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Polymorphisms in thrombophilic genes are associated with deep venous thromboembolism in an Iranian population

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ABSTRACT

It has been revealed that the inherited thrombophilia increases the risk of thrombosis in the venous system. To study the association of factor V G1691A, factor V HR2 (4070A/G), prothrombin G20210A, and PAI-1 (−675 I/D, 5G/4G) polymorphisms with deep venous thromboembolism (DVT), these polymorphisms were investigated.

A total of 193 patients who presented clinical symptoms of deep venous thromboembolism including 103 men and 90 women, and 500 healthy individuals without both personal and family histories of thromboembolic disorders including 275 men and 225 women were recruited into the study. Genotyping was carried out using the amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) technique.

Our results showed that the genotype distribution for FV (G1691A and A4070G) and PAI-1 4G/5G polymorphisms in DVT patients were significantly higher than healthy control ($P < 0.05$). Also, the mutant allele frequencies for all studied polymorphisms differed significantly between the case and control groups ($P < 0.05$).

We concluded that the prevalence of FV (G1691A and A4070G) and PAI-1 4G/5G polymorphisms increased the risk of DVT occurrence in subjects. These findings provide additional evidence to support the

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hypothesis that thrombophilic gene polymorphisms are involved in vascular thromboembolism.

Introduction

Deep venous thromboembolism (DVT) is a major health problem as a result of thrombosis in the deep venous of the legs (Lopez et al., 2004). The annual incidence of DVT has been estimated between 0.1 and 0.2% of the adult population (Heit, 2006). DVT is a complicated and multi-factorial disorder which can be caused by acquired and genetic risk factors. Acquired risk factors include age, surgery, major trauma, hormone therapy, pregnancy, prolonged immobilization, plaster cast, and some types of cancer that can predispose an individual to an increased risk for DVT (Franco and Reitsma, 2001; Smalberg et al., 2011). According to the results of family and twin studies, genetic factors account for nearly 60% of the risk for DVT (Rahimi et al., 2010).

Three major molecular mechanisms which effectively contribute to DVT are venous stasis, hypercoagulability, and blood vessel wall changes (Lopez et al., 2004; Previtali et al., 2011). Hypercoagulability states promoting thrombosis, collectively termed "thrombophilias", may be inherited or acquired, and approximately in 40% of cases are inherited (Coulam et al., 2008). There is much evidence that inherited thrombophilia plays a major role in thrombosis development. To date, several thrombophilic gene polymorphisms have been identified that are involved in the pathogenesis of thromboembolic disorders. Activated protein C resistance (APCR) due to the factor V (FV) G1691A polymorphism and the G20210A polymorphism in the prothrombin gene are well-characterized genetic variants causing thrombophilia. The methylentetrahydrofolate reductase (MTHFR) C677T polymorphism which causes hyperhomocysteinemia has been also considered to be a risk factor for thromboembolism (Sykes et al., 2000). Nevertheless, these genetic variants only explain a fraction of all thromboembolic events. Therefore, it seems that there should be other genetic variants that are also involved in clot formation. Lunghi et al. (1996) have reported novel polymorphisms in the factor V gene. The G4070A polymorphism in FV gene leads to an amino acid substitution His to Arg at position 1299. This polymorphism which is marked by the HR2 haplotype is associated with an increased risk for thromboembolic disease (Alhenc-Gelas et al., 1999). Additionally, previous studies have reported that the increases in plasminogen activator inhibitor-1 (PAI-1) serum level could lead to a thrombotic tendency (Francis, 2002; Sartori et al., 2003; Tsantes et al., 2007). The PAI-1 (−675 I/D, 5G/4G) polymorphism affects the binding of nuclear proteins involved in the regulation of PAI-1 gene transcription. The 4G allele appears to bind only an enhancer, whereas the 5G allele binds both an enhancer and a suppressor. So, the 4G allele is associated with higher rates of PAI-1 synthesis and thromboembolism (Francis, 2002).

This study was design to determine the prevalence of FV G1691A, FV A4070G, prothrombin G20210A and PAI-1 (−675 I/D, 5G/4G) polymorphisms in patients with DVT and healthy control, and to address the question "whether these polymorphisms are associated with DVT" by examining a large study population.

Table 1
The mean and range of age in all studied groups.

	Mean age ± SD (years)	Range (years)
Case group (n = 193)	46.18 ± 4.72	38–57
Control group (n = 500)	46.27 ± 5.82	36–59
Men of the case group (n = 103)	45.38 ± 4.44	38–54
Women of the case group (n = 90)	47.10 ± 4.89	39–57
Men of the control group (n = 275)	45.79 ± 6.23	36–59
Women of the control group (n = 225)	46.85 ± 5.23	37–58

Abbreviation: SD, standard deviation.