

The association of Factor XIII 100 G/T polymorphism and the risk of deep venous thromboembolism: An in silico and experimental study

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ABSTRACT

Introduction: Several lines of evidence suggest that the Factor XIII (FXIII) 100 G/T polymorphism may influence susceptibility to deep venous thromboembolism (DVT). To explore this hypothesis, we investigated whether this polymorphism is associated with the predisposition to DVT. We also predict the possible impact of residue substitution at codons 34 (Val34Leu) in A subunits of the FXIII coagulation factor on the structure and function of it.

Methods: A total of 693 individuals were included in the current study, 193 patients with DVT clinical symptoms, and 500 healthy subjects without both personal and family histories of thromboembolic disorders. Genotyping was carried out using the amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) technique. To predict the potentially effects of residue changes at codons 34 on the structure and function of the FXIII, we used Polymorphism Phenotyping (PolyPhen) online software.

Results: No significant difference in the genotypes distribution of the FXIII 100 G/T gene polymorphism was detected between DVT patients and healthy controls ($P > 0.05$). Our results showed that the frequency of the mutated FXIII 100T allele was not statistically significant different between two group. Using PolyPhen online software, residue substitution at codons 34 of the FXIII was predicted to be benign.

Conclusion: Our in silico and experimental findings indicated that the FXIII 100 G/T gene polymorphism is not associated with DVT.

Key words: Deep Venous Thromboembolism, FXIII 100 G/T Polymorphism, Thrombophilia, PolyPhen

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Table 2. The genotype distribution of the FXIII 100 G/T polymorphism in case and control groups

	Case group (n=193) %	Control group (n=500) %	P value ^a
FXIII 100 G/T ^b			0.517
GG	72.02	74.60	
GT	24.87	23.60	
TT	3.11	1.80	

Abbreviations: F XIII; Factor XIII.

^a P value calculated by chi-square test^b FXIII, at nucleotide position 100 on the gene a G was exchanged by a T**Table 3. The heterozygote and homozygote genotypes and mutant allele frequencies of the FXIII 100 G/T polymorphism in case and control groups**

	Case group (n=193) %	Control group (n=500) %	P value ^a	OR	95 % CI
FXIII 100 G/T ^b					
GT	24.87	23.60	0.766	0.933	0.634 - 1.373
TT	3.11	1.80	0.381	0.571	0.201 - 1.627
Frequency of T allele	15.54	13.60	0.346	0.855	0.615 - 1.189
Carrier (GT+ TT) ^c	27.98	25.40	0.500	0.876	0.603 - 1.273

Abbreviations: F XIII; Factor XIII, OR; Odds Ratio, CI; Confidence Interval

^a P value calculated by chi-square test^b FXIII, at nucleotide position 100 on the gene a G was exchanged by a T^c Carriers: individuals who had either heterozygous or homozygous specified mutation

The frequencies of mutated FXIII 100T allele in case and control subjects was also calculated (see Table 3). We found that the prevalence of mutated FXIII 100T allele was more frequent in the case subjects but, did not show a statistically significant difference ($P>0.05$) (see Table 3).

Finally, we unified the heterozygote and homozygote genotypes of each group into a new group (carrier group) and then the odds ratios (OR) and 95% confidence intervals (CI) were calculated. Our data showed that the FXIII 100 G/T polymorphism is not associated with the increased risk of DVT (see Table 3).

Prediction of Functional Effect of Factor XIII Val34Leu polymorphism

The substitution of valine by leucine at codon 34 was predicted to be benign by PolyPhen online software (see Figure 1).



Figure 1. In silico analysis of the Factor XIII 100 G/T polymorphism using PolyPhen. The substitution of leucine a valine for a valine at codon 34 in FXIII coagulation factor was predicted to be benign.

Conclusion:

As indicated earlier, increasing evidences suggest that the procoagulant, anticoagulant and fibrinolytic systems deficiencies play a fundamental role in susceptibility to thromboembolic disorders [6]. To our knowledge, here, the possible association between FXIII 100 G/T polymorphism with DVT in Northwestern Iran was investigated in the current study for the first time. Our results revealed that the prevalence of the FXIII 100 G/T polymorphism was not statically significant different between case and control subjects in our population ($P>0.05$).

However, a high prevalence of this polymorphism in the patient group was detected. We also found that the frequency of mutated FXIII 100T allele was higher in the DVT patients than in healthy controls, but this difference was not statistically significant ($P>0.05$). Therefore, it seems that the presence of the FXIII 100T allele is not associated with DVT, based upon our experimental results. Our results are in accordance with the findings of several previous studies that have been published in this field. Corral *et al*, reported that Factor XIII 100T allele does not has any effect on the risk of venous thrombosis in the Spanish population [10]. Le Gal *et al*, studied 286 patients with idiopathic VTE and 286 healthy controls for FXIII 100 G/T polymorphism and reported that FXIII 100T allele was significantly associated with a lower risk of VTE [11]. Similar data were obtained in a

study by Renner *et al*, who investigated FXIII 100 G/T polymorphism in 154 DVT patients and 308 healthy controls in Austrian population and reported that presence of the FXIII 100T allele is associated with a decreased risk for DVT [13]. Moreover, Van Hylckama Vlieg *et al*, demonstrated that FXIII 100T allele was associated with a slightly decreased thrombotic risk [14]. In light of these studies and meta-analysis studies by Wells *et al*, and Gohil *et al*, provided additional evidence to support the hypothesis that the FXIII 100 G/T polymorphism has a significant protective effect against VTE [15, 16]. It has been proposed that the Leu34 FXIII is activated by thrombin more rapidly than their Val34 variant [17]. Although, the presence of FXIII Leu34 allele increases the catalytic activity of FXIII but it decreases clot stability and resistance to fibrinolysis through alteration of clot structure [16]. A study by Ariens *et al*, suggested that fibrin clots formed in the presence of Leu34 FXIII allele have finer structures with thinner fibers, smaller pores, and altered permeation characteristics when compared with fibrin clots formed in the presence of the Val34 variant [17, 18]. The findings of these studies have suggested that thinner and less porous fibrin clots relatively resistant to plasmin degradation [17,18]. Hence, it is conceivable that the FXIII 100 G/T polymorphism is associated with pathogenesis of VTE. Therefore, the role of FXIII 100 G/T polymorphism in pathogenesis of DVT remained controversial.

In conclusion, our in silico and experimental results revealed that the FXIII 100 G/T polymorphism is not associated with DVT. However, in spite of the negative association reported in the current study, the possible role of FXIII 100 G/T polymorphism in DVT pathogenesis could not be completely ruled out, and further studies will be needed to conclusively find association between this polymorphism and DVT.

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Declaration of conflicting interests

There are no potential conflicts of interest for each author, concerning the submitted manuscript.

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