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# Polymorphisms in FVL, prothrombin, and MTHFR genes in samples tested for thrombophilia in Saudi Arabia

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## ABSTRACT

**Background:** Thrombophilia is a multifactorial condition influenced by both genetic and acquired risk factors and plays a key role in the development of venous thromboembolism (VTE). The present study aims to assess the prevalence of thrombophilia-associated genetic variants—Factor V Leiden (FVL), Prothrombin G20210A, and MTHFR polymorphisms—in samples referred to Al Borg Diagnostic Laboratory, while also exploring gender differences and regional variations in their distribution.

**Methods:** The present study is a retrospective study conducted on 13,728 samples of Saudi individuals referred for thrombophilia screening at Alborg Diagnostics Laboratory (2014–2024). Genomic DNA was isolated from blood samples, and mutations were identified using Reverse Dot Blot Hybridization (RDBH)-based multiplex PCR. Statistical analysis was performed using SPSS (v21.0).

**Results:** Among 7,634 samples tested for FVL, 7.7% (n = 588) were positive, whereas only 2.9% (n = 94) of the 3,278 samples tested for Prothrombin G20210A carried mutations. In contrast, mutations in MTHFR were more common, with 32.6% (918 of 2,816) positive for the 677C>T variant and 55.8% (1,572 of 2,816) positive for the 1298A>C variant, making them the most frequent mutations identified in the cohort. Significant gender differences were observed for FVL and Prothrombin G20210A (p  T (p < 0.03).

**Conclusions:** The study highlights notable differences in mutation frequencies based on region and gender, underscoring their potential impact on thrombotic risk evaluation and the advancement of personalized medical approaches within the Saudi population.

**Keywords:** factor V Leiden, MTHFR, prothrombin, Saudi Arabia, thrombophilia

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## INTRODUCTION

Thrombophilia is a multifactorial disorder that encompasses both genetic and acquired risk factors, resulting in an imbalance between procoagulant and anticoagulant factors and thereby increasing the risk of thrombosis [1]. The interplay between genetic predisposition and environmental influences determines the likelihood of clinical symptoms. Thrombophilia is a major contributor to Venous thromboembolism (VTE), with hereditary factors contributing to 50-60% of VTE occurrence [2]. The most common causes of congenital thrombophilia are mutations in factor V Leiden (FVL), prothrombin G20210A, protein C, protein S, and antithrombin III (ATIII) deficiencies. These conditions increase people's risk of thrombotic events such as pulmonary embolism, arterial thrombosis, and deep vein thrombosis (DVT) [3].

Factor V Leiden (FVL) is the most common genetic cause of inherited thrombophilia [4]. Factor V is primarily synthesized in the liver and plays a critical role in the coagulation cascade. It is activated by thrombin, after which it functions to convert prothrombin into thrombin, thereby amplifying the clotting process. Under normal physiological conditions, activated protein C (APC) serves as a major anticoagulant by inactivating factor V. Thrombin, when bound to thrombomodulin on endothelial cells, shifts from a procoagulant to an anticoagulant

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role by activating protein C. Thus, the levels and function of protein C are vital in the negative feedback loop that limits excessive thrombin generation [5]. Factor V Leiden is an autosomal dominant genetic disorder characterized by incomplete penetrance, meaning that not all individuals carrying the mutation will manifest clinical symptoms. This condition, also referred to as factor V R506Q or factor V Arg506Gln, is caused by a single nucleotide substitution (guanine to adenine at position 1691) in the factor V gene. This results in the replacement of arginine with glutamine at amino acid position 506, a critical site for cleavage by activated protein C. The mutation disrupts the inactivation of factor V by APC, as the cleavage site is no longer functional. Consequently, the persistent activity of factor V promotes continued thrombin formation, significantly increasing the risk of thrombosis [5].

