Original Article

The Founder Effect? - FXIII Deficiency in Southeast Iran: A Molecular Study Report

Hojat Shahraki[1], Akbar Dorgalaleh[1], Majid Fathi[2], Shadi Tabibian[1], Shahram Teimourian[3], Hasan Mollanoori[3], Majid Naderi[4], Farhad Zaker[1*]

Abstract

Background: Congenital factor XIII (FXIII) deficiency is an extremely rare bleeding disorder (RBD) with different clinical coagulation disorders and great impacts on the perioperative patient outcome. Its prevalence in Southeast Iran is approximately 4,000 times higher than the worldwide prevalence, with Trp187Arg (c.559T> C) as the only causative mutation of FXIII deficiency (FXIIID) there. We investigated the founder effect of rs1742924, rs4960181, rs3778360 and rs4142290 using haplotype analysis to define the genetic phenomenon in this geographic region.

Materials and Methods: In a case-control study, 10 patients with FXIIID and 10 healthy individuals were assessed. Initially, Trp187Arg (c.559T>C) mutation was assessed in all study populations using a PCR-RFLP technique, then haplotype analysis was performed by assessing rs1742924, rs4960181, rs3778360, and rs4142290 polymorphisms. Data were analyzed using a two-proportion z-test.

Results: All patients were homozygote for Trp187Arg (c.559T>C), and this mutation was not observed in any form of homozygote or heterozygote in the control group. Polymorphisms in rs1742924, rs4960181, and rs377836 were homozygote (TT, GG, GG, respectively) and T, G, and G alleles distribution in cases and controls with significant difference (P<0.001, P<0.001, and P=0.01 respectively). Rs4142290 polymorphism showed no significant difference between patients and controls (P=0.3). Two types of haplotypes were observed in the case group, and haplotype number 1* was observed among 90% of them, while not observed in the control group.

Conclusion: It seems that founder effectors of haplotype number *1 have more antiquity versus other haplotypes, and probably founder effect is responsible for this high prevalence of FXIIID in the southeast of Iran.

Keywords: Factor XIII deficiency, Rare bleeding disorder, Founder effect

1. Department of Hematology and Blood Transfusion, School of Allied Medicine, Iran University of Medical Sciences, Tehran, Iran
2. Department of Medical Biotechnology, School of Allied Medicine, Iran University of Medical Sciences. Tehran, Iran
3. Department of Medical Genetics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
4. Department of Pediatrics, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

Corresponding Author: Farhad Zaker, Professor of Hematology, Department of Hematology and Blood Transfusion, School of Allied Medicine, Iran University of Medical Sciences, Tehran, Iran
Phone: (+98) 21 88652267
Email: Hojat93.shahraki@gmail.com

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Introduction

Coagulation Factor 13 (FXIII) is a member of the transamidases family that is present in the blood circulation system in the form of heterotetramer (FXIII-A2B2), including two catalytic A subunits (FXIII-A2) and two non-catalytic (carriers) B subunits (FXIII-B2) (1). FXIII at the end of the coagulation cascade will create a strong and stable fibrin clot by creating cross-linking and isopeptide bonds between the amino acids lysine and glutamine of fibrin monomers (2).

Congenital Deficiency of Coagulation FXIII (FXIIID) is one of the extremely rare bleeding disorders with a prevalence of 1 in 2 million people in the general population and with autosomal recessive inheritance (3). Deficiency of this coagulation factor is due to mutations in the A subunit or B subunit gene, but the mutations of A subunit are much more than B subunit, so far more than 155 mutations have been observed in A subunit gene (4, 5). FXIIID causes a lack of consistency and persistence of fibrin clots at the end of the coagulation process, and subsequently, the fibrin clots formed by the body's fibrinolytic system decompose, and in this spontaneous miscarriage and delayed wound healing occur in the patient (2).

