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The Val34Leu genetic variation in the A Subunit of Coagulation Factor XIII in recurrent spontaneous abortion

Morteza Bagheri,[1*] Isa Abdi Rad,[2] Mir Davood Omrani,[1] and Fariba Nanbaksh[3]

[1]*Faculty of Medicine, Department of Genetics, Urmia University of Medical Sciences,* [2]*Center for Cellular and Molecular Research (CMRC-UMSU), Urmia University of Medical Sciences,* [3]*Department of Obstetrics and Gynecology, Urmia University of Medical Sciences, Urmia, Iran*

The present study was carried out to assess the frequencies of factor XIII (FXIII) Val34Leu genetic variation in the patients with recurrent spontaneous abortion and healthy fertile women of Azeri Turkish origin. A total of 54 patients with recurrent spontaneous abortion and 46 healthy fertile women as controls were studied for the FXIII Val34Leu genetic variation by a RFLP-PCR method. Statistical analysis showed that patients ($\chi^2 = 2.4$, p value = 0.292) and controls ($\chi^2 = 1.035$, p value = 0.596) were in agreement with Hardy-Weinberg equilibrium. The Leu allele frequency was 0.18 and 0.13 in patients and controls, respectively. FXIII Leu34Leu (homozygous for 34Leu) genotype was not found in patients and controls. FXIII Val/Leu and Val/Val genotype frequencies were 19 (35.19%) and 31 (64.81%) in patients and 12 (26.09%) and 34 (73.91%) in controls, respectively. FXIII 34Leu allele and Val34Leu genotypes were more common in the case group containing individuals with unexplained RSA but the differences of FXIII Val34Leu (G/T genotype) (odds ratio = 0.65 (0.25 < OR < 1.67) corresponding to 95% CI, $\chi^2 = 0.96$, p value = 0.32) and FXIII 34Leu (T allele) (odds ratio = 0.70 (0.30 < OR < 1.64) corresponding to 95% CI, $\chi^2 = 0.78$, p value = 0.37) was not statistically significant. These results suggest that factor XIII Val34Leu genetic variation is not associated with recurrent spontaneous abortion.

Keywords factor XIII, RSA, Val34Leu

Abbreviations FXIII: factor XIII; FSF: fibrin stabilizing factor; F13A: FXIII A subunit gene; F13B: FXIII B subunit gene; RSA: recurrent spontaneous abortion.

Introduction

Factor XIII (FXIII) is well defined as fibrin stabilizing factor (FSF), transglutaminase, and fibrinoligase. It regulates the state of hemostasis and blood coagulation. FXIII glycoprotein is composed of heterotetramer (FXIII-A_2B_2) subunits including 2A and 2B [Chung et al. 1974]. FXIII 2A subunits have catalytic activity and the coagulation A subunit gene (F13A) is located on chromosome 6p24–p25 [Chung et al. 1974; Board et al. 1988]. FXIII 2B subunits have non-catalytic functions and the coagulation FXIII B subunit gene (F13B) is located on chromosome 1q31–32.1 [Chung et al. 1974; Webb et al. 1989]. During blood coagulation, thrombin is produced and along with calcium ions and fibrin catalyze the conversation of activated FXIII from FXIII proenzyme [Lewis et al. 1985]. Plasma FXIII plays an important role in cross-linking fibrin monomers [Meyer 2004]. Several nucleotide variations were reported in the FXIII A-subunit gene. A point mutation of G → T in the 2nd exon of the FXIII A-subunit gene leads to conversion of Val to Leu within codon 34 (FXIIIVal34Leu) and impacts the cross-linking activity as well as clot stability [Kohler et al. 1998; Suzuki et al. 1996]. FXIII deficiency results in lifelong episodes of bleeding and recurrent spontaneous abortion (RSA) [Duckert 1972; Lorand et al. 1980; Kohler et al. 1998; Ivaskevicius et al. 2007]. To the best of our knowledge, there is no official report on the frequencies of FXIII gene Val34Leu genetic variation in patients with unexplained RSA in the Azeri Turkish population. This study was carried out to assess whether FXIII gene Val34Leu genetic variation is associated with unexplained RSA.

