Expanding the genetic landscape of hereditary thrombophilia: classical defects, novel variants, and genomic perspectives. A narrative review

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ABSTRACT

Hereditary thrombophilia encompasses a spectrum of genetic conditions predisposing to venous thromboembolism (VTE). Traditionally, it has been attributed to a limited number of well-defined defects, including deficiencies of natural anticoagulants—antithrombin, protein C, and protein S—and two common gain-of-function mutations, Factor V Leiden and prothrombin G20210A. These classical abnormalities remain clinically relevant but explain only a minority of early-onset, recurrent, or familial cases. Advances in molecular genetics have uncovered a broader landscape of inherited susceptibility. Next-generation sequencing, whole-exome sequencing, and genome-wide association studies have identified rare and population-specific variants in genes such as *SERPINC1*, *PROS1*, *F2*, and *F5*, as well as regulatory and intronic changes influencing coagulation pathways. Additional contributors include elevated factor VIII, IX, or XI levels, fibrinogen structural variants, and abnormalities in fibrinolytic regulators such as TAFI and PAI-1. Beyond single-gene defects, evidence supports a polygenic model in which multiple low-effect alleles and modifier genes act synergistically with environmental triggers to determine thrombotic risk. This expanding genetic and functional complexity challenges the traditional binary concept of thrombophilia. Integrating genomic tools into clinical evaluation—while avoiding indiscriminate testing—may improve risk stratification in selected patients, particularly those with strong family history or unusual thrombotic phenotypes. Hereditary thrombophilia should therefore be regarded as a continuum of genetic predisposition rather than a categorical disorder, calling for a refined, personalized approach to prevention and management of VTE in the genomic era.

Key words: hereditary thrombophilia, venous thromboembolism, genetic predisposition.

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Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality.[1,2] While many events are linked to acquired risk factors such as surgery, trauma, malignancy, or hormonal therapy, a substantial proportion—particularly in younger, recurrent, or familial cases—remains unexplained.[3-6] This led to the investigation of inherited factors, collectively termed hereditary thrombophilia.

In the 19th century, Rudolf Virchow first described thrombosis as the result of three interacting factors—endothelial injury, blood stasis, and hypercoagulability.[7,8] Since then, this conceptual framework has progressively evolved, incorporating a broader and more dynamic understanding of thrombotic risk. Antithrombin (AT) deficiency, reported in 1965, became the prototype of a hereditary "loss-of-function" defect. Protein C (PC) and protein S (PS) deficiencies, described in the early 1980s, reinforced the model that the absence of natural anticoagulants drives hypercoagulability. During the 1990s the spectrum widened with two prevalent "gain-of-function" variants—Factor V Leiden (FVL)

and the G20210A prothrombin mutation (PTM)—showing that common alleles can also underlie thrombophilia.

However, conventional screening detects pathogenic variants in only a minority of patients. The advent of next-generation sequencing (NGS), whole-exome sequencing (WES), and genome-wide association studies (GWAS) revealed rare variants and polygenic influences. These discoveries are reshaping our understanding of thrombophilia, from a binary to a continuum of genetic susceptibility.

Although evidence exists in the literature supporting an association between inherited thrombophilia and arterial thrombotic events,[9,10] the present review focuses on VTE, where the clinical relevance of genetic thrombophilic defects is more clearly defined. To provide an overall framework for the conditions discussed in the following sections, Supplementary Table 1 summarizes their prevalence and estimated thrombotic risk.[10-17]

Classical hereditary thrombophilia

Historically, hereditary thrombophilia has been categorized according to two main molecular mechanisms: loss-of-function and gain-of-function defects. Loss-of-function variants typically involve deficiencies of natural anticoagulants, such as AT, PC, and PS, leading to insufficient regulation of thrombin generation. In contrast, gain-of-function mutations result in hyperactivity or increased expression of procoagulant proteins, exemplified by FVL—resistant to inactivation by activated PC (APC)—and the PTM, which increases plasma prothrombin levels.[18]