The Prothrombin G20210A mutation (FII G20210A) is recognized as the second most common genetic contributor to thrombophilia. This mutation is inherited in an autosomal dominant pattern and occurs in the 3′ untranslated region (3′ UTR) of the prothrombin gene (F2 gene), located on chromosome 11 [4,6]. This genetic alteration leads to increased production of prothrombin, a crucial protein in the blood coagulation pathway. Elevated prothrombin levels result in greater thrombin generation, which increases the risk of blood clot formation and contributes to a hypercoagulable state [4,6]. The prothrombin G20210A mutation occurs in approximately 2% of the general population in its heterozygous form. While homozygous cases are far less common, with just 70 documented by 2006, the mutation exhibits distinct ethnic patterns, showing higher prevalence in Southern Europeans and lower frequency in African and Asian populations [4].

Methylenetetrahydrofolate Reductase (MTHFR) is a crucial enzyme for folate metabolism and homocysteine conversion. The MTHFR gene is located on chromosome 1p36.22. A common genetic variant, C677T, reduces MTHFR's enzymatic activity and increases plasma homocysteine levels. The 677T allele is associated with thrombotic disorders, including venous thromboembolism and arterial thrombosis, and pregnancy-related complications [7]. Individuals with homozygous mutations have been found to have mild hyperhomocysteinemia. The 1298A>C (rs1801131) polymorphism is a single-nucleotide change that replaces glutamate (Glu) with alanine (Ala) at position 429 (E429A). Unlike the 677C>T variant, the 1298A>C mutation alone does not cause elevated homocysteine levels. However, when combined with heterozygosity for 677C>T, the enzyme activity is reduced to levels similar to those seen in 677C>T homozygotes. Both mutations can impair MTHFR function, potentially disrupting folate metabolism and the associated pathway [7].

Up to 10% of the population may be afflicted by one or more of the currently known inherited thrombophilias, making thrombophilia a common problem [8]. Compared to a healthy person of wild type, those who inherit a heterozygous mutation have a 5–10-fold increased risk of thrombosis, while those who inherit a homozygous mutation have a 50–100-fold increased risk [9]. The prevalence of thrombophilia varies among different ethnic groups in the general population [2,10]. Middle Eastern populations have one of the world's highest rates of Factor V Leiden. Mutations in the MTHFR and prothrombin genes differ depending on the population [10].

In Saudi Arabia, preliminary data from the Saudi Thrombosis and Familial Thrombophilia (S-TAFT) Registry report a high incidence of Thrombophilia and suggest regional differences in the incidence of thrombophilia-related gene variants within Saudi provinces [11]. The high incidence of thrombophilia highlights its clinical significance. Thus, this study aims to determine the prevalence of FVL, prothrombin G20210A, and MTHFR variants across Saudi regions, examine gender disparities, and investigate regional differences in the distribution of thrombophilia-related genetic variants within the Saudi population.

## METHODS

### Ethical considerations

This study has been approved by the Ethics Committee at Alborg Diagnostic Laboratory (approval no. 09/24).

### Study design

This retrospective study analyzed assay-level results from referred samples (n=13,728) tested at Al Borg Diagnostic Lab and processed between 2014 and 2024 in Saudi Arabia. Test selection was determined solely by the treating physician: Factor FV Leiden (FVL), Prothrombin G20210A (FII G20210A), and methylenetetrahydrofolate reductase (MTHFR 677C>T and MTHFR 1298A>C) The laboratory information system did not retain a persistent, study-linkable patient identifier across separate orders; therefore, analyses are reported per assay rather than per unique patient.

The inclusion criteria include Saudi individuals who have been referred to Alborg diagnostic laboratory for FVL, FII G20210A, MTHFR 677C>T, and MTHFR 1298A>C. Patients who do not meet the inclusion criteria and non-Saudi individuals were excluded.

