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Environmental and genetic risk factors associated with venous thromboembolism

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Abstract

Venous thromboembolism (VTE) includes deep vein thrombosis and pulmonary embolism; a combination of environmental and genetic risk factors contributes to VTE risk. Within environmental risk factors, some are provoking (e.g. cancer, surgery, trauma or fracture, immobilization, pregnancy and the postpartum period, long distance travel, hospitalization, catheterization, and acute infection) and others are non-provoking (e.g. age, sex, race/ethnicity, body mass index and obesity, oral contraceptive or hormone therapy use, corticosteroid use, statin use, diet, physical activity, sedentary time, and air pollution). Additionally, VTE has a strong genetic basis, with approximately 50–60% of the variance in VTE incidence attributed to genetic effects. Some genetic susceptibility variants that contribute to risk have been identified in candidate genes, mostly related to the clotting system and responsible for inherited hypercoagulable states (e.g., factor V Leiden, prothrombin, fibrinogen gamma, or blood group non-O). Other susceptibility single nucleotide polymorphisms have been identified from genome-wide association studies, such as the two new loci in TSPAN15 (rs78707713) and SCL44A2 (rs2288904) genes. Risk factors are not always associated with VTE in isolation, however, and an understanding of how environmental and genetic factors interact may provide insight into the pathophysiology of VTE, possibly identifying opportunities for targeted prevention and treatment.

Keywords

Venous thromboembolism; Epidemiology; Genetics; Risk factors

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Introduction

Venous thromboembolism (VTE) is a disease classification that includes clots that have formed in the veins of the legs and arms, known as deep vein thrombosis (DVT), as well as clots that have embolized and traveled to the lungs, known as pulmonary embolism (PE). Among persons of European ancestry, VTE is estimated to occur at an incidence rate of approximately 1 to 2 per 1,000 person-years, with approximately 60% all VTE cases presenting as DVTs-only and the other 40% presenting as PEs with or without DVT.[1] After a first (incident) VTE event, the risk of a recurrent event is high, with approximately 30% of persons who experience an incident VTE event experiencing a recurrence within 10 years.[1]

Although VTE is a type of cardiovascular disease, the etiology of VTE is unique from that of arterial thrombosis and likewise, only some traditional arterial thrombotic risk factors are thought to contribute to VTE risk.[2] Multifactorial in nature, VTE includes both environmental and genetic risk factors. Within environmental risk factors for VTE, some are provoking (e.g. cancer, surgery, trauma or fracture, immobilization, pregnancy and the postpartum period, long distance travel, hospitalization, catheterization, and acute infection) and others are considered to be non-provoking (e.g. age, sex, race/ethnicity, BMI and obesity, oral contraceptive [OC] or hormone therapy [HT] use, corticosteroid use, statin use, diet, physical activity and sedentary time, and air pollution) (Figure 1).

In this review we will discuss a selection of environmental and genetic risk factors for VTE from a public health perspective. Importantly, our discussion will place special emphasis on risk factors that are controversial or of emerging interest. We will not attempt to be all-inclusive. In addition, while we acknowledge that “venous thrombosis” can include superficial thrombophlebitis, splenic, hepatic, ovarian vein, or cavernous sinus thrombosis, or other entities, this review will focus only on the most common forms of VTE: DVT and PE. Furthermore, our discussion in this review will focus on risk factors for incident and not for recurrent VTE. We have divided this review into several sections. In the first section we will discuss non-modifiable risk factors and their relationship to VTE, including: age, race/ethnicity, and sex. In the second section, we discuss the role of a selection of potentially modifiable environmental risk factors, including traditional risk factors for arterial thrombosis, medication use (exogenous hormones, corticosteroids, and statins), and emerging or controversial risk factors (diet, physical activity, and air pollution). While we acknowledge the importance of provoking environmental risk factors, these are well studied and characterized elsewhere, and thus will not be the focus of our review. In the third section we turn our attention to genetic risk factors for VTE, and in the final fourth section, we discuss gene-environment interactions in relation to VTE risk (Figure 1).

Non-Modifiable Risk Factors for VTE: Age, Sex, and Race/Ethnicity

Age

Although age, sex, and race/ethnicity are non-modifiable characteristics, understanding how VTE risk differs by these characteristics is critical to improving VTE diagnosis and treatment. While VTE can occur at any age, incident VTE more commonly occurs in older individuals. In young adult life until approximately midlife, VTE occurs at a low rate of 0.5

to 1 event per 1,000 person-years.[3] This rate increases in midlife and by age 80, VTE incidence is substantially higher, occurring at a rate of approximately 5 to 7 VTE events per 1,000 person-years.[3,4] Although the role of older age as an independent risk factor for VTE is not well understood, it has been proposed that blood coagulability may increase with age.[5] In addition, age effects are likely mediated by a higher prevalence of provoking risk factors for VTE, such as cancer, immobility, hospitalization, and surgery.

