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COMPARATIVE EVALUATION OF FXIII VAL34LEU AND PAI 4G/5G POLYMORPHISMS IN WOMEN WITH RECURRENT PREGNANCY LOSS AND SPONTANEOUS MISCARRIAGE

TEKRARLAYAN GEBELİK KAYBI VE KENDİLİĞİNDEN DÜŞÜK YAŞAYAN KADINLARDA FXIII VAL34LEU VE PAI 4G/5G POLİMORFİZMLERİNİN KARŞILAŞTIRMALI DEĞERLENDİRİLMESİ

AYÇA KOCAAĞA[1], ECE AKÇA SALIK[2]

[1] Eskisehir City Hospital, Department of Medical Genetics, Eskişehir, Turkey
[2] Eskisehir City Hospital, Department of Gynecology and Obstetrics, Eskişehir, Turkey

ABSTRACT

Introduction: Thrombophilia is a condition that increases the tendency to thrombosis and can be acquired or hereditary. If thrombophilia is present during pregnancy, it can lead to various complications such as preeclampsia, intrauterine growth retardation and miscarriage. The aim of this study was to comparatively investigate the association between FXIII Val34Leu and PAI 4G/5G polymorphism in spontaneous and recurrent pregnancy loss (RPL).

Methods: A total of 536 people participated in this case-case study, including 408 women diagnosed with RPL and 128 women diagnosed with spontaneous abortion (SA) with a similiar family history. SPSS-22 was used to statistically investigate the genotype and allele frequencies of these variants and the significance between the two groups.

Results: The mean age of the RPL and SA patients was 29.50 ± 5.46 and 30.02±6.03 years, respectively. The most common variant in both groups was Val/Val, while the least common variant was Leu/Leu FXIII Val34Leu. There was no significant difference in genotype and allele distributions for the Leu/Leu FXIII Val34Leu variant between RPL and SA patients (p=0.167 and 0.174). In our study, no significant difference was observed between SA and RPL groups in terms of genotype and allele frequencies of PAI-1 4G/5G polymorphism (p=0.110 and 0.092). PAI 4G/4G and FXIII Val/Val double mutations were dominant in patients with spontaneous abortion (23.4%) compared to RPL patients (21.0%).

Conclusions: The absence of a significant difference in the frequency and combination of plasminogen activator inhibitor-1 4G/4G and FXIII Val/Val genetic variants in both groups suggests that these variants are important both in patients with recurrent pregnancy loss and in patients with a spontaneous abortion.

Keywords: Chemotherapy, gastric cancer, elderly, first-line treatment

Keywords: FXIII Val34Leu, PAI-1 4G/5G, recurrent pregnancy loss, spontaneous abortion, thrombophilia.

ÖZET

Giriş: Trombofili, tromboza eğilimi artıran, edinilmiş veya kalıtsal olabilen bir durumdur. Gebelikte trombofili preeklampsi, intrauterin büyüme geriliği ve düşük gibi çeşitli komplikasyonlara yol açabilir. Bu çalışmanın amacı, spontan ve tekrarlayan gebelik kaybında (TGK) FXIII Val34Leu ve PAI 4G/5G polimorfizmi arasındaki ilişkiyi karşılaştırmalı olarak araştırmaktır.

Yöntemler: Bu vaka-vaka çalışmasına 408 TGK tanılı kadın ve 128 spontan abort (SA) ve benzer aile öyküsü tanılı kadın olmak üzere toplam 536 kişi katıldı. Bu varyantların genotip ve alel frekanslarını ve iki grup arasındaki anlamlılığı istatistiksel olarak araştırmak için SPSS-22 kullanıldı.