Results and Discussion

The cases examined had a history of three (3.2 ± 1.1; range: 2 – 6) pregnancy losses, all occurring between the 8th and the 12th week of gestation. Patients with RSA were > 20 years old and < 38 years old and of Azeri Turkish decent. Patient DNA was extracted from blood then analysis performed in a manner essentially as described [Kangsadalampai and Board 1998]. The samples were then genotyped following restriction digestion with Dde I enzyme as shown in Figure 1. A summary of the entire dataset and results is presented in Table 1. Statistical analysis showed that patients ($\chi^2 = 2.4 < 3.84$, p value = 0.292 > 0.05) and

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*Address correspondence to Morteza Bagheri MSc, Department of Genetics, Urmia University of Medical Sciences, Urmia, Iran. E-mail: mortazabagheri@yahoo.com and mortezabagheri@umsu.ac.ir

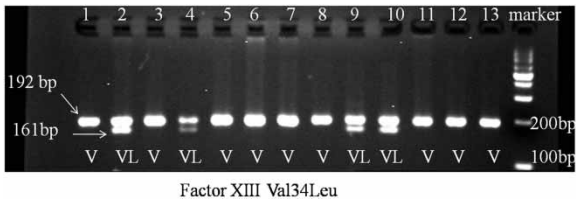

Figure 1. Electrophoresis of digested PCR products. The presence of Leu mutation in FXIII gene provides a restriction site for Dde I enzyme, whereas, the amplified fragment remains un-cut (192 bp) in the presence of Val nucleotide variation. (Lane Marker, 100 bp DNA ladder; Lanes 1,3,5,6,7,11,12,13, V34V - G/G genotype - (192-bp PCR product); Lanes 2,4,9,10 V34L - G/T genotype - (192 and 161-bp).

controls ($\chi^2 = 1.035 < 3.84$, p value = 0.596 > 0.05) were in agreement with Hardy-Weinberg equilibrium. The leu allele frequency was 0.18 and 0.13 in patients and controls, respectively. The FXIII Leu34Leu (homozygous for 34Leu) genotype was not found in patients and controls. The FXIII Val/Leu and Val/Val genotype frequencies were 19 (35.19%) and 31 (64.81%) in patients, and 12 (26.09%) and 34 (73.91%) in controls, respectively. Interestingly the FXIII 34Leu allele and Val34Leu genotypes were more common in the case group containing individuals with unexplained RSA but the differences of FXIII Val34Leu (G/T genotype: odds ratio = 0.65 (0.25 < OR < 1.67; corresponding to 95% CI, $\chi^2 = 0.96$, p value = 0.32) and FXIII 34Leu (T allele: odds ratio = 0.70 (0.30 < OR < 1.64; corresponding to 95% CI, $\chi^2 = 0.78$, p value = 0.37) was not statistically significant. To the best of our knowledge, this is the first report on the frequencies of FXIII Val34Leu genetic variation in patients with recurrent spontaneous abortion and healthy female controls in the Azeri Turkish population. The pattern of inheritance in the case of congenital FXIII deficiency is autosomal recessive [Lorand et al. 1980]. FXIII gene Val34Leu genetic variation in the patients with unexplained RSA and healthy controls was identified based on the cleavage site of the Dde I enzyme as described above [Kangsadalampai and Board 1998]. The cases and controls are summarized in Table 1, indicating that the G allele (Val34) was more frequent compared to the T allele (34Leu) (cases: 89 (82.41%) vs. 19 (17.59%), controls: 80 (86.96%) vs. 12 (13.04%). In addition, FXIII Leu 34Leu (homozygous for 34Leu) genotype was not found in patients and controls and was of similar frequency as observed by others [López Ramírez et al. 2006; Cho et al. 2002; Attié-Castro et al. 2000]. FXIII Val34Leu and Val/Val genotypes did not significantly differ between patients and controls. The findings reported in this study are in agreement with others that showed no statistically significant difference between patients with unexplained RSA and controls [López Ramírez et al. 2006; Dossenbach-Glaninger et al. 2003; Barbosa et al. 2004; Jeddi-Tehrani et al. 2010]. In contrast, Goodman et al. [2006] concluded that a panel of thrombogenic markers could be useful in identifying individuals at high risk for pregnancy loss. Further, Coulam et al. [2006] suggested that multiple inherited thrombophilic markers rather than specific gene mutations were associated with recurrent miscarriage. Both of these recent studies indicated that FXIII V34L gene mutations in combination with other thrombophilic markers promotes polymerization or cross-linking of fibrin and fibrinolysis of the fibrin and may result in pregnancy loss [Goodman et al. 2006; Coulam et al. 2006]. Jeddi-Tehrani et al. [2010] reported that the FXIII A614T and FXIII C1694T polymorphisms have been associated with RSA, but failed to indicate any association between FXIII (Val34Leu) (G103T) polymorphism and RSA. Anwar et al. [1999] reported that both plasminogen activator inhibitor 1 polymorphism, and Phe204Tyr polymorphism in exon 5 of the FXIII gene were associated with recurrent pregnancy loss.

