RESEARCH ARTICLE

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Factor XIII Polymorphism and Risk of Coagulation Factor XIII A Subunit Deficiency: Evaluation of Risks

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ABSTRACT

The coagulation factor deficiency XIII- A subunit (F XIII A) is a rare autosomal recessive disorder marked by lifelong hemorrhage and challenging wound healing. This study evaluates the association between factor XIII polymorphism and coagulation factor XIII A subunit deficiency risk. The study groups are comprised of twenty patients with FXIII deficiency and twenty-five healthy individuals, including the sex (female: 10 and male: 10), mean of ages 30.48± 15.09 years, the controls sex (female: 11 and male; 14) and age mean 31.3± 10.07 years. Single nucleotide polymorphisms (SNPs) was used. Direct sequencing is use to identify the polymorphisms of the FXIIIA gene on chromosomes 6p24-25. The results view information of five unique mutations were identified in the FXIIIA gene on chromosome 6p24-25; the distribution of single nucleotide polymorphisms (SNPs) were located on exon 9, rs5977, rs5978. In patients with coagulation factor XIII-A Subunit deficiency, SNPs were located on exon 10, rs2274391, rs41302861, and rs924669371. Among the individuals, 20 (100%) have carried the rare polymorphisms of 8 (40%) rs5977 and 8 (40%) rs5978, along with 10 (50%) rs2274391, 1 (50%) rs41302861, and 10 (50%) rs924669371. The genotypes and allelic frequencies of the FXIIIA gene were compared between the two groups, namely the patients and the controls. In this population, the rs5978 allele frequency and the susceptibility of the FXIIIA gene with polymorphisms were correlated (OR =28.33, P = 0.001). The study found ten distinct haplotypes in patient samples on exon 9, 10 and exon 13, which was the first time such haplotypes were identified in Iraq. The haplotype CCGGA frequency was considerably higher in controls than in FXIIIA patients (OR=0.369), (P = 0.02) this results consider a protective factor. In contrast, the haplotypes CTGGG and CTGGA were more frequent in patients than controls (OR=6.988), (p = 0.04) and (p = 0.005) respectively, this result consider as risk factor.

Keywords: Blood Coagulation, Factor XIII subunit A, Polymorphism, FXIII deficiency.

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INTRODUCTION

Blood coagulation factor (F) XIII is a plasma protransglutaminase that is responsible for stabilizing the fibrin clots by creating cross-links between c-glutamyl and e-lysine residues of fibrin chains during the last stage of blood coagulation[1]. Factor XIII circulates in plasma as a heterotetramer consisting of paired A subunits with a catalytic domain and B subunits (A2B2) that protect and stabilize the A subunits[2]. However, A subunit gene has been definitively localized to chromosome 6p24–25[3]. This gene encodes a 4-kb mRNA transcript and a substantial 731 amino acid protein[4]. A recent analysis of the gene structure revealed that the gene spans more than 160 kb and is divided into 15 exons and 14 introns[5]. Moreover, the three-dimensional structure of FXIII A protein is comprised of a b-sandwich (residues 43–184), the catalytic core domain (residues 185–515), and b-barrel domains 1 and 2 (residues 516–628 and 629–727, respectively)[6]. FXIII deficiency is an uncommon hereditary bleeding illness passed down through families in an autosomal recessive manner[7] it affects individuals of all races and genders[8]. Clinical evaluation, along with family and patient history, is crucial for early diagnosis and raising suspicion[9]. It is most widely assumed that the prevalence of this phenomenon is higher among communities' incidence of consanguineous unions[10]. The majority of FXIII deficiency cases are caused by mutations in the A subunit, such as in homozygous patients who experience severe, lifelong bleeding, most commonly from the umbilical cord after delivery and cerebral bleeding. Furthermore, women have reported recurrent miscarriages, and some patients experience delayed wound healing[11,12]. Many specialist researchers have reported more than 50 mutations in the FXIII A gene, including twenty-five missense mutations, four nonsense mutations, nine splice site mutations, twelve small deletions or insertions, and one gross deletion[13]. In contrast, a few modifications were described in the B subunit[14]. The first mutations in the FXIII-A genes were discovered in 1992, and since then, a diverse spectrum of mutations has been identified[15]. Herein, this research study aims to evaluate the association between Factor XIII polymorphism and the risk of coagulation factor XIII A subunit deficiency in Iraqi families.

