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Genetic links between HLA-G and recurrent pregnancy loss: a global perspective

Abstract

Recurrent spontaneous abortion (RSA), defined as the loss of three or more fetuses during the first trimester of pregnancy, is a significant reproductive health issue. The Human Leukocyte Antigen (HLA)-G, a non-classical major histocompatibility complex (MHC) class I molecule, plays a crucial role in maternal-fetal immune tolerance. This study investigates the relationship between HLA-G alleles and RSA across various populations globally. Allelic frequencies were analyzed using data from the Anthony Nolan and Allele Frequencies databases, focusing on populations with genetic ties to Colombia due to historical migration patterns. Results indicate that the HLA-G01:01 allele is most prevalent in Denmark, Germany, Portugal, and the United States, with frequencies of 56.7%, 87.47%, 77.19%, and 79.8%, respectively. Conversely, the HLA-G01:03 and HLA-G01:05N alleles are the least frequent, with HLA-G01:05N particularly associated with RSA. The study underscores the importance of HLA-G in pregnancy outcomes and suggests that genetic screening for specific HLA-G alleles in women with a history of RSA could provide insights into the risk factors and mechanisms underlying recurrent pregnancy loss.

Keywords: recurrent spontaneous abortion, HLA-G alleles, maternal-fetal immune tolerance, genetic screening, pregnancy loss

Volume 13 Issue 1 - 2025

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Received: December 28, 2024 | **Published:** January 13, 2025

Introduction

A recurrent abortion is the loss of three or more fetuses during the first trimester of pregnancy, consecutive or not.[1] Spontaneous loss is the most common cause, corresponding to 20% of the abortions detected out of the total abortions in the first trimester. The risk of a subsequent abortion after a spontaneous loss is about 24% and 26% after 2 abortions. Women who have had 3 consecutive spontaneous abortions have a 68% chance of having a successful pregnancy according to a study conducted in 2001 by Makhseed.[2]

The immunological interaction between the embryo and its mother has been conceived as a successful allograft. Communication between the fetoplacental boundary and the maternal immune system is essential for the success of pregnancy, since immune system cells, such as Natural Killers (NK), are responsible for regulating trophoblastic invasion and angiogenesis.[3] The blastocyst, upon implanting, continuing the invasion and replacing the muscular layer of the maternal spiral arteries with trophoblastic cells, causes cellular and tissue damage in the uterus, which is described as an 'open wound'.[4] This is why adequate cellular and tissue repair is required, which may be possible due to the presence of NK cells, macrophages, and T lymphocytes. The development of the fetus will depend on the regulation of the immune response to prevent the occurrence of the rejection of the fetal allograft, this can be perceived in the response of cytotoxic LTs, since they allow the activation of cell-mediated immunity and the production of Th1 cytokines.[5] The expression of HLA-G by extravillous cytotrophoblast cells and its recognition by NK cells through their KIR (Killer-cell immunoglobulin-like receptor) receptors prevents antibody-mediated cytotoxicity induced by them, destroying the musculature that responds to catecholamines, thus avoiding abortion.[6]

HLA-G molecules, which are part of the Major Histocompatibility Complex, are expressed mainly in the fetal vascular endothelium and amniotic cells, and is exactly that of the cells that come into contact with the maternal immune system. Unlike other HLA genes, the HLA-G isoform presents a complete absence of polymorphism in the nucleotide sequence, and when measuring this protein it is essentially the same in the entire world population and for this reason the immune system does not recognize trophoblast cells how I miss. In contrast, the complete absence of expression of the major histocompatibility complex class I by the trophoblast may expose trophoblast cells to attack by cells of the immune system.[7]

The HLA -G molecule adopts seven isoforms, four membrane-bound (HLA-G1, - G2, -G3, -G4) and three soluble (-G5, -G6, -G7), the former are expressed in cytotrophoblast cells. extravillous of the placenta, epithelial cells of the amnion, fetal endothelial cells, macrophages of the mesenchyme of the chorionic villi and in the epithelial cells of the medulla of the thymus; the latter in the amniotic fluid, in the maternal peripheral blood and in the cord blood. It has also been observed that the HLA-G molecule participates in the immune response against tumors.[8]

The HLA-G molecule is associated with some pregnancy pathologies such as eclampsia and preeclampsia,[9] since its absence or poor expression in extravillous cytotrophoblast cells is accompanied by abortion.