Unfortunately, it is not possible to diagnose this coagulation disorder with routine coagulation tests, Bleeding Time, Prothrombin Time, Partial Thromboplastin Time, and platelet count tests are normal in these patients (6). Typically, clot solubility in 5-molar urea or monochloroacetic acid (1%) is used to diagnose the disease. Of course, this method does not identify all types of coagulation FXIII deficiency, so more accurate tests such as quantitative and antigenic measuring of factors and molecular studies are used to confirm patients (7).

For the treatment of patients with coagulation FXIIID, preventive treatments such as fresh frozen plasma (FFP) and cryo-precipitation are usually recommended. Today, however, drugs such as Fibrogammin P as well as recombinant FXIII have been used, which are helpful (8, 9).

Although the congenital deficiency of factor 13 in coagulation has a very low prevalence in the world (1 in 2 million people), but the prevalence of this hemorrhagic disorder in Iran is very high, since more than 500 patients with the disorder have been identified. Sistan and Baluchestan province, with a population of 2.775 million and a high rate of consanguineous marriages, with 410 patients and approximately 4,000 times higher than the worldwide prevalence, has the highest frequency of coagulation FXIIID, not only in Iran but throughout the world (10, 11). Several molecular studies have been performed on a significant number of patients, all of them suggest that a common homozygous mutation (Trp187Arg (c.559T> C)) causes TGG to CGG deformity in Exon 4 of A subunit gene on chromosome 6 is present in all patients, which change Arginine to Tryptophan (8, 10, 12-15).

The presence of such a same mutation in all patients with coagulation FXIIID in Sistan and Baluchestan province may indicate a common ancestry or a founder effect in this population (12-14). In general, the founder effect occurs when a small group of immigrants creates a new genetic population in an area. Populations affected by the founder effect often have small populations with intra-racial marriages and therefore are sensitive to genetic drift, which in turn reduces genetic diversity in these populations, and subsequently, due to a significant decrease of genetic diversity, the newly formed population may be genetically and phenotypically distinct from the original population (16-20). The present study used molecular analysis of rs1742924, rs4960181, rs3778360, rs4142290) to molecularly investigate the founder effect to examine the possible role of the founder effect in increasing the prevalence of this disease in southeast Iran.

Methods

Case and control population (Samples): The present case-control study was performed on 10 patients with congenital FXIIID and 10 healthy individuals. Initially, a questionnaire on demographic characteristics including age, sex, city of residence, age of diagnosis, first clinical sign, family history of FXIIID, and type of treatment for each patient was completed by experienced laboratory staff.

DNA extraction: To isolate the DNA, 2 ml of blood samples were collected from healthy controls and patients in a tube containing anticoagulant EDTA, then genomic DNA was extracted from the white blood cells of the samples by Kit (Yekta Tajhiz Azma, Iran),

and to determine the quality of the extracted DNA, the concentration of the samples was determined by Biophotometer (Eppendorf), and also all samples were electrophoresed on 1% agarose gel to ensure the presence of DNA samples.

Molecular studies: FXIII mutation; Trp187Arg; (c.559T> C): Initially, all patients and the control group were examined for Trp187Arg mutation (c.559T> C). To perform this, genomic DNA was replicated using PCR (Polymerase chain reaction), and then 861 basepairs product of PCRs were treated by the restrictive enzyme Eco130I (Fermentas Life Sciences, York, UK). This enzyme produces three fragments of 601, 192, and 68 base pairs (bp) in those without mutations, while homozygotes produce only two fragments of 669 and 192 bp, and heterozygotes produce fragments with the size of 601, 669, 192, and 68 bp (Table 1).

Polymorphisms of rs1742924, rs4960181, rs3778360, and rs4142290: To investigate the haplotype polymorphisms, rs1742924, rs4960181, rs3778360, rs4142290 were selected within the FXIII gene (chromosome 6). All selected polymorphisms are approved by Hapmap and have a Global MAF of about 0.5 to be Informative. Initially, all studied patients and the control group were evaluated for these polymorphisms. To do this, genomic DNA was amplified using PCR, then the products were sequenced, and finally, the sequences were viewed by CLCSequenceViewer-6-8-1 and Chromas261 software (Table 2).

