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Relation between Endothelial Protein C Receptor Gene Polymorphisms rs867186 and rs9574, and the Risk of Deep Vein Thrombosis in Sudanese

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Abstract

Background: Deep venous thrombosis (DVT) can lead to a serious fatal pulmonary embolism. Many genetic risk factors may predispose to DVT; one of these is the mutation in the *PROCR* gene responsible for the production of endothelial protein C receptor (EPCR), which plays an important role in activation of protein C (PC). The objective of the present study was to examine the association between the rs867186 and rs9574 polymorphism in the *PROCR* gene and the occurrence of DVT in Sudanese individuals. Methods: A total of 100 Sudanese DVT patients and 100 apparently healthy individuals were recruited for this study. Ethylene diamine tetraacetic acie (EDTA)-anticoagulated blood samples were collected from all participants. Genomic DNA was extracted and *PROCR* gene product was amplified by a standard ploymerase chain reaction (PCR) reaction. PCR products were sequenced to identify *PROCR* gene polymorphisms. Results: The frequency of mutated allele of rs867186 was significantly higher in the DVT patient (41%) than in healthy control (21%). The presence of mutated allele of rs867486 increases the risk of DVT 3 folds. There was no significant difference in the frequency of mutated allele of rs9574 polymorphism between the DVT patients and the healthy control subjects. Further, it does not show an increase in the risk of DVT. The adjustment of gender, ethnic group, and body mass index (BMI) does not change the significance of each single nucleotide polymorphism (SNP) as a risk factor for DVT. Conclusion: It can be concluded that Sudanese individuals carrying the mutated allele rs867186 polymorphism were at risk to develop DVT, while the mutated allele of rs9574 polymorphism is not a risk factor for DVT in Sudanese individuals.

Keywords

Deep Vein Thrombosis, Pulmonary Embolism, EPCR, rs867186, rs9574, Sudanese

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1. Introduction

DVT is the formation of blood clots (thrombi) in deep veins, associated with a number of risk factors [1] and preventable morbidity and mortality [1]. An accurate diagnosis of DVT is extremely important to prevent potentially fatal acute complication of pulmonary embolism (PE) and long-term complications of postphlebitic syndrome and pulmonary hypertension [1]. Many genetic and acquired factors impede the natural anticoagulation process which in turn results in a hypercoagulable state and eventually thrombus formation. Protein C system is one of the most important naturally occurring anticoagulants affected by these factors, activated by thrombin-thrombomodulin complex [2]. This activation is enhanced by an endothelial cell surface receptor, EPCR [3]. Centelles M.N. *et al*. [4] reported that blocking EPCR can accelerate thrombus development. The gene encodes for this receptor; *PROCR* gene located in chromosome 20q11.2 and comprised of four exons and 3 introns. The first exon encodes for the 5' untranslated region (UTR) and signal peptides; the fourth exon encodes an additional 10 residues of extracellular domain, the transmembrane domain, the cytoplasmic tail and 3'UTR, while the second and third exons encode for most of the extracellular domain [5]. Many studies [6]-[8] reported an association between the presence of rs867186 polymorphism in exon 4 of *PROCR* gene and risk of venous thrombosis, while other studies [9] [10] concluded an association between a 3'UTR polymorphism (rs9574), and decreased risk of thrombosis. A lack of association between the latter polymorphism and the risk of venous thrombosis was also reported [11]-[14]. The aim of this study is to examine the association between the rs867186 and rs9574 polymorphisms and DVT in Sudanese patients.

2. Materials and Methods

In a case control study carried out during the period between January 2013 and May 2015, a sample of 200 participants were recruited, 100 Doppler ultrasonographically confirmed DVT patients (45% male and 55% female) with age ranged from 18 to 59 years, attended different Khartoum state hospitals, designated as cases group. Patients with hematological diseases, history of DVT, liver and kidney dysfunctions, infections, autoimmune diseases, tumors, or those receiving thrombolytic treatment or anticoagulant treatment were excluded. While the control group comprised of 100 apparently healthy individuals (58% male and 42% female) with age ranged from 17 to 55 years. All controls were the co-patients of the DVT patient to ensure the maximum homogeneity between the cases and controls. Participants with history of thrombosis were excluded from the control group.

The study was approved by the ethical committee of research department, Ministry of Heath, Khartoum state, Sudan, and an informed written consent was also obtained from all participants. The study results were used for research purpose only, and were made available for all participants.