### Techniques / instruments

Reverse Dot Blot Hybridization (RDBH)-based multiplex PCR (CVD strip Assay, Vienna Lab Diagnostics, Vienna, Austria) genotyping was used to identify polymorphic

variants of FVL, FII G20210A, and MTHFR 677C>T, and MTHFR 1298A>C. Genomic DNA was isolated from patient blood samples according to the commercial instructions using QIAamp blood mini kit (Qiagen, Hilden, Germany). Genetic variants were identified through PCR amplification of specific gene regions, followed by reverse hybridization on a test strip with allele-specific probes. Biotin-labeled PCR products will bind to these probes, and detection will be accomplished using a streptavidin-alkaline phosphatase conjugate and color substrates, allowing for visual confirmation of the alleles.

### Data collection method

The data were collected from existing medical records of patients who were followed at the Alborg Diagnostic Laboratory from January 2014 to 2024.

### Statistical analysis

Research data were statistically analyzed using SPSS (version 21.0). The data were expressed as counts and percentages. The chi-square test was used to assess significant differences between groups. Statistical significance was established at $p<0.05$.

## RESULTS

### Gender-based screening for thrombophilia

The study cohort consisted mainly of females (80.7%, n=11,083) compared to males (19.3%, n=2,645), with a mean age of 39.7 ± 9.9 years. Table 1 presents the number and percentage of male and female participants tested for three thrombophilia-associated genetic variants: Factor V Leiden (FVL), MTHFR, and Prothrombin G20210A (FII G20210A). Approximately four times more females than males were tested for thrombophilia-associated variants. Most Factor V Leiden (75.9%), MTHFR (88.5%), and Prothrombin G20210A (85.2%) tests were conducted in females.

### Genotyping of thrombophilia-associated genetic variants in the sample population

Figure 1 demonstrates genotype distributions across thrombophilia-associated genes. The FVL and Prothrombin G20210A genes were predominantly wild-type (92.3% and 97.1%, respectively), with relatively few heterozygous or homozygous mutants. In contrast, MTHFR 677C>T showed 32.6% combined mutant genotypes, while MTHFR 1298A>C had the highest overall mutation frequency, with over half of participants carrying heterozygous (43.1%) or homozygous (12.7%) variants.

Thrombophilia gene genotyping among genders. The genotypic analysis revealed notable gender differences in thrombophilia-related variants (Figure 2). Factor V Leiden (FVL) mutations were significantly more common in males than females, both in heterozygous (13.4% vs. 4.4%) and homozygous (2.9% vs. 0.6%) forms, while wild-type alleles predominated in females ($p<0.001$). For MTHFR 677C>T and MTHFR 1298A>C variants, genotype distributions showed minor gender variations, with heterozygous and homozygous mutations slightly higher in females for 1298A>C, and homozygous 677C>T mutations more frequent in males. However, these differences were not statistically significant ($p>0.05$). In the Prothrombin gene, both heterozygous (5.2% vs. 2.1%) and homozygous (0.8% vs. 0.2%) mutations were significantly more frequent in males, whereas wild-type alleles were more common in females ($p<0.001$).

### Distribution of genotyping of thrombophilia among Saudi provinces

The distribution of thrombophilia-related genes was analyzed using statistical testing, revealing significant regional variation ($p<0.05$) in the Factor V and MTHFR 677C>T genotypes across different provinces in Saudi Arabia (as shown in Tables 2 and 3, respectively). In contrast, no statistically significant differences were observed in the distribution of MTHFR 1298A>C and Prothrombin genotypes among the regions.

The regional distribution of FVL genotypes showed notable variation across Saudi Arabia. The Western Area had the highest frequency of the heterozygous mutation at 8.8%, followed closely by the Central Region at 7.8%. Homozygous mutants were most frequent in the Central Region (1.4%) and Western Area (1.3%), while the Eastern Area, Northern Area, and Southern Area showed lower frequencies, ranging from 0.6% to 1.5%. The wild-type genotype was most prevalent in the Southern Area (96.7%) and Eastern Area (94.9%), and slightly lower in the Western (89.9%) and Central (90.8%) regions.

