Electronic Journal of General Medicine
2025, 22(6), em706
e-ISSN: 2516-3507
https://www.ejgm.co.uk/

MODESTUM

Original Article **OPEN ACCESS**

Association between single nucleotide polymorphisms in the ribosomal protein L5 gene and the risk of deep vein thrombosis in Saudi population

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Citation: Hassan F, Alsultan A, Albuali W, Bubshait DK, Abass E, Elbasheer M, Shaikh SS, Alkhanbashi A, Alzahrani FM. Association between single nucleotide polymorphisms in the ribosomal protein L5 gene and the risk of deep vein thrombosis in Saudi population. Electron J Gen Med. 2025;22(6):em706. https://doi.org/10.29333/ejgm/17525

ARTICLE INFO

Received: 03 Jan. 2025

Accepted: 02 Apr. 2025

ABSTRACT

Purpose: This study investigates the association between single nucleotide polymorphism in RPL5 and the risk of deep vein thrombosis (DVT) in the Saudi population.

Materials and methods: The case-control study included 98 DVT patients and 97 age- and sex-matched healthy controls. Peripheral blood samples were collected for genetic analysis after ethical clearance. DNA extraction was performed using a standard protocol, and RPL5 gene primers were designed for PCR amplification. Sanger sequencing was performed using the ABI 3730×L system.

Results: Findings showed a significant correlation between DVT patients and controls for two alleles: RPL5 rs558220259 G ($p = 0.000$); rs576892621 G ($p = 0.031$). Genotype analysis showed significant associations for rs138979590 (C/T) ($p = 0.0001$), rs558220259 (G/A) ($p = 0.0087$), and rs576892621 (G/A) ($p = 0.0272$) with DVT.

Conclusions: Our findings indicate that variants (rs138979590, rs558220259, and rs576892621) significantly contribute to DVT risk in Saudi patients.

Keywords: DVT, SNPs, RPL5, risk factors

INTRODUCTION

Thrombosis directly affects the quality of life and results in increased mortality rate [1]. The risk of Crohn's disease thrombosis in patients with ulcerative colitis is higher than in patients deprived of inflammatory bowel pathology [2-5]. Each year, more than 500,000 cases in the US are diagnosed with deep vein thrombosis (DVT) [6]. The prevalence of DVT was approximately 3% and larger than 15% after the occurrence of pulmonary thromboembolism. Extended immobilization, malignancy, obesity, oral contraceptives, smoking, corticosteroids, abortion, heart and lung diseases are associated with venous thromboembolism (VTE); in turn, mucosal damage occurs, which may increase the danger of thrombosis.

Numerous studies have described a wide difference in the postsurgical tendencies of DVT [1, 7-11]. In addition, climatic or racial factors are presumed to be an important risk for DVT complications [10]. Ribosomes are organelles that participate in protein synthesis. Ribosomes comprise of tiny subunits, 40S and 60S, which contain 4 RNA types, and in which 80 different protein structures have been observed. These ribosomal proteins encode the gene of the 60S subunit located in the cytoplasm. The structure of ribosomal proteins is stable. These proteins are recognized as ribonucleoprotein molecules and are significant for transporting a nucleolus by ribosomes through the non-ribosome-associated 5S rRNA cytoplasm [12].

Though there was no association between the level of expression and severity of DVT, compared to normal tissues, there was a variable expression of the gene of the ribosome protein after its interaction in colorectal cancers with a casein kinase II beta subunit. This gene is transcribed in intron with a small nuclear RNA gene, which is typical for encoded ribosomal proteins, in which many genes are spread throughout the genome; better rRNA arrangement is required for ribosome development [13]. However, 2 transcript alternates encoding the same protein have been observed in the gene of the ribosome protein [14].

Recent studies have also emphasized the importance of RP as novel suppressors of tumors, together with the role of RPL5 as a regulator of p53 [15-18]. According to these reports, RPL5 defects cause type 6 Diamond-Blackfan anemia (DBA6) and may also cause intrinsic non-regenerative hypoplastic anemia in initial childhood [19, 20].

RPL5 (L5) genes in intron six on chromosome 1p22, rs6604026 are linked to the threat of multiple sclerosis [21].