2.1. Blood Sample Collection

Five ml venous blood were drawn from all participants into an EDTA blood container and stored at −80˚C until further processing.

2.2. DNA Extraction and Genotyping Analysis

The genomic DNA was extracted from the blood samples using modified salting out method [14]. Specified regions in *PROCR* gene were amplified using conventional thermal cycler with the following set of in silico designed primers; F-5'taaacgggtccctttcctct3' and R-5'ctcccctccctcaaatcttc3' for exon 4 (384 bp). Two single nucleotide polymorphisms, (rs867186); located in exon 4 with ancestral allele A and reference SNP allele G, and (rs9574); located in the 3' UTR with ancestral allele C and reference SNP allele G, were selected in silico, the selection of these SNPs based on minor allele frequency (MAF > 5%) and validation status using Ensemble and single nucleotide polymorphism database (dbSNP) of national center for biotechnology information (NCBI) tools. The cycling conditions for polymerase chain reaction (PCR) were 30 cycles of denaturation (95˚C for 30 seconds), annealing (54˚C - 66˚C for 50 seconds) and extension (72˚C for 60 seconds). A preheating step at

95˚C for 5 minutes and a final extension step for 7 minutes at 72˚C were also carried out. The PCR products were stored at 4˚C. Prior to sequence determination of each DNA fragment with advanced sequencing technique, the size of each fragment was ascertained with agarose gel electrophoresis, later all PCR products were sent for purification and DNA sequencing to Macrogen Inc., Seoul, Republic of South Korea.

2.3. Data Analysis

The sequencing data were analyzed using the basic local alignment search tool (BLAST) program of NCBI, and SPSS 16. Level of significance for the statistical tests was set at 0.05.

3. Results

The demographic data of this study showed that cases group comprised of 45% males and 55% females with age ranged from 15 to 59 years, 26% Nilo-Saharan, 60% Afro-Asiatic, and 14% Congo-Niger, and 10% underweight, 72% normal weight, 12% overweight and 6% obese. While the control group were 58% males, 42% females, with age ranged from 17 to 55 years. 22% Nilo-Saharan, 56% Afro-Asiatic, and 22% Congo-Niger and, 4% underweight, 70% normal weight, 20% over weight, and 6% obese, as showed in **Table 1**.

In this study the frequency of the mutated allele of rs867186 polymorphism was significantly high in DVT patients than in healthy individuals (*P* value < 0.05). The allele frequency of this polymorphism was 21% in control group and 41% in the case group for the mutated allele, while the normal allele was 79% and 59%, in the two study groups respectively as shown in **Table 2**. On the other hand no statistically significant difference was observed in the allele frequency of the rs9574 polymorphism between DVT patients and healthy individuals (*P* value > 0.05). The frequency of the mutated allele of rs9574 were 23% as for controls and 18 for cases, and for normal allele were 77% and 82%, respectively shown in **Table 3**.

The results of regression analysis showed that the mutated allele of rs867186 significantly increases the risk of DVT (OR = 2.614; 95% CI, 1.400 - 4.883) (*P* value < 0.05) as shown in **Table 4**. Further adjustment of the

Table 1. Demographic data for DVT patients and healthy controls.

		DVT Patients	Healthy Controls
Gender	Male %	45	58
	Female %	55	42
BMI	Under Weight %	10	4
	Normal Weight %	72	70
	Over Weight %	12	20
	Obese %	6	6
Ethnic Groups	Nilo-Saharan %	26	22
	Afro-Asiatic %	60	56
	Congo-Niger %	14	22

Table 2. Cross-tabulation between rs867186 and the study groups.

			rs867186		Total	Pearson Chi-Square (*P* value)
			Normal	Mutated		
Study groups	Control	Count	79	21	100	0.002
		%	79.0%	21.0%	100%	
	Case	Count	59	41	100	
		%	59.0%	41.0%	100%	

regression model to gender, ethnicity and BMI showed slight increase of risk of DVT with the mutated allele (OR = 2.817; 95% CI, 1.467 - 5.410) (*P* value < 0.05) as shown in **Table 5**.

Single nucleotide polymorphism rs9574 does not show statistically significant effect as a risk factor for DVT (*P* value > 0.05), as shown in **Table 6**. The lack of rs9574 effect as risk factor has not changed after addition of other potential risk factors to the regression model as shown in **Table 7** (**Figures 1-3**).

