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Genetic factors in miscarriages

Ricardo A Galván-Márquez [1,*], Sebastián Díaz-Alanís [1], Paula V Lujan-Valles [1], Fernanda G Parra-García [1], Karla M Vázquez-Macias [1] and Brissia Lazalde [2]

[1] *Faculty of Medicine and Nutrition, Universidad Juárez del Estado de Durango, Dgo., México.*
[2] *Department of Genetics, Faculty of Medicine and Nutrition, Universidad Juárez del Estado de Durango, Dgo., México.*

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Abstract

Miscarriage is defined as the unexpected loss of the pregnancy before the 20th week of gestation. The importance of this article is to acknowledge the varied genes involved in miscarriage, such as thrombophilia genes (factor 5 and factor 2); Immune-related genes (HLA-G and IL-10); and placental development genes (KIR genes).

Keywords: Miscarriage; Thrombophilia; Factor 5; Factor 2; HLA-G; KIR genes; IL-10

1. Introduction

Miscarriage is defined as the unexpected loss of the pregnancy before the 20th week of gestation. Overall, almost all miscarriages occur in an early stage of the pregnancy or even before the woman notices she is pregnant [1].

Genetics is key to understanding the factors behind miscarriage, especially when these events emerge from genetic anomalies such as an abnormal number of chromosomes or rearrangements inside the embryo. Taking advantage of big data technology has allowed researchers to identify specific genetic mutations that may contribute to these losses [2].

Genetics is an important factor in miscarriages, and chromosomal abnormalities are diagnosed in over 50% of first-trimester losses. A karyotype analysis gives definitive perspectives, revealing that the primary causes come from numerical genetic abnormalities: aneuploidy accounts for 30-60% of cases, while triploidy and monosomy represent 11-13% and 10-15%, respectively [1].

Besides genetic factors, there are other causes related to miscarriage, such as uncontrolled diabetes, uterine anomalies, woman's age, previous miscarriages, BMI, smoking, ingestion of alcohol and drugs, man's age, and infections caused by pathogens [3].

This article's central point is to review the monogenic disorders that contribute to the development of a miscarriage.

2. Disorders related to miscarriage

2.1. Thrombophilia

Thrombophilia is a group of disorders in which the blood has an increased tendency to clot. It can be caused by inherited or acquired diseases. Thrombophilia can have autosomal dominant, autosomal recessive, or X-linked inheritance, and one of its increased risks of venous thrombosis may be associated with an increased incidence of miscarriage [4].

* Corresponding author: Ricardo A Galván-Marquez

A recent meta-analysis evaluated a total of 31 studies and found that mutations in factor V Leiden and prothrombin are associated with miscarriage. In addition, mutations in the MTHFR (methylenetetrahydrofolate reductase) gene are also implicated in miscarriage [5].

2.2. F5 (Factor 5 Leiden)

Paternal Factor (F) V Leiden in pregnancy loss. The FV Leiden mutation is inherited in an autosomal dominant manner, so it can also be inherited from the father. Fetal carriage of FV Leiden can lead to a hypercoagulable state in the fetal vessels and even cause infarction along the fetal portion of the placenta and miscarriage (fig-1) [6].

Large deletions/duplications have been described in the F5, F2 SERPINC1, PROS1, PROC, F9, FGA, FGB, and F5 genes encoding coagulation factor V [7].