PATIENTS & METHODS

Study design and participants

Twenty patients from unrelated families in Baghdad City were investigated for FXIII deficiency based on clinical and laboratory features. All patients were selected and recruited from the Department of Hemorrhagic Disorders at Child Protection Hospital in Medicine City, Baghdad, Iraq, who had experienced severe bleeding. Further, twenty-five healthy control samples were randomly selected from the general population from November 2022 to January 2023. The healthy controls had no family ties to the patients but were of the same ethnicity. The healthy controls were identified as having no complaints of bleeding or inherited familial hemorrhage. The Biotechnology Department, College of Science, University of Baghdad, authorized the research work with the CSEC/0222/0023 reference number. Factor XIII deficiency was diagnosed and classified according to the 2010 EULAR/ACR criteria, depending on the time of diagnosis. All participants provided informed consent and completed a questionnaire regarding each patient and control information.

DNA Extraction and Genotyping

Genomic DNA was extracted from peripheral blood leukocytes using a standard procedure (Promega USA kit); the genotyping analysis utilized DNA with a purity between 1.75 and 1.85. Genomic DNA consisting of the coding region was amplified by polymerase chain reaction (PCR) using Taq DNA polymerase (Macro gene company, Korea) and specifically designed primers Fo rward..5'TGTAAAACGACGGCCAGTGCAGAGTAGATG CAGGAATAG3', Reverse..5'CAGGAAACAGCTATGAC GGATGGCAGGA 3'. The PCR products were purified using a High Pure PCR Product Purification kit (Promega, USA) and subjected to direct sequencing. The procedure of polymerase chain reactions (PCRs) was conducted using a 25μl total volume, which consisted of a 10μl mixture of the GoTaq Green Master Mix (Promega, USA) and 1μl of the forward primer solution. After that, 1μl of reverse primer (10pmol/μl), and 2 μl of the DNA template, and 6 μl of the distilled nuclease-free water. The temperature program utilized in this study involved an initial denaturation step at 94°C for 4 min, followed by a series of 30 cycles. Each cycle consisted of denaturation at 94°C for 30 sec, annealing at 55°C for 30 sec, and extension at 72°C for 30 sec. The ultimate incubation temperature was sustained for 7 min, followed by a 10 min incubation at 4°C to cease the reactions. The products amplified by PCR were undergone to forward and reverse Sanger DNA sequencing. After aligning with reference-DNA-sequences in the National Centre for Biotechnology Information (NCBI), Geneious software was employed to recognize the FXIIIA gene SNPS.

Statistical Analysis

All clinical data of the study groups were compared using the statistical software package (SPSS and WinPep) version 26, along with the Student T-Test for age. P-value significance was established at 0.05. The distribution of genotypes was analyzed in autosomal recessive inheritance. Under this mode, the Odds Ratio (OR) calculation with a 95% Confidence Interval (CI) and the determination of the P-value was performed to assess the presence of an association. The WinPepi program was utilized to estimate calculations, whereas the Haploview program was employed to calculate D' and r^2 values for analyzing the PCR and LD results.

RESULTS

Participant Characteristics

The study consisted of 45 subjects, divided into two groups: 20 patients and 25 controls; the groups were

carefully matched in terms of sex and age. The patients' demographic profiles had a mean age of 30.48–15.09 years (female: 10 and male: 10). The control group involved sex (female: 11 and male: 14) and an age mean of 31.310.07 years. The characteristics of patients with FXIII deficiency and controls are summarized in **(Table 1)**. The demographic characteristics of patients differed significantly from those of the healthy group.

Routine Coagulation Tests

Standard coagulation tests, like Prothrombin time and Partial Thromboplastin time, revealed significant differences between the two groups (patients and controls) with a P-value of 0.001 **(Table 2)** shows, there were no statistically significant differences between the mean platelet counts of patients and healthy individuals.

