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Association Between - 675 ID, 4G/5G PAI-1 Gene Polymorphism and Pregnancy Loss: A Systematic Review

Grazyna Adler[1], Emir Mahmutbegovic[2], Amina Valjevac[3], Mateusz A Adler[4], Nevena Mahmutbegovic[5], Krzysztof Safranow[6], Ewa Czerska[7], Anna Pawinska-Matecka[7], Iwona Ciechanowicz[8], Damir Marjanovic[9,10]

1Department of Studies in Antropogenetics and Biogerontology, Pomeranian Medical University, Szczecin, Poland

2Institution of Health Protection of Women and Motherhood Canton Sarajevo, Sarajevo, Bosnia and Herzegovina

3Laboratory for Molecular Medicine, Center for Genetics, Medical Faculty, University of Sarajevo, Sarajevo, Sarajevo, Bosnia and Herzegovina

4Warsaw School of Economics, Warsaw, Poland

5Neurology Clinic, Clinical Center of University of Sarajevo, Sarajevo, Bosnia and Herzegovina

6Department of Biochemistry and Medical Chemistry, Pomeranian Medical University, Szczecin, Polandl

7Central Laboratory, Regional Hospital, Szczecin, Poland

8Pomeranian Medical University, Szczecin, Poland

9International Burch University, Bosnia and Herzegovina

10Institute for Anthropological Research, Zagreb, Croatia

Corresponding author: Grazyna Adler, Associate Professor, Department of Studies in Antropogenetics and Biogerontology, Pomeranian Medical University, ul. Żołnierska 48, 70-111 Szczecin, Poland, ORCID ID: http://www.orcid.org: 0000-0001-8792-553X. E-mail: gra2@op.pl

ABSTRACT

Introduction: Several analysis for different population conclude that endothelial plasminogen activator inhibitor 1 gene polymorphism, -675 ID, 4G/5G *PAI-1* (ref SNP ID: rs1799889, also described as rs34857375, has merged into rs1799762) may increase risk of pregnancy loss (PL). However, there is a disagreement as to the association 4G allele with pregnancy loss. **Aim:** Therefore, we decided to investigate the -675 ID, 4G/5G *PAI-1* as a potential genetic factor linked to PL in European and worldwide populations. A systematic review of the scientific literature was conducted with the use of the PubMed and Scopus electronic databases (1991-present), using the following search terms: pregnancy loss, miscarriage, genetic risk of thrombophilia, rs1799889 *PAI*-1 gen, 4G/5G *PAI-1* gene polymorphism, *PAI-1* gene locus 4G/5G polymorphism. **Results:** Among European populations, the statistically significant association between 4G allele and recurrent PL only in Czechs and Bulgarian women was found ($p<0.002$ and $p=0.018$, respectively); while, among populations outside Europe in Iranian, Tunisian and Turkish women (each $p<0.001$). **Conclusions:** We concluded, that both in Europe and elsewhere in the world, the high frequency of 4G allele in population, is not unambiguously linked with the risk of pregnancy loss.

Keywords: pregnancy loss, genetic risk, polymorphism, *PAI-1* gene.

1. INTRODUCTION

Pregnancy is a physiological state that predisposes to hypercoagulability and thrombosis. Due to thrombosis changes in the blood flow (venous stasis), changes in the vascular wall (hypotonia, endothelial damage) and increased levels of coagulation factors such as: VII, VIII, X, XII as well as decreased activity levels of natural anticoagulants, protein C and S, which increase the risk of venous thromboembolism in women with a thrombophilia even further are observed. Pregnancy loss (PL) can be caused due to diverse factors with thrombophilia being one of them (1).

