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Fibrinogen gamma gene *rs2066865* and risk of cancer-related venous thromboembolism

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ABSTRACT

Venous thromboembolism (VTE) is a frequent complication in patients with cancer. Homozygous carriers of the fibrinogen gamma gene (*FGG*) *rs2066865* have a moderately increased risk of VTE, but the effect of the *FGG* variant in cancer is unknown. We aimed to investigate the effect of the *FGG* variant and active cancer on the risk of VTE. Cases with incident VTE (n=640) and a randomly selected age-weighted sub-cohort (n=3,734) were derived from a population-based cohort (the Tromsø study). Cox-regression was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for VTE according to categories of cancer and *FGG*. In those without cancer, homozygosity at the *FGG* variant was associated with a 70% (HR 1.7, 95% CI: 1.2-2.3) increased risk of VTE compared to non-carriers. Cancer patients homozygous for the *FGG* variant had a two-fold (HR 2.0, 95% CI: 1.1-3.6) higher risk of VTE than cancer patients without the variant. Moreover, the six-months cumulative incidence of VTE among cancer patients was 6.4% (95% CI: 3.5-11.6) in homozygous carriers of *FGG* and 3.1% (95% CI: 2.3-4.7) in those without risk alleles. A synergistic effect was observed between *rs2066865* and active cancer on the risk of VTE (synergy index: 1.81, 95% CI: 1.02-3.21, attributable proportion: 0.43, 95% CI: 0.11-0.74). In conclusion, homozygosity at the *FGG* variant and active cancer yielded a synergistic effect on the risk of VTE.

Introduction

Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease associated with substantial short- and long-term morbidity and mortality.^{1,2} The incidence of VTE is 1-2 in 1,000 people/ year, and it increases steeply with age.³ Malignant disease is associated with a four- to seven-fold increased risk of VTE, and 20-25% of all first lifetime VTE-events are cancer-related.^{4,5} VTE, particularly in cancer, leads to prolonged and more frequent hospitalizations, and has a substantial impact on quality of life.^{6,7} Complications of VTE, such as recurrence, post-thrombotic syndrome and treatment-related bleeding, occur more frequently in cancer patients,^{6,8,9} and the risk of death is higher in cancer patients with than without VTE.^{10,11}

Family and twin studies suggest that VTE is highly heritable, and likely results from an interplay between inherited and environmental factors.^{12,13} Fibrinogen, the precursor of fibrin, is an essential component in the final stage of the coagulation cascade. The fibrinogen molecule has three subunits called A α , B β and γ , which occur in pairs for a total number of six subunits. The γ chain, transcribed from the

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fibrinogen gamma gene (*FGG*) located on chromosome 4, has two isoforms, γA and γ' . In the Leiden Thrombophilia Study, the *FGG* *rs2066865* single nucleotide polymorphism (SNP) was first proposed as a risk factor for VTE by reducing fibrinogen γ' levels.¹⁴ Several later genotyping^{15,16} and genome-wide association studies (GWAS)^{17,18} confirmed an association between *rs2066865* and VTE risk, whereas two cohort studies found no significant association.^{19,20} In a recent meta-analysis including seven studies, *rs2066865* was associated with an increased risk of VTE (OR 1.61, 95% CI: 1.34-1.93).²¹

The majority of the genetic studies have excluded individuals with cancer-related thrombosis. However, as prothrombotic genotypes are fixed, and not influenced by disease, interventions and complications, they may be attractive candidates as biomarkers of VTE risk in cancer patients. Recent studies have suggested that interactions between cancer and other prothrombotic genotypes (factor V variants *rs6025* and *rs4524* and prothrombin *G20210A*) have synergistic effects on the risk of VTE.²²⁻²⁵ To the best of our knowledge, no study has investigated the impact of *rs2066865* on the risk of VTE in cancer patients. Therefore, we aimed to investigate the joint effect of *rs2066865* and active cancer on the absolute and relative risks of VTE in a population-based case-cohort.