FXIIIA gene SNP data

Several SNPs were identified in the exon 9, and exon 10 region, including, five polymorphisms of the FXIII A gene were detected by direct sequencing. The observed genotype distributions of factor XIII carried the rare polymorphisms, 8 (40%) rs5977 and 8 (40%) rs5978, as well as 10 (50%) rs2274391, 1 (50%) rs41302861, and 10 (50%) rs924669371 SNPs. The SNPs rs5977, rs2274391, rs41302861, and rs924669371 exhibited insignificant differences between the study groups. The SNPs' rs5978 location on exon 9 revealed a significant difference between patients and healthy people. The heterozygous showed (40%), up or =0.52, CI =0.16-1.68, p-value=0.3, and the genotype homozygous recessive displayed (35%) up or =28.33, CI=1.59-504.4, p-value=0.001. This polymorphism was significant, with a p-value of 0.001 and a high-risk odds ratio. The genotype of the polymorphisms rs5977 heterozygous showed (40%), and the homozygous recessive genotype (5%). The SNP rs2274391 genotype showed (50%) and (5%) of the heterozygous and the genotype homozygous recessive, respectively. The genotype of the SNP rs41302861, heterozygous, showed (5%). The SNP rs924669371 had a genotype of heterozygous, which was ten times higher than the SNP rs41302861, and Table 3 shows the calculated allele frequencies among the subjects **(Table 3)**.

Two models (Dominant and Recessive models) were calculated to detect the association between SNPs of the FXIIIA gene and risk with the disease. Negative associations were observed between the rs5977 and rs2274391 in the dominant and recessive model, prevalent in rs5977 odds ratio =2.10, p-value=0.3, recessive or =0.125, p-value =0.4 and dominant in rs2274391 or=1.13, P-value=1.0 and recessive or=0.25, p-value=0.4. Significance was observed in rs5978 polymorphism dominant model or =2.36, p-value =0.2 and recessive model or =0.03, p-value =0.025, as presented in **(Table 4)**.

Linkage Disequilibrium (LD) and Haplotype analysis of Factor XIII Gene

The link imbalance was established among the five FXIIIA SNPs genes, as shown in **(Figure 1)**. There was a linkage disequilibrium with the following pairwise parameters between the SNPs rs5977, rs5978; D'=0.862, r2=0.26, rs5977, rs2274391; D'=1, r2=0.605, rs5977, rs41302861; D'=0.994, r2=0.016; rs5977, rs924669371; D'=0.127, r2=0.014, rs5978, rs2274391; D'=0.919,r2=0.488, rs5978, rs41302861; D'=0.997,r2=0.047, rs5978, rs924669371; D'=0.597,r2=0.143, rs2274391,

Table 1: Participant characteristics of study groups.

Parameters	No (20)	No (%)
Gender	Male: 10	50%
	Female: 10	50%
Age groups; years	May-25	10(50%)
	26-46	6(30%)
	47-67	4(20%)
Family history	Positive 20	100%
	Negative 0	0
Bleeding At birth	7	35%
Bleeding joint	4	20%
Bleeding skin	5	25%
Bleeding muscle	3	15%
Bleeding epistaxis	2	10%
Bleeding After trauma	5	25%

Table 2: Platelet, PT and PTT in Patients and controls.

Groups	NO	Patient	NO	Control	P-value	Reference range platelet (X10 ^ 3/ uL)
		Mean ± S. D		Mean ± S. D		PT, PTT (second)
Platelet count	20	303.8±55.5	25	296.5± 88.9	0.8	150-400
(PT)	20	14.4±1.3	25	11.9± 0.8	>0.001	Nov-15
(PTT)	20	34.5±4.4	25	30.3±2.3	>0.001	28-40

PT: Prothrombin time, PTT: Partial Thromboplastin Time

Table 3: Five factor XIII genotype and allele frequency distribution SNPs.