Table 3. Cross-tabulation between rs9574 and the study groups.

			rs9574		Total	Pearson Chi-Square (*P* value)
			Normal	Mutated		
Study groups	Control	Count	77	23	100	0.381
		%	77%	23%	100%	
	Case	Count	82	18	100	
		%	82%	18.0%	100%	

Table 4. Odd ratio of rs867186 as a risk factor for DVT.

		P value	Exp(B)	95.0% CI for EXP(B)	
				Lower	Upper
Step 1	rs867186	0.003	2.614	1.400	4.883
	Constant	0.090	0.747		

Table 5. Odd ratio of rs867186 and confounders as a risk factor for DVT.

		P value	Exp(B)	95.0% CI for EXP(B)	
				Lower	Upper
Step 1	rs867186	0.002	2.817	1.467	5.410
	Female	0.061	1.792	0.974	3.299
	Nilo-Saharan	0.341			
	Afro-Asiatic	0.781	0.905	0.446	1.835
	Congo-Niger	0.171	0.512	0.197	1.335
	Under Weight	0.371			
	Normal Weight	0.129	0.377	0.107	1.329
	Over Weight	0.077	0.286	0.071	1.148
	Obese	0.255	0.372	0.068	2.037
	Constant	0.444	1.715		

Table 6. Odd ratio of rs9574 as a risk factor for DVT.

		P value	Exp(B)	95.0% CI for EXP(B)	
				Lower	Upper
Step 1	rs9574	0.382	0.735	0.368	1.466
	Constant	0.692	1.065		

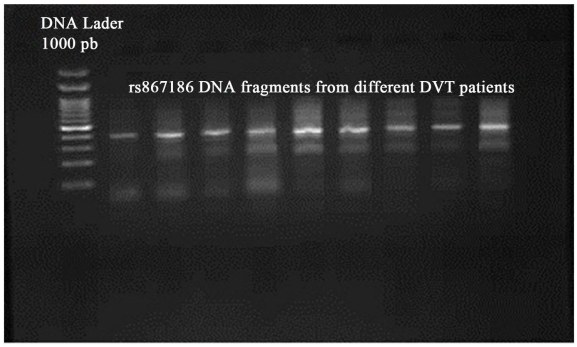

Figure 1. Results of gel electrophoresis for DVT patients.

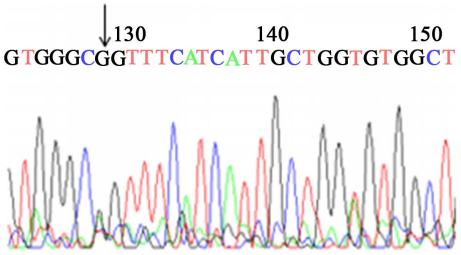

Figure 2. DNA sequence of the mutated allele of rs867186.

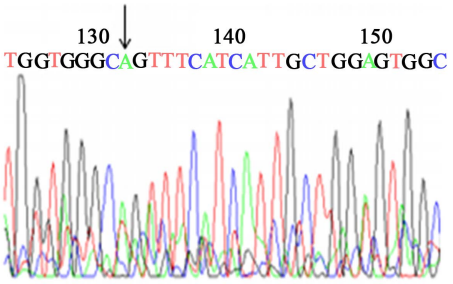

Figure 3. DNA sequence of the normal allele of rs867186.

Table 7. Odd ratio of rs9574 and confounders as a risk factor for DVT.

		P value	Exp(B)	95.0% CI for EXP(B)	
				Lower	Upper
Step 1	rs9574	0.492	0.778	0.380	1.591
	Female	0.108	1.624	0.899	2.934
	Nilo-Saharan	0.331			
	Afro-Asiatic	0.904	0.958	0.478	1.920
	Congo-Niger	0.185	0.530	0.207	1.355
	Under Weight	0.373			
	Normal Weight	0.165	0.419	0.122	1.432
	Over Weight	0.078	0.293	0.075	1.147
	Obese	0.328	0.435	0.082	2.307
	Constant	0.231	2.274		

4. Discussion

A reliable accurate diagnosis of DVT is extremely important to prevent potentially fatal acute complications such as pulmonary embolism (PE) and the long-term complications of post-phlebitic syndrome and pulmonary hypertension. It is also important to avoid unjustified therapy with anticoagulants associated with high risk of bleeding in patients misdiagnosed with the condition. In the human body the anticoagulation process is influenced by a number of genetic and acquired factors that may lead to hypercoagulable states and eventually thrombus formation. The PC system is one of the key anticoagulants produced by the human body, activated by thrombin-thrombomodulin complex and an endothelial surface receptor known as EPCR [6]. Therefore, a decrease in the activity of EPCR as a result of mutation in the gene coding for this receptor will emphatically alter PC activation process.