According to definition, miscarriage is every unwanted pregnancy loss until the age of 24 weeks of pregnancy, while according to epidemiological definition, miscarriage is considered as extrusion of the fetus weighting less than 500 grams, or less than 25 cm, which matches to the 20 to 22 week pregnancy (2). Routine gynecological, endocrine and cytogenetic diagnostics could not clarify the reason up to 40% of cases of pregnancy losses worldwide. Recently, the heritable factors of thrombophilia that may predispose to obstetrical complications attract a great attention. In recent studies it was found that -675 ID, 4G/5G endothelial plasminogen activator inhibitor 1 gene (Serpine 1, *PAI- 1*) polymorphism, as referred to "a new thrombophilic factor" may increase the pregnancy loss, and knowledge of its variants may improve the predictive ability (3,4). The -675 ID, 4G/5G *PAI-1* polymorphism consisting of a single insertion/deletion of a guanine base at position 675 in the promoter region of *PAl-1* gene gives rise to 2 alleles 4G and 5G which differ in their regulation of the concentration of plasminogen activator inhibitor-1 (PAl-1) (5, 6). Individuals who are homozygous 4G have higher concentrations of PAI-1 than those who are homozygous 5G, and individuals who are heterozygous 4G/5G, which have intermediate levels of PAI-1 (7). Some studies have reported that the increases in PAI-1

Ref.	Country/Area, total no. of women	No. of women with/ without PL	Women with PL n, (%) 5G5G	5G4G	4G4G	5G	4G	Women without PL n, (%) 5G5G	5G4G	4G4G	5G	4G
(11)	Bosnia and Herzegovina, 308	154/154	30 (19.5)	77 (50)	47 (30.5)	137 (44.5)	171 (55.5)	22 (14.3)	80 (51.9)	52 (33.8)	124 (40)	184 (60)
(12)	Bulgaria, 384	52/125	15 (28.9)	23 (44.2)	14 (26.9)	53 (51)	51 (49)	26 (26.8)	45 (46.4)	26 (26.8)	97 (50)	97 (50)
(13)		110/97	20 (18.2)	44 (40)	46 (41.8)	84 (38.2)	136 (61.8)	26 (26.8)	45 (46.4)	26 (26.8)	97 (50)	97 (50)
(14)	Czech Republic, 231	157/74	23 (14.6)	75 (47.8)	59 (37.6)	121 (38.5)	193 (61.5)	10 (13.5)	54 (73)	10 (13.5)	74 (50)	74 (50)
(15)	Egypt, 250	120/130	75 (62.5)	37 (30.8)	8 (6.7)	187 (77.9)	53 (22.1)	99 (76.2)	28 (21.5)	3 (2.3)	226 (86.9)	34 (13.1)
(16)	Germany, 462	49/102	7 (14.3)	25 (51)	17 (34.7)	39 (39.8)	59 (60.2)	20 (19.6)	50 (49)	32 (31.4)	90 (44.1)	114 (55.9)
(17)		184/127	37 (20.1)	75 (40.8)	72 (39.1)	149 (40.5)	219 (59.5)	28 (22)	58 (45.7)	41 (32.3)	114 (44.9)	140 (55.1)
(18)	Indie, 500	200/300	55 (27.5)	100 (50)	45 (22.5)	210 (52.5)	190 (47.5)	95 (31.6)	131 (43.6)	74 (24.6)	321 (53.5)	279 (46.5)
(19)	Iran, 1034	89/50	26 (29.2)	49 (55.1)	14 (15.7)	101 (56.7)	77 (43.3)	15 (30)	28 (56)	7 (14)	58 (58)	42 (42)
(20)		595/100	184 (30.9)	289 (48.6)	122 (20.5)	657 (55.2)	533 (44.8)	72 (72)	27 (27)	1 (1)	171 (85.5)	29 (14.5)
(21)		100/100	60 (60)	31 (31)	9 (9)	151 (75.5)	49 (24.5)	72 (72)	27 (27)	1 (1)	171 (85.5)	29 (14.5)
(22)	Korea, 531	227/ 304	31 (13.6)	123 (54.2)	73 (32.2)	185 (40.7)	269 (59.3)	48 (15.8)	154 (50.6)	102 (33.6)	250 (41.1)	358 (58.9)
(23)	Serbia, 203	112/91	31 (27.7)	45 (40.2)	36 (32.1)	107 (47.8)	117 (52.2)	18 (19.8)	45 (40.2)	28 (30.8)	81 (44.5)	101 (55.5)
(24)	The Gaza Strip, 200	100/100	40 (40)	44 (44)	16 (16)	124 (62)	76 (38)	36 (36)	48 (48)	16 (16)	120 (60)	80 (40)
(25)	Tunisia, 675	304/371	139 (46)	128 (42)	37 (12)	406 (66.8)	202 (33.2)	257 (69)	104 (28)	10 (3)	618 (83.3)	124 (16.7)
(26)	Turkey, 854	543/106	91 (16.8)	331 (60.9)	121 (22.3)	513 (47.2)	573 (52.8)	34 (32)	62 (58.5)	10 (9.5)	130 (61.3)	82 (38.7)
(27)		113/92	28(25)	53(47)	32(28)	109(48)	117(52)	28(31)	50(54)	14(15)	106(58)	78(42)