Genotype rs5977	Patients (N=20)		Controls (N=25)		OR	95%CI	P-value
	N	%	N	%			
CC	11	55	18	72	0.48	0.14-1.60	0.3
CT	8	40	7	82	1.49	0.44-5.05	0.5
TT	1	5	0	0	3.59	0.15-86.72	0.4
Allele Frequencies							
C	30	75	43	86	0.49	0.17-1.41	0.27
T	10	25	7	14	2.05	0.71-5.91	0.27
Genotype rs5978	**Patients (N=20)**		**Controls (N=25)**		**OR**	**95%CI**	**P-value**
	N	**%**	**N**	**%**			
CC	5	25	11	44	0.42	0.12-1.49	0.2
CT	8	40	14	56	0.52	0.16-1.68	0.3
TT	7	35	0	0	28.33	1.59-504.45	0.001
Allele Frequencies							
C	18	45	36	72	0.32	0.13-0.76	0.017
T	22	55	14	28	3.14	1.32-7.48	0.017
Genotype rs2274391	**Patients (N=20)**		**Controls (N=25)**		**OR**	**95%CI**	**P-value**
	N	**%**	**N**	**%**			
GG	9	45	12	48	0.89	0.28-2.81	1
AG	10	50	13	52	0.92	0.29-2.91	1
AA	1	5	0	0	3.92	0.16-95.03	0.44
Allele Frequencies							
G	28	70	37	74	0.82	0.33-2.05	0.8
A	12	30	13	26	1.22	0.49-3.05	0.8
Genotype rs41302861	**Patients (N=20)**		**Controls (N=25)**		**OR**	**95%CI**	**P-value**
	N	**%**	**N**	**%**			
GG	19	95	20	80	4.75	0.54-42.13	0.2
AG	1	5	5	20	0.21	0.02-1.87	0.2
AA	0	0	0	0	-	-	-
Allele Frequencies							
G	39	97.5	45	90	4.33	0.5 -37.6	0.2
A	1	2.5	5	10	0.23	0.03-2.01	0.2
Genotype rs924669371	**Patients (N=20)**		**Controls (N=25)**		**OR**	**95%CI**	**P-value**
	N	**%**	**N**	**%**			
AA	10	50	16	64	0.56	0.17-1.81	0.37
AG	10	50	9	36	1.78	0.55-5.73	0.37
GG	0	0	0	0	-	-	-
Allele Frequencies							
A	30	75	41	82	0.66	0.24-1.80	0.44
G	10	25	9	18	1.52	0.56-4.15	0.44

rs41302861; D'=0.991,r2=0.027, rs41302861, rs924669371; D'=0.997,r2=0.019. Haploview software was used to estimate the LD between the two-studied groups. It can be observed that among the polymorphisms was no significant LD (D' = 0.17) in Fig 1, which refers to the most substantial evidence of recombination **(Table 5,6)**.

The study analyzed haplotypes in FXIII deficiency patients using polymorphisms and a control table. Ten distinct haplotypes were found. The haplotype CCGG A frequency was considerably higher in controls than in FXIIIA patients (OR=0.369), (p = 0.02). In contrast, the haplotypes CTGGG and CTGGA were more frequent in patients than controls (OR=6.988), (p = 0.04 and p = 0.005, respectively). The haplotype frequency estimation among patients and controls is shown in **(Table 7)**. Haplotype frequency distribution among patients and control (All those frequencies<0.03 will be ignored in analysis).

Table 4: Genetic Model of rs5977 C>T polymorphisms, rs5978 C>T polymorphisms, rs2274391 G>A polymorphisms.

Genetic Model rs5977 C>T	Genotypes	Patients	Control	OR	95% C.I.	P-value
Dominant	CT+TT	08-Jan	7/0	2.1	0.63-7.07	0.3
	CC (Ref.)	11	18	1	-	-
Recessive	CT+CC	08-Nov	Jul-18	0.25	0.009-6.603	0.4
	TT (Ref.)	1	0	1	-	-
Genetic Model rs5978 C>T	**Genotypes**	**Patient**	**Control**	**OR**	**95% C.I.**	**P-value**
Dominant	CT+TT	08-Jul	14/0	2.36	0.67-8.26	0.2
	CC (Ref.)	5	11	1	-	-
Recessive	CT+CC	08-May	14-Nov	0.03	0.0019-0.66	0.025
	TT (Ref.)	7	0	1	-	-
Genetic Model rs2274391 G>A	**Genotypes**	**Patients**	**Control**	**OR**	**95% C.I.**	
Dominant	AG+AA	10-Jan	13/0	1.13	0.36-3.57	1
	GG (Ref.)	9	12	1	-	-
Recessive	AG+GG	10-Sep	13-Dec	0.25	0.0098-6.6	0.4
	AA (Ref.)	1	0	1	-	-