Methods

Study population

The Tromsø Study is a single-center population-based cohort, following residents of the municipality of Tromsø, Norway, with repeated health surveys. The case-cohort was derived from the fourth survey (Tromsø 4), which included 27,158 participants aged 25-97 years. A detailed cohort profile of the Tromsø study has been published previously.²⁶ The study was approved by the Regional Committee for Medical and Health Research Ethics in Northern Norway, and all participants provided informed written consent to participation. From enrolment in Tromsø 4 (1994/95), subjects were followed until December 31, 2012. Detailed information regarding identification and validation of VTE-events are described in the *Online Supplementary Material and Methods*.

In total, 710 participants developed VTE during follow-up. Of these, 26 did not have blood samples available or of sufficient quality for DNA analyses. The remaining 684 subjects were included as the cases in our study. A subcohort (n=3,931) was composed by randomly sampling individuals from Tromsø 4 weighted for the age distribution of the cases in 5-year age-groups. Due to the nature of the case-cohort design, where each participant has the same probability of sampling, 72 of the cases were also in the subcohort. Subjects with a history of cancer prior to inclusion (n=232) and subjects with missing information on *rs2066865* (n=9) were excluded from the analysis. The final case-cohort consisted of 4,374 subjects, with 640 cases and 3,734 in the subcohort. A flow chart of the case-cohort is displayed in Figure 1.

Baseline measurements and genotyping

Baseline measurements and genotyping methods are described in the *Online Supplementary Materials and Methods*.

Cancer exposure

Cancer assessment is described in the *Online Supplementary Materials and Methods*. Previous studies have shown a strong temporal relation between cancer diagnosis and incident VTE, and up

to 50 % of cancer-related VTE events presents within a 2.5-year interval (from six months preceding the cancer diagnosis until 2 years following the cancer diagnosis).^{27,28} Therefore, a VTE was defined as related to active cancer if it occurred within this time period.

Subjects who survived the active cancer period without a VTE were censored at the end of the active cancer period (*i.e.* 2 years after cancer was diagnosed). The censoring was performed because information regarding remission and relapse of cancer was unavailable, and extension of the observation period of cancer could result in the dilution of the estimates due to inclusion of VTE cases not necessarily caused by cancer. This approach resulted in censoring of 14 VTE cases that occurred after the active cancer period. Thus, 626 VTE cases were included in the final analyses.

Statistical analysis

Statistical analyses were performed using STATA version 15.0 (Stata Corporation LP, College Station, TX, USA). Cox proportional hazards regression models were used to obtain age- and sex-adjusted HR with 95% CI for VTE across categories of cancer status (no cancer/active cancer) and *FGG* risk alleles. Cancer was assessed as a time-dependent covariate in the model. Subjects who developed cancer contributed person-time as unexposed from the inclusion date until six months prior a cancer diagnosis, and thereafter contributed person-time in the active cancer group as exposed. Absolute incidence rates (IR) were calculated based on person-time from the original cohort (n=27,128). To calculate joint effects conferred by active cancer and *FGG* risk alleles, subjects with no cancer and no risk alleles were used as the reference group in the Cox model. Based on the total active cancer person-time at risk derived from the source cohort, 1-Kaplan-Meier curves were used to estimate the cumulative incidence of VTE in subjects with active cancer according to the presence of *FGG* risk alleles. Methods for assessing synergism between *FGG* and active cancer on the risk of VTE are described in detail in the *Online Supplementary Materials and Methods*.

Results

The mean follow-up of the case-cohort was 12.6 years. In total, 854 subjects had active cancer, of which 167 experienced an incident VTE. The baseline characteristics of

Table 1. Baseline characteristics in the entire case-cohort and in the active cancer group.

	Entire case-cohort	Active cancer
Subjects (n)	4374	854
Age (years)	58 ± 13	62 ± 10
Sex (males)	47.0 (2,048)	53.0 (456)
BMI (kg/m ²)	26.0 ± 4	26.0 ± 4
Daily smoking	34.5 (1,464)	43.5 (364)
WBC count (10 ⁹ /L)	7.1 ± 1.8	7.2 ± 1.8
Platelet count (10 ⁹ /L)	251 ± 60	250 ± 58
<i>rs2066865</i> *	0.26	0.26
1 risk allele	1,723	334
2 risk alleles	289	51

Values are numbers or percentages with numbers in parenthesis or means ± standard deviation (SD). Active cancer: period from six months before a cancer diagnosis until two years after; BMI: body mass index; Daily smoking indicates smoking at the time of enrollment; WBC: white blood cell; *: allele frequency.