Sex

VTE incidence across the lifespan also differs by sex, with a higher age-adjusted incidence rate among men (130 per 100,000 person-years) than women (110 per 100,000 person-years).[3] However, it is controversial whether men are inherently at a greater risk of VTE than women. In younger adult life, the annual incidence of VTE is slightly higher among women than men,[3] a difference that has been attributed to hormonal exposures that impact women in their childbearing years, such as pregnancy, the postpartum period and OC use.[6] Following midlife, VTE incidence increases more rapidly among men than among women, resulting in a higher VTE incidence among older men than women.[3] Although it is unclear as to why VTE incidence is higher among older men than women, it has been proposed that there may be differences in lifestyle-based risk factors between men and women. Alternatively, this difference may be mediated by body height.[7]

Race/Ethnicity

The risk of incident VTE is also thought to differ by race, with the highest risk thought to be among Black individuals, then White individuals, and the lowest risk among Asian or Hispanic individuals.[8] Few studies have been able to appropriately evaluate the race-VTE association while controlling for appropriate confounders, however, and so the association of race with VTE remains controversial.[9] Recently, a large study combined data from three United States-based cohorts: the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), and the Reasons for Geographic and Racial Differences in Stroke study (REGARDS). In the CHS, blacks had an 81% greater risk of incident VTE than did whites (hazard ratio [HR]=1.81; 95% confidence interval [CI]: 1.20–2.73) but in ARIC, there was no significant difference (HR=1.21; 95% CI: 0.96, 1.54).[10] In REGARDS, the only one of the three cohort studies to include a substantial population of blacks residing outside of the Southeast, there was significant interaction between region of residence (Southeast vs. rest of country) and race (p=0.01), suggesting that regional differences in comorbid illnesses, environmental risk factors, or in quality and access to medical care may mediate a potential race-VTE association.[10] Further complicating our understanding of a race-related gradient in VTE risk is the understanding that factor V Leiden (FVL) and prothrombin gene mutations (that will be discussed in detail in section 3) are both less common among persons of Black race than White race.[8,11]

Potentially Modifiable Environmental Risk Factors for VTE

In contrast to age, sex, and race/ethnicity, other risk factors for VTE may be modifiable, and are therefore relevant not only to diagnosis, but to VTE prevention. In this section, we will discuss potentially modifiable risk factors for VTE. We will focus on some risk factors that

are common across both venous and arterial thrombosis. We will also discuss medications that are associated with VTE risk. Finally, we will discuss some risk factors for which the association with VTE is controversial or only just becoming clearer.

Traditional Arterial Thrombotic Risk Factors

Although venous and arterial thrombotic disease have been historically regarded as distinct diseases with differing etiologies, these two classes of thrombotic events share common characteristics. Both hypercoagulability and inflammation contribute to the development of arterial and venous thrombi and risk factors for the two diseases are not altogether dissimilar.[2,12] A 2008 meta-analysis by Ageno et al. included 21 case-control and cohort studies that evaluated the association between traditional risk factors for arterial thrombosis and VTE risk. Obesity (odds ratio [OR]=2.33; 95% confidence interval [CI]: 1.68, 3.24), hypertension (OR=1.51; 95% CI: 1.23, 1.85), and diabetes mellitus (OR=1.42; 95% CI: 1.12, 1.77) were significantly associated with VTE risk, but there was no statistically significant evidence of an association between smoking (OR=1.18; 95% CI: 0.95, 1.46) or hypercholesterolemia (OR=1.42; 95% CI: 0.67, 2.02) and VTE risk.[2] In this meta-analysis, there was no evidence that mean total and low-density lipoprotein cholesterol levels were associated with VTE risk, though mean high-density lipoprotein cholesterol levels were lower among VTE patients than controls (weighted mean difference=-2.86 mg/dL; 95% CI: −4.34, −1.38).[2]

The findings of Ageno et al. suggest that some traditional arterial thrombotic risk factors are also associated with VTE.[2] However, the magnitude of VTE risk associated with some of these risk factors is not as high as with arterial disease, and in some studies do not reach statistical significance (for example, the borderline significant 18% greater VTE risk associated with smoking). Thus, while there are shared risk factors for arterial and venous disease, the etiologies of these two classes of thrombotic disease are distinct.

Medication Use

Exogenous Hormones—When evaluating medication use in relation to VTE risk, it can be difficult to disentangle risk associated with the medication from that associated with a medication's underlying condition. However, the use of exogenous hormones (OC or HT) has been well established as positively associated with a 1.5 to >3-fold greater risk of incident VTE.[13–16] Comparative studies of VTE risk associated with OC and HT type, dose, and formulation remain warranted especially as women's use of OCs and indication for HTs remain common. Among women at risk for pregnancy, birth control use of any type ranges from 55% to 81% by state in the United States,[17] and 30–80% of women experience hot flashes and night sweats at some point during the menopausal transition,[18] which may prompt symptomatic treatment with HT. Moreover, different formulations are thought to be associated with different risks of VTE. In a 2014 systematic review and meta-analysis, OCs containing ethinyl estradiol with levonorgestrel were associated with a 50 to 80% lower risk of VTE than were OCs containing gestodene, desogestrel, cyproterone acetate, or drospirenone.[19] Differences in VTE risk associated with the use of non-oral methods of contraception have also been reported. For example, in a Danish historical national registry-based cohort study, transdermal patch and the vaginal ring use were each separately

associated with a greater risk of VTE than use of OCs containing levonorgestrel (relative risk [RR]=2.3; 95% CI: 1.0, 5.2, and RR=1.9; 95% CI: 1.3, 2.7, respectively).[20] In contrast, the use of a levonorgestrel intrauterine device or an implant was associated with a lower risk of VTE (RR=0.18; 95% CI: 0.12, 2.6, and, RR=0.43; 95% CI: 0.18, 1.05, respectively) than the use of OCs containing levonorgestrel.[20] Differences in VTE risk by oral HT type have also been identified. A population-based case-control study reported that among oral HT users, current use of conjugated equine estrogens was associated with a 2-fold greater risk of incident VTE as compared with current estradiol use (OR=2.08; 95% CI: 1.02, 4.27).[21] In addition, a recent meta-analysis reported a greater VTE risk associated with oral estrogen HT as compared with transdermal HT use (RR=1.63; 95% CI: 1.40, 1.90).[22] Given these reported differences in VTE risk by OC and HT type, dose, and formulations, additional research in this area is warranted.