Through evolution, the functions of RPL5 have been highly preserved, which leads to bigger biological detections in research; the raised expression of RPL5 can be used as a marker for molecules in the early detection of thrombosis, which has been confirmed by former research on the causal relationship between the ribosomal protein (RPL5) and thromboembolism [22]. In addition, determination of whether RPL5 gene variants in Saudi DVT patents may differ from the normal control may result in the considerable association of this gene to the clinical situation and may be a diagnostic marker for DVT patients. Therefore, this study aimed to determine the association between single nucleotide polymorphisms in the ribosomal protein L5 gene and the risk of DVT in Saudi population.

MATERIALS AND METHODS

Study Setting and Design

The study was conducted at a university hospital, a four-story building with a capacity of 440 beds. Each floor has different rooms and represents a particular patient group. This case-control analysis included 98 patients registered between February 2019 and October 2019. All patients have been diagnosed with DVT. In addition, the study included 97 Saudi individuals (both male and females) with no known history of chronic illness or immunosuppressive conditions, and with age distribution similar to the patient group; these individuals were included in the control group.

The ethical clearance of the Institutional Review Board (IRB) was obtained from the Deanship of Scientific Research (IRB number: IRB-2019-03-188), and the hospital was granted permission to interview people and collect data and blood samples. After the investigator approached all patients registered with DVT, they were asked to enrol in the study and were explained the purpose of the study. Patients provided verbal and written informed consent, and data were collected using structured questionnaires to obtain demographic data. EDTA peripheral blood samples were collected from both the patients and controls and kept in a deep freezer at -80 °C prior to genetic analysis.

DNA Extraction and PCR

The frozen samples of EDTA blood were completely thawed and combined at room temperature for 10 min in a rotisserie shaker. DNA extraction was performed with a ReliaPrep™ Blood gDNA Miniprep System (Promega). DNA was taken out from the whole blood according to standard protocols, and Denovix/ND-1000 Nanodrop was used to test the DNA concentration. The RPL5 gene was observed in chromosome 1. The design and primers of PCR are established on the assembly of homo sapiens (RPL5) references NC 000001.11.

The PCR primers were designed to target regions in the RPL5 genes to screen for polymorphisms. PCR amplification was carried out using 25 ng of prepared DNA containing 2 µL of Template DNA, 15 µL of Taq PCR Master Mix (MOLECULE-ON ®), 9 µL of deionized water (dH2O), 2 µL of forwarding priming, and 2 µL of reverse priming. All reactions were conducted in 0.2-mL PCR tubes, which were gently mixed and tightly capped to prevent evaporation. The tubes were placed in a Swift™ Maxi thermal cycler, and the reaction was programmed according to the primer and DNA used. The temperature cycling conditions started by initial denaturation at 94 °C for 7 minutes, followed by amplification cycling for (35 cycles) starting with denaturation at 94 °C for 1 minute, annealing of the primer at 59 °C for 1 minute, extension at 72 °C for 1 minute, and final extension at 72 °C for 7 minutes [23]. After the amplification of DNA using specific primers, agarose gel electrophoresis was used to determine the size of PCR products and to make sure that DNA amplification was accomplished. The MOLEQULE-ON® PCR/Gel product purification kit was used to purify PCR products.

DNA Sequencing

Purified DNA samples were sent for automated DNA sequencing to the MYA trading company. Sanger sequencing was performed using an Applied Biosystems ABI 3730×L DNA analyzer (Hong Kong). The DNA sample of each participant was added to the tubes and mixed with DNA polymerase, primer, nucleotides of DNA (dTTP, dATP, dGTP, and dCTP), and four dideoxynucleosides, This mixture was heated to denature the DNA template and to separate DNA strands and then cooled to keep the primer bound to the single-stranded template. The temperature increased to allow DNA polymerase to synthesize new DNA starting from the primer. DNA polymerase continued to add nucleotides to the chain until the dideoxynucleoside was added. Thus, the strand was ended with dideoxynucleoside, and no additional nucleotides were added. This procedure was repeated for several cycles. The fragments were run through a gel matrix in a thin and long tube. This process is called capillary gel electrophoresis. Long fragments moved slowly through gel pores, while short fragments moved more quickly. At the end of the tube, each fragment crossed the finish line and was illuminated by a laser to detect the attached dye by a detector. The data registered by the detector contained a series of fluorescent peaks. Thus, the sequence of DNA was read in the chromatogram from these peaks. The chromatogram data was analyzed by a FinchTV DNA analyzer to view the DNA sequence of the patient. Then, the sequence was incorporated into Blast National Center of Biotechnology Information (https://rb.gy/eec44k) to relate nucleotide sequences to the reference sequence in the databank. Using the alliance graphics, the variant particulars were recognized and chosen depending on 1,000 genomes phase 3 and db SNP b153 v 2.