Loss-of-function defects

Antithrombin deficiency

AT deficiency was the first inherited thrombophilia to be identified. It was discovered in 1965 by the Norwegian physician Olav Egeberg, who described a family with recurrent VTE affecting several generations.[9] Laboratory investigations demonstrated reduced plasma anticoagulant activity, assessed by measuring AT activity in heat-defibrinated plasma using a plasma thrombin system, which was later attributed to AT deficiency. AT is a serine protease inhibitor produced by hepatocytes that plays a key anticoagulant role by inactivating thrombin and FXa, as well as FIXa, FXIa, and FXIIa to a lesser extent. Its activity is significantly enhanced by heparin and endothelial glycosaminoglycans, and it also exerts anti-inflammatory and endothelial-protective functions.[10,19]

Encoded by the *SERPINC1* gene, AT is affected by over 350 reported mutations that lead to two principal types of hereditary deficiency (Table 1).[9-17,16,20] Type I is a quantitative defect characterized by reduced levels of both antigen and activity, whereas type II is a qualitative defect, with normal antigen levels but impaired function. Type II is further divided into reactive site mutations (IIa), heparin-binding site variants (IIb), and pleiotropic or conformational defects (IIc).[10,16,20]

Laboratory diagnosis begins with chromogenic anti-FXa or anti-IIa assays, which may miss type II mutations, especially those affecting the heparin-binding site or glycosylation.[16,19] These tests do not distinguish type II subtypes, and in cases with normal ac-

Table 1. Molecular classification of hereditary antithrombin deficiency. The traditional distinction between quantitative (type I) and qualitative (type II) defects is expanded to include conformational and glycosylation-related variants, reflecting the molecular heterogeneity revealed by recent genetic and proteomic studies.

Type/subtype	Mechanism	Examples (mutation/variant)	Clinical/diagnostic implication	References
Type I (quantitative)	Reduced synthesis or secretion leading to decreased antigen and activity	Null mutations, large deletions, frameshifts	Low antigen and activity levels; complete deficiency incompatible with life	Egeberg 1965; Patnaik & Moll 2008[9,10]
Type IIa - Reactive site	Alteration of the thrombin inhibition site	Variants near Arg393	Normal antigen, reduced activity; variable thrombotic risk	Pabinger 2019[11]
Type IIb - Heparin-binding site	Impaired interaction with heparin	AT Toyama (Arg79Cys), AT Budapest 3 (Leu131Phe)	Decreased heparin cofactor activity; often mild phenotype in heterozygotes, severe in homozygotes	Olds 1992; Luxembourg 2014[12,13]
Type IIc - Conformational/pleiotropic	Abnormal folding or conformational instability affecting multiple domains	Pro439Thr, Pro461Ser, AT Cambridge II (A384S)	May present with normal antigen and activity but increased thrombotic risk	Martínez-Martínez 2012; Corral 2007[14,15]
Glycosylation-related variants (borderline Type I/II)	Mutations at or near N-glycosylation sites altering secretion or folding	Asn224His, Glu227Lys	May reduce secretion or modify glycan structure; activity may appear normal in routine assays; associated with early or recurrent thrombosis	de la Morena-Barrio 2022; Kruijt 2025[16,17]

tivity but strong clinical suspicion, antigenic quantification and molecular testing are essential.[19] Some conformational variants may mimic type I due to impaired secretion. Accurate classification requires integrated biochemical, functional, and genetic analysis.[16,20]

AT deficiency is the most thrombogenic inherited thrombophilia, with up to a 50-fold increased VTE risk and recurrence rates exceeding 60% without prophylaxis, and an estimated prevalence of 1:500-1:5000 in the general population.[10,16,19,20] Heterozygotes may remain asymptomatic, while compound heterozygotes can present with in utero thrombosis or neonatal purpura fulminans. Complete homozygous deficiency is presumed incompatible with life. During pregnancy, AT deficiency has been linked to placental complications and fetal loss.[10,19]

Management depends on clinical history and laboratory phenotype. Symptomatic patients usually receive long-term anticoagulation; asymptomatic carriers may receive thromboprophylaxis in high-risk settings.[10,20] AT supplementation or anti-FXa-guided monitoring may be required, as the anticoagulant effect of heparin depends on adequate AT levels. In selected clinical settings, such as the perioperative period or pregnancy, short-term AT replacement may be considered.[20]