Table 1. Distribution of PAI-1 gene polymorphism

serum level lead to a thrombotic tendency (8-10). Furthermore, PAI-1 plays crucial role in the process of fibrinolysis and any changes in concentrations and activity may cause thrombotic changes in the utero-placental unit.

2. AIM

The aim of our study was to investigate the relationship between -675 ID, 4G/5G *PAI-1* polymorphism and pregnancy loss in European women and women elsewhere in the world.

Statistical analysis

Significance of *PAI-1* alleles frequency differences between women with pregnancy loss and control group (without pregnancy loss) was assessed using Fisher's exact test in Statistica 12 software package (StatSoft, Tulsa, OK, USA). P value <0.05 was considered as statistically significant.

By the end of June 2017, PubMed and Scopus electronic databases were searched. The objective was to identify case-control studies on the association between frequency of 4G allele of *PAI-1* polymorphism and pregnancy loss, using the following search terms: pregnancy loss, miscarriage, genetic risk of thrombophilia, rs1799889 *PAI*-1 gen, 4G/5G *PAI-1* gene polymorphism, *PAI-1* gene locus 4G/5G polymorphism. The following data were extracted for each study included in systematic review: authors (reference number), country/area, total number of women, number of women with and without pregnancy loss for each population, distribution of genotypes and alleles in women with and without PL. Reports in English and Bulgarian language were taken into consideration.

The geographical regions excluding Korea and the Gaza Strip by the United Nations were divided (United Nations Statistics Division- Standard Country and Area Codes Classifications, http://www.unstats.un.org/unsd/methods/m49/m49regin.htm#europe).

3. RESULTS

Our results, PubMed and Scopus databases posted as of 30/06/2017, and literature research yielded a dataset containing data from 17 populations belonging to 12 countries

(see Table 1). The total number of women across all 17 populations was 3209 and 2423 in the study and control group, respectively.

4. DISCUSSION

It is estimated that the frequency of pregnancy loss is about 10-25% of all clinically recognized pregnancies, wherein the reasons about 50% of all miscarriages are unidentifiable causes (28, 29).

The pregnancy loss is considered as a multifactorial disease occurring as the result of external factors, many variants of genes among which are mentioned responsible for hemostatic disorders and endothelial dysfunction and behavioral risk factors. Recently, the polymorphism -675 ID, 4G/5G of *PAI-1* gene, linked with hemostasis and endothelial function is eagerly studied in the context of PL and recurrent PL in Europe and worldwide (Figure 1 and Figure 2). The Figure 1 shows the frequency of 4G allele of *PAI-1* gene in some populations of European women with and without pregnancy loss (controls).