Statistical Analysis

Statistical analysis was performed using both the SPSS version 21 and Microsoft Excel software 2016. The descriptive statistics of genotypic data was analyzed. The frequency of Saudi DVT patients as well as age- and sex-related incidence was clarified. An independent t-test was used, and $p \leq 0.05$ was chosen as a cut-off for statistical significance. Pearson correlation analysis and the p-value of genotypic features were calculated to compare DVT patients and Saudi healthy individuals who participated in this study.

RESULTS

98 cases in total that were diagnosed with DVT were enrolled over one year. Their sex age ratio was male/female 66.7/57.4, and the mean age was 61.2 years old. The majority of the patients were self-identified and lacking the former history of DVT (60.2%). The majority of the patients were recently identified, i.e., within the past 5 years (73.5%), as shown in **Table 1**.

Table 1. Characteristics of the Saudi DVT patients

Characteristics	Cases (n = 98)	Controls (n = 97)	p-value
Age, M ± SD	61.2 ± 4.8	57.4 ± 6.2	0.0001
Sex, male/female	66.7/57.4	65.8/62.4	0.4878
Degree of relative, n (%)			
First	39 (39.8)	-	
Others	59 (60.2)	-	
Family history, n (%)			
Yes	39 (39.8)	-	
None	59 (60.2)	-	
Duration of DVT, n (%)			
0-5 years	72 (73.5)	-	
5-10 years	22 (22.4)	-	
>10 years	4 (4.1)	-	

Note. M: Mean & SD: Standard deviation

Table 2. Allele frequency of RPL5 genetic polymorphisms in DVT patients and comparison with the control subjects

db SNP b153 v 2	Alleles	n (%) Patients	n (%) Control	p-value
rs138979590	C	393 (91.4)	386 (88.5)	0.180**
	T	37 (8.6)	50 (11.5)	
rs558220259	G	306 (71.2)	171 (65.3)	0.000*
	A	124 (28.8)	91 (34.7)	
rs576892621	G	360 (72.0)	187 (64.5)	0.031**
	A	140 (28.0)	103 (35.5)	
rs182018447	A	232 (52.7)	220 (50.9)	0.540**
	G	208 (47.3)	216 (49.5)	
rs559377519	T	466 (89.6)	475 (89.3)	0.860*
	A	54 (10.4)	57 (10.7)	

Note. *p-values were calculated by Chi-square analyses; **p-values were calculated by the Fisher exact probability test; & differences were considered to be statistically significant at $p < 0.05$

Table 3. Genotype frequency of RPL5 genetic polymorphisms in DVT patients compared the control subjects

db SNP b153 v 2	GT	n (%) Patients	n (%) Control	UOR	p-value
rs138979590	C/C	186 (78.8)	152 (64.1)	Reference	
	C/T	42 (17.8)	80 (33.8)	0.43 (0.28-0.67)	0.0001*
	T/T	8 (3.4)	5 (2.1)	0.34 (0.11-1.16)	0.1398*
rs558220259	G/G	120 (42.7)	58 (31.2)	Reference	
	G/A	132 (47.0)	110 (59.1)	0.58 (0.39-0.88)	0.0087**
	A/A	29 (10.3)	18 (9.7)	1.78 (0.93-3.35)	0.0824**
rs576892621	G/G	142 (43.6)	66 (33.0)	Reference	
	G/A	152 (46.6)	110 (55.0)	0.64 (0.44-0.94)	0.0272**
	A/A	32 (9.8)	24 (12.0)	0.62 (0.34-1.13)	0.1524**
rs182018447	A/A	80 (27.4)	72 (24.5)	Reference	
	A/G	144 (49.3)	152 (51.7)	0.85 (0.58-1.26)	0.4849**
	G/G	68 (23.3)	70 (23.8)	0.87 (0.55-1.38)	0.6381**
rs559377519	T/T	212 (70.2)	218 (71.5)	Reference	
	T/A	84 (27.8)	78 (25.5)	1.12 (0.77-1.59)	0.644**
	A/A	6 (2.0)	9 (3.0)	0.69 (0.24-1.95)	0.602**