Statistical analysis: all data were analyzed by Minitab software using a two-proportion z-test, and the results were considered statistically meaningful with a P value less than 0.05.

Results

Characteristics of the studied individuals

Among 10 patients with coagulation FXIIID, 4 were male (40%) and 6 were female (60%). The mean age and mean age of diagnosis were 15 and 1.9 years, respectively. The average age of male patients was 7.75 years and in women, it was 19.83 years. The mean age of diagnosis in male patients was 1.54 years and in female patients was 2.10 years. Among the 10 control group members, 3 were males (30%) and 7 were females (70%), and the mean age of healthy males was 23.33 years and 17.57 years in females.

FXIII mutation (Trp187Arg; c.559T> C)

Trp187Arg mutation (c.559T> C) was observed in people with suspected coagulation FXIIID as 669 and 192 bp fragments, which indicate the same form of homozygous (C / C) of the disease. In the control group, fragments with the size of 601, 192, and 68 bp were observed, which indicates the absence of mutation and consequently no FXIIID (Figure 1).

Polymorphism rs1742924 (NC_000006.12: g.6242713T> C): After obtaining the single-band

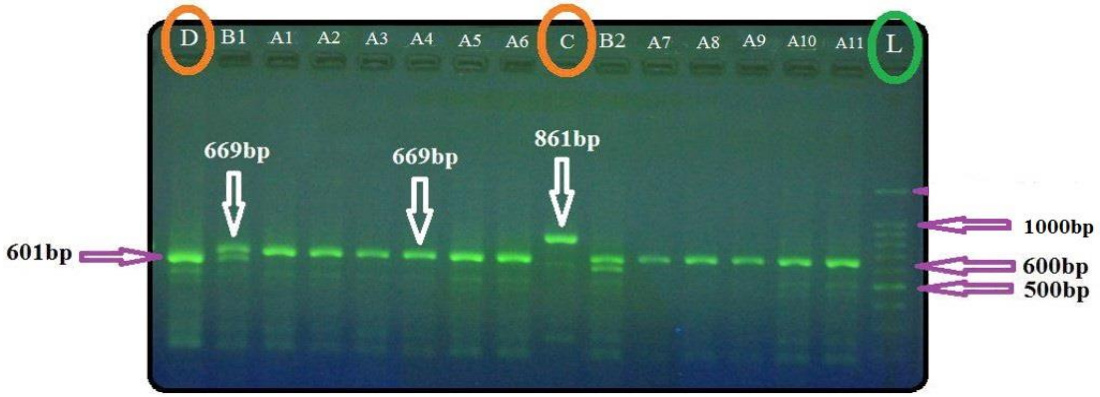

Figure 1. PCR enzyme digestion result for Trp187Arg mutation (c.559T> C)
L: Ladder (100bp)
A1-12: Homozygous (669bp-192bp)
B1-2: Hetrozygote (669bp-192bp-68bp-601bp)
C: PCR product (861bp)
D: Non mutant sample (601bp-192bp-68bp).

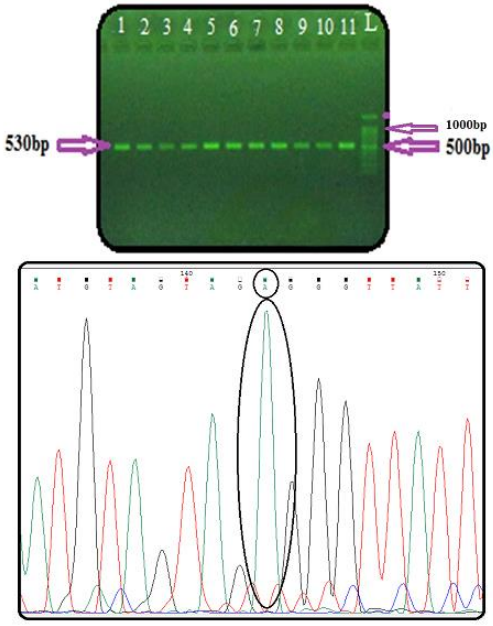

Figure 2. Results of PCR reaction sequence and genotyping for polymorphism rs1742924 (Negative Strand).