Corticosteroids—Emerging research suggests that the use of corticosteroids may also be associated with VTE risk. Early studies of individuals with disease-based indications for corticosteroids reported a positive association between corticosteroid use and VTE. However, as corticosteroids are used to treat inflammation-associated conditions including asthma and arthritis, it has been difficult to control for residual confounding from the underlying disease in these studies. Only recently have studies evaluated VTE risk associated with corticosteroid use, either in relatively healthy populations or with improved adjustment for potential confounders. In a large (n=38,765 VTE cases) population-based case-control study using national databases in Denmark, glucocorticoid prescription fulfillment within the past 90 days was associated with more than a 2-fold greater risk of incident VTE (incidence rate ratio [IRR]=2.33; 95% CI: 2.18, 2.45), after adjustment for indicators of underlying disease severity.[23] In a cohort study set in the British General Practice Research Database (n=6,550 VTE cases), current use of corticosteroids was associated with a 3-fold greater risk of incident VTE (OR=3.1; 95% CI: 2.5, 3.7).[24] Of course, while the authors of these studies were able to adjust for cancer and for other inflammatory conditions, it is possible that residual confounding by inflammatory conditions may remain. However, one mechanism by which corticosteroids may increase VTE risk is via altered levels of hemostatic factors. In a study of 10-day randomized prednisolone vs. placebo use (total n=31) among healthy participants, levels of von Willebrand factor (VWF), plasminogen activator inhibitor type 1, and in vitro thrombin generation were all higher among prednisolone users.[25]

Statins—Statins, which are commonly prescribed to reduce low-density lipoprotein cholesterol levels for a reduction in the risk of arterial thrombotic events, have also been associated with a lower risk of incident VTE. In 2009, results from the Justification for the Use of Statins in Prevention: an Interpretation Trial Evaluating Rosuvastatin (JUPITER) suggested that rosuvastatin was associated with more than a 40% lower risk of incident VTE (HR=0.57; 95% CI: 0.37, 0.86) among apparently healthy persons.[26] However, this association remains controversial.[27] In a separate trial of pravastatin among men and women aged 70–82 years, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), randomization to pravastatin was not associated with a lower VTE risk (HR = 1.42; 95% CI: 0.80, 2.52), but confidence intervals were wide.

Emerging and/or Controversial Risk Factors of Interest

Diet—Although the role of diet in the risk of arterial thrombosis is commonly considered, the relation of diet to venous thrombosis is more controversial. Some studies have evaluated the relation between specific nutrients or food groups, and some evidence has suggested that fruits and vegetables,[28] fish,[28,29] whole grains,[30] and alcohol[30] may be negatively associated and that red/processed meat intake may be positively associated[28,31] with VTE risk. Evidence remains inconsistent between studies, however.

Several studies have also evaluated patterns of diet in relation to VTE. The study of dietary patterns can be important since these patterns may more closely represent real-life food consumption than do studies of specific food groups of nutrients. Three studies have evaluated the Western Diet as compared to the Prudent Dietary Pattern in relation to VTE risk, but results have been inconsistent.[28,30,31] The Western Diet, which is characterized by high intakes of refined grains, cured and red meats, desserts, sweets, French fries, and high-fat dairy products, is hypothesized to be associated with a greater VTE risk than is the Prudent Dietary Pattern, which is defined by high intakes of fruits, vegetables, fish, poultry, whole-grain products, and low-fat dairy products.[31] Results from the ARIC study suggested (p-trend=0.04) that the Western Dietary Pattern was associated with a greater risk of VTE (top quintile of Western Diet Pattern score compared with bottom quintile HR: 1.6; 95% CI: 0.97, 2.66) although quintiles of Prudent Dietary Pattern intake were not linearly associated with VTE risk.[28] In the Health Professionals Follow-up Study, the top two quintiles of Western dietary pattern intake were associated with an approximate 40% greater risk of incident VTE compared to the lowest value of intake (top quintile HR=1.43; 95% CI: 1.16, 1.78), and there was a significant linear trend by quintile ($p<0.001$).[31] In contrast, analyses from the Iowa Women's Health Study[30] and the Nurses' Health Study (NHS)[31] suggested no significant association between the Western or Prudent Dietary Patterns and VTE risk. Inconsistent results have also been found when other dietary patterns have been studied. In an EPIC-NL analysis of the Mediterranean Diet Score, which assigns positive point values to above-median intake of vegetables, fruits, legumes/nuts, grains, fish/seafood, the ratio of unsaturated to saturated fatty acids, and to consumption of 1 or more alcoholic drinks per month, and negative point values for above-median intake of meat and dairy products, each 2-unit increase in intake was negatively associated with PE risk (HR=0.74; 95% CI: 0.49, 0.92).[32] In contrast, studies have not reported strong evidence of an association between the Dietary Approaches to Stop Hypertension (DASH) dietary pattern[33] and the Smart Diet Score[34] with VTE risk. Thus, the relationship between diet and VTE risk remains challenging to understand.