Note. GT: Genotype; UOR: Unadjusted odds ratio (95% confidence interval); *p-values were calculated by Chi-square analyses; **p-values were calculated by the Fisher exact probability test; & differences were statistically significant at $p < 0.05$

We sequenced the RPL5 gene in intron 6 from DVT patients with uncommon RPL5 gene expression arrangements in PCR analysis. 5 SNPs in the RPL5 gene were testified after sequencing, and each patient SNP was compared with the control to identify the association of DVT risk with the RPL5 gene in both subjects.

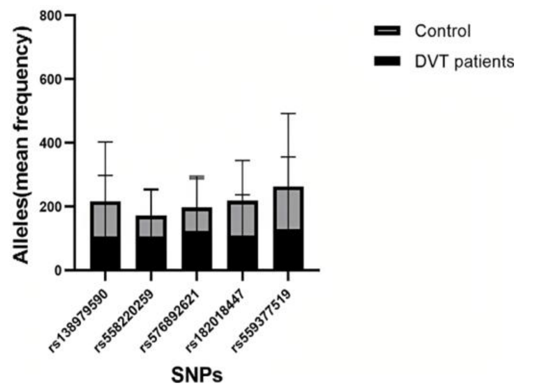

Figure 1. Mean allele's frequency of RPL5 gene SNPS in DVT Saudi patients and control, the alleles in both rs559377519 and rs138979590 were increased in patients and controls when compared with other SNPs (Source: Authors' own elaboration)

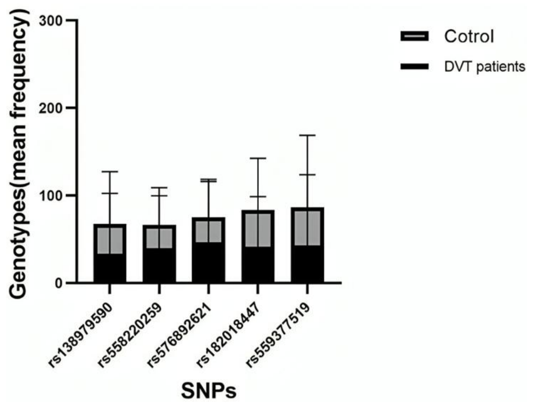

Figure 2. Mean genotype's frequency of RPL5 gene SNPS in DVT Saudi patients and control, the genotypes in both rs559377519 were increased in patients and controls compared to other SNPs (Source: Authors' own elaboration)

Two alleles showed significant difference between DVT patients and controls: RPL5 rs558220259 G allele ($p = 0.00$) and RPL5 rs576892621 G allele ($p = 0.031$) (**Table 2**).

Table 3 shows the genotype analyses. The results revealed that genotypes rs138979590 (C/T), rs558220259 (G/A), and rs576892621 (G/A) were statistically significantly associated with DVT patients ($p = 0.0001$, $p = 0.0087$, $p = 0.272$, respectively) compared with the control groups.

The frequency of allele SNPs (rs559377519 and rs13879590) and genotypes SNP rs559377519 were most common among DVT patients compared with other SNPs (**Figure 1** and **Figure 2**).

DISCUSSION

Ribosomes are dynamic to lifecycles and produce all proteins required to cultivate cells and tolerate them. A developed ribosome in eukaryotes comprises of 4 diverse ribosomal RNAs [1]. Current research revealed that RPL5 gene polymorphisms were associated with DVT. The allele distributions of two SNPs (rs558220259 and rs576892621) and genotype frequencies of three SNPs (rs138979590, rs558220259, and rs576892621) were significantly different between DVT patients and control subjects.

Our findings showed the existence of genotype association with the existence of DVT in Saudi participants. This finding settles with that in former research, which recognized that these genes were upregulated in cases with VTE [22]. Previous studies have identified ribosomes during platelet preparation. Specifically, the ribosomal protein RPS6 has been described as existing in circulating thrombocytes, exclusive cellular regulators of hemostasis, and thrombosis [24]. Thrombocytes back up the gathering of innate immune cells and endorse the construction of neutrophil extracellular traps, which contributes to the spread of DVT [25, 26].