fragments, the products of PCR were sequenced. The results of sequencing were checked in Chromas software. The results analysis of patient and control group sequence in Chromas software, CLC sequence viewer, and Minitab and using two-proportion z-test for polymorphism rs1742924 showed that this polymorphism occurs in all patients as T / T homozygote; however, it was different in the control

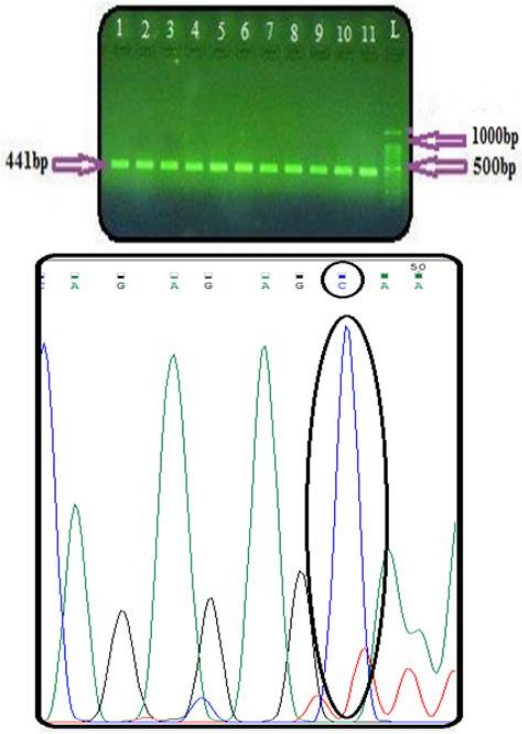

Figure 3. Results of PCR reaction product sequence determination and genotyping for polymorphism rs4960181 (Negative Strand).

group (C / C and T / C), and statistical studies showed that the distribution of allele T was significantly different between the two groups of patients and control (P <0.001) (Figure 2).

Polymorphism rs4960181 (NC_000006.12: g.6269065G> C): After obtaining the single-band fragments, the products of PCR were sequenced. The results of sequencing were checked in Chromas software. The results analysis of patient and control group sequence in Chromas software, CLC sequence viewer, and Minitab and using two-proportion z-test for polymorphism rs4960181 showed that this polymorphism occurs in all patients as G / G homozygous but differs in the control group (G / G and C / C), Statistical studies also showed that the distribution of allele G was significantly different in the two groups of patients and control (P <0.001) (Figure 3).

Polymorphism rs3778360 (NC_000006.12: g.6150132G> A): After obtaining the single-band fragments, the products of PCR were sequenced. The results of sequencing were checked in Chromas software. The results analysis of patient and control group sequence in Chromas software, CLC sequence viewer, and Minitab and using two-proportion z-test for polymorphism rs3778360 showed that this polymorphism occurs in all patients as G / G homozygous; however, it was different in the control group (G / G, A / A, and G / A), and statistical studies also showed that the distribution of allele G was significantly different in the two groups of patients and control (P = 0.01) (Figure 4).