HLA-G*0105N is the first null allele of HLA-G described, it presents a deletion of a cytosine (1597 of C) in the third base of codon 129 or in the first base of codon 130, this causes a structural change that It alters the amino acid sequence in exon 3 (domain a2) and generates a premature stop codon in exon 4. The relationship between recurrent spontaneous abortions and the presence of this allele has been demonstrated, which is considered a risk factor for them; This association led to a study being carried out to demonstrate the relationship between the HLA-G*01:05N allele and the spontaneous abortions that occur in Colombia, since it is estimated that between 40-50% of pregnancies end in abortion spontaneous.[10,11]

This study aims to find the relationship between the Human Leukocyte Antigen HLA-G and recurrent spontaneous abortions in various populations around the world; determining the HLA-G allelic

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sequences with the highest and lowest incidence within the studied populations. At the same time, the rate of spontaneous abortions during the first trimester of pregnancy in South America is identified and the ethnic and genetic relationship between the studied populations and the South American countries is determined, since these countries have a diversity of extra-regional migrants throughout the region extension of the continent. Among these migratory flows, Africans, Asians, Europeans, North Americans and Caribbeans stand out. One of the South American countries with the most ethnic diversity due to constant migrations is Colombia. According to the 2014-2015 Annual Statistics Bulletin, 490,116 people from the United States, 437,265 people from Europe, 63,393 from Asia and 4,218 from Africa entered the Colombian country, influencing the settlement of many of these populations in the different polymorphisms found in our country.[12,13]

Methods

A systematic search was carried out in the PubMed, Elsevier and Scielo databases, with the following MeSH: ››pregnancy‹‹, ››abortions/spontaneous‹‹, ››Major Histocompatibility Complex/HLA Antigens‹‹, ››HLA-G allele/frequencies/risk factor‹‹. As a result of the exhaustive bibliographic review in the databases, a series of review articles[5,6] and experimental studies[14] were obtained, which showed the relationship of HLA-G with recurrent spontaneous abortions, providing a basis theory to research. The bibliography of the selected articles and studies was reviewed in search of other relevant articles.

Using the Anthony Nolan and Allele Frequencies databases,[15] the allelic frequencies of HLA-G were identified in populations genetically related to Colombia, such as Iran, Brazil, Ghana and India, taking into account the constant migrations that have developed over the years; In addition, the HLA-G allelic sequences were aligned using software such as MEGA7, BLAST and FASTA.

Results

From the allelic sequences obtained from the Allele Frequencies[15] and Anthony Noland database, it was found that the genes of the HLA-G*01:01 family were the most frequent in Denmark, Germany, Portugal and the United States. United with a frequency of 56.7%, 87.47%, 77.19% and 79.8% respectively.

In the same way, it was evident that the HLA-G*01:03 and HLA-G*01:05N genes were the least frequent. The HLA.G*01:03 allele occurs with a frequency of 8% in Brazilian populations, 0.30% in China, 2.30% in Germany, 24.20% in India, 6.14% in Portugal, 1.4% in Denmark and 2.70% in the United States; while, the HLA-G*01:05N allele had a lower frequency in the following countries: Brazil (1%), China (1.40%), Germany (2.30%), Ghana (4.8%), India (15.40%), Iran (18.10%), Poland (1.70%), Portugal (0.88%), South Korea (1.90%), Spain (3.90%), United States (8.30 %) and in Zimbabwe (11.10%) (Table 1).

Table 1 HLA-G polymorphisms of higher and lower frequency in different populations around the world, highlighting HLA-G*01:05N, related to recurrent spontaneous abortions, and phylogenetically close alleles

* https://www.allelefrequencies.net/

Allele Frequencies - HLA G					
Countries	**Alleles**	**Population**	**Allele frequency**	**Sample size**	**Ref**
Brazil	G*01:01:02	Brazil Parana Mixed	0.24	52	
	G*01:01:02	Brazil Sao Paulo pop 2	0.199	103	
	G*01:03	Brazil Parana Mixed	0.14	52	
	G*01:03	Brazil Sao Paulo Pop 2	0.087	103	
	G*01:05N	Brazil Parana Mixed	0.01	52	
	G*01:05N	Brazil Sao Paulo Pop 2	0.01	103	
	G*01:06	Brazil Sao Paulo Pop 2	0.049	103	
China	G*01:01:02	China Zhejiang Province Han	0.116	146	
	G*01:03	China Zhejiang Province Han	0.003	146	
	G*01:05N	China Zhejiang Province Han	0.014	146	
Denmark	G*01:01	Denmark pop 2	0.567	150	
	G*01:03	Denmark pop 2	0.432	150	
Germany	G*01:01	Germany pop 5	0.8749	132	
	G*01:03	Germany pop 5	0.023	132	
	G*01:05N	Germany pop 5	0.023	132	
Ghana	G*01:01:02	Ghana	0.024	42	
	G*01:05N	Ghana	0.048	42	
India	G*01:01:02	India Lucknow pop 2	0.163	120	
	G*01:03	India Lucknow pop 2	0.242	120	
	G*01:05N	India Lucknow pop 2	0.154	120	*
	G*01:06	India Lucknow pop 2	0.029	120	
Iran	G*01:01:02	Iran Tehran pop 2	0.299	102	
	G*01:05N	Iran Tehran pop 2	0.181	102	
Poland	G*01:01:02	Poland pop 2	0.207	58	
	G*01:05N	Poland pop 2	0.017	58	
	G*01:06	Poland pop 2	0.052	58	