Physical Activity and Sedentary Time—Physical activity is a well-characterized protective risk factor for arterial thrombosis, but like diet, its association with VTE is complex and uncertain.[35–39] For example, in the CHS analysis of adults aged 65 years and older, self-reported exercise at baseline was not associated with the risk of VTE (HR=1.16; 95% CI: 0.84, 1.61), but when exercise was modeled in a time-varying fashion, the effect estimate shifted higher and nearly reached statistical significance, suggesting that physical activity among older adults may be associated with a greater risk of VTE (HR=1.38; 95% CI: 0.99, 1.91).[39] There was also evidence that VTE risk may differ by intensity of physical

activity. Whereas there was no association between mild intensity exercise and VTE risk (HR=0.75; 95% CI: 0.49, 1.16), strenuous exercise was associated with a greater risk of VTE than no physical activity (HR=1.75; 95% CI: 1.08, 2.83).[39] In contrast, the Multiple Environmental and Genetic Assessment of risk factors for VTE (MEGA) case-control study, found that regular participation in leisure-time sports was associated with reduced risk of VTE (OR=0.71; 95% CI: 0.64, 0.78). However, investigators found no evidence of a dose-response relationship between sports intensity, frequency, and duration and risk of VTE.[36] Other analyses, of the NHS,[35] the Longitudinal Investigation of Thromboembolism Etiology (LITE) study,[37] and the Tromsø study,[38] reported no statistically significant evidence of an association between physical activity and VTE risk.

Contrasting findings between studies may stem from differences in the intensity, frequency, and duration of physical activity conducted by study participants, and how each study was able to evaluate these factors in relation to VTE risk. It is possible, for example, that physical activity may be associated with an increased short term VTE risk – perhaps by increasing the risk of injuries – whereas consistent physical activity may plausibly reduce VTE risk similarly to arterial thrombosis. It is also possible, especially given the results from the CHS that the association between physical activity and VTE varies depending on age.[39]

Air Pollution—Air pollution is emerging as a potential risk factor of interest, given its positive association with the risk of arterial thrombotic events[40] and its proposed association with hypercoagulability and lung disease. However, like smoking, which is a strong risk factor for arterial thrombotic events, but a weak risk factor for VTE,[2] the relationship between air pollution and VTE is inconsistent. Some studies suggest a positive association between air pollution and VTE risk,[41–44] whereas others suggest no association.[44–46] A recent systematic review of 11 studies concluded that there is a positive association between air pollution and VTE risk, but acknowledged that heterogeneity existed between studies.[47] This heterogeneity likely stems from varied study settings[41,4245,46] with a wide range of pollutant levels.[47] Like smoking, air pollution may be associated differently with venous versus arterial thrombotic risk, but further work is required to clarify this relationship.

Genetics

In this section, we will discuss genetic susceptibility for VTE. We will primarily focus on the genetic variants from candidate genes that have a large effect on VTE risk. We will also discuss the single nucleotide polymorphisms (SNPs) identified from genome-wide association studies that have been described to date.

Heritability and Family History

In addition to its association with environmental risk factors, VTE has a strong genetic basis: it has been shown that VTE is highly heritable and about 50–60% of the variance in VTE incidence is attributable to genetic effects.[48–50] VTE inheritance follows a multifactorial, or non-Mendelian, inheritance model, with multiple genetic factors contributing to risk.[48,51–54] The risk of VTE is greater among monozygotic twins (OR=13.5; 95% CI: 7.3, 24.8) than dizygotic twins (OR=3.8; 95% CI: 1.8, 8.3), providing further evidence of the importance of genetic influence to VTE risk.[55] Family-based studies have confirmed these findings, and

have reported that the risk for VTE in individuals with an affected sibling is 2.5 times higher than risk in the general population.[48] Carriers of a familial thrombophilic genetic risk variant have a 0.8% risk per year of developing VTE.[49,50]

Susceptibility Variants from Candidate Gene Approaches

The genetic basis of VTE is only partly understood.[56] At present 20–30 genetic VTE risk factors are known,[56,57] and most of the identified genetic risk factors involve mutations in the clotting system (Figure 2). There are seven well-established genetic risk factors for VTE, all responsible for inherited hypercoagulable states. Four, which include variants in factor V (FV) (e.g. the FVL mutation), prothrombin (e.g. prothrombin 20210-A), fibrinogen gamma (FGG), and blood group non-O, are more frequent in the general population. The prevalence in European-descent individuals is around 5% for FVL and prothrombin 20210-A, and around 25% for FGG and non-0 blood group. The increase in VTE risk is about 3-fold for the FVL and prothrombin mutations, 1.5-fold for FGG, and 2-fold for non-O blood group.[58–83] The other three are heterozygous deficiencies of the natural coagulation inhibitors (antithrombin, protein C, and protein S). Their effect is relatively large, increasing VTE risk by approximately 10 fold. However, these deficiencies are relatively rare, affecting less than 1% of the general population.

Factor V—The strongest genetic variant identified to date in association with VTE risk is known as the FVL mutation. The rs6025 SNP represents an autosomal dominant genetic variant in the FV gene, encoding a change in the protein from an arginine at position 506 to a glutamine. This is found in 4–5% of individuals in most populations. FVL is a mutation in one of the genes involved in the intrinsic coagulation pathway (Figure 2), and causes resistance to activated protein C[84,85]. The missense variant rs6025 has been associated with a 2 to 7 fold increase in VTE risk for heterozygous carriers, and a 15- to 20-fold increase for homozygous carriers.[86–90]

Recently, a large meta-analysis successfully validated two missense variants located in FV; specifically the previously mentioned SNP rs6025, associated with an increased odds of VTE of 3.25 ($p=1.10x10^{-96}$), and the SNP rs4524, associated with VTE risk independently of the previously described variant with an odds of VTE of OR=1.20, $p=2.65x10^{-11}$.[91]

Other independent SNPs in FV gene (including rs3753305, rs9332695) have also been associated with alterations in FV, and consequently have been associated with increased VTE risk.[92] Even though the risk allele frequencies for some of those SNPs might be higher in the general population, the effect sizes are lower than those at rs6025.