Bulgular: TGK ve SA hastalarının ortalama yaşları sırasıyla 29,50 ± 5,46 ve 30,02 ± 6,03 yıldı. Her iki grupta en sık görülen varyant Val/Val iken, en az görülen varyant Leu/Leu FXIII Val34Leu idi. Leu/Leu FXIII Val34Leu varyantı için TGK ve SA hastaları arasında genotip ve alel dağılımları açısından anlamlı bir fark yoktu (p=0,167 ve 0,174). SA ve TGK grupları arasında PAI-1 4G/5G polimorfizminin genotip ve alel frekansları açısından anlamlı bir fark gözlenmedi (p=0,110 ve 0,092). Spontan düşük öyküsü olan hastalarda PAI 4G/4G ve FXIII Val/Val kombine mutasyonları (%23,4) TGK hastalarına (%21,0) göre daha baskındı.

Sonuç: Her iki grupta plazminojen aktivatör inhibitörü-1 4G/4G ve FXIII Val/Val genetik varyantlarının sıklığı ve kombinasyonu açısından anlamlı bir fark bulunmaması, bu varyantların hem tekrarlayan gebelik kaybı olan hem de tek düşük yapan kadın hastalarda önemli olabileceğini göstermektedir.

Anahtar kelimeler: XIII Val34Leu, PAI-1 4G/5G, tekrarlayan gebelik kaybı, spontan düşük, trombofili.

INTRODUCTION

Spontaneous abortion (SA) is pregnancy loss before 20 weeks gestation. Recurrent pregnancy loss (RPL) is when this happens two or more times. (1). To date, a number of etiologies have been identified for RPL and SA, including chromosomal abnormalities, anatomical problems, endocrinological and autoimmune disorders, and thrombotic defects. In more than half of the cases the cause is unknown (2). Thrombotic disorders include the antiphospholipid syndrome, FV Leiden and FII (Prothrombin G20210A) mutations, MTHFR and PAI-1 polymorphisms, dysfibrinogenemia, deficiencies of protein C, protein S, and

Corresponding Author: Dr. Ayca Kocaağa, Department of Medical Genetics, Eskisehir City Hospital. 71 Evler Mahallesi, Çavdarlar Sk., 26080 Odunpazarı/Eskişehir
E-mail: dr.aycacelikmakas@hotmail.com
ORCID: 0000-0003-0434-8445

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antithrombin III. Recent studies indicate that the strength of the correlation between certain hereditary causes of thrombophilia and RPL is controversial (3). Plasma FXIII is a tetrameric structure (A2B2) arranged by two active A (FXIII-A) and two carrier/protective B subunits (FXIII-B). Val34Leu, located in the FXIII A-subunit gene, is the most functional polymorphism affecting FXIII activation (4). This polymorphism is a G to T substitution at position 34 in exon 2, three amino acids away from the thrombin cleavage site that encodes the Val/Leu change (5). The presence of leucine at this position results in an increased FXIII-specific fibrinolytic activity and appears to be associated with a reduced risk of both arterial and venous thrombosis (6). Previous studies have associated the FXIII Val34Leu polymorphism with a reduced risk of arterial and venous thrombosis, but its association with RPL has not been convincingly established (7). The human plasminogen activator inhibitor-1 (PAI-1) gene has nine exons and eight introns and is found on the long arm of chromosome 7 (8). A deletion/insertion polymorphism (4G or 5G) in the promoter of the PAI-1 gene has been suggested to be involved in the regulation of the synthesis of the inhibitor, the 4G allele being associated with enhanced gene expression, and therefore related to thrombosis (9). Individuals who are homozygous for the 4G allele have the highest levels of PAI-1 in their plasma, while heterozygote intermediates and 5G homozygotes have the lowest levels. There are many studies investigating the potential impact of the PAI-1 4G/5G polymorphism and RPL, but the results are unclear or contradictory (10). Until recently, routine screening for genetic markers of RPL in most laboratories in Turkey included only FV Leiden, FII (Prothrombin G20210A) mutations and MTHFR polymorphisms. However, for the last 3 years, PAI 4G/5G and FXIII Val34Leu have been added to these markers and are being examined in all patients diagnosed with RPL. Although there are some publications examining the relationship between PAI 4G/5G and RPL in Turkey, there is very limited information about FXIII Val34Leu polymorphism and RPL (11). The aim of our study was to determine the frequency of these two polymorphisms in women with RPL and SA and investigate whether there was a relationship through comparative analysis.