Protein C deficiency

PC deficiency was first described in 1981 by Griffin and colleagues, who reported two families with a strong history of recurrent VTE and markedly reduced plasma PC activity.[21] PC is a vitamin K-dependent serine protease encoded by the *PROC* gene, activated by thrombin bound to thrombomodulin (TM). APC inactivates FVa and VIIIa and modulates inflammation via EPCR and PAR-1.[22-24]

More than 270 mutations in *PROC* have been reported, including missense, nonsense, and splicing variants.[23,25] Hereditary deficiency is typically inherited in an autosomal dominant manner in heterozygous individuals, while severe neonatal presentations occur in the setting of biallelic deficiency, consistent with recessive inheritance.[24,26] The molecular and clinical classification of hereditary PC deficiency is summarized in Table 2.[21,26-30]

Type I deficiency, with reduced antigen and activity levels, is more common than type II, which involves normal antigen but reduced function and is often underdiagnosed due to the limited sensitivity of chromogenic assays.[31,32] Clot-based assays are more reliable for detecting type II variants.[31,33] In selected cases—particularly those with neonatal onset or familial clustering—genetic analysis may aid diagnostic confirmation by integrating clinical and laboratory data.[23,25]

Variants affecting the activation peptide or catalytic site can compromise APC function.[25,34] While no single mutation is predominant, the pathogenic role of rare or population-specific variants must be assessed in the context of laboratory data due to variable penetrance.

Heterozygous PC deficiency increases VTE risk 7- to 10-fold, with an estimated prevalence in the general population of approximately 1:200-1:500, particularly in the presence of concomitant acquired risk factors such as surgery, pregnancy, or hormonal exposure.[23,24,35] Homozygous or compound heterozygous forms are rare and typically manifest at birth with purpura fulminans, disseminated intravascular coagulation (DIC), or cerebral thrombosis.[26,36,37] Long-term anticoagulation is reserved for symptomatic cases; prophylaxis is used in high-risk settings.[22,38] Severe neonatal forms require replacement therapy and ongoing prophylaxis.[26,36] In refractory cases, liver transplantation may be considered.[26]

Protein S deficiency

Association of familial protein S deficiency with recurrent thrombosis was reported in 1984.[39] PS is a vitamin K-dependent glycoprotein synthesized in hepatocytes and endothelial cells.[40-42] It acts as a cofactor for APC in inactivating FVa and FVIIIa and also participates in APC-independent inhibition of coagulation via interactions with TFPI and the intrinsic tenase and prothrombinase complexes.[40,42,43] In plasma, about 60% of PS is bound to C4b-binding protein (C4BP) and is functionally inactive, while 40% circulates in the free, active form.[40,43,44]

Hereditary PS deficiency is categorized into three types (Table 3).[25,30,39,45-47]

Type I involves reduced total and free antigen levels along

Table 2. Molecular and clinical classification of hereditary protein C deficiency. Quantitative (type I) and qualitative (type II) defects represent the heterozygous forms associated with increased risk of venous thrombosis, whereas compound heterozygous or homozygous mutations cause severe neonatal phenotypes such as purpura fulminans.

Type/subtype	Mechanism	Examples (mutation/variant)	Clinical/diagnostic implication	References
Type I (quantitative)	Reduced synthesis or secretion of protein C, leading to decreased antigen and activity levels	Nonsense or frameshift mutations, large deletions, splice-site variants	Low antigen and activity; classical hereditary form	Griffin 1981; Bertina 1982[21,27]
Type II (qualitative)	Normal antigen but reduced functional activity due to structural or post-translational alterations	Missense variants affecting the catalytic or activation domain (*e.g.* His160Arg, Arg169Trp, Lys193del)	Normal antigen with low activity; may be missed if only antigen assays are used	Reitsma 1993; Esmon 1987[28,29]
Compound heterozygous/ homozygous forms	Presence of two pathogenic *PROC* alleles causing complete or near-complete loss of function	Various combinations of null or missense variants	Severe neonatal purpura fulminans or early-onset thrombosis	Marlar 1989; Dreyfus 1991[26,30]

with reduced activity.[22] Type II is characterized by normal antigen levels but impaired function, often due to defects in APC interaction.[45] Type III features normal total PS but reduced free PS and activity, possibly due to increased C4BP binding or altered protein expression.[40,44] Differentiating these subtypes requires combined antigenic and functional testing, though interpretation is often complicated by physiological modifiers such as estrogen use, pregnancy, liver dysfunction, or anticoagulant therapy.[44,48]