Prothrombin—A prothrombin gene mutation is the second most common cause of inherited thrombophilia. It is caused by mutation in the prothrombin gene (also known as Factor II), another key element in the blood clotting cascade (Figure 2). A prothrombin G to A SNP at position 20210 (rs1799963) in the untranslated 3’ region of the prothrombin gene leads to overproduction of prothrombin, consequently making carriers of this mutation prone to blood clots. This variant is present in 2–4% of the population, and is associated with a two-to-three fold increased risk of VTE for the heterozygous state and 5–10-fold for the

homozygous state.[87,93–96] The intronic variant in FII rs1799963 was also validated in the meta-analysis previously mentioned and with an odds ratio of 2.29 ($p=1.73x10^{-9}$).[91]

ABO Blood Group—ABO blood group is known to be a major determinant of plasma levels of factor VIII, one of the proteins involved in the clotting cascade (Figure 2). Specifically, factor VIII and VWF undergo extensive post-translational modification by the ABO blood group-encoded glycosyltransferases.[58,97] Increased plasma factor VIII and VWF levels are associated with an increased risk for VTE.[98,99] ABO phenotype correlates with plasma levels of factor VIII and VWF, such that individuals with type O blood group have about 25% lower plasma factor VIII and VWF levels[63,100] and accordingly, a lower risk of VTE. It is worth noting however, that non-O ABO blood type has been associated with an 86% (95% CI: 1.35, 2.57) increase in VTE risk independent of factor VIII, so there may be additional mechanisms behind this association as well.[63]

Different ABO SNPs have been independently associated with VTE. These include: rs8176719, an ABO exon 6 deletion determining type O blood group, and rs2519093, and ABO intron 1 tag SNP.[101,102] Additionally, the SNP rs529565, an intronic variant in the ABO gene, was replicated on meta-analysis.[91] The risk allele for this SNP is associated with a 55% increased risk of VTE ($p=4.23\times10^{-75}$).

The SNPs described above have a large effect on VTE risk. The joint population-attributable risk (PAR) for the four SNPs including FVL (rs6025), prothrombin (rs1799963), ABO non-O blood group (rs8176719) and ABO rs2519093 account for a large proportion of VTE among non-Hispanic adults of European-ancestry: population attributable risk (PAR)=0.40.[103]

Other Genes—Polymorphisms in other genes, including factors VIII, IX, XI and XIII also produce thrombophilia and consequently they have been associated with increased risk of VTE.[83] One of the better established is FGG. Individuals with mutations in the FGG gene have a reduced FGG level, which increases binding of proteins that promote cleavage to fibrin monomers (Figure 2). Several studies have found the 455GA polymorphism of β-fibrinogen gene (rs2066865) to be associated with risk of VTE in Caucasian population. Carriers of the A allele have a slight (around 15%) protective effect against VTE.[57] The large genome wide association study (GWAS) meta-analysis also validated the SNP rs2066865, located in the 3’ untranslated region (UTR) of the FGG gene, associated with odds of VTE of 1.24 ($p=1.03\times10^{-16}$).[91]

Moreover, deficiencies of protein C and antithrombin, two natural plasma anticoagulants, are known risk factors for VTE. Deficient protein C or antithrombin is typically present in 4% to 9% of the patients with familial thrombophilia. In contrast, the prevalence of protein C deficiency in the general population is less common and has been estimated to be between 0.2% and 0.4%.[104,105] A number of mutations of the protein C and antithrombin genes contribute to deficiencies of these anticoagulant proteins.[104] Hereditary protein S deficiency has also been associated with an increased risk of VTE.[106] Protein S assists in the downregulation of thrombin formation by stimulating the activity of both activated protein C

and tissue factor pathway inhibitor. The genetic basis of protein S deficiency is heterogeneous and several mutations in PROS1 have been described to date.

Other variants in genes coding for alpha and beta-fibrinogen, protein C, and plasminogen activator inhibitor, have been also associated with VTE risk. Some of these variants were validated in the aforementioned meta-analysis,[91] specifically: the SNP rs4253417, an intronic variant in factor XI (FXI) gene, associated with VTE risk with an OR of 1.27 ($p=1.21x10^{-23}$), and the SNP rs6087685, an intronic variant located in the protein C receptor (PROC) gene, associated with VTE risk with an OR of 1.15 ($p=1.65x10^{-8}$). The majority of SNPs associated with VTE have been identified in populations of European ancestry. However, a genetic variant in the gene encoding for the methylenetetrahydrofolate reductase (MTHFR), the SNP rs1801133 (also known as C677T mutation) has been identified in Asian ancestry populations (OR=1.57; 95% CI: 1.23, 2.00); and the insertion/deletion polymorphism of the angiotensin-converting enzyme gene has been specifically described in African ancestry populations as associated with VTE risk (OR=1.50; 95% CI: 1.03, 2.18).

Susceptibility Variants from GWAS Approaches

Despite the accumulated evidence that genetic factors play a major role in the pathophysiology of VTE, only 35% of VTE patients undergoing testing for thrombophilia carry a polymorphism known to increase VTE risk.[107] Given the high estimated heritability of VTE, additional genetic risk factors likely exist. All of the factors discussed above were identified based on their relevance to the clotting cascade, using candidate-gene approaches. GWAS are a powerful method to identify common SNPs associated with a complex disorder without a pre-specified hypothesis. GWAS have proven highly efficient in identifying novel susceptibility loci for other complex diseases.

Despite this promise, early GWAS were unable to identify any previously unknown variants associated with VTE.[91,102,108–110] Most of these GWAS had limited samples sizes, and were underpowered to detect novel associations at the rigorous genome-wide-significance level. To overcome this limitation, the International Network on VENous Thrombosis (INVENT) Consortium came together to perform a meta-analysis of existing GWAS.[91] The main objective was to identify additional common variants associated with VTE risk in the context of a large study. The INVENT network currently comprises 15 cohort and case-control studies worldwide and includes 10,676 VTE cases and more than 71,752 controls.