Reports on the influence of the -675 ID, 4G/5G *PAI-1* polymorphism on risk of pregnancy loss in the countries of
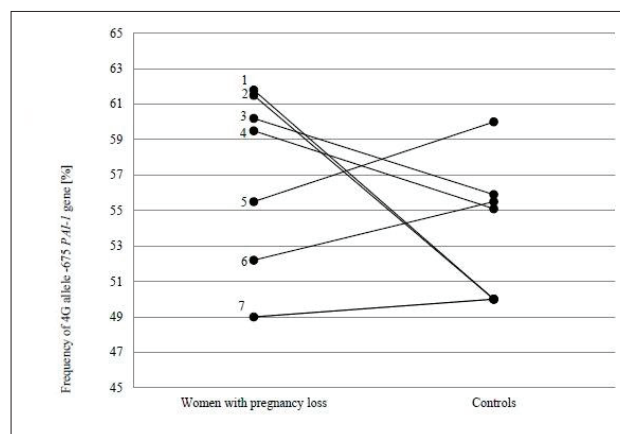
Figure 1. Frequency of 4G allele PAI-1 gene in European women, with and without PL. 1- Bulgaria (13), 2- Czech Republic (14), 3- Germany (16), 4- Germany (17), 5- Bosnia and Herzegovina (11), 6- Serbia (23), 7- Bulgaria (12). Note that data 1-4, 7 but not 5 and 6 are for recurrent PL
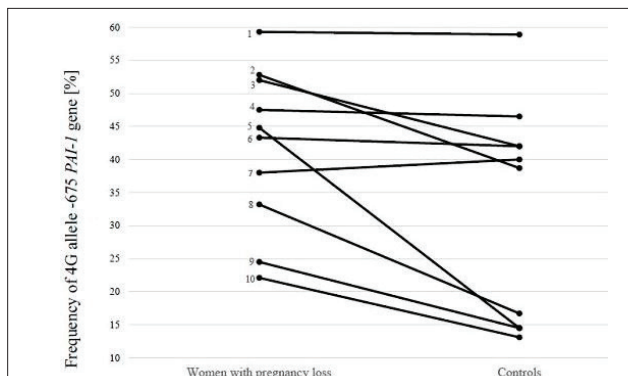
Figure 2. Frequency of 4G allele PAI-1 gene in some populations outside Europe, both in women with and without PL. 1- Korea (22), 2- Turkey, (26), 3-Turkey (27), 4- India (18), 5- Iran (20), 6- Iran (19), 7- the Gaza Strip (24), 8- Tunisia (25), 9-Iran (21), 10- Egypt (15). All data for recurrent PL
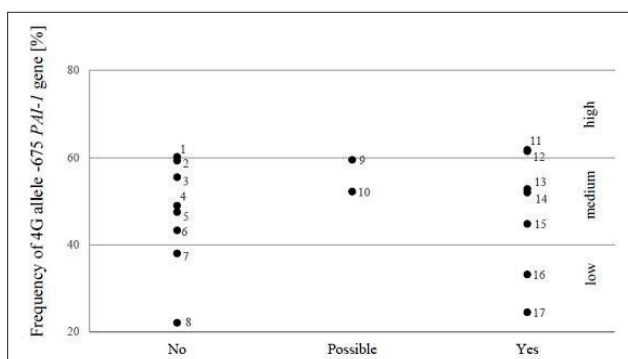
Figure 3. The relationship between statistically significant effect linked with women with PL and the frequency of 4G allele, both in and outside Europe. 1- Germany (16), 2- Korea (22), 3- Bosnia and Herzegovina (11), 4- Bulgaria (12), 5- India (18), 6- Iran (19), 7- the Gaza Strip (24), 8- Egypt (15), 9- Germany (17), 10- Serbia (23), 11- Bulgaria (13), 12- Czech Republic (14), 13- Turkey (26), 14-Turkey (27), 15- Iran (20), 16- Tunisia (25), 17- Iran (21)

southern Europe are rare, and results for European populations are opposing (12-14, 16, 17, 23, 26).