Prevalence in the general population is estimated between 0.03% and 0.21%, but it rises significantly among VTE patients.[48,49] Founder variants (*e.g.*, Tokushima) contribute regionally.[25,48] PS deficiency increases the risk of VTE, including DVT, PE, and pregnancy complications such as recurrent fetal loss.[48,49] Recurrence risk is elevated, though diagnostic challenges and phenotypic variability hinder precise estimation.[49] Genetic testing is limited by the presence of the *PROS2* pseudogene and by a weak genotype-phenotype correlation, which complicate variant interpretation.[25,49] Asymptomatic carriers require prophylaxis only in high-risk settings.[22,48] In neonatal purpura fulminans, fresh frozen plasma is the only available replacement.[41]

Gain-of-function disorders

Factor V-related activated protein C resistance

The archetype of inherited APC resistance is FVL: a single G→A substitution at nucleotide 1691 in *F5* replaces Arg506 with Gln, erasing a critical APC-cleavage site, prolonging FVa activity, and accelerating thrombin generation.[50-52] FVL is the most common inherited thrombophilia in Caucasians (~5% in Europe; up to 15% in countries like Sweden, Greece, and Lebanon), and is rare in Asian, African, and Indigenous American populations.[53,54] Heterozygotes have a 3-7-fold increased VTE risk, while homozygotes may reach 10-80-fold, particularly with additional triggers (*e.g.*, surgery, pregnancy, estrogen).[51,53] Estrogen-containing contraceptives may raise the risk up to 35-fold in heterozygotes.[51,53] FVL is detected in ~25% of first VTEs and >50% of inherited thrombophilias[53]. Diagnosis relies on APC resistance assays or genotyping.[51,55] Treatment decisions depend on genotype and clinical history; long-term anticoagulation is considered in homozygotes or in patients with recurrent events.[51,53]

A related condition, FVL pseudo-homozygosity, arises when FVL is co-inherited with a loss-of-function *F5* mutation on the other allele.[56-58] The mutant FVL protein is the only one expressed, resulting in functional homozygosity.[57-59] This state leads to pronounced APC resistance and enhanced thrombin generation, often exceeding that of true homozygotes.[57,58] It may be misclassified by genotyping alone and requires functional assays or FV antigen/activity measurements for accurate identification.[51,55] These patients may present with early or unprovoked VTE and often benefit from the same preventive strategies used for homozygotes.[60]

Beyond FVL, several rare *F5* variants can cause APC resistance through different mechanisms (Table 4).[61-68]

Mutations at cleavage sites—such as FV Cambridge (Arg306Thr)[62] and FV Hong Kong (Arg306Gly)[63]—reduce FVa inactivation.[50,52] Structural variants like FV Liverpool (Ile359Thr),[64] FV Bonn (Ala512Val),[65] and Glu666Asp[66] affect nearby domains or introduce abnormal glycosylation, while FV Nara (Trp1920Arg)[67] and FV Besançon (Ala2086Asp),[68] located in the C-terminal domains, impair phospholipid binding and PS interaction. These mutations variably affect FVa inactivation and cofactor functions, potentially increasing thrombosis risk.[50,52]

Clinically, these non-Leiden variants range from asymptomatic to recurrent or unusual site thromboses.[50,69] Their identification is challenging, often requiring extended molecular analysis, as standard FVL genotyping may miss them. Functional APC resistance assays can be helpful, particularly in FVL-negative patients not on anticoagulation.[51,55]

Table 3. Molecular and clinical classification of hereditary protein S deficiency. Quantitative (type I) and qualitative (type II) defects are the most common heterozygous forms associated with increased risk of venous thrombosis, while type III involves selective reduction of free protein S. Homozygous or compound heterozygous mutations cause severe neonatal thrombosis or purpura fulminans.