Citation: Parga-Lozano C, Santodomingo N, Parga M, et al. Genetic links between HLA-G and recurrent pregnancy loss: a global perspective. *Pharm Pharmacol Int J.* 2025;13(1):1–5. DOI: 10.15406/ppij.2025.13.00458

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Table 1 Continued.....

South Korea	G*01:01:02	South Korea Pop 7	0,066	486
	G*01:05N	South Korea pop 7	0.019	486
Spain	G*01:01:02	Spain Pop 2	0,251	114
	G*01:05N	Spain Pop 2	0,0309	114
Portugal	G*01:01	Portugal Azores Terceira Island	0.7719	130
	G*01:03	Portugal Azores Terceira Island	0.0614	130
	G*01:05N	Portugal Azores Terceira Island	0.0088	130
	G*01:06	Portugal Azores Terceira Island	0.0746	130
USA	G*01:01	USA South Dakota Hutteritie	0,798	80
	G*01:01:02	USA African American Pop 6	0,06	42
	G*01:05N	USA African American Pop 6	0,083	42
Zimbabwe	G*01:01:02	Zimbabwe Harare Shona Pop2	0,144	108
	G*01:05N	Zimbabwe Harare Shona pop2	0,111	108

A comparison of all HLA-G alleles was carried out, using the sequence information of exons 2, 3 and 4 provided by the IMGT database and based on this, a phylogenetic tree was created based on genetic distances (Figure 1). The relationship between the HLA-G*01:05N allele and the alleles: -G*01:06, - G*01:08 and –G*01:01:02:02 was observed. The HLA-G*01:01:02:02 allele was found with a frequency of 24% and 19% in two populations from Brazil, a frequency of 11.6% in China, 2.4% in Ghana, 16.3 % in India, 29.9% in Iran, 20.7% in Poland, 6.6% in South Korea, 25.1% in Spain, 6% in the United States and 14.4% in Zimbabwe. While HLA-G*01:06 was found in Brazil (4.9%), in India (2.9%), Poland (5.2%) and in Portugal (7.46%) and was not found presence of the HLA-G*01:08 allele in none of the populations studied (Table 1).

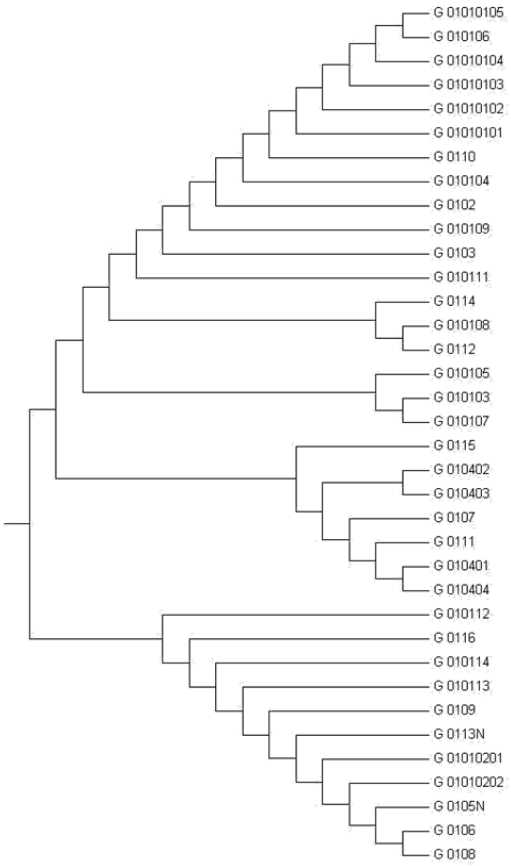

Figure 1 Neighbor-Joining dendrogram obtained using HLA-G allele frequencies.