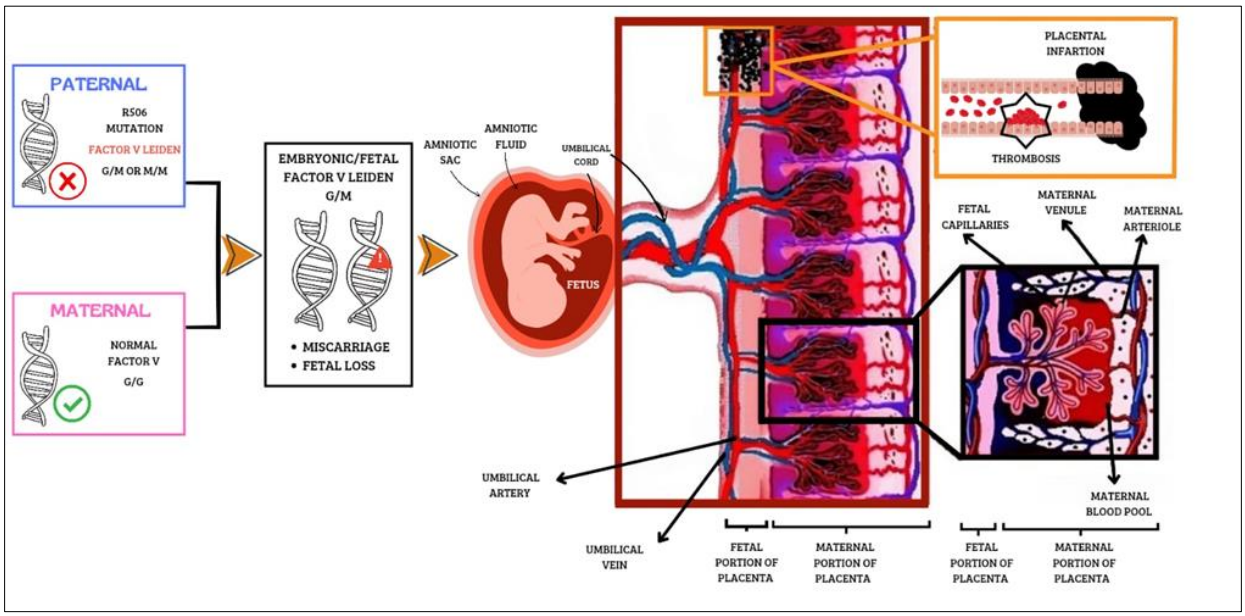

Figure 1 Paternal Factor (F) V Leiden in pregnancy loss

Taken and modified:

Udry S, Aranda FM, Latino JO, de Larrañaga GF. Paternal factor V Leiden and recurrent pregnancy loss: a new concept behind fetal genetics? J Thromb Haemost [Internet]. 2014;12(5):666–9. Available from: http://dx.doi.org/10.1111/jth.12526

2.3. F2 (Prothrombin G20210A)

The F2 gene encodes coagulation factor II, or prothrombin, a vitamin K-dependent glycoprotein synthesized in the liver as an inactive) zymogen. The activated enzyme thrombin plays an important role in hemostasis and thrombosis: it converts fibrinogen to fibrin for blood clot formation, stimulates platelet aggregation, and activates coagulation factors V, VIII, and XIII (Lancellotti and De Cristofaro, 2009) [8].

2.3.1. Another Gen- Prothrombin

Susceptibility to RPRGL2 is conferred by a mutation in the coagulation factor II gene on chromosome 11p11; RPRGL3 by a mutation in the ANXA5 gene on chromosome 4q27; and RPRGL4) by a mutation in the SYCP3 gene on chromosome 12q23 [7].

3. Immune-related genes

3.1. HLA-G Genes

NK cell receptor recognition of the absence of HLA-Ia on leukemic cells and upregulation of HLA-G on those cells devoid of HLA-Ia is a tightrope walk for a sick immune system. The insusceptibility of some patients to these therapies 50 % suggests an unknown inhibitory receptor of NK cells. For personalized NK cell-based immunotherapies, it is imperative to thoroughly evaluate the role of HLA-G [9].

In contrast, HLA-G has been identified as a key molecule in immunological tolerance, whose main function is to protect the fetal allograft from attack by cytotoxic T lymphocytes and to inhibit NK cell-mediated cytolysis at the maternal-fetal interface [10].

HLA G antigens are non-classical major histocompatibility complex (MHC) class I molecules. They were initially identified as a distinct type of HLA selectively expressed at the maternal-fetal interface, specifically on cytotrophoblast cells. In addition, these molecules have been found to bind to inhibitory receptors on uterine NK cells, thus promoting mother-embryo tolerance [11].

Table 1 Alterations related to miscarriage

Alteration	Factor	Mutation	Ubication	Gene/Locus MIM number	Burden
Thrombophilia	Factor V F2	Leiden mutation	11:46,719,21 311:11.2	176930	Miscarriage
	Prothrombin F5	G20210A mutation	1:169,463,90 91q24.2	612309	Miscarriage
HLA	HLA-G	725G allelo	6:29,826,474 6p22.1	600807	Miscarriage

3.2. KIR Genes

KIR (Killer Cell Immunoglobulin Receptor) genes are polymorphic genes that play a crucial role in regulating the maternal immune response during pregnancy [12].

They encode inhibitory and activating genes that are expressed not only in NK cells but also in CD4, CD8, and T cells [13].

KIRs interact with human leukocyte antigens (HLA) on the trophoblast, these complementary ligands help identify self from foreign, resulting in immune tolerance, and this may influence the pathogenesis of recurrent miscarriage disease [14].