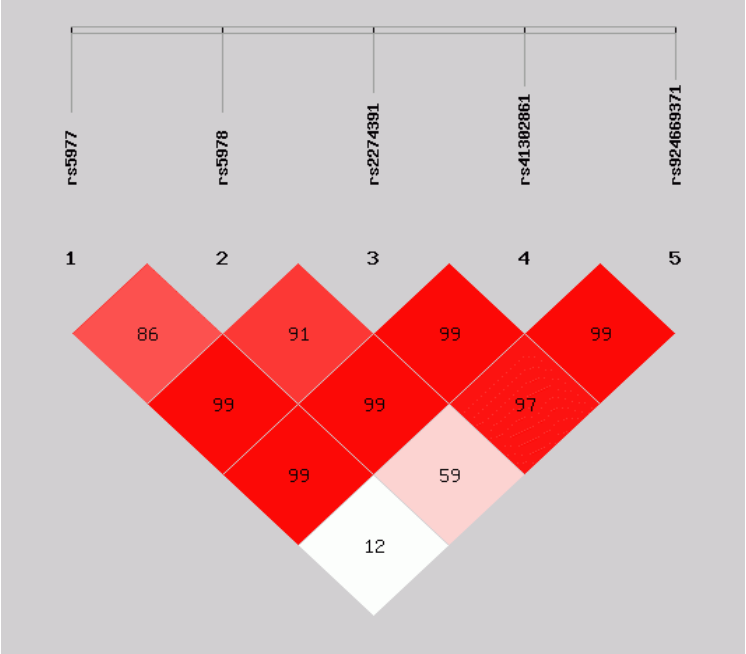

Figure 1: Linkage disequilibrium test of FXIIIA (exon 9 and exon 10) SNPs. Linkage disequilibrium (LD) was calculated with the software Haploview. A D0 value of 100 signifies complete linkage disequilibrium between two markers, while a D value denotes full linkage equilibrium. The greater the linkage disequilibrium between SNPs, the darker the cell.

Table 5: Linkage Disequilibrium tests of five SNPs of FXIIIA gene (exon 9 and exon 10).

D':	rs5978	rs2274391	rs41302861	rs924669371
rs5977	0.862	1	0.994	0.127
rs5978	-	0.919	0.997	0.597
rs2274391	-	-	0.991	0.972
rs41302861	-	-	-	0.997

Table 6: Linkage Disequilibrium test of five SNPs of FXIIIA (exon 9 and exon 10).

r2:	rs5978	rs2274391	rs41302861	rs924669371
rs5977	0.26	0.605	0.016	0.014
rs5978	-	0.488	0.047	0.143
rs2274391	-	-	0.027	0.097
rs41302861	-	-	-	0.019