Table 1. Genotypes and Alleles. Values for genotypes/alleles are n (%); FXIII Val34Leu genotype distribution and allele frequency in patients and controls.

	Patients with RSA (n = 54)		Controls (n = 46)	
FXIII gene Val34Leu	Observed frequency (%)	expected frequency	Observed frequency (%)	expected frequency
Val/Val (G/G)	35 (64.81)	36.7	34 (73.91)	34.8
Val/Leu (G/T)	19 (35.19)	15.7	12 (26.09)	10.4
Leu/Leu (T/T)	0 (0)	1.67	0 (0)	0.78
Val (G)	89 (82.41)		80 (86.96)	
Leu (T)	19 (17.59)		12 (13.04)	
Leu allele frequency	0.18		0.13	

The trophoblast, endoderm, and extraembryonic mesoderm are specialized cells of the placenta. They have an important role in implantation and the development of vascular connections for blood supply and nutrient transport that supports metabolic functions and are necessary for a healthy pregnancy [Cross et al. 1994]. These processes are under control of coagulation factor FXIII Val34Leu and plasminogen activator inhibitor 1 and are essential for homeostasis mutations [Muszbek 2000; Anwar et al. 1999; Feng et al. 2000]. Floridon et al. [2000] reported that plasminogen activator inhibitor-1 controls proteolysis during trophoblast invasion [Floridon et al. 2000]. The presence of Leu instead of Val within codon 34 (FXIIIVal34Leu) in the 2nd exon of the FXIII A-subunit gene has been associated with high FXIII specific activity [Anwar et al. 1999]. The FXIIIVal34Leu (G → T) mutation has been associated with myocardial and brain infarction [Kohler and Grant 1998; Elbaz et al. 2000; Rallidis et al. 2008; Shafey et al. 2007; Wartiovaara et al. 1999], venous thrombosis, and familial thrombophilia [Catto et al. 1999; Balogh et al. 2000; Franco et al. 2000; Vossen and Rosendaal 2005; Wells et al. 2006]. It has been observed that severe FXIII deficiency is a rare homozygous disorder, but, heterozygous FXIII deficiency is more common [Ichinose and Davie 1988; Ivaskevicius et al. 2010]. Individuals with heterozygote for FXIII deficiency are not aware of their state and might be at high risk [Ivaskevicius et al. 2010]. The distribution of the FXIIIVal34Leu (G → T) genetic variation was different in ethnic groups [Ariëns et al. 2002] and may be useful as a susceptibility marker.

In conclusion, the FXIII gene Val34Leu (G → T) genetic variation is not associated with RSA within Iranian women with Azeri origin. Whether this can be extended to other ethnic groups requires consideration. Additional samples are warranted to strengthen this conclusion considering the strict inclusion and exclusion criteria, the limited ethnic diversity, and number of subjects. The role of more genes (such as prothrombin (factor II) polymorphism G20210A, and Factor V Leiden) in conjunction with environmental factors should be considered.