Type/subtype	Mechanism	Examples (mutation/variant)	Clinical/diagnostic implication	References
Type I (quantitative)	Reduced synthesis or secretion of protein S leading to decreased total and free antigen, and reduced activity	Nonsense, frameshift, or splicing mutations in *PROS1*	Low total and free antigen and reduced activity; classical form of hereditary deficiency	D'Angelo 2008; Reitsma, 1991[25,45]
Type II (qualitative/functional)	Normal antigen levels but reduced functional activity due to structural alterations of the cofactor domain	Missense variants affecting the APC cofactor or C4b-binding regions	Normal antigen, low activity; often underdiagnosed if only antigen assays are used	Comp 1990; Reitsma 1991[25,39]
Type III (free protein S deficiency)	Normal total antigen but decreased free protein S and reduced activity due to increased binding to C4b-binding protein	Variants influencing C4BP-binding site or regulatory regions	Normal total, low free protein S and activity; phenotypically similar to Type I	Lauer 1990[46]
Compound heterozygous/ homozygous forms	Two pathogenic *PROS1* alleles causing severe or complete deficiency	Various null or missense variants	Neonatal purpura fulminans, DIC, or early-onset thrombosis	Dreyfus 1991; Tang 2022[30,47]

Prothrombin gain-of-function mutations

The G20210A mutation in the *F2* gene, located in the 3′ untranslated region, increases mRNA stability and prothrombin levels by ~30%, enhancing thrombin generation.[70,71] PTM is the most common prothrombotic variant in prothrombin, with an allele frequency of 1-6% in Europeans and is rare in other populations.[71,72] Inherited dominantly with incomplete penetrance, it confers a 2-4-fold increased risk of VTE in heterozygotes, further amplified by acquired triggers (*e.g.*, surgery, pregnancy, estrogen) or coexisting thrombophilias like FVL.[71,73] Homozygosity is rare but associated with higher thrombotic risk.[72,74] PTM has also been repeatedly linked to unusual-site thrombosis, particularly cerebral venous sinus and splanchnic vein thrombosis.[70,75]

The mutation is not detectable by functional assays and requires molecular testing.[70,74] Long-term anticoagulation is not generally recommended for asymptomatic carriers, but thromboprophylaxis is indicated in high-risk situations.[70,73]

Non-O blood group

The ABO blood group system, first described by Karl Landsteiner in the early 20th century, is a major determinant of thrombotic risk: individuals with non-O blood types (A, B, or AB) have a 1.5- to 2.5-fold higher VTE risk than those with group O, making it the most prevalent inherited thrombophilic factor worldwide.[76-80] This association mainly reflects higher plasma von Willebrand factor (VWF) and FVIII levels in non-O individuals.[79-81] ABO glycosyltransferase activity modifies VWF glycosylation, leading to reduced VWF clearance and impaired ADAMTS13-mediated proteolysis, thereby favoring the presence of thrombogenic high-molecular-weight multimers.[79-81] VWF and FVIII are approximately 25-30% higher in non-O subjects, particularly in AA or A1B genotypes.[77,80,82] Large studies confirmed this association for both first and recurrent VTE (hazard ratios up to 2.0).[76,78,83,84] Additional mechanisms—such as ABO-related differences in adhesion molecules (*e.g.*, selectins,

Table 4. Molecular and clinical characteristics of factor V variants associated with activated protein C (APC) resistance. Factor V Leiden (Arg506Gln) is the archetypal and most prevalent cause, but several rare non-Leiden variants can impair FVa inactivation or its cofactor interactions, contributing variably to thrombotic risk.