Presently, limited studies are available on the association among these ribosomal protein family genes and thrombosis. Therefore, we guess that RPL5 and DVT might be narrowly related owing to their relationship with thrombocytes. In intron 6, the identified SNPs were significantly associated with DVT threat amongst Saudi patients. We didn't detect any noteworthy relationship with other SNPs, which might be because of observed OR and the number of DVT cases in the choice of the study sets, which might replicate alterations. Of memo, for RPL5 SNPs, this difference is pretty important, which shows a strong relationship with this pathology.

Our findings don't deliver any indication that these alternates are related with DVT, which also designates differential effects through the mechanisms of pathology, as has been detected with some SNPs. Though, new research proposes that the strong effects of RPL5 depletion on p53 induction can be credited to condensed global translation and not reducing solidity at p53. Therefore, in relations of biogenesis of ribosomal reactions, RPL5 seems to be the solitary RP mandatory for p53 induction, which harms 60S translation of ribosomal subunit to the similar grade as other important RPs [27]. Some RP transcripts alter cellular stages as a job of development, manufacture, and cancers [28].

Moreover, it is identified that numerous RPs have vital roles in numerous other cellular courses. In latest years, alterations in ribosomal proteins have been recognized in patients with several illnesses; these alterations might lead to structural abnormalities in people [29]. Hylomorphic alterations in RPL along with other RPs, leading to the disease of DBA6 [30]. Since most studies thus far have been limited to cancer cells, it is uncertain whether a decline in the ribosome content owing to the translation loss of a p53 checkpoint or the stimulation of an alternative p53-independent cell cycle are the fundamental mechanism for regulatory cell production and declining RPL5 stages [16].

The impairment of ribosome biogenesis backs to the stimulation of p53 and to the disruption of cell cycle tangled in DVT. RPL5 brings a p53 reaction, and the formerly described effects on p53 can be attributed to global translation inhibition. This reaction consequences in the hindering of G1, and an original block of G2/M is not detected when either subunit is disordered [16]. Therefore, the p53 induction mechanisms in DVT patients may be vital for RPL5, more than localization. Saudi DVT patients were defined to have numerous alternates of the RPL5 gene matched to the controls, which specified that the role of the RPL5 gene and its role in DVT might be significant for splicing or translational control. Current study, by concentrating on the coding intron, we might have overlooked possibly significant polymorphisms in controlling non-coding areas.

In summary, owing to the importance of understanding the genome, the gene analysis of RPL5 in chromosome 1 is of considerable interest; the large quantities of RPs, especially RPL5, allow obtaining their full description. The structures of RPL5 genes are more complicated. In 2001, the first full description of human ribosomal proteins has been published [28, 30]. Overall, our findings confirm the essential role of variants (rs138979590, rs558220259, and rs576892621) as a risk factor for DVT in the RPL5 gene. Nevertheless, the pattern of genetic association is complex, with multiple variants contributing differently across the DVT spectrum. Additional work will be required to confirm the unusual associations identified in this study and to recognize polymorphisms in non-coding regions that may contribute to the disease risk in Saudi patients, which may help to identify a new biomarker for the diagnosis and therapy of DVT. RPL5 may have the ability to act as DVT diagnosis and treatment targets. However, we need more genetic and experimental research on a larger sample size to confirm our results.

Author contributions: FH, WA, DKB, SSS, & FMA: validation; **FH & FA:** conceptualization and formal analysis; **AA, EA, ME, & AA:** methodology; **FH:** writing–original draft preparation, supervision, project administration, and funding acquisition; **AA:** investigation; & **SS & FA:** writing–review and editing. All authors have agreed with the results and conclusions.

Funding: This study was supported by the Deanship of Scientific Research, Imam Abdulrahman Bin Faisal University with grant number 2019-014-CAMS.

Acknowledgments: The authors would like to thank all research assistants at the King Fahad University Hospital, Al-Khobar medical staff who helped us during the conduction of this study.

Ethical statement: The authors stated that the study was approved by the Institutional Review Board of Deanship of Scientific Research at Imam Abdulrahman Bin Faisal University with approval number IRB-2019-03-188. Written informed consents were obtained from the participants.

AI statement: The authors stated that generative AI tools were used to assist in improving the English language clarity. All content was reviewed, edited, and verified by the authors to ensure accuracy and integrity.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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