METHODS

The patients who applied to Department of Medical Genetics or Obstetrics and Gynecology (Eskişehir City Hospital) due to spontaneous abortion or RPL (more than two abortions before 20th gestational weeks) between January 2022 and January 2025 were included in the study. Patients with a single miscarriage history have a similar family history. The demographic characteristics and clinical history (age, gravida, parity and abortion) were recorded. Each participant filled an informed consent form. DNA isolation was performed from blood samples taken into tubes containing ethylene diamine tetra acetic acid (EDTA). Genomic DNA was isolated from individuals by using the QIAamp DNA Blood Mini Kit (Qiagen Inc., Germany). To determine the prevalence of the polymorphisms in THE CVD panel, the subjects were genotyped for PAI 4G/5G and FXIII Val34Leu by using Real-time PCR with Cobas Z 480 LightCycler (Roche Molecular Diagnostics). LightCycler FastStart DNA Master mix was used containing specific primers and probes for each of them. We investigated the frequency of PAI 4G/5G and FXIII Val34Leu thrombophilic variants calculated for this retrospective study. All statistical calculations were performed using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22 for Microsoft Windows. Data were statistically described in terms of mean ± standard deviation (±SD), median (range), or frequencies (number of cases) and percentages where appropriate. The study was approved by our institution's ethics committee (ESH/BAEK/2025/134). The chi-square test was used to compare the genotype and allele distribution between the two groups. P-values less than 0.05 were considered statistically significant.

RESULTS

A total of 408 women with RPL and 128 women with SA were included in the study. The mean age of the RPL patients was 29.50 ± 5.46 (range 18-46). The mean numbers of gravida, parity and abortion were found as 3.23±1.46, 1.28±0.96, and 3.65±1.24, respectively. The mean age of the SA patients was 30.02±6.03 (18-46). The mean numbers of gravida and parity were found as 2.94±1.03 and 2.58±1.76, respectively. Demographic and clinical characteristics of the patients were listed in Table 1.

Table 1. Demographic characteristics of the study group.

Demographic characteristics	**RPL** Mean±SD Min-Max	**SA** Mean±SD Min-Max
Age	29.50 ± 5.46 (18-46)	30.02±6.03 (18-46)
Gravida (n)	3.23±1.46 (2-8)	2.94±1.03 (1-6)
Parity (n)	1.28±0.96 (0-4)	2.58±1.76 (0-5)
Abortion (n)	3.65±1.24 (2-7)	1

Note: This table displays descriptive statistics for each data. The statistics estimated are mean, minimum, maximum and standard deviation (SD). RPL: Recurrent pregnancy loss, SA: spontaneous abortion

Among the RPL patients, women 112 (27.5%) were heterozygous (Val/Leu) for the FXIII Val34Leu polymorphism, and 5 (1.2%) were homozygous (Leu/Leu). FXIII Val34Leu polymorphism was detected as Val/Val

Table 2. The genotype and allele frequencies of FXIII Val34Leu and PAI 4G/5G in study group.

Genotypes frequencies	**RPL** (n=408) (%)	**SA** (n=128)(%)	**P value**
FXIII Val34Leu			
Val/Val	291 (71.3)	92 (71.9)	0.167
Val/Leu	112 (27.5)	31 (24.2)	
Leu/ Leu	5 (1.2)	5 (3.9)	
PAI 4G/5G			
4G/4G	119 (29.2)	35 (36.8)	0.110
4G/5G	190 (46.5)	50 (57.3)	
5G/5G	99 (24.3)	43 (33.9)	
Allel frequencies			
FXIII Val34Leu			
Val	694 (85.04)	215 (83.99)	0.174
Leu	122 (14.96)	41 (16.01)	
PAI 4G/5G			
4G	428 (52.45)	120 (46.8)	0.092
5G	388 (47.55)	136 (53.2)	