Regional analysis of Factor V Leiden (FVL) genotypes in Saudi Arabia showed the highest heterozygous frequencies in the Western (8.8%) and Central (7.8%) regions,

**Table 1. Distribution of thrombophilia-associated genes in the referred samples by gender**

| Gender | Thrombophilia-Associated Genes | | | Total |
|---|---|---|---|---|
| | FVL | MTHFR | FII G20210A | |
| Male | 1,836 (24.1%) | 325 (11.5%) | 484 (14.8%) | 2,645 (19.3%) |
| Female | 5,798 (75.9%) | 2,491 (88.5%) | 2,794 (85.2%) | 11,083 (80.7%) |
| Total | 7,634 (100.0%) | 2,816 (100.0%) | 3,278 (100.0%) | 13,728 (100.0%) |

Table 2. Distribution of Factor V Leiden (FVL) genotyping among Saudi provinces

| Area | | FVL | | | Total | *p* value |
|---|---|---|---|---|---|---|
| | | Mutant (heterozygous) | Mutant (homozygous) | Normal (wild type) | | |
| Central Region | Count | 115 | 21 | 1,335 | 1,471 | < 0.001 |
| | % | 7.8% | 1.4% | 90.8% | 100.0% | |
| Eastern Area | Count | 92 | 21 | 2,103 | 2,216 | |
| | % | 4.2% | 0.95% | 94.9% | 100.0% | |
| Northern area | Count | 2 | 1 | 65 | 68 | |
| | % | 2.9% | 1.5% | 95.6% | 100.0% | |
| Southern Area | Count | 22 | 5 | 790 | 817 | |
| | % | 2.7% | 0.6% | 96.7% | 100.0% | |
| Western Area | Count | 269 | 40 | 2,753 | 3,062 | |
| | % | 8.8% | 1.3% | 89.9% | 100.0% | |
| Total | Count | 500 | 88 | 7,046 | 7,634 | |
| | % | 6.5% | 1.2% | 92.3% | 100.0% | |

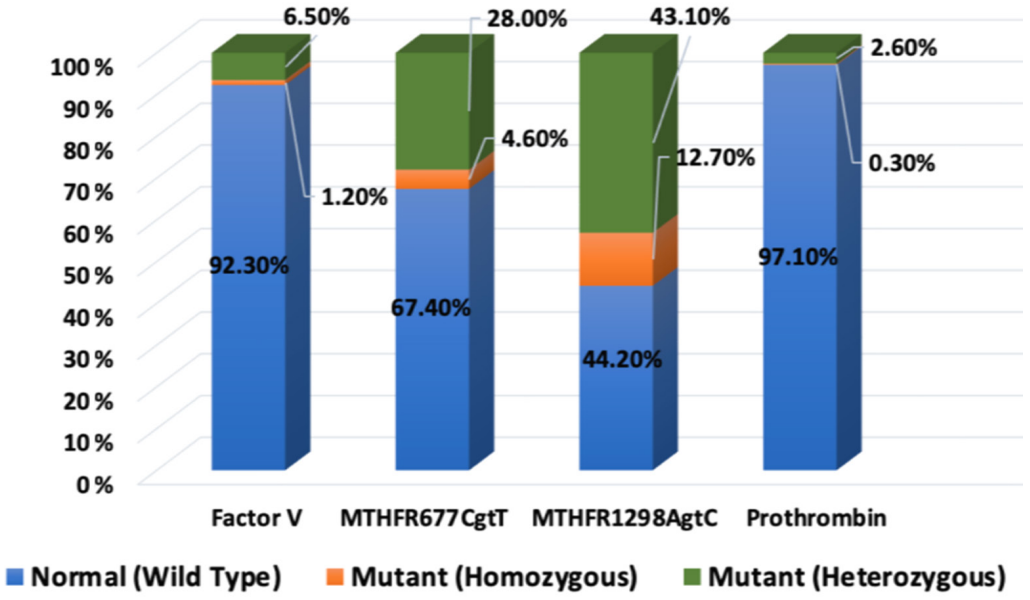


Figure 1. Genotyping of thrombophilia-associated genetic variants in the sample population