The INVENT meta-analysis is the largest investigation to date on the influence of common genetic variation on VTE risk. It included GWAS findings from 12 studies, including a total of 7,505 VTE cases and 52,632 controls and was the first study to identify new genetic loci involved in VTE susceptibility using modern, agnostic genotyping methods.[91] Out of a total of 6,751,884 SNPs tested after quality-control measures, nine loci reached the genome-wide significance ($5x10^{-8}$) and were successfully replicated in independent samples. Those included loci in six genes previously identified as associated with VTE: rs529565 in ABO, rs1799963 in FII, rs6025 and rs4524 in FV, rs4253417 in FXI, rs2066865 in FGG, rs6087685 in PROC; and two new loci in TSPAN15 (rs78707713) and SCL44A2 (rs2288904) genes. Interestingly, neither of the two new loci identified in this large meta-analysis belong to conventional pathways for thrombosis, nor have they been associated to

other cardiovascular diseases. This suggests that they may represent novel pathophysiological mechanisms of VTE.[91,102]

The lead SNP at the TSPAN15 locus is the intronic variant rs78707713, and has an OR of 1.31 ($p=1.67x10^{-16}$) for VTE. *TSPAN15* codes for tetraspanin 15, a member of the tetraspanin superfamily that act as scaffolding proteins, anchoring multiple proteins to the cell membrane [reference]. Members of the tetraspanin family have roles in cells that regulate hemostasis. However, the *TSPAN15* rs78707713 has not been linked to any regulatory elements supporting a functional role of this particular SNP. It is likely that the SNP is in strong linkage disequilibrium with yet unidentified functional variants.

The lead SNP at the SCL44A2 locus is the non-synonymous rs2288904, which has an OR of 1.21 ($p=2.75x10^{-15}$) for VTE.[91] The risk allele at the *SLC44A2* locus (rs2288904-G) is probably the functional variant since it codes for the Arg154 isoform of the choline transporter-like protein 2 (CTL-2). CTL-2 has been associated with several human diseases, including transfusion-related acute lung injury (TRALI). TRALI is a life-threatening complication of blood transfusion and the leading cause of transfusion-associated mortality in developed countries. Severe TRALI is due to antibodies in blood components directed against the human neutrophil alloantigen-3a, which is determined by the Arg154 isoform.

Genetic Risk Scores

While specific genetic variants can have large effects on VTE risk, VTE is a complex disease. Thus, an individual's risk of VTE may be better described by the sum of their genetic risk factors, or in other words, their overall genetic predisposition. In order to assess overall genetic predisposition, a few studies have constructed genetic risk scores (GRS) and assessed their association with VTE risk.

Soria et al. performed a systematic review and meta-analysis to select variants that contribute to VTE risk and created a GRS called Thrombo inCode (TiC).[111] They concluded that TiC, which includes SNPs on FVL, FII, FXIII, SERPINC1, SERPINA10, and A1 blood group genes, improved VTE risk prediction compared to using variants in FVL and prothrombin genes alone. De Haan et al. also created a GRS based on 31 SNPs associated with VTE, identified through candidate gene approaches.[112] In this case-control study of 2712 patients and 4634 controls, a GRS including five SNPs was highly associated with VTE risk (OR 7.48; 95% CI: 4.49, 12.46) and performed similarly to a GRS including all 31 studied SNPs. Both of these studies were performed in predominantly European ancestry subjects. Folsom et al[113] recently tested the ability of a GRS based on five well-established VTE SNPs in the FVL, FII, ABO, FGG, and FXI genes to predict VTE incidence in African Americans. While this five-SNP GRS had identified white adults at risk of VTE, the GRS did not identify future VTE occurrence in African Americans. Recently, Crous-Bou et al[114] constructed a GRS based on SNPs associated with VTE risk from previous GWAS. In this nested case-control study of 1,040 incident VTE cases and 16,637 controls, VTE risk increased with the number of risk alleles, and the risk of VTE among individuals with a high GRS was 1.93 times that of individuals with a low GRS (p for trend = $1.63x10^{-16}$).

In combination, these studies demonstrate that selected SNPs can be combined into a GRS with a strong, linear, positive association with VTE. In the coming era of personalized medicine, GRS may be incorporated into clinical decision making. Identifying individuals at high risk of VTE may provide opportunities for targeted prevention and testing of the most appropriate patients.

The Genetic Risk of DVT versus PE

Although much of the discussion thus far has focused on VTE (i.e. both DVT and PE), it is worth noting that genetic factors may affect the risk of DVT and PE differently. For example, studies repeatedly report that carriers of the FVL variant have a substantially (three-fold) increased risk of DVT, whereas the risk of PE is only mildly increased (up to two-fold) compared with non-carriers. The observation that patients at higher risk of VTE are more likely to present with the less severe manifestation of the disease has been called the "Factor V Leiden paradox".[115,116] Few studies have investigated possible mechanisms for this so-called paradox.[115,117,118] Some of the proposed mechanisms take into account whether FVL affects thrombus location, number of affected veins, time until diagnosis, clot propagation speed or density and whether these factors differ in in patients with DVT compared to patients with PE.[117] Further investigation into the FVL paradox is required.