DISCUSSION

Coagulation factor XIII is a transglutaminase that plays a crucial function in cross-linking fibrin during the final stages of the blood coagulation pathway[16]. Statistically significant demographic factors for diagnosis include bleeding tendencies at birth, after vaccinations and trauma, joint and muscle hemorrhage, cutaneous bleeding, and family history, which are compared between the patient and control groups. The results agree with the findings of[17] research finding, the majority of patients have a severe bleeding diathesis characterized by postnatal umbilical cord bleeding, cutaneous bruising, hematomas, intramuscular and joint hemorrhage, postoperative hemorrhage, impaired wound healing, spontaneous abortions in early pregnancy, intracranial hemorrhage, leading to cause of death. In this study, family history is positive in 100% of patients due to a higher incidence of interfamilial marriages. These results agree with[18], family history was positive in more than half of the patients. The thromboplastin and thrombin times were examined, and a p-value of >0.001 indicated a significant difference between patients and healthy individuals, although it was still within the normal range. These findings agree with research study published by[19], due to the disorder's rarity and the normal expected of standard coagulation screening tests, such as prothrombin time, activated partial thromboplastin time, thrombin time, platelet count, or bleeding time, diagnosing FXIIID might be difficult. Twenty patients with factor XIII deficiency were studied in the exon 9, and exon 10 regions of the coagulation factor XIII gene A. These regions have five SNPs: rs5977, rs5978, rs2274391, rs41302861, and rs924669371. Polymorphisms between individuals revealed the presence of congenital homozygous and heterozygous deficiencies in the individuals. The genotypic distribution of rs2274391 heterozygous (50%) was higher than homozygous recessive (5%). The genotypic distribution of rs41302861 heterozygous (5%) and the mutant allele did not appear, homozygous recessive (0%), and the genotypic distribution of rsA.924669371G>A, heterozygous (50%), was higher than homozygous mutant (5%). All these SNPs were insignificant, except for the rs5978 polymorphism. There was a significant difference in the genotypic distribution of the rs5778 polymorphism between FXIII patients and controls, with a p-value of 0.001 and a high-risk odds ratio of 28.33 for the homozygous recessive genotype (35%). In comparison, the percentage frequency to heterozygous (40%) and allele frequencies to allele T (55 %) high than allay C (45%), the C allele was protective, and the T allele was harmful when patients were compared to controls, A studies that support this date[20], severe disease may be caused by either homozygous or compound heterozygous mutations at either locus. These SNP, rs5978, were found in a family where both parents were disease carriers and had consanguineous marriage. The symptoms for the thirteen-year-old male appeared after the trauma, whereas for the fifteen-year-old girl, they appeared seven days after her birth, which agrees well with the claimed findings of[21] Patients with severe FXIII deficiency display symptoms in the neonatal period; it is essential to acquire a family history, particularly a history of consanguineous marriages. The presence of the T/T genotype may be a risk factor for the FXIIIA gene; these results are consistent with those of[22], who found that the TT genotype of a functional factor XII (FXII) C46T gene polymorphism was a risk factor for peripheral venous thrombosis. In the present investigation, the frequency of the haplotypes CTGGG and CTGGA was considerably greater in FXIIIA patients than in controls; the most prevalent haplotypes were CTGGG ($p = 0.04$) and CTGGA ($p=0.005$) this result considers a risk factor. In comparison, the haplotype CCGG was considerably greater in control than patients ($OR=0.369$), ($p = 0.02$), this result considers a protective factor. Results agree with[23], haplotypes are formed when SNPs are close to one another on a chromosome and are inherited in clusters. These SNPs occurred in the intron region and have not changed the amino acid type from one to another[24] Found that owing to degeneration of the genetic code, SNPs within a coding sequence do not necessarily alter the amino acid sequence of the protein produced. Therefore, global research on this polymorphism may be limited, and the current study is the first to demonstrate a correlation between the rs5978 gene and the risk of the FXIIIA gene. Although the SNPs are listed in the NCBI, no articles have been made about them. Due to the disease's rarity and insufficient samples available in Baghdad and Iraq, as well as the lack of information regarding the cause of the disease's emergence in the SNPs, it is impossible to draw conclusions from this comparison.

CONCLUSION

It was found that the tests Prothrombin time, Partial thromboplastin time, and platelet count helped diagnose the disease, as well as the appearance of five rare SNPs rs5977, rs5978, rs2274391, rs41302861, and rs924669371, for the first time in the samples of Iraq, which are located in the exon 9, and exon 10 on the gene A on chromosome 6p24-25, all four SNPs rs5977, rs.2274391, rs41302861, and rs924669371 was not significant, except rs5978 was effective in patients who were related by consanguineous marriage. The most common haplotypes were CTGGG and CTGGA were risk factor; CCGG was a protective factor.

CONFLICT OF INTEREST

The authors declare no conflict of Interest.

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