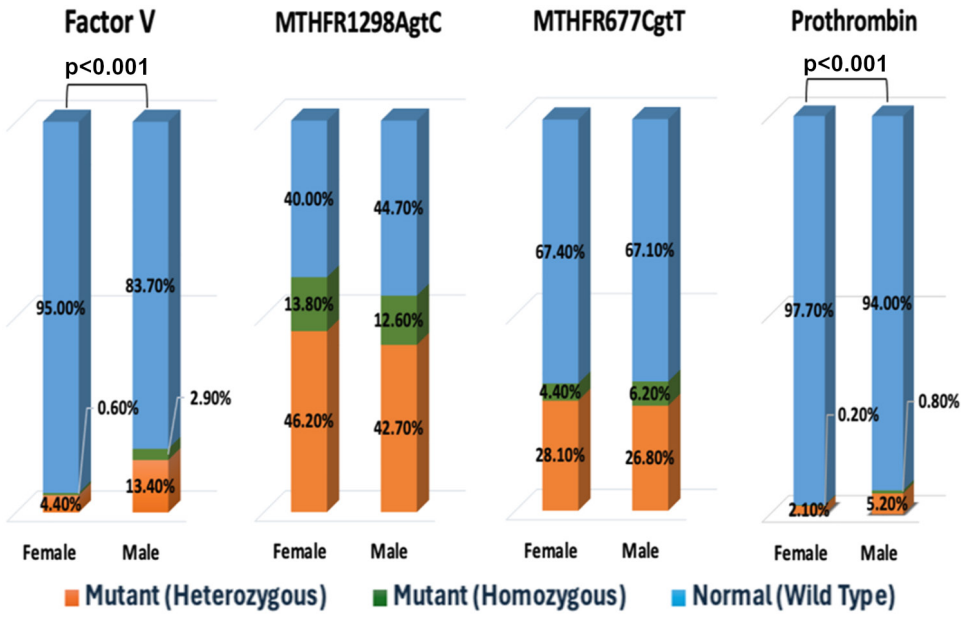


Figure 2. Thrombophilia genes genotyping among genders

**Table 3. Distribution of MTHFR 677C>T genotyping among Saudi provinces**

| Area | | MTHFR 677C>T | | | Total | *p* value |
|---|---|---|---|---|---|---|
| | | Mutant (heterozygous) | Mutant (homozygous) | Normal (wild type) | | |
| Central Region | Count | 101 | 9 | 204 | 314 | 0.03 |
| | % | 32.2% | 2.9% | 65.0% | 100.0% | |
| Eastern Area | Count | 380 | 57 | 969 | 1,406 | |
| | % | 27.0% | 4.1% | 68.9% | 100.0% | |
| Northern area | Count | 6 | 1 | 18 | 25 | |
| | % | 24.0% | 4.0% | 72.0% | 100.0% | |
| Southern Area | Count | 26 | 5 | 96 | 127 | |
| | % | 20.5% | 3.9% | 75.6% | 100.0% | |
| Western Area | Count | 275 | 58 | 611 | 944 | |
| | % | 29.1% | 6.1% | 64.7% | 100.0% | |
| Total | Count | 788 | 130 | 1,898 | 2,816 | |
| | % | 28.0% | 4.6% | 67.4% | 100.0% | |

while the Eastern, Northern, and Southern regions had lower rates (2.7%–4.2%). Homozygous mutants were rare, with the highest prevalence in the Northern (1.5%) and Central (1.4%) regions. Wild-type alleles predominated in the Southern (96.7%) and Northern (95.6%) regions but were less common in the Western and Central regions, consistent with their higher mutation rates. These regional differences were statistically significant ($p<0.001$) (Table 2).