Future Directions: Identification of Rare Variants associated with VTE Risk

It has been estimated that common variants captured by existing GWAS arrays explain 35% of the genetic variance underlying VTE susceptibility.[109] However, as we have discussed, existing GWA studies for VTE have had limited success identifying previously undiscovered variants and a large proportion of variants associated with VTE are yet to be identified.[108,109] Variants that have been discovered tend to be rare (<5% prevalence), functional, and have relatively strong effects.[57,119–121] If heretofore-unknown risk factors for VTE are similar, an approach focused on low-frequency coding variants may outperform GWAS approaches at detecting potential susceptibility variants. Efforts to identify new rare variants associated with VTE risk are currently ongoing through a meta-analysis of exome-wide association studies of VTE being performed by the INVENT consortium. Future steps towards the identification of new genetic variants associated with VTE risk may also include approaches like targeted exome sequencing, or whole genome sequencing.

Gene-Environment Interactions

As we have discussed, both environmental and genetic risk factors contribute to VTE risk. However, these risk factors do not act in isolation. Previous research suggests that VTE risk is greatest when genetic predisposition is combined with an environmental risk factor.[48,58,122–124] Understanding how genes and environmental risk factors interact may provide key insight into the pathophysiology of VTE and may identify opportunities for targeted prevention and treatment.[125–127] However, few interactions have been explored in prospective cohort studies, with work focusing mostly on short-term environmental risk factors such as trauma or surgery.[93,127–149]

One of the first gene-environment interactions explored was the effect of exogenous hormone use (either OCs or HT) and VTE risk in FVL mutation carriers. Studies support gene-environment interaction between the FVL mutation and exogenous hormone use, with a 35-fold increased risk of VTE in women with the FVL mutation who also used hormones.[130–133,136–139] One study also suggested that VTE risk associated with FXI risk alleles is blunted by statin use.[150] However, in a case-control study of the association between FXI variants and VTE risk, Harrington et al. showed that VTE risks were similar across strata of statin use and that there was no statistical evidence of a FXI-statin interaction.[151] In another analysis, Wolpin et al[58] found that the risk of PE with non-O blood type was higher among smokers (HR=2.56; 95% CI: 1.60, 4.07) than never smokers (HR=1.31; 95% CI: 0.83, 2.07; p for interaction = 0.04).[58] In order to build on those finding, Crous-Bou et al[114] explored interactions between genetic risk factors and two key environmental risk factors, BMI and smoking. This study represented the first detailed exploration of interactions between BMI, smoking, and genetic risk factors for VTE. Although the authors did not find evidence of multiplicative interactions between genetic and environmental risk factors, they did demonstrate additive effects of both on VTE risk.[114] Gene-environment interaction studies have the potential to provide key insight into the relative contribution of genetic and environmental risk factors for VTE, but result remain sparse. Further work into the interaction between genes and environment are needed.

Conclusions

In summary, both environmental and genetic factors contribute to the risk of VTE. Environmental factors can be characterized in a number of different ways, such as non-modifiable and modifiable factors; both of those have significant contribution in risk of VTE. Similarly, genetic risk factors influence the risk of VTE. Many of these were found through candidate gene studies, and only recently modern high-throughput techniques have increased our understanding of the genetic risk of VTE. Ultimately, however, VTE is a complex disease and is related to interactions between both environmental and genetic risk factors. This we are now beginning to understand, but future research should focus on a holistic approach that includes both genetic and environmental risk factors for VTE.

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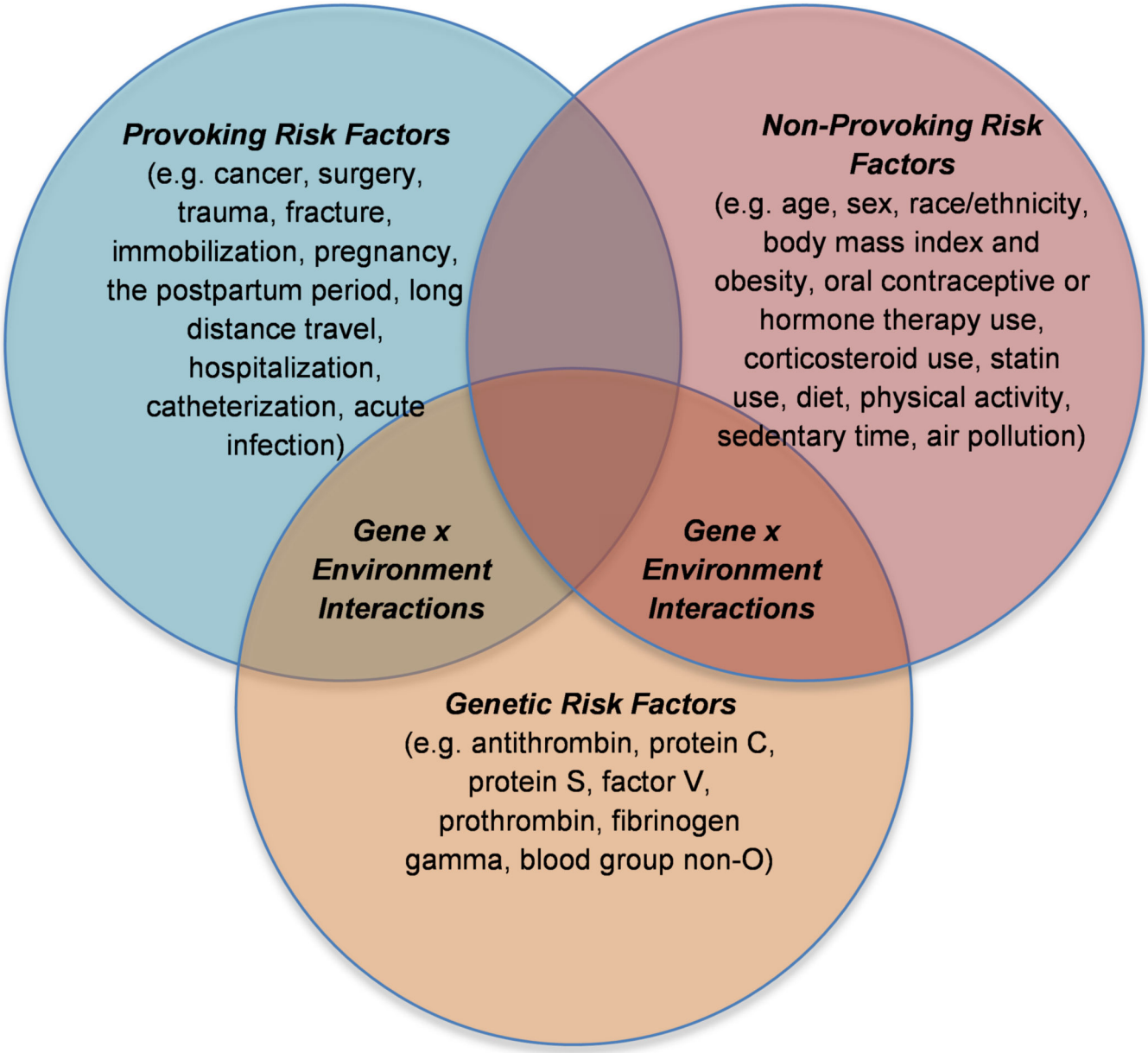