Polymorphism rs4142290 (NC_000006.12: g.6154374G> C): After obtaining the single-band fragments, the products of PCR were sequenced. The results of sequencing were checked in Chromas software. The results analysis of patient and control group sequence in Chromas software, CLC sequence viewer, and Minitab and using two-proportion z-test for polymorphism rs3778360 showed that this polymorphism occurs in patients as G/G and C/C

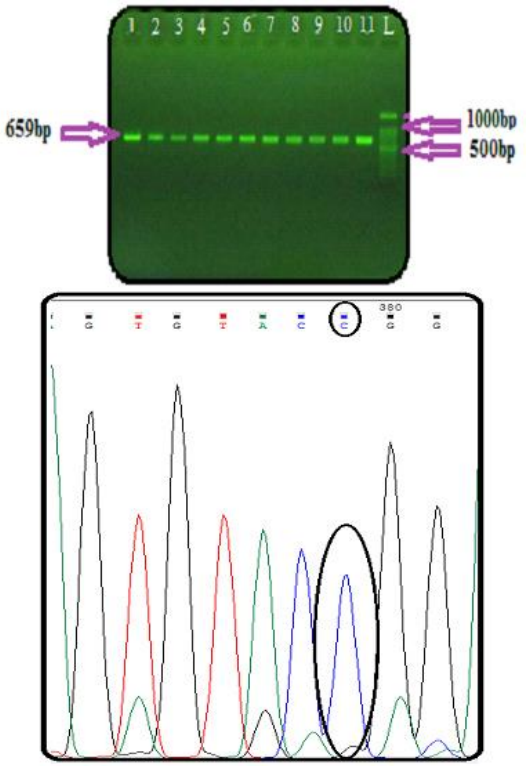

Figure 4. Results of PCR product sequencing and genotyping evaluation for polymorphism rs3778360 (Negative Strand).

Table 1: Primers used in PCR reaction for Trp187Arg mutation (c.559T> C).

Mutation	Primers	PCR product (bp)	Restriction enzyme
Trp187Arg	Forward: 5′ GTAACTTATGTCCGCACCTCC 3′ Reverse: 5′ TAACCTCCAACTCCCGAACT 3′	861	Eco130I

homozygous; however, it is different in the control group (G / G and C / C), and statistical studies also showed that there is no significant difference in the distribution of allele G between the two groups of patients and control (P <0.3) (Figure 5).

Haplotype analysis: Interpretation and haplotype analysis results showed that there are 2 different types of haplotypes in patients (No. 1 *, 2 *) that haplotype

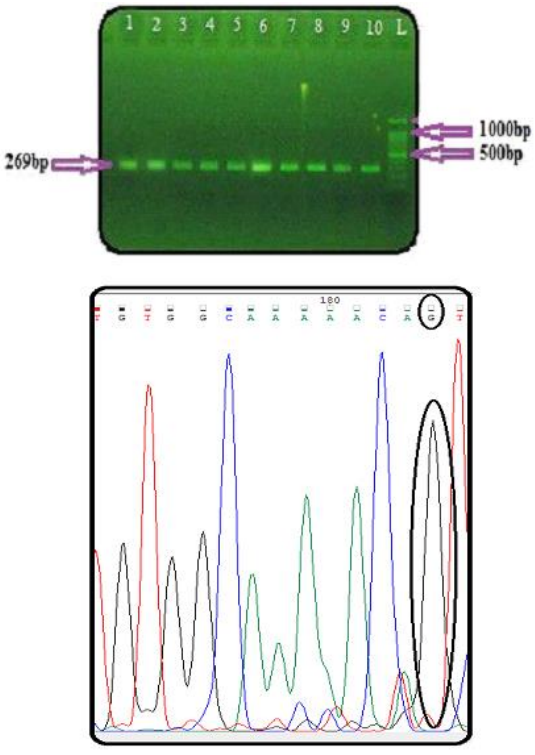

Figure 5. Results of PCR product sequencing and genotyping for polymorphism rs4142290 (positive Strand).

