

## Full Length Article

## Prothrombotic genotypes and risk of venous thromboembolism in cancer

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## A B S T R A C T

Venous thromboembolism (VTE) is a common and potentially life-threatening complication in cancer. Patients with cancer are at a higher risk of VTE-related complications such as major bleeding during anticoagulant treatment, recurrence and mortality. Therefore, it is important to identify cancer patients with high risk of VTE in order to implement targeted prevention to those with a favorable benefit-to-harm ratio for thromboprophylaxis. VTE is strongly heritable, and during the last decades, several prothrombotic genotypes associated with VTE-risk have been identified. However, most of these studies were conducted in non-cancer patients, and the role of prothrombotic genotypes in cancer-related VTE is scarcely studied. In this review, we summarize current knowledge on the role of prothrombotic genotypes in cancer-related VTE, with particular focus on factor V Leiden, the prothrombin G20210A mutation and polymorphisms in the ABO gene. In general, many of the studies were small and performed in selected cancer populations, and they showed somewhat diverging results. Results from recent, larger, studies indicated that there is an association between these prothrombotic genotypes and cancer-related VTE. However, their predictive capability has not been assessed and the clinical implications are yet unclear. Future research should be conducted in larger cancer patient populations, and should be extended to include recently identified prothrombotic genotypes and assess the predictive value of genetic risk scores.

## 1. Introduction

Venous thromboembolism (VTE) is a frequent and severe complication of cancer, and the incidence of cancer-related VTE is increasing [1,2]. Compared to cancer-free subjects, subjects with cancer are at a four- to sevenfold increased risk of VTE [3,4], and about 15% of all cancer patients develop symptomatic VTE during the course of their disease [5]. Clinical consequences of VTE, including recurrence, post-thrombotic syndrome and anticoagulant-related bleeding, occur more often in cancer patients [6–8], and the risk of death following a VTE is threefold higher in cancer patients than in those without [9,10]. Despite the high risk of VTE in cancer, international guidelines do not recommend routine prophylactic anticoagulation to ambulatory cancer patients without additional risk factors due to the uncertain benefit-to-harm ratio [11–13].

Thrombophilia describes an abnormality of blood coagulation that increases the risk of thrombosis. The term thrombophilia was first introduced into scientific literature in 1937, when Kaare Nygaard and George Brown used the term “essential thrombophilia” in a report on five patients with arterial vascular disease [14]. Later, in 1965 Olav Egeberg described a Norwegian family with familial aggregation of

symptomatic venous thrombi at early age and established the clinical connection between thrombophilia and heritability (antithrombin deficiency) of VTE [15]. VTE is strongly heritable, and a family history of VTE is associated with a two- to threefold increased risk of VTE [16,17]. Further, family and twin studies estimate that 50–60% of the variation in susceptibility to VTE can be attributed to genetic factors [18,19]. During the last decade, genome-wide studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) associated with VTE (Table 1) [20–24]. The majority of these SNPs are relatively common in the population with risk allele frequencies ranging from 0.02 to 0.88, but they have a modest effect on VTE risk with relative risks ranging between 1.1 and 3.0 [25].

Several risk factors for VTE have been identified among cancer patients. These can broadly be stratified into patient-, cancer- and treatment-related factors (Fig. 1). VTE is a multicausal disease, which often occur as the result of an accumulation of several risk factors [26]. Although major advances during the last decades have increased our understanding of the role of genetics on the risk of VTE [27], the role of pro-thrombotic genotypes in the complex interplay of risk factors for cancer-related is not yet well established, as only a few of these genotypes have been studied in cancer cohorts.

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**Table 1**  
Known prothrombotic single nucleotide polymorphisms [27,96].

Gene	Site	Phenotype	Frequency	VTE OR
Genes associated with VTE identified before GWAS				
F2	rs1799963	VTE	0.02	2.50
F5	rs6025	VTE	0.05	3.00
FGG	rs2066865	VTE	0.25	1.47
ABO	rs8176719	VTE	0.3	1.50
PROC	Multiple	VTE	rare	~10
PROS1	Multiple	VTE	rare	~10
SERPINC1	Multiple	VTE	rare	~10
Novel SNPs associated with VTE identified by GWAS				
VWF	rs1063856	Increased vWF	0.37	1.15
STXBP5	rs1039084	Increased vWF	0.46	1.11
GP6	rs1613662	Increased platelet function	0.82	1.15
F11	rs2289252	Increased FXI	0.41	1.35
F11	rs2036914	Increased FXI	0.52	1.35
C4BPB/C4BPA	rs3813948	Increased C4BP	0.08	1.18
KNG1	rs710446	Increased aPTT	0.45	1.2
SERPINC1	rs2227589	Decreased antithrombin	0.10	1.29
TSPAN15	rs78707713	Unknown	0.88	1.28

The influence of prothrombotic genotypes on the risk of VTE among cancer patients may be illustrated using the thrombosis potential model (Fig. 2) [26]. The thrombosis potential model demonstrates how several risk factors must be present simultaneously to exceed the thrombosis threshold leading to a VTE event. Alone, inherited risk factors may only mildly increase the risk of VTE. However, in the presence of cancer, prothrombotic genotypes may increase the thrombosis potential enough for a VTE event to occur (Fig. 2). Several cancer treatments like surgery, chemotherapy, and central venous catheters are well-established risk factors for VTE, and will further contribute to increase the thrombosis potential. These treatment-related factors and their complications (e.g. acute infections, hospitalizations etc.) may explain why there is a considerable rise in the incidence of VTE in the initial months following a cancer diagnosis, particularly in subjects with prothrombotic polymorphisms.