A study by Akbari et al. where the population was only women with a history of at least three miscarriages, demonstrated the relationship between KIR and recurrent miscarriage, describing that KIR2DS1 (the KIR gene), with paternal HLA-C2, may be a risk factor for RSA (recurrent spontaneous abortion) [15].

These findings were supported by Wang et al. who found that activation of KIR genes such as KIR2DS1 is a risk factor for RSA demonstrating that there is increased activation of KIR genes and decreased HLA-C alleles in patients with RSA [16].

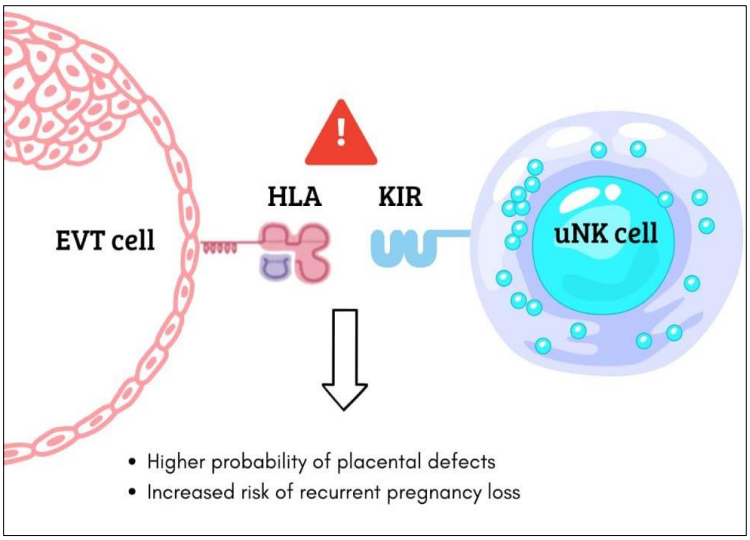

Figure 2 HLA and KIR interaction

Taken and modified

Cuadrado-Torroglosa I, García-Velasco JA, Alecsandru D. Maternal–fetal compatibility in recurrent pregnancy loss. J Clin Med [Internet]. 2024;13(8):2379. Available from: http://dx.doi.org/10.3390/jcm13082379

4. IL-10

Interleucine-10 (IL-10) is an anti-inflammatory cytokine that plays an important role in preventing inflammatory and autoimmune pathologies [17].

In the context of pregnancy, IL10 levels usually increase significantly in women during the early stages of pregnancy and remain elevated until the third trimester, before the onset of labor. Role of IL10 during pregnancy as an active maternal immune suppressor by facilitating fetal allograft acceptance [18].

Several studies have been conducted linking IL10 deficiency to adverse pregnancy outcomes, such as recurrent spontaneous abortion (RSA), preterm birth, and preeclampsia. Mechanisms by which IL10 production may be deficient at the maternal-fetal interface and polymorphisms in the IL10 gene promoter have been detected. They have been associated with deregulated IL10 production and several diseases [18].

Recurrent miscarriages have been associated with increased CD56+ cells as well as increased TNFa. However, this historical inflammatory balance with cytokines may be indicated as a result of insufficient IL-10 production [19].

5. Conclusion

Genetics is key to understanding factors that can lead to miscarriage since the study of genetic factors in miscarriage has revealed a complex interaction of chromosomal abnormalities and genetic mutations that play a fundamental role in gestational losses.

There are different genes involved in spontaneous abortions, which, depending on their characteristics, can vary the effect that the anomaly has on fetal development.

Thrombophilia, characterized by an increased tendency to blood clotting, is associated with mutation of the F5 (Factor 5 Leiden) and F2 (Prothrombin G30210A) genes, to the risk of miscarriage. In addition, abnormal expression of the HLA-G gene contributes to embryo rejection.

Likewise, KIR genes are related to the maternal immune response and their abnormal expression contributes to recurrent miscarriage.

Finally, interleukin-10 (IL-10) contributes to the prevention of inflammatory and immune pathologies, and its deficiency is associated with miscarriage and preeclampsia.

It is also important to take into account other factors that contribute to miscarriage, such as the advanced age of the parents, smoking, stress, etc. The detection of these anomalies allows us to detect patterns and risk factors that contribute to recurrent miscarriages and to guide us toward new diagnostic and counseling strategies.

Compliance with ethical standards

Disclosure of conflict of interest

The author declares that there is no conflict of interest.

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