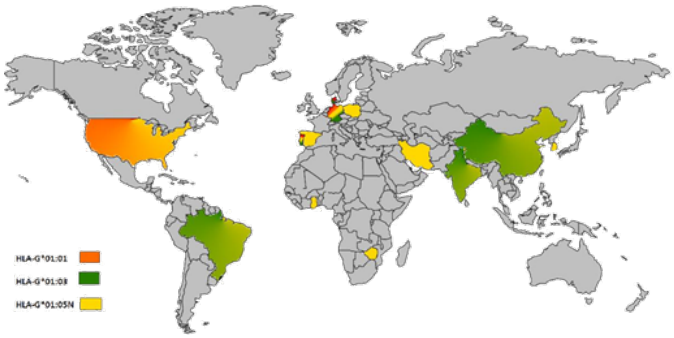

Image Countries of the world where HLA-G polymorphisms are found with greater and lesser frequency, excluding the HLA-G*01:05N allele which is related to spontaneous abortions.

Discussion

In the United States, Sabbagh A et al.,[16] sought to characterize the variation in the regulatory sequence of the HLA-G 3'UTR in several populations worldwide, in order to understand the patterns of variation in this locus, and provide information on the expression mechanisms of this molecule, for which 444 individuals from Africa, from different regions, 239 from Senegal, 175 from Congo and 30 from Benin were taken 4 variation sites and 13 single nucleotide variants were found, of which 4 were identified for the first time, 3 of these variants were only in the Congo individuals and the other was present in both Congo and Senegal individuals, all with a frequency less than 0.02, the other ten variants had already been described in previous studies. Two of the new variants found in this study for these populations had been previously described in Kenya, England, Puerto Rico and China.[16.]

Another study in the United States, Castelli E et al.,[17] through the analysis of databases such as 1000 Genomes where misnamed genotypes and haplotypes were recovered, evidence was made that the global structure of the HLA-G molecule has been maintained during the evolutionary process and that most of the variation sites found in the HLA-G coding region are encoding synonymous or intronic mutations. And through this study, they came to the conclusion that African populations have greater variability of this molecule than European and Asian populations, and in America high variability of this molecule was also found.[17.]

The HLA-G*01:015N allele is implicated as a risk factor for spontaneous abortions; A study carried out by Pfeiffer et al in 2001 found an increase in the frequency of the HLA-G*01013 and HLA-

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G*0105N alleles in 78 couples with recurrent abortion compared to 52 controls.[18] In Colombia, 352 cases of deaths of fetuses of less than 22 weeks of gestation affected by certain maternal conditions were recorded, according to the statistics provided by the DANE death bulletin for 2016. Based on the study of allele frequencies in the analyzed populations, the countries that showed a significant allele frequency were: Iran (18.10%), India (15.40%), Zimbabwe (11.10%), United States (8.30%), Ghana (4.8%), Spain (3.90%) and Germany (2.30%), these countries have stood out for their migratory flow to Colombia throughout history, which has been increasing in the last century.

Unfortunately, the search for data on spontaneous abortions that have occurred in each of the aforementioned countries has turned out to be quite a challenge since there is no specific data or reliable information that can show us how the allele frequency of HLA-G*01:05N affects in these countries. This is because the WHO/OPS suggests that early fetal deaths (those that correspond to what is generally called "abortion" or products less than 22 weeks of gestation) should not be included in national statistics for the following reasons:

I. The under-registration of abortions is extremely high, given that in many countries, such as Colombia, it is totally illegal.

II. Assigning causes and a basic cause is very difficult, and the information recorded by doctors on death certificates almost always leads to an "undetermined or unknown cause."

III. In most cases it is very difficult to clearly determine the cause of early fetal death, given that the required studies are not usually carried out throughout the country due to lack of the necessary resources.

Despite the above, Colombia has a special interest in being able to establish the number of early fetal deaths, therefore it has continued to be certified. Knowledge of this data was one of the motivations to carry out this study and search for the possible causes of said abortions.

However, an article published in The Lancet magazine was taken as a reference, which analyzed the global, regional, national and subnational situation of some countries regarding the levels of intrauterine, neonatal and infant deaths under 5 years of age in the 2015. The study analyzed the situation of 195 countries, territories and selected subnational geographical regions around the world in terms of the number of intrauterine fetal deaths and also analyzed how great the progress of each country was in this matter in the last 15 years.