the entire case-cohort and in those with active cancer during follow-up are presented in Table 1. Subjects who developed active cancer were slightly older (61±10 years vs. 58±13 years) and reported a higher frequency of daily smoking (46% vs. 35%) compared to the entire case-cohort. The minor allele frequency of rs2066865 was 0.26, which is comparable to reference populations.^{14,29} The homozygous variant of the FGG was present in 289 (6.6%) subjects, the heterozygous variant in 1,723 (39.4%) subjects, while 2,362 (54.0%) subjects were non-carriers of the FGG variant. The allele frequency was essentially similar in subjects who developed cancer. Expected versus observed proportions of hetero- and homozygous individuals in the subcohort according to the Hardy-Weinberg equilibrium are presented in *Online Supplementary Table S1*.

The clinical characteristics of the VTE events stratified by the presence of active cancer are shown in Table 2. Compared to the non-cancer-related VTE, cancer-related VTE were more often a DVT (59.2% vs. 55.5%) than a PE (40.7% vs. 44.4%). The prevalence of provoking factors such as acute medical conditions, immobilization and surgery were essentially similar between the two groups, as were the total proportion of VTE with one or more concurrent provoking factors (44.3% vs. 44.7%). Non-cancer related VTE were more likely to be associated with traumas (9.6% vs. 2.4%) while other provoking factors (*i.e.* venous catheters) were more frequent in cancer-related VTE (8.4% vs. 3.7%).

In participants without cancer, the IR of VTE increased from 1.2 (95% CI: 1.1-1.4) per 1,000 people/year among non-carriers of FGG rs2066865 to 2.0 (95% CI: 1.5-2.7) per 1,000 people/year among those with two risk alleles. Accordingly, the risk of VTE was 70% (HR 1.7, 95% CI: 1.2-2.3) higher in those with two risk alleles at FGG compared to non-carriers (Table 3). In subjects with active cancer, the risk was 12-fold higher (HR 11.9, 95% CI: 9.3-15.2) in those with no FGG risk alleles, and 22-fold higher (HR 22.2, 95% CI: 12.9-38.1) in those with two FGG risk alleles, compared to cancer-free subject without risk alleles. Cancer patients with two risk alleles at FGG had a two-fold higher (HR 2.0, 95% CI 1.1-3.6) risk of VTE compared to cancer patients without risk alleles. In sub-analyses, the effect of active cancer and homozygosity at FGG yielded higher risk estimates for PE (HR 2.9, 95% CI: 1.3-6.6) than for DVT (HR 1.6, 95% CI: 0.7-3.5).

The cumulative incidence of VTE during the active can-

cer period is shown in Figure 2. The cumulative incidence of VTE increased particularly during the first six months following a cancer diagnosis, where we found a substantially steeper incline in the incidence curve for subjects with two risk alleles at FGG rs2066865. The cumulative incidence of VTE among homozygous carriers was 5.0% (95% CI: 2.4-9.6), 6.4% (95% CI: 3.5-11.6), and 8.0% (95% CI: 4.6-13.9) at three months, six months and 24 months after cancer diagnosis, respectively. The corresponding figures for cancer patients who were non-carriers were 2.1% (95% CI: 1.5-3.0), 3.1% (95% CI: 2.3-4.7), and 4.8% (95% CI: 3.8-6.2), respectively.

A supra-additive effect on the risk of VTE was observed for the combination of homozygosity at the FGG variant and active cancer (Table 4). The Relative excess risk by

Table 2. Characteristics of subjects with cancer-related and non-cancer-related first venous thromboembolism.

	Cancer-related VTE	
	Yes (167)	No (459)
Age at VTE diagnosis (years)	69 ±11	68±14
Sex (Males)	44.9 (75)	47.3(217)
VTE type		
Deep vein thrombosis	59.2 (99)	55.5 (255)
Proximal upper limb	5.1 (5)	2.0 (5)
Distal upper limb	1.0 (1)	0 (0)
Proximal lower limb	62.6 (62)	65.9 (168)
Distal lower limb	12.1 (12)	28.2 (72)
Other localizations	19.1 (19)	3.9 (10)
Pulmonary embolism	40.7 (68)	44.4 (204)
Unprovoked event	NA	54.9 (252)
Provoking factors		
Surgery ^a	12.6 (21)	15.3 (70)
Trauma ^a	2.4 (4)	9.6 (44)
Acute medical condition ^b	15.0 (25)	14.2 (65)
Immobilization ^c	20.4 (34)	20.0 (92)
Other provoking factor ^d	8.4 (14)	3.7 (17)
Total provoked ^e	44.3 (74)	44.7 (205)