Table 2: Charactristics and PCR conditions of polymorphisms rs1742924, rs4960181, rs3778360, rs4142290

Polymorphism	Accession ID	Strand	PCR Cycles				Primers	PCR product (bp)
				Denaturation	Annealing	Elongation		
rs1742924	NC_000006.12: g.6242713T> C	Negative Strand	**Cycles**	1	30	1	**Forward:** 5′CTCTATCTAGATGCTATAGG 3′ **Reverse:** 5′AAGGCATACCTGAACGAAGT 3′	530
			Time(Sec)	5 min	30, 30, 30	5 min		
			Temperature	95° C	95°, 57°, 72°	72° C		
rs4960181	NC_000006.12: g.6269065G> C	Negative Strand	**Cycles**	1	31	1	**Forward:** 5′TCCCCTTAGATCGATCGTCTC3′ **Reverse:** 5′AGGACTACTGCGTAGCGCCAC3′	441
			Time(Sec)	5 min	30, 30, 30	5 min		
			Temperature	95° C	95°,56°,72°	72° C		
rs3778360	NC_000006.12: g.6150132G> A	Negative Strand	**Cycles**	1	30	1	**Forward:** 5′GGCTATCGGTACGTTCTTTCA3′ **Reverse:** 5′CCATCATCGCGTGTAGATTCA3′	659
			Time(Sec)	5 min	30, 30, 30	5 min		
			Temperature	95° C	95°, 58°,72°	72° C		
rs4142290	NC_000006.12: g.6154374G> C	Positive Strand	**Cycles**	1	30	1	**Forward:** 5′GGCAGTATGCGTATGTGGGAG3′ **Reverse:** 5′CCAGCATCGGTAAGATAGTAG3′	269
			Time(Sec)	5 min	30, 30, 30	5 min		
			Temperature	95° C	95°,56°,72°	72° C		

Table 3: Results of genotypes analysis of polymorphisms rs1742924, rs4960181, rs3778360, rs4142290.

No	rs1742924		rs4960181		rs3778360		rs4142290	
	Patient	**Control**	**Patient**	**Control**	**Patient**	**Control**	**Patient**	**Control**
1	T/T	C/C	G/G	C/C	G/G	G/G	G/G	G/G
2	T/T	C/C	G/G	C/C	G/G	G/A	G/G	G/G
3	T/T	C/C	G/G	G/G	G/G	A/A	G/G	G/G
4	T/T	C/C	G/G	G/G	G/G	G/G	G/G	G/G
5	T/T	C/C	G/G	G/G	G/G	A/A	G/G	G/G
6	T/T	C/C	G/G	C/C	G/G	G/G	G/G	C/C
7	T/T	T/C	G/G	G/G	G/G	G/A	G/G	G/G
8	T/T	T/C	G/G	C/C	G/G	G/G	G/G	G/G
9	T/T	T/C	G/G	G/G	G/G	A/A	C/C	G/G
10	T/T	C/C	G/G	G/G	G/G	G/G	G/G	C/C
	P <0.001		P <0.001		P = 0.01		P <0.3	

No. 2* was seen in 10% of the study population; however, there was a significant point about haplotype No. 1 * that this haplotype was observed in 90% of patients, in other words, 90% of the patients had the same haplotype block. In the control group, different types of haplotypes were observed compared to patients (Tables 3 and 4).

Discussion

Congenital Coagulation FXIII deficiency is known as an extremely rare bleeding disorder with a prevalence of approximately 1 in 2 million people worldwide; despite the very low prevalence of this disease in the world, the prevalence rate of the disease has increased significantly due to consanguineous marriages in some geographical regions. Statistical studies and researches conducted in this field have shown that Sistan and Baluchestan province in Iran, with a prevalence more than of 130 patients per 1 million people; has the highest prevalence of congenital FXIIID in the world (13, 21).

Trp187Arg mutation (c.559T> C) has been observed in all patients in the present study as the main

Table 4: Results of Haplotype analysis of patients with coagulation FXIIID.