The highest frequency of the 4G allele in women without pregnancy loss was in Bosnian, Serbian and German women (in two groups): 60%, 55.5% and 55.9% and 55.1%, respectively. The lowest and identical frequency was observed in two Bulgarian and one Czech group of women, each 50% (11, 12, 13).

The highest frequency of the 4G allele in women with recurrent PL was in German (in two groups): 59.5% and 60.2%, Bulgarian, 61.8% and Czechs women, 61.5% (13, 14, 16, 17). Once again, Ivanov studied another group of Bulgarian women and this time, the frequency of the 4G allele was 49.0% (23). Results from Bosnian women are arranged in other European populations, and the frequency of the 4G allele in women with PL was 55.5% (11).

Among women from European countries, the statistically significant association between 4G allele and recurrent PL only in Czechs and Bulgarian women was found (p<0.002 and p= 0.018, respectively) (13, 14). Also, authors of several studies state that 4G allele may affect pregnancy loss, but their results were not statistically significant (p>0.05) (17, 23, 26). In other group of Bulgarian and German women, there was no association between the presence of 4G allele and pregnancy loss (p>0.05) (12, 16). We would like to note that, similar as in Bosnian women, in Serb women frequency

of 4G allele in the control group was higher than in women with pregnancy loss; 55.5% and 60% and 55.5% and 52.2%, respectively (23). The frequency of 4G allele in European populations is relatively high and varies from about 50% to 60% (11-14).

We noticed that, in recent years, interest in the role of the 4G allele of *PAI-1* gene in PL outside of European countries is also growing (15, 18, 19, 20, 22, 25). The Figure 2 shows the frequency of 4G allele of *PAI-1* gene in some populations women outside Europe.

The highest frequency of the 4G allele in women without pregnancy loss was in Korean women, 58.9%, and the lowest in Egyptian, Iranian (two consecutive groups) and Tunisian 13.1%, 14.5%, 20.5% and 16.7%, respectively (15, 20-22, 25). Intermediate values of frequency 4G allele were observed in Indian women and women from the Gaza Strip, 46.5% and 40.0%, respectively (18, 24). Also, it should be noted, that other Iranian author, Poursadegh reports frequency of the 4G allele, 42.0% (19).

The highest frequency of the 4G allele in women with pregnancy loss was in Korean women, 59.3%, while intermediate values was in Indian, Iranian (in two consecutive groups) and Palestinian women: 47.5%, 43.3%, 44.8% and 38%, respectively (18-20, 22, 24). Also, it should be noted, that other Iranian author, Torabi reports frequency of the 4G allele 24.5% [21]. The lowest frequency of 4G allele was in Tunisian and Egyptian women, 33.2% and 22.1%, respectively (15, 25).

Among populations outside Europe, the statistically significant association between 4G allele and pregnancy loss in Iranian (two groups) and Tunisian women was found (p<0.001; p<0.05; p<0.001, respectively) (20, 21, 25). However, in another group of Iranian women, there was no association between the presence of 4G allele and pregnancy loss (19). Additionally, several studies also state that 4G allele did not affect pregnancy loss in Korean, Egyptian, Indian and Palestinian women (p>0.05) (15, 18, 22, 24).

In presented results the fact, that the frequency of 4G allele in European populations compared to non European populations is higher, draws attention. Furthermore, there is a disagreement as to the association 4G allele with pregnancy loss. We asked ourselves the question, whether the countries where the allele frequency is higher, the statistically significant relationship between 4G allele and pregnancy loss more often occurs (see Figure 3).

Based on presented results we deduce that, the high frequency of 4G allele in population, is not unambiguously linked with the risk of pregnancy loss.

5. CONCLUSION

Both in Europe and elsewhere in the world, the high frequency of 4G allele in population, is not unambiguously linked with the risk of pregnancy loss.

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