Original Article

Coagulation Factor XIII-A A614T gene Variation is Suggestive of Founder Effect in Iranian Patients with Severe Congenital Factor XIII Deficiency

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Abstract

Background: Factor XIII (FXIII) is a heterotetramer consisting of two subunits, FXIII-A and FXIII-B. Several common gene variations were observed in the FXIII-A gene with an obvious ethnic difference. This study assessed the prevalence of A614T as a common FXIII-A gene variation among Iranian patients with FXIII deficiency (FXIIID).

Materials and Methods: This study was conducted on eighty Iranian unrelated individuals with FXIIID. Genotype analysis for FXIII-A A614T gene variation was performed for all individuals.

Results: Molecular analysis of these Iranian populations revealed that all studied patients were homozygous for the T allele at codon 204 of the FXIII-A1 subunit.

Conclusion: Present of T allele at codon 204 of FXIII-A1 subunit among all study population can be suggestive of founder effect.

Keywords: Factor XIII, Polymorphism, Mutation

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Introduction

Coagulation factor XIII (FXIII) or fibrin stabilizing factor is a zymogen composed of two A-subunits and two B- subunits that are held together no covalently in a tetrameric form (1). The gene coding FXIII-A subunit consists of 15 exons, covers a genomic region of 160 kb, and maps to the 6p24-25 chromosomal region. This subunit consists of 731 amino acids and characterized by 5 domains including the activation peptide (residues of 1-37), β-sandwich (residues of 38-183), the central domain of catalytic core region (residues 184-515), β-barrel 1, and 2 (residues 516-627 and residues 628-731, respectively) (2, 3). The gene coding FXIII-B subunit located on 1q31-32 covers a 28 kb genomic region and compromise of 12 exons which are separated by 11 introns. This subunit consists of 10 tandem repeats named sushi domains (2, 3). The active form of factor cross-links the fibrin monomer and stabilizes the fibrin clot during the final stage of the coagulation cascade. In addition, FXIII has an essential role in wound healing, angiogenesis, and maintaining the pregnancy (1, 4, 5).

Until now, a considerable number of polymorphisms have been identified in FXIII-A subunits and the most common of them are Val34Leu in exon 2, Tyr204Phe in exon 5, Pro(CCA)331(CCC)Pro in exon 8, Pro564Leu, Glu (GAA)567Glu(GAG) in exon 12, Val650Ile, and Glu651Gln in exon 14. Also, in the factor XIII-B subunit two common polymorphisms were reported,

His95Arg and C29759G change in intron K29756 (1-5, 8, 9). Studies on the structural and functional effects of these mutations lead to a better understanding of the causes of and accurate diagnosis of this disorder. Thus, our study aims to evaluate one of the most common polymorphisms of the FXIII-A subunit.

Methods

This descriptive study was conducted on eighty unrelated Iranian patients with FXIII deficiency (FXIIID). All participants gave informed by written consent according to the protocol approved by the local medical ethics committee.

Blood sample from each patient was collected in Ethylene-diaminetetraacetic Acid (EDTA) anticoagulant tube. Blood specimens were lysed with sodium dodecyl sulfate (SDS) and genomic DNA of each sample was isolated from the leucocytes according to the standard protocol. DNA was purified using phenol-chloroform and ethanol precipitation. The quality and quantity of obtained DNA were determined through spectrophotometry and also using agarose gel electrophoresis.

After DNA extraction, genotyping of FXIII-A A614T gene variation was performed by polymerase chain reaction amplification of genomic DNA followed by restriction enzyme digestion (PCR-RFLP) (Table 1). Primer and DNA sequences were selected from reports published previously (9). For all PCR amplification, positive control DNA samples of known genotype were included as well as a negative control without template DNA.

Results

This descriptive study was conducted on eighty patients with severe FXIID from same number of unrelated families. Among our patients, 52.5% (n: 42) were male and 47.5% (38) were female and the mean age of them was 26±3 years. In all patients, genetic analysis revealed that homozygous for T allele at codon 204 of FXIII-A1 subunit. In every case, the sequencing results agreed with the PCR-RFLP genotyping result.

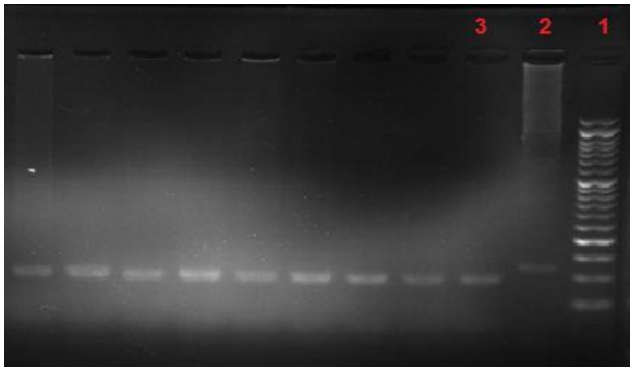

Fig. 1. Results of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) of factor XIII-A A614T gene variation among Iranian patients with severe congenital factor XIII deficiency.
1- 50bp ladder, 2- 113 bp undigested band, 3- Two 91 and 22 bp band after digestion with Rsa I restriction enzyme.

Table 1: Characteristics of used primers and restriction enzymes.

Polymorphism	Ref.	Primers	Hybridization	PCR product	Digestion	Bands (bp)
FXIII-A A614T	(9)	5´-GGAAACAGTCTGGTTTGGTAA-3´ 5´-ACCCCGATGTCATTCAGGACG-3´	60°	113bp	*Rsa I*	91, 22

Discussion

FXIII is a coagulation factor with multiple intra- and extracellular functions (1, 9, 10). Several studies revealed that there are five common gene variations in the FXIII-A gene including Val34Leu, Tyr204Phe, Pro564Leu, Glu567Glu, and Glu651Gln (1-5). These common gene variations show a significant difference in various ethnicities. No comprehensive study was performed in Iranian patients with severe FXIIID to asses' prevalence of these polymorphisms among this population.

After careful selection of the study population, we chose A614T as a common mutation of FXIII-A. We found that all patients were homozygous for the T allele at codon 204 of the FXIII-A1 subunit.

We previously found that all of these patients were homozygote for c559t mutation in the FXIII-A subunit (4, 10, 11). This mutation of a disease-causing mutation and cause severe FXIIID in Iranian patients. These two findings are a sign of founder effect in these individuals but further studies are required for confirmation of this issue. A few studies were performed on Iranian patients to the determined prevalence of this common polymorphism. Jeddi-Tehrani et al. were found that these common FXIII-A gene variations with a frequency of 84% in women with miscarriage and with a prevalence of 48% in healthy Iranian individuals (12). Their finding showed that this FXIII-A polymorphism is common among Iranian patients such other ethnicities in the world. A comparison with the results of the Jeddi-Tehrani et al. study it seems that all of our patients were inherited this common FXIII-A gene variation similarly and further studies on FXIII-A short tandem repeat (STR) can confirm this issue that c559t mutation in FXIII-A is the result from a founder effect. Meanwhile, investigation of other FXIII-A common polymorphisms such as Val34Leu in exon 2, Pro(CCA)331(CCC)Pro in exon 8, Pro564Leu, Glu (GAA)567Glu(GAG) in exon 12 as well as Val650Ile and Glu651Gln in exon 14 can be used for confirmation of founder effect in these patients (1, 13, 14).

Conclusion

The presence of a similar single nucleotide polymorphism (SNP) in all of the study population unlike the normal Iranian population can be suggestive of the founder effect but further investigations are required for confirmation of this issue.

Acknowledgment

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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