The demographic data of the DVT group in this study showed a younger mean age 35.89 years which compares favorably with 45 years in Uganda [15] and 42 years in Senegal [16], this young age can be attributed to the young demographic structure of the Sudanese population, and to some extend to the lack of a reliable and precise tool for age determination other than the reliance on the patient's own estimation. Another contributing factor could be the limited travel and access of old patients to healthcare due to socio-cultural constrains.

The results of this study indicated that the frequency of the mutated allele of rs867186 polymorphism is higher among DVT patients than in healthy control group. This finding is consistent with that reported by many studies [9] [11] [17] [18]. While no difference was observed in the allele frequency of rs9574 polymorphism between the DVT patients and the healthy individuals.

The high frequency of mutated allele of rs867186 in the patients group is indicative of possible role in the etiology or pathogenesis of the disease, Navarro, S *et al*. [19], and Karabiyik A *et al*. [11] reported that mutated allele of rs867186 increases the risk of VTE by approximately two-folds in the carriers of prothrombin 20210A allele, in another study Saposnik, B *et al*. [9] reported an association between rs867186 and elevated levels of plasma sEPCR as well as the risk of DVT. The possible role of rs867186 polymorphism as a risk factor for DVT was also suggested by Yin, G *et al*. [17] and Chen, X *et al*. [20] in two separate studies carried out to explore the distribution of allele frequency of rs867186 among both thrombotic patients and healthy individuals, they reported high allele frequency of the SNP in the patients group as compared to their healthy counterparts. A strong supportive evidence of the role of this SNP in the disease comes from the conclusion of meta-analysis of observational studies conducted by Jessica Dennis *et al.* [21] who reported a significant association between the SNP and the disease. In contrast to our finding, Uitte de WS *et al*. [10], Yamagishi K *et al*. [22], and Medina P *et al*. [10] [22] [23] reported no association between rs867186 polymorphism and the risk of DVT. The relation between the rs867186 single nucleotide polymorphism and deep venous thrombosis can be explained by the fact that rs867186 polymorphism has been documented to cause conformational change in EPCR as a result of substitution of serine amino acid in position 219 with glycine leading to increased shedding of this receptor as sEPCR [24] which has high affinity towards PC and activated protein C (APC), a consequent binding of sEPCR to APC interferes with its anticoagulant action this will ultimately result in a hypercoagulable state and thrombosis. The relation between rs867186 and DTV can also be explained under the light of the findings of study conducted by Saposnik B *et al*. [25] who concluded that cells carry the mutated allele of rs867186 polymorphism produce an abnormal mRNA that encodes a truncated protein lacks the transmembrane and intracellular domains which gets secreted directly into the plasma as sEPCR.

The findings of the present study are suggestive to the lack of significant synergistic or antagonistic effect of gender, ethnicity, and BMI on the potential risk of rs867186 for thrombosis.

On the other hand no relation was observed between rs9574 polymorphism and the risk of DVT, this goes in concordance with the reports by Medina P *et al*. [23] [26] and Saposnik B *et al*. [9], while Espana F *et al*. [27] reported that this polymorphism reduces the risk of VTE by 3 folds and attributed this protective effect to its association with high level of APC.

5. Conclusion

In conclusion the findings of the current study suggest that Sudanese carriers of the mutated allele of rs867186 polymorphism are at high risk to develop DVT, while rs9574 polymorphism plays a neither risky nor protective role for DVT in Sudanese individuals.

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Abbreviations

APC	Activated protein C
BLAST	Basic local alignment search tool
BMI	Body mass index
dbSNP	Single nucleotide polymorphism data base
DNA	Deoxyribonucleic acid
DVT	Deep vein (venous) thrombosis
EDTA	Ethylene diamine tetra-acetic acid
EPCR	Endothelial protein C receptor
MAF	Minor allele frequency
NCBI	National center for biotechnology information
OR	Odd ratio
PC	Protein C
PCR	Polymerase chain reaction
PE	Pulmonary embolism
SNP	Single nucleotide polymorphism
SPSS	Statistical package for social science
UTR	Untranslated region