Values are numbers or percentages with numbers in parenthesis or means ± standard deviation (SD); VTE: venous thromboembolism; NA: not applicable; ^awithin eight weeks before the VTE-event; ^bmyocardial infarction, ischemic stroke of major infectious disease; ^cbedrest >3 days, wheelchair, long haul travel >4 hours in the past 14 days; ^dpresence of other provoking factors noted by the physician (*e.g.* intravenous catheters); ^eone or more provoking factor above

Table 3. Age and sex adjusted hazard ratios for venous thromboembolism according to categories of fibrinogen gamma (FGG) risk alleles and cancer status.

	Risk Alleles	Events	VTE		Events	PE		Events	DVT	
			HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)		HR (95% CI)	
No cancer	0	242	Ref.	–	112	Ref.	–	130	Ref.	–
	1	170	1.0 (0.8-1.2)	–	70	0.9 (0.6-1.2)	–	100	1.1 (0.8-1.4)	–
	2	47	1.7 (1.2-2.3)	–	22	1.7 (1.1-2.7)	–	25	1.6 (1.1-2.5)	–
Active cancer	0	89	11.9 (9.3-15.2)	Ref.	32	8.3 (5.6-12.5)	Ref.	57	15.3 (11.2-21.1)	Ref.
	1	64	12.2 (9.2-16.1)	1.1 (0.8-1.5)	29	10.6 (7.1-16.3)	1.3 (0.8-2.2)	35	13.4 (9.2-19.6)	1.0 (0.6-1.5)
	2	14	22.2 (12.9-38.1)	2.0 (1.1-3.6)	7	22.8 (10.6-49.1)	2.9 (1.3-6.6)	7	21.6 (10.0-46.4)	1.6 (0.7-3.5)

Active cancer: period from six months before a cancer diagnosis until two years after; CI: confidence interval; DVT: deep vein thrombosis; HR: hazard ratio; PE: pulmonary embolism; VTE: venous thromboembolism.

interaction (RERI) was 9.61 (95% CI: -2.38-21.61) and the Rothmans synergy index (RSI) was 1.81 (95% CI: 1.02-3.21). The proportion attributable to interaction (AP) was 0.43 (95% CI: 0.11-0.74). In sub-group analysis, the estimates of biological interaction were stronger for PE (RSI=2.37, 95% CI: 1.05-5.39) than for DVT (RSI=1.46, 95% CI: 0.65-3.27).

Discussion

In the present study, we aimed to investigate the joint effect of the *rs2066865* SNP at *FGG* and active cancer on the risk of VTE in a case-cohort recruited from the general population. Homozygosity at *rs2066865*, occurring in 6.6% of the study population, was associated with an increased risk of VTE. The combination of an *rs2066865* homozygous risk genotype and active cancer showed a synergistic effect on VTE risk (on an additive scale). The effect was particularly strong for PE. The cumulative incidence of VTE increased substantially during the first six months following a cancer diagnosis, especially among patients with two risk alleles at *FGG rs2066865*. Our findings suggest that homozygosity at *FGG rs2066865* may aid to differentiate patients at high and low risk of cancer-related VTE.

Several observational studies have reported an association between homozygous genotype of *rs2066865* and increased risk of VTE in Caucasians.^{14-16,21} In a recent meta-analysis including seven observational studies, the odds ratio of VTE was 1.61 for homozygosity at *rs2066865*.²¹ Accordingly, in cancer-free subjects, we found that those with two *rs2066865* risk alleles had a 1.7-fold higher VTE risk than those with 0 risk alleles. The risk estimates for DVT and PE were essentially similar in cancer-free subjects.