Material and Methods

Unexplained recurrent miscarriage or unexplained recurrent spontaneous abortion is defined as the occurrence of two or more consecutive fetal losses between the 8th and the 12th week of gestation without a known reason with the same partner [Dossenbach-Glaninger et al. 2008; Dossenbach-Glaninger et al. 2003]. A minimum sample size of 49 cases among the patients had a statistical power of approximately 85% (two-tailed, $\alpha = 0.05$) and thus, 54 patients with unexplained RSA (2 to 6 history of miscarriages) were sequentially selected among cases referred to the Department of Genetics at Motahari Hospital (Urmia, West Azerbaijan, Iran) from the Obstetrics and Gynecology Department at Urmia University of Medical Sciences and other centers. The karyotypes of the patient and respective partner were normal. Patients with abnormal medical findings such as a history of systemic diseases (e.g., endocrine, metabolic, cardiovascular diseases, diabetic mellitus, thyroid dysfunction), obesity, immunological disorders, autoimmunity, antiphospholipid and anticardiolipin disorders, thrombophilic disorders, polycystic ovarian syndrome, and uterine abnormalities were excluded from the study. In total, 46 unrelated controls (fertile females) were randomly selected from the general population who had experienced live births of singletons without any obstetric problems (Urmia, Iran) and no history of pregnancy loss. Controls were matched for cases regarding ethnicity, age, geographical region, and body mass index; and selected among participants in genetic counseling sessions which occurred in the Genetic Center at Urmia University of Medical Sciences. They were selected in regards to their past medical history and exclusion of any specific disorders such as genetic, congenital diseases, and history of pregnancy loss. The inclusion and exclusion criteria was described previously by Dossenbach-Glaninger et al. [2008; 2003].

This case–control study was approved by the ethical committee of Urmia University of Medical Sciences and was performed in the city of Urmia, Iran. Written informed consent was obtained from cases and controls who participated in the present study. Cases and controls completed a detailed questionnaire. Blood samples of cases and healthy Azeri Turkish controls were obtained from persons referred for testing in our laboratory and from the Obstetrics and Gynecology Department, Motahari Hospital (Urmia, Iran). A 3-5 mL aliquot of peripheral blood was collected in EDTA-containing tubes for extraction of genomic DNA by standard method [Miller et al. 1988]. The forward primer "5′-CAT GCC TTT TCT GTT GTC TTC-3′" and reverse primer "5′-TAC CTT GCA GGT TGA CGC CCC GGG GCA CTA-3′" were used for amplification of 192 bp fragment. PCR reaction was performed in 35 cycles (denaturation at 94 °C for 30 sec, annealing at 58 °C for 30 sec, extension at 72 °C for 30 sec). The final cycle was followed by extension at 72 °C for 7 min [Kangsadalampai and Board 1998]. Restriction digestion with Dde I enzyme was used for FXIII (Val34Leu) genotyping. Digestion of the amplified fragments was carried out at 37 °C for two h. After digestion reaction, fragments were resolved by electrophoresis through a 3% agarose gel that was then stained with ethidium bromide. Then presence or absence of fragments was determined by a UV transilluminator. The presence of Leu mutation in FXIII gene provides restriction site for Dde I enzyme (161 and 31 bp fragments), whereas, the amplified fragment remains un-cuted (192 bp) in the presence of Val nucleotide variation [Kangsadalampai and Board 1998]. The FXIII Val34Leu allele frequencies were calculated by direct gene counting in the case and control groups. In order to test for genotyping quality control and to better understand the genetic background of the population by Hardy-Weinberg equilibrium, observed and expected genotype frequencies were compared using the goodness-of-fit χ^2 test. χ^2 and p value, the odds ratio (OR) corresponding to 95% confidence interval (CI) were computed by EpiInfo version 6 and Microsoft Excel 2003 to assess whether FXIII gene Val34Leu genetic variation has been associated with recurrent spontaneous abortion. A two-tailed p value of less than 0.05 was considered to be statistically significant.

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