Regional distribution of MTHFR 677C>T genotypes in Saudi Arabia showed the highest heterozygous prevalence in the Central (32.2%) and Western (29.1%) regions, with lower rates in the Northern (24.0%) and Southern (20.5%) regions. Homozygous mutations were most frequent in the Western (6.1%) and Eastern (4.1%) regions but least common in the Central (2.9%). Wild-type alleles predominated in the Southern (75.6%) and Northern (72.0%) regions, while being less frequent in the Western and Central regions. These regional differences were statistically significant ($p=0.03$) (Table 3).

## DISCUSSION

The present study comprehensively analyzes the prevalence and distribution of thrombophilia-associated genetic variants, including Factor V Leiden (FVL), MTHFR (677C>T and 1298A>C), and Prothrombin G20210A (FII G20210A) across different regions of Saudi Arabia. While Factor V Leiden (FVL) is recognized as the most prevalent hereditary thrombophilia, the frequency of these genetic mutations varies across different ethnic groups. It has been reported that FVL is more common in Caucasian populations, while rare or absent in African, Asian, and some Arab populations [12]. Alfeel's study (2016) supported the regional distribution pattern of thrombophilia genes, which underscores the importance of considering the unique genetic makeup of each population when evaluating the risk of inherited thrombosis [13].

In Saudi Arabia, it has previously been reported that the prevalence of FVL among healthy individuals is 1.3% [11]. However, this study showed that 7.7% of samples tested for FVL were positive (6.5% heterozygous and 1.2% homozygous). This value is higher than that reported in the other two recent studies [14,15]. The higher current frequencies may be attributed to the large sample size and the fact that the testing was conducted among a high-risk group presenting with clinical signs of thrombosis.

Also, we found that the frequency of the heterozygous allele was much higher than the homozygous allele (6.5% vs 1.2%). This trend has been documented in several previous studies. For instance, [14] showed a prevalence of 5.9% positive FVL in Saudi Arabia, with 5.5% being heterozygous and 0.39% homozygous. Moreover, Maalej et al. (2011) reported that the prevalence of the FVL mutation in southern Tunisia was 13.6%, comprising 12.4% heterozygous and 1.2% homozygous cases [16].

The distribution of FVL varied significantly across different regions of Saudi Arabia, with a notably higher prevalence of the heterozygous FVL genotype in the Western (8.8%) and Central (7.8%) regions, while the Eastern, Northern, and Southern provinces exhibited lower frequencies. The homozygous mutant genotype was rare in all regions. FVL was found to be common (14.9%) among Saudi women who had experienced miscarriage [17]. However, this study found that a significantly higher prevalence of positive FVL was observed in males compared to females. Several studies have reported a higher prevalence of FVL mutations in males. A case-control study observed that activated protein C resistance, primarily due to the FVL mutation, was 2.3 times more likely in men than in women [18]. In addition, Tzoran et al. (2017) found that among patients with VTE, men with FVL had a six-fold higher rate of VTE recurrences during anticoagulant therapy compared to major bleeds, and a three-fold higher rate of deep vein thrombosis (DVT) recurrences after discontinuing anticoagulation [19].

Regarding the Prothrombin G20210A mutation, our findings showed that 2.9% of the tested samples were positive, with 2.6% being heterozygous and 0.3% ho-

mozygous. These results are consistent with those who reported a 2.9% prevalence [14], suggesting that this mutation is relatively rare in Saudi Arabia, especially when compared to the higher prevalence observed in European populations [20]. Similar to FVL, FII G20210A was found in this study with a higher frequency in males than females (2.1% heterozygous and 0.2% homozygous in females vs 5.2% heterozygous and 0.8% homozygous in males). However, a study conducted by Rahimi (2008) among the Kurdish population reported a similar distribution of this mutation across sexes [21].