To develop the data on intrauterine deaths, a variable was included that represented different definitions of fetal death, covering the seven definitions found within its database. These definitions included fetal death after 28 weeks gestation, 26 weeks gestation, 24 weeks gestation, 22 weeks gestation, 20 weeks gestation, weighing at least 1000 g, or weighing at least 500 g.

The rate of total stillbirths of the countries that have a significant frequency of HLA-G*01:05N and that are related to Colombia was: India (533,140), Zimbabwe (16,960), Ghana (16,160), United States (11,450), Iran (9,270), Germany (1,400) and Spain (750). Colombia, in turn, was included in the study with a result of 7,180 stillbirths in 2015 (Table 2).[19]

Although the study did not take spontaneous abortions into account, the results of the stillbirth rate in countries where the frequency of the HLA-G*01:05N allele is high is significant enough to develop an interesting number of spontaneous abortions in each country, therefore, it should be included in the death statistics. Although it is known that the cause of spontaneous abortions is most of the time unknown or difficult to resolve, this does not exclude the possibility of leading to carry out studies that help find it. Colombia, being one of the few countries that continues to certify the number of abortions, should determine the frequency of the HLA-G*01:05N allele in order to justify its presence as a possible cause for spontaneous abortions.

Table 2 Stillbirth rate in 2015 in countries with significant frequencies of HLA-G*01:05N, Colombia and the global rate

Rate and Total of stillbirths in 2015		
Countries	**Estimated rate per 1,000 Births**	**Total stillbirths (x1000)**
Global	14,89	2124,96
India	20,25	533,14
Zimbabwe	30,48	16,96
Ghana	17,93	16,16
USA	2,84	11,45
Iran	6,82	9,27
Colombia	9,52	7,18
Germany	2,1	1,44
Spain	1,81	0,75

Taking these migrations into account, the frequency of the HLA-G*01:05N allele in these countries and its relationship with spontaneous abortions can lead us to conclude that there is a relationship between this allele and the rate of spontaneous abortions that occur in Colombia.

The Neighbor-Joining dendrogram shows that the alleles: HLA-G*01:06, - G*01:08 and –G*01:01:02:02 are very close genetically to the HLA-G*01:05N allele (Figure 1). The HLA-G*01:06 allele has been associated with preeclampsia in French and Singaporean populations.[20] In a study, an increase in the frequency of this allele in recurrent spontaneous abortions has been reported, but it was not significant enough to relate it as a cause of these.

However, no described cases or information were found that relate the HLA-G*01:08 and HLA-G*01:01:02 alleles to pregnancy or any of its complications. Likewise, these alleles are genetically related to both the HLA-G*01:05N allele and the HLA-G*01:06 allele. Based on this, it can be inferred that these alleles could in turn be related to recurrent spontaneous abortions due to their genetic similarity. However, it is worth highlighting that the HLA-G*01:06 and HLA-G*01:02:02 alleles are not only related in the dendrogram to the null allele but also their frequency stands out in some of the countries in which that is located, such as Brazil, China, Ghana, India, Iran, Poland, South Korea, Spain, United States, Zimbabwe, Portugal.

Considering the above, when carrying out genetic studies in women who have suffered recurrent spontaneous abortions, the frequency of the HLA-G*01:05N, HLA-G*01:06, HLA-G*01 alleles should be looked for: 08 and HLA-G*01:01:02 to determine the increase that these could or could not have and thus determine their relationship with recurrent spontaneous abortions, in turn, the populations where these alleles are found at high frequencies must be taken into account as possible risk factors for said abortions.

Colombia, being a country with a significant rate of spontaneous abortions, should carry out studies to determine the polymorphisms of the HLA-G molecule found in its population, which would facilitate the determination of the cause of recurrent spontaneous abortions,

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showing its relationship with the null allele and those associated with it.

Conclusion

The relationship between the presence of the HLA-G molecule in the cytotrophoblast and the spontaneous abortions present in the Colombian population is evident, according to the HLA-G allelic frequencies of highest (18.10%) and lowest incidence (4, 8%) in populations that have a direct ethnic relationship with Colombia such as Iran, Ghana and India, in which the presence of the G*01:05N allele was evident. Based on the results obtained on the frequency of the HLA-G*01:05N allele in the aforementioned populations, it is suggested that further research be carried out to demonstrate the degree of frequency of this allele in the Colombian population due to constant migrations that occur in the country to relate said frequency as the cause of recurrent spontaneous abortions that occur in Colombia.

Acknowledgments

We thank Natalia Peñaranda Múnera for collecting the data and for making a high contribution to the development of the research.

Conflicts of interest

There is no conflict of interest.

Funding

None.

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