Prothrombotic genotypes may be attractive candidates as biomarkers of VTE risk in cancer patients. Genetic markers are fixed, they only need to be measured once, and they are not influenced by the disease, its interventions or complications. The aim of this review is to present the current knowledge on the impact of established

prothrombotic genotypes on the risk of cancer-related VTE.

The PubMed database was searched for articles on the relationship between cancer, prothrombotic genotypes and incident VTE. The following text-words and MeSH headings were combined: (“venous thromboembolism”, “venous thrombosis”, “deep vein thrombosis”, “pulmonary embolism”), (“neoplasm”, “cancer”, “malignancy”,) and (“genetic”, “single nucleotide polymorphism”, “genotype”, “gene”, “genetic”, “inherited”, “factor V Leiden”, “prothrombin G20210A”, “ABO”). Additional articles were identified by following PubMed links and by cross-referencing from the reference list of the articles retrieved.

## 2. Factor V Leiden

Factor V plays an important role in the coagulation cascade. Although not enzymatically active, it functions as a cofactor in the conversion of prothrombin to thrombin and promotes the degradation of activated factor VIII [28,29]. Factor V Leiden (FVL) is a single point gain-of-function mutation, where arginine is replaced by glutamine at position 506 [30]. This mutation results in attenuated down-regulation of activated factor V by activated protein C (APC), and in abnormal factor VIII degradation by APC [31,32]. FVL is present in 3–7% of the European population, is very rare in Asian and African populations, and known to increase the VTE risk two to fourfold [33,34].

Several studies have investigated the role of FVL in cancer-related VTE [35–50] (Table 2). Several studies reported no association between FVL and VTE in unselected [45,48], gynecological [46], pediatric [50], breast [38,41] and gastrointestinal cancers [38,51], as well as in acute promyelocytic leukemia [49]. It is important to note, however, that these were predominately small studies, with the size of the study populations ranging from 67 to 281 patients.

In more recent years, larger studies have reported an increased risk of cancer-related VTE in patients with the FVL mutation. In the Multiple Environmental and Genetic Assessment (MEGA) study, a large case-control study, the risk of VTE was threefold higher in subjects with FVL, fivefold higher in patients with cancer and 12-fold higher in patients with both FVL and cancer [42]. Similarly, in an Austrian cohort of 982 patients with cancer, Pabinger and colleagues reported a twofold higher risk of VTE in patients with the FVL mutation, and the one-year probability of developing a VTE was 15% in those with and 7.3% in those without FVL [44]. In a case-cohort derived from the Tromsø Study, a large population-based cohort, heterozygosity for FVL was associated

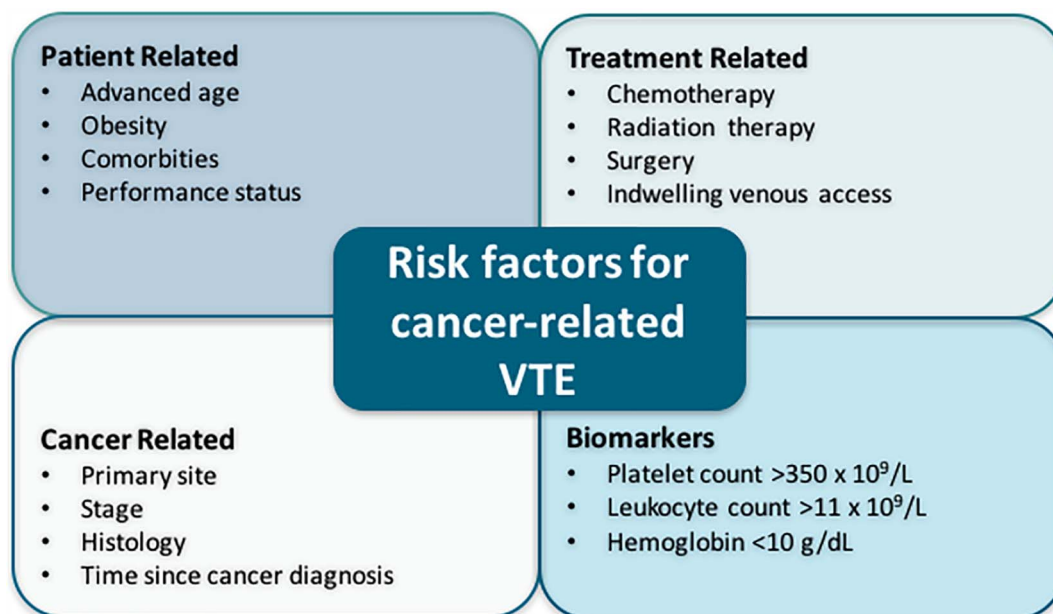


Fig. 1. Risk stratification for cancer-related VTE [2,3,6,42,86].

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