genotype in 291 (71.3%) patients. The allele frequency of Val for FXIII Val34Leu polymorphism was found to be 0.85 (Table 2). The prevalence of the PAI 4G/5G polymorphism among cases was 119 (29.2%) for the homozygous (4G/4G), 190 (46.5%) for the heterozygous (4G/5G), and 99 (24.3%) for the wild state (5G/5G). The 4G allele frequency was 0.52 of PAI-1 4G/5G (Table 2). The most common variant in this group was Val/Val, while the least common variant was Leu/Leu FXIII Val34Leu (71.3% and 1.2% Table 2). The number of patients with the combined genotype of 4G/4G (PAI) and Val/Val (FXIII) was 86 and the incidence rate was 21%. The number of patients with the combined genotype of 5G/5G (PAI) and Leu/Leu (FXIII) was detected only one patient and the incidence rate was 0.25%. Among the SA patients, women 31 (24.2%) were heterozygous (Val/Leu) for the FXIII Val34Leu polymorphism, and 5 (3.9%) were homozygous (Leu/Leu). FXIII Val34Leu polymorphism was detected as Val/Val genotype in 92 (71.9%) patients. The allele frequency of Val for FXIII Val34Leu polymorphism was found to be 0.83 (Table 2). The prevalence of the PAI 4G/5G polymorphism among cases was 35 (36.8%) for the homozygous (4G/4G), 50 (57.3%) for the heterozygous (4G/5G), and 43 (33.9%) for the wild state (5G/5G). The 4G allele frequency was 0.46 of PAI-1 4G/5G (Table 2). The most common variant in this group was Val/Val, while the least common variant was Leu/Leu FXIII Val34Leu (71.9% and 3.9% Table 2). The number of patients with the combined genotype of 4G/4G (PAI) and Val/Val (FXIII) was 30 and the incidence rate was 23.4 %. The number of patients with the combined genotype of 5G/5G (PAI) and Leu/Leu (FXIII) was detected in 2 patients and the incidence rate was 1.4%. There was no significant difference between RPL and SA patients in terms of the distribution of Leu/Leu FXIII Val34Leu genotypes (p=0.167; Table 2). No significant difference was found in FXIII Leu allele frequency between the patient groups (p=0.174; Table 2). There were no differences with regard to the PAI 4G/5G genotype or 4G allele distribution in RPL and SA groups (p > 0.05; Table 2). There was no significant relationship between the groups in terms of combined genotype (PAI 4G/5G + FXIII Val34Leu) (Table 3).

DISCUSSION

This causes of RPL and SA include anatomic and endocrine disorders, antiphospholipid syndrome, and parental or fetal chromosomal abnormalities (12). The cause of 30-50% of cases is still unclear. Thrombophilia is also a common cause of RPL and can be seen in almost half of the cases (1). More commonly, the diagnosis is based on the demonstration of a gene mutation such as a Factor V Leiden mutation, prothrombin II (PTII) mutation, MTHFR C677T and A1298G (13). To our knowledge, this is the first study to investigate FXIII Val/Leu and PAI-1 4G/5G polymorphisms together in the Turkish population and to comparatively associate them with RPL and SA. The frequency distribution of FXIII genotypes in RPL patients was 71.3% Val/Val, 27.5% Val/Leu and 1.2% Leu/Leu and in SA patients was 71.9% Val/Val, 24.2% Val/Leu and 3.9% which is consistent with previous studies. The FXIII Val/Leu genotype frequencies were found as follows; 65.1% Val/Val, 32.0%

Table 3. Distribution of genotype frequencies in FXIII Val34Leu and PAI 4G/5G complex variants.

