytokines may affect trophoblast invasion and angiogenesis. EVT — extravillous trophoblast cells; VEGF — vascular endothelial growth factor [23]

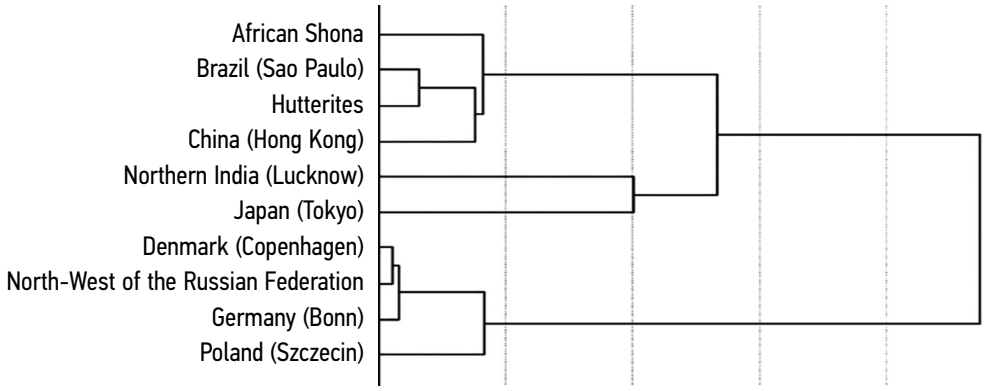

Fig. 3. The similarity of different populations for the G*0101–0107 alleles of the *HLA-G* gene. Clustering by Ward's method using the Euclid distance measure [25]

expression by inducing RNA degradation upon binding to specific sites in the 3'-regions of mRNA. They represent a class of RNAs that do not code for proteins that regulate 30% of all genes in animals by binding to specific sites in the 3' untranslated region (UTR). Through target repression, miRNAs induce critical changes in gene expression programs that underlie such concepts and processes as development time, differentiation, proliferation, cell death, and cell metabolism. MiRNA expression is tissue-specific. Moreover, miRNAs are highly expressed in the human placenta. The fetus is semi-allogenic to the mother, and *HLA-G* is expected to provide fetal and maternal immune tolerance for a favorable pregnancy course. This is similar to a mechanism in tumor cells that escapes immune surveillance. Further studies revealed that miRNA-133a plays a key role in tumor cell proliferation and invasion processes [22]. Therefore, dysfunction of T-cell proliferation and invasion is one of the main causes of pregnancy interruption.

In studying the mechanisms underlying RM, Wang et al. found that miRNA-133a is significantly more expressed in chorionic villi in patients with RM compared to chorionic villi in patients with induced abortion [21]. Multiple program prediction and real-time polymerase reaction confirmed that miRNA-133a most likely binds to the 3'UTR of *HLA-G*, and decidual NK cell functions may be downregulated by reduced *HLA-G* expression, suggesting a possible mechanism for repetitive reproduction losses (Fig. 2). Guo et al. demonstrated that miRNA-133a negatively regulates *HLA-G* expression, affecting the function of decidual NK cells through KIR2DL4 in patients with RM [23]. The *HLA-G* expression status differs among embryos, tissues, and cell population groups. It turned out that *HLA-G* expression is reduced by miRNA-133a in JEG-3 cells due to translation blockade and not due to mRNA degradation. These findings reveal the critical role of *HLA-G* in the development of physiological pregnancy and *HLA-G* expression suppression by miRNA-133a overexpression in patients with reproductive losses. Moreover, high miRNA-133a expression contributes to RM pathogenesis.

POLYMORPHISM OF THE *HLA-G* GENE

HLA-G differs from classical *HLA* genes since it has very limited polymorphic alleles; for example, *HLA-B* has 1431 alleles and *HLA-C* has 569 alleles, while *HLA-G* has only 46 alleles [24]. Polymorphic changes affect both coding and non-coding regions of a gene. Alenichev et al. showed that the frequency of the G*0101 allele in the population of the North-West Russian Federation was 86.5%. The G*0101 allele is considered the most widespread among Caucasoids (the frequency is 72.5% in the Hutterite population, 87% in Denmark, 86% in Germany, 55% in Japan, and 39% in India) [25].

Based on the cluster analysis performed for the G0101–0107 alleles in different populations, two distinct clusters can be distinguished, namely European (Denmark, North-West Russian Federation, Germany, and Poland) and Asian (Japan and North India) (Fig. 3).

HLA-G gene analysis as one of the possible candidate genes that contribute to the development of multifactorial diseases is extremely important for medical genetics.

Cluster analysis and further study of the *HLA-G* gene will individualize the approach to predict and treat patients with immunological disorders and reproductive problems based on their origin and "genetic roots."

CONCLUSION

Based on immunological interaction with immune cells and limited tissue distribution, *HLA-G* appears to suppress maternal alloattack on the fetus during pregnancy. Therefore, much effort has been made to elucidate how *HLA-G* expression influences the development of pregnancy complications, such as recurrent pregnancy losses, in which immunological factors are thought to play a critical role. A detailed study of candidate genes may lead to an understanding of the pathogenesis of immune system-related pregnancy loss.

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Informed consent was obtained from each of the participants included in the study.

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All authors made a significant contribution to the study and the article preparation, as well as read and approved the final version before its publication.

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