MTHFR 677C>T and 1298A>C polymorphisms also vary significantly across different ethnic and geographic populations, likely due to genetic and environmental influences. Our study found that the MTHFR mutation had the highest frequency among the tested thrombophilia genes. However, the MTHFR 677C>T mutation is considered relatively rare in the Saudi population compared to other populations [22]. The MTHFR 1298A>C variant was much more frequent and may have a greater clinical role in Saudi patients. Alhumaydhi et al. (2021) suggested a potential association between the 677C>T mutation and male fertility issues, highlighting a possible protective role of folic acid supplementation [23]. Also, a study conducted in the Qassim region involving 273 healthy Saudi adults reported allele frequencies of 18.7% for MTHFR 677C>T and 29.45% for MTHFR 1298A>C [24]. Another study focusing on Saudi children (aged 6–12 years) from the Western Province found even higher frequencies, 36.2% for MTHFR 677C>T and 91.3% for MTHFR 1298A>C [25]. These findings confirm that the MTHFR 1298A>C mutation is more prevalent than the 677C>T mutation in the Saudi population, with notable regional variations. Eloualid et al. (2012) in their study supported the association between MTHFR gene variants and unexplained severe male infertility [26]. The study reported that the homozygous 1298A>C genotype was significantly more frequent among men with severe oligozoospermia compared to the control group, indicating a possible association between this variant and male infertility [26]. It is worth noting that this disparity in the distribution of genetic mutations may be related to demographic and cultural factors, most notably the high rate of consanguineous marriage in Saudi society, a factor also noted by Madkhaly et al. (2021) as a potential factor in promoting the genetic transmission of these mutations [14]. Therefore, this study highlights the need to implement proactive genetic screening programs, particularly in regions with high rates of consanguineous marriage, to mitigate the health risks linked to hereditary thrombosis and fertility-related disorders.

This study has several important limitations. First, its retrospective design, based on pre-existing medical records, may introduce selection bias and result in incomplete data. Second, because patient-level deduplication was not feasible, we could not determine how many assays were performed on the same individual or how many patients received multiple tests; therefore, all reported counts and genotype frequencies are presented at the assay level. Additionally, the genetic analysis was limited to a narrow set of mutations—Factor V Leiden, Prothrombin G20210A, and MTHFR variants—excluding other potentially relevant inherited thrombophilia markers and acquired risk factors that could provide a more comprehensive assessment of thrombotic risk.

## CONCLUSIONS

This study provides a comprehensive analysis of thrombophilia-associated genetic variants (Factor V Leiden, Prothrombin G20210A, and MTHFR mutations) in Saudi Arabia. The study found that approximately four times more females were tested than males. MTHFR 1298A>C and MTHFR 677C>T were the most frequently observed mutated variants. Factor V Leiden and Prothrombin G20210A mutations exhibited significant gender differences ($p < 0.001$), with a higher prevalence in males. Additionally, significant regional variations were detected in the distribution of FVL variants and MTHFR 677C>T ($p < 0.03$). These findings underscore the importance of population-specific genetic screening, particularly in regions with high rates of consanguineous marriage, to better identify individuals at risk of thrombosis and fertility-related complications.

## ABBREVIATIONS

APC – activated protein C
ATIII – antithrombin III
FVL – factor V Leiden
MTHFR – methylenetetrahydrofolate reductase
PC – protein C
PCR – polymerase chain reaction
PS – protein S
RDBH – reverse dot blot hybridization
S-TAFT – Saudi Thrombosis and Familial Thrombophilia
VTE – venous thromboembolism

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## AUTHORS' CONTRIBUTION

HMA: conceptualization, resources, writing (review and editing)

AA: methodology, data collection, writing (original draft)

RA: methodology, data collection, writing (original draft)

MA: writing (review and editing)

AFG: formal analysis, data management

SA: data curation, writing (original draft)

AAA: data curation, writing (original draft)

HA: data curation, writing (original draft)

EFA: formal analysis, data management

HME: resources, writing (review and editing)

## CONFLICT OF INTEREST

None to declare.

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