Genotype frequencies		**RPL n (%)**	**SA n (%)**	**P value**
PAI 4G/4G	FXIII Val/Val	86 (21.0)	30 (23.4)	
	FXIII Val/Leu	31 (7.5)	9 (6.3)	
	FXIII Leu/Leu	2 (0.50)	2 (1.4)	0.528
PAI 5G/5G	FXIII Val/Val	69 (16.9)	24 (18.7)	
	FXIII Val/Leu	29 (7.1)	9 (6.3)	
	FXIII Leu/Leu	1 (0.25)	2 (1.4)	0.196
PAI 4G/5G	FXIII Val/Val	136 (33.5)	38 (32.7)	
	FXIII Val/Leu	52 (12.7)	13 (9.1)	
	FXIII Leu/Leu	2 (0.50)	1 (0.7)	0.144
Total		408 (100%)	128 (100%)	

Val/Leu and 2.9% Leu/Leu in a Spanish population with thrombosis (14). In another study, FXIII genotype frequency ratios in RPL patients were reported as Val/Val (60.93%), Val/Leu (34.37%) and Leu/Leu (4.68%) (15). In a different group, 67.5% of individuals had wild-type FXIII; 21.7% were heterozygous and 10.8% were homozygous for the FXIII Val34Leu polymorphism (16). The frequency of the Leu allele of FXIII varies among different populations. The frequency of the Leu allele is higher in Whites (0.25-0.30), American Indians (0.29), and Pima Indians than in our patient group. In South Asians, Africans and Japanese populations, the Leu allele frequency is lower: 0.13, 0.17 and 0.01, respectively (17-19). In this study, the Leu allele frequencies were determined as 0.14 in RPL group and as 0.16 in the SA group (Table 2).

The prevalence of the FXIII variant 34Leu allele was consistent with most of the literature data reported worldwide. The Leu34 allele has been shown to protect against deep vein thrombosis (20). Another study has shown that the carrier status or homozygous status (Val/Leu + Leu/Leu) of the Leu allele has a protective role in patients with myocardial infarction (21). In an RPL group, the FXIII Leu34Leu genotype was absent in the patient group and the 34Leu allele was shown to be a protective factor for the RPL (22). Elmahgoub et al. found the Leu frequency in women with RPL to be 21.7%, which was quite high compared to the literature (16). The researchers found significant associations between FXIII Val34Leu mutations and the risk of RPL in Asian populations; however, the association between Europeans and South Americans was insignificant (23). An in vivo study has shown that the FXIII-A Val34Leu polymorphism protects against venous thrombosis by reducing clot mass (24). The frequencies of 4G allele (PAI-1) were 0.52 and and 0.46 in patients. In PAI-1 4G/5G polymorphism, the 4G/4G genotypes were found to be 29.2% and 36.8% in patients (RPL and SA, respectively, Table 2) In a Greek group with recurrent miscarriages, the 4G/4G and 4G/5G genotypes were found to be 32.1% and 49.1% (25). Shaala et al. reported that the 4G allele frequency was found 0.18 in a patient group with RPL, which was a considerably lower value compared to our study group (26). The limitation of the study is the lack of a control group. The Leu allele frequency of FXIII and the 4G allele frequency of PAI-1 were determined as 0.14 and 0.52 in the RPL group, respectively. The Leu allele frequency of FXIII and the 4G allele frequency of PAI-1 were determined as 0.16 and 0.46 in the RPL group, respectively, in SA.

CONCLUSION

In conclusion, we found similar results for both variants in the group of patients with a single miscarriage, as in RPL patients in this study. This shows that the indication group should be expanded and these genetic variants should be examined in patients. The allele and genotype frequencies of FXIIIVal34Leu and PAI-1 4G/5G polymorphisms are important as a sample of Turkish population data since they are compatible with other previous population studies in this research area.

Ethics Committee Approval: The study protocol was approved by the ethical committee of Eskisehir City Hospital (Protocol Number: ESH/BAEK/2025/134).

Informed Consent: This study was done retrospectively.

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