Figure 1. Environmental and Genetic Risk Factors for Venous Thromboembolism

Risk factors for venous thromboembolism are provoking, non-provoking, and genetic in nature.

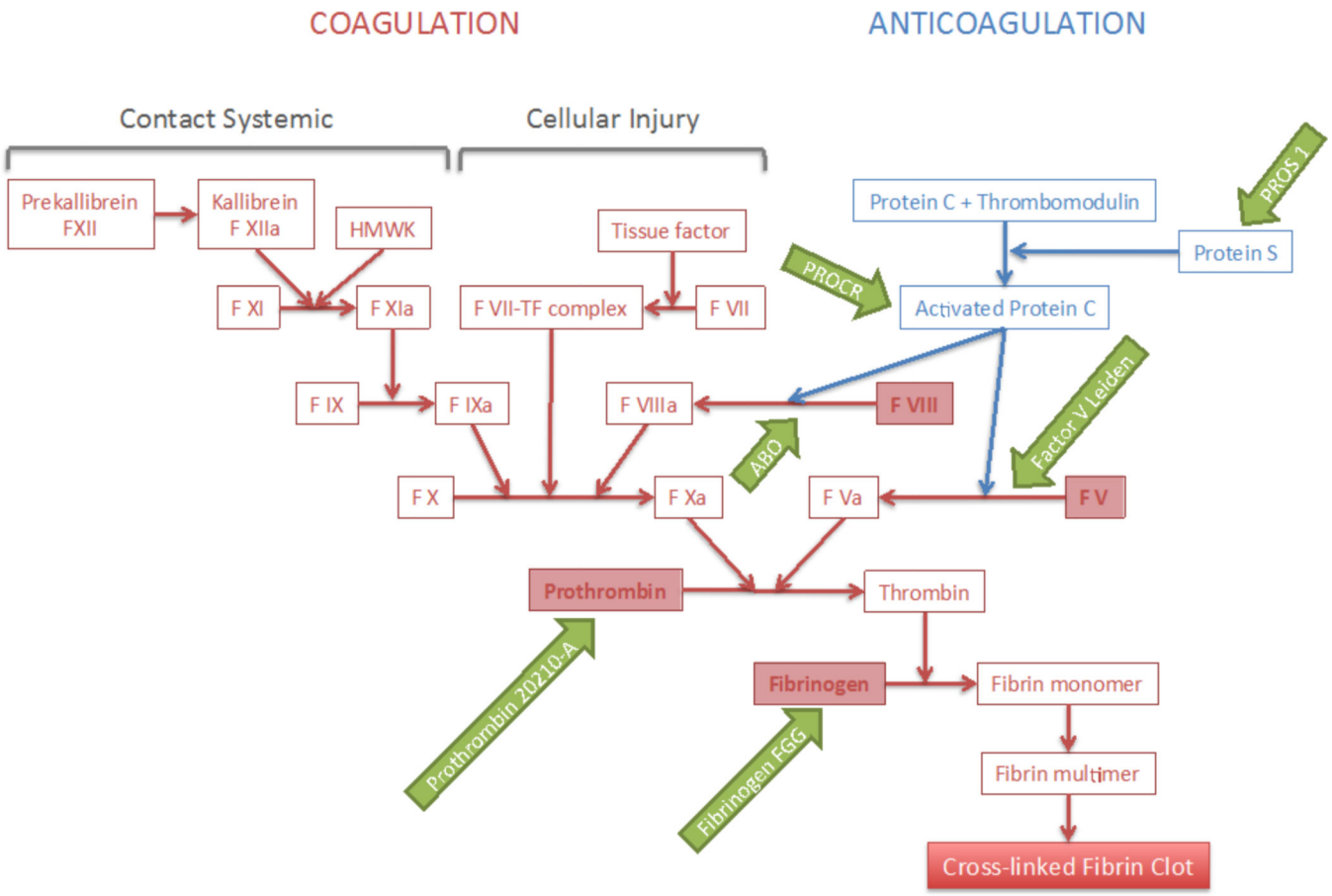

Figure 2. The Clotting Cascade

HW=high-molecular-weight kininogen. TF=tissue factor.