Haplotype	rs4142290	rs3778360	rs4960181	rs1742924	Frequency
1*	**G**	**G**	**G**	**T**	**9/10 (90%)**
2*	C	G	G	T	1/10 (10%)

cause of coagulation factor XIII deficiency in Sistan and Baluchestan province (12). In 2010, Tamaddon et al, conducted a study on 23 people (including 10 patients and 13 members of patients' families) from non-consanguineous families. They used molecular methods such as sequencing, PCR-RFLP, and CFGE to evaluate all exons of coagulation FXIII in these patients, and they concluded that the mutation in c.559T> C was homozygous (CC) in all patients studied (22).

Trinh et al suggested that the presence of a similar mutation in different non-related families with FXIIID in southeastern Iran (Sistan and Baluchestan Province) may indicate a common ancestry or founder effect in this population (14). The founder effect is one of how nature creates new species from the original population. In fact, in population genetics, the reduction in genetic diversity caused by the creation of a new population by a small number of people belonging to a large population is called the founder effect. The newly formed population may be genetically and phenotypically distinct from the original population (23-25).

Important examples in this regard include the Ashkenazi Jewish population, which has the highest prevalence of congenital factor XI deficiency in the world, in one study, haplotype analysis was performed to examine a group of patients with factor XI deficiency which confirmed the founder effect in the mutation of type II of factor XI and concluded that the mutation of type II factor XI occurred more than 120 generations ago (26, 27).

In the present study, a significant point was related to polymorphisms rs1742924, rs4960181, and rs377836; which were homozygous in patients (TT, GG, and GG, respectively); besides, in each polymorphism, the distribution of alleles (T, G, and G, respectively) had a significant difference between the two groups of patients and control (P <0.001, P <0.001, and P = 0.01, respectively), however, polymorphism rs4142290 was present in 9 patients in the form of GG homozygote and one patient as CC homozygote; also, no significant difference was observed between the distribution of allele G between the two groups of patients and control (P = 0.3).

Following the interpretation and analysis, the haplotype results showed that there are 2 different types of haplotypes in patients (1 *, 2 *) that haplotype number 2 * was seen in 10% of the study population, but there was a significant point about haplotype No. 1 * that this haplotype was present in 90% of patients, in other words, 90% of the patients had the same haplotype block. In the control group, different haplotypes were observed compared to patients.

The rs1742924, rs4960181, and rs377836 polymorphisms were significantly different in the patient and control group; besides, it was noted that haplotype No. 1 * of the patients' group was observed in 90% of this group, it could indicate the genetic association of the polymorphisms with the mutation Trp187Arg (c.559T>C), and subsequently, this genetic association could indicate a kind of founder effect in this disease. In other words, there have been people with pathogenic genes in previous generations who have increased the prevalence of the pathogenic gene in the population of southeast Iran as a result of interracial marriages and lower genetic diversity.

According to the above, one of the most important and influential factors in increasing the prevalence of the disease is congenital coagulation FXIIID in Sistan and Baluchestan province is consanguineous marriages. Interestingly, all patients in this study have parents with a first-degree family relationship (cousins). Previous studies have also

shown that more than 70% of patients with FXIIID in southeast Iran have parents with a close relationship (cousins); while only 10% of patients' parents have no relationship (12, 21).

The highest number of patients in this province lives in Khash and less in Zahedan and Saravan (45.9%, 18.5%, and 13.7%, respectively). Interestingly, according to studies, the source of the disease in the city of Khash, and almost all patients or their ancestors have migrated from this city to other cities in the province (11, 28-29). This resemblance in the race is an important and helpful factor in increasing consanguineous marriages and consequently increasing the prevalence of the disease in this province (29-31).

Conclusion

The present study showed that there is a genetic linkage between polymorphisms rs1742924, rs4960181, and rs377836 with a mutation in Trp187Arg (c.559T> C). It seems that founder effectors of haplotype number *1 have more antiquity versus other haplotypes, and probably founder effect is responsible for this high prevalence of FXIIID in the southeast of Iran.

Acknowledgment

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Conflicts of Interest

The authors declare that they have no conflict of interest based on this study.

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