Even though the role of prothrombotic genotypes in cancer-related VTE have been scarcely studied, previous studies have found that some prothrombotic genotypes (e.g. factor V Leiden and prothrombin G20210A) are associated with increased risk of cancer-related VTE.^{22,23,30,31} Further, the combined effect of cancer and factor V variants (factor V Leiden and *rs4524*) exceeded the sum of the individual effects, implicating a biological interaction on VTE risk.^{22,24} Accordingly, we found that the combination of *FGG* and active cancer yielded a synergistic effect on VTE risk.

In cancer patients, the cumulative incidence curve of VTE was substantially steeper in individuals homozygous for *FGG* during the first six months following the cancer diagnosis. According to the thrombosis potential model,³² several risk factors need to be present concurrently to exceed the thrombosis potential and facilitate development of a VTE. In the period following a cancer diagnosis, treatment with surgery and/or chemotherapy is typically initiated, and treatment-related complications such as acute infection and immobilization frequently occur. Thus, the accumulation of several treatment-related risk factors, which adds to the background risk in patients with cancer and risk alleles at *FGG*, may partly explain the substantial increase in VTE incidence the first half year following a cancer diagnosis.

In contrast to cancer-free subjects, we found that the effect of *rs2066865* was stronger for PE than for DVT in cancer patients. This suggests that the *FGG* variant may

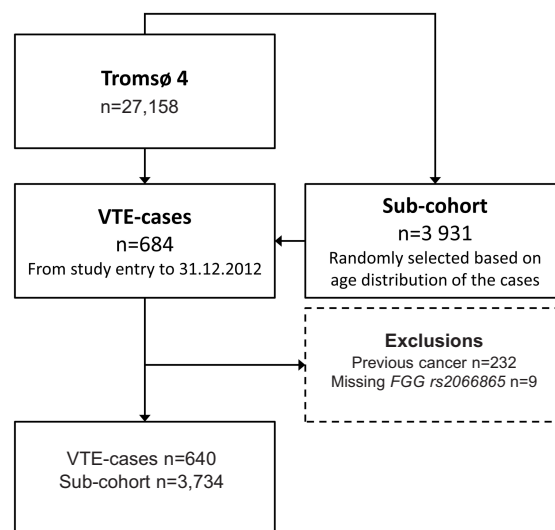


Figure 1. Flow chart for the case-cohort.

play a more essential role in the pathogenesis of PE than DVT in cancer patients. The underlying mechanism(s) for the latter observation is unknown, but may imply that *rs2066865* is associated with fragile thrombi, which are prone to embolization and manifest clinically as PE rather than DVT in cancer patients.

The mechanism by which the *rs2066865* affects susceptibility to VTE is not fully elucidated. However, the current hypothesis is that it acts through a phenotype with altered fibrinogen composition and formation. The *rs2066865* SNP tags the *FGG-H2* haplotype. Previous studies have shown that homozygous carriers of the *FGG-H2* haplotype had lower levels of γ' fibrinogen and γ' fibrinogen/total fibrinogen concentration¹⁴ without alterations in the total fibrinogen level.³³ The suggested mechanism is that the *FGG* variant favors formation of the abundant γ -chain isoform (γA) above the minor γ -chain (γ') through alternative splicing of the mRNA of the *FGG*-gene.^{14,33} Fibrinogen γ' exhibits an inhibitory activity towards thrombin, due to a high affinity binding site on the γ' chain for thrombin exosite II,³⁴ which inhibits thrombin-mediated activation of factor VIII,³⁵ factor V³⁶ and platelets.³⁷ Moreover, fibrinogen γ' has been shown to increase the activated protein C (APC) sensitivity.³⁸ However, studies on the association between low plasma levels of fibrinogen γ' and VTE risk have shown somewhat inconsistent results.^{14,20}

Current anticoagulant prophylaxis regimens efficiently prevent first VTE in cancer patients, but at the expense of a substantial risk of major and life-threatening bleedings.³⁹ Therefore, current international guidelines do not recommend prophylactic anticoagulation to all ambulatory cancer patients.^{40,41} Thus, it is vital to recognize patients that are at high risk of cancer associated VTE, in order to identify those who would benefit most from thromboprophylaxis. Prothrombotic genotypes are attractive biomarker candidates, which could be used to distinguish between high and low risk of VTE in cancer patients, since they are fixed and not affected by the clinical status or treatment-related factors. In the present study, 6.4% of cancer

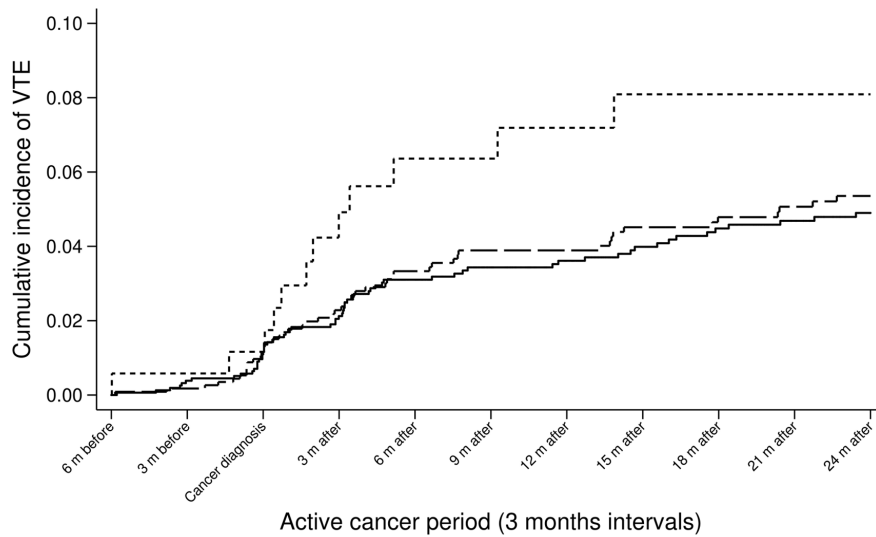


Figure 2. Cumulative incidence of venous thromboembolism in the presence of FGG rs2066865 risk alleles during the active cancer period. VTE: venous thromboembolism; m: months.

Table 4. Measures of interaction between the homozygous fibrinogen gamma (FGG) variant and active cancer on venous thromboembolism.

	Rothmans synergy index (RSI) (95% CI)	Relative excess risk by interaction (RERI) (95% CI)	Proportion due to interaction (AP) (95% CI)
FGG rs2066865			
VTE	1.81 (1.02-3.21)	9.6 (-2.4-21.6)	0.43 (0.11-0.74)
PE	2.37 (1.05-5.39)	13.4 (-4.8-31.7)	0.56 (0.21-0.90)
DVT	1.46 (0.65-3.27)	6.3 (-9.6-22.1)	0.30 (-0.24-0.83)

Rothmans synergy index (RSI) >1 indicates a positive interaction or more than additivity; Relative excess risk by interaction (RERI) >0 indicates a positive interaction or more than additivity; Proportion due to interaction (AP) >0 indicates a positive interaction or more than additivity. VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; CI: confidence interval.

patients with two risk alleles at FGG rs2066865 developed VTE during the first six months after cancer diagnosis compared to 3.1% of cancer patients without risk alleles. Our findings suggest that FGG may be an attractive gene candidate to pursue in future research on prediction models of VTE risk in cancer patients. We and others have previously reported similar discriminative power of two variants in the F5 gene (rs6025 and rs4524),^{23,24} and a genetic model including nine SNP reported promising predictive capacity on VTE risk in breast cancer.⁴² Recently, a new risk prediction model for cancer-related VTE, including clinical characteristics and genetic variants, reported a strong predictive capacity with an area under the curve (AUC) of 0.73 and performed better than the Khorana score (AUC 0.58).⁴³

The main strengths of present study are the prospective design, high participation rate and long-term follow-up, making it possible to capture a large quantity of both incident cancer- and VTE-events in the study population. Since all participants live within a single hospital catchment area, the probability of missing outcomes is low.

Moreover, both incident VTE-events and cancer diagnoses were systematically validated and objectively confirmed. The study was limited by the lack of statistical power in sub-group analysis (i.e. DVT/PE), illustrated by wide CI for our risk estimates. In addition, we did not have access to information on treatment regimens or medical complications among cancer patients. Although there is no reason to believe that the type or intensity of treatment would be influenced by the genetic makeup, such data could have provided further insights into the possible interplay between genes and treatment-related risk factors.

In conclusion, we found that homozygosity at FGG rs2066865 was associated with an increased risk of VTE, and yielded a synergistic effect on the VTE risk in combination with active cancer, particularly on the risk of PE.

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