Variant/condition	Genetic/molecular defect	Functional effect	Clinical/diagnostic features	References
Factor V Leiden (Arg506Gln)	G→A substitution at nucleotide 1691 in *F5*; loss of Arg506 APC-cleavage site	Markedly reduced APC-mediated inactivation of FVa; prolonged FVa activity	Most common inherited thrombophilia (~5% of Europeans); 3-7× VTE risk in heterozygotes, up to 80× in homozygotes; detected by APC resistance assay or genotyping	Bertina 1994[61]
Pseudo-homozygous FVL	FVL on one allele + null *F5* mutation on the other	Only protein expressed → functional homozygosity	Enhanced APC resistance exceeding true homozygotes; may be missed by genotyping alone; requires FV antigen/activity testing	Simioni 1996[56]
FV Cambridge (Arg306Thr)	Mutation at APC-cleavage site Arg306	Partial APC resistance; slower FVa inactivation	Rare; may occur alone or with FVL; detected by functional APC resistance assay	Williamson 1998[62]
FV Hong Kong (Arg306Gly)	Mutation at Arg306 cleavage site	Reduced cleavage by APC; partial resistance	Very rare; mild phenotype, often coexisting with FVL	Chan 1998[63]
FV Liverpool (Ile359Thr)	Missense mutation near APC-interaction region	Altered FVa conformation; reduced susceptibility to APC	Rare; reported in VTE and pregnancy complications	Mumford 2003[64]
FV Bonn (Ala512Val)	Missense variant in A2 domain	May alter glycosylation and FVa stability	Rare; associated with mild APC resistance	Pezeshkpoor 2003[65]
FV Glu666Asp	Substitution in A2 domain	Affects FVa-APC interaction and stability	Functional APC resistance; rare	Cai 2010[66]
FV Nara (Trp1920Arg)	Mutation in C2 domain	Impaired phospholipid binding and reduced cofactor function for APC	Reported in familial thrombosis; FVL-negative APC resistance	Nogami 2014[67]
FV Besançon (Ala2086Asp)	Mutation in C-terminal region	Disrupts protein S interaction and membrane binding	May increase thrombotic tendency; rare	Castoldi 2021[68]

ICAM-1, TNF-α) and platelet function—may further increase risk, especially when combined with other thrombophilias like FVL or PTM.[81,85,86] Unlike the major hereditary thrombophilias, ABO blood group—as well as other additional genetic modifiers described in the following sections—acts as a risk modulator rather than a determinative defect and therefore does not influence anticoagulant duration or prophylaxis, which remain guided by clinical factors.

Congenital dysfibrinogenemia

Congenital dysfibrinogenemia is a rare qualitative fibrinogen disorder traditionally associated with mild bleeding or incidental laboratory findings.[87,88] Recent data suggest that some variants may predispose to thrombosis, particularly in familial cases or postpartum.[89,90] Structural defects in fibrinogen can impair thrombin binding or fibrinolysis despite normal antigen levels, creating a prothrombotic state.[88,90] Thrombosis rates may exceed bleeding, with VTE or arterial events reported in up to 30% of patients by age 50.[90] Mutations such as FGA Arg35His and FGB Arg44Cys have been linked to thrombotic phenotypes, although genotype-phenotype correlation is inconsistent.[89,90] Prolonged thrombin or reptilase times with discordant antigen and activity levels may suggest the diagnosis, which is confirmed by fibrinogen gene sequencing.[87,90]

Elevated FVIII, FIX, and FXI

Persistent elevation of FVIII, FIX, and FXI is an important yet often underrecognized contributor to VTE. These quantitative gain-of-function traits, shaped by genetic and environmental factors, bridge the spectrum between polygenic predisposition and rare monogenic hypercoagulability.

Elevated FVIII is one of the most consistent laboratory findings in unprovoked or recurrent VTE. Levels above 150 IU/dL (approximately the 90th percentile) confer a three- to fivefold higher, dose-dependent, and persistent risk. Although FVIII is an acute-phase reactant, many individuals show chronically elevated levels, suggesting a stable prothrombotic trait. Familial clustering and twin studies indicate heritability, with about 40% of first-degree relatives similarly affected. High FVIII results from combined genetic and environmental influences, including variants regulating *F8* expression or VWF clearance, non-O blood group, age, sex, BMI, inflammation, and estrogen exposure.[91]

High FIX levels confer a two- to threefold increased risk of VTE, as first demonstrated in the Leiden Thrombophilia Study and confirmed in subsequent epidemiological cohorts.[92,93] More broadly, FIX levels are influenced by hormonal status, aging, BMI, and FVIII concentration.[93,94]

While several factors are associated primarily with the risk of a first VTE, others—most notably elevated FXI levels—appear to confer a disproportionate risk of recurrence. In most clinical and epidemiological studies, FXI levels have been assessed as coagulant activity. Persistently elevated FXI levels (above the 90th percentile) have been associated with a twofold risk of first VTE and a fivefold risk of recurrence.[95,96] Genetic predisposition has been linked to *F11* variants such as c.539A>G and rs2289252, which increase FXI levels and correlate with both first and recurrent VTE.[97-99] FXI elevation enhances thrombin generation and reduces fibrinolysis, sustaining coagulation activation over time.[95,99]

Novel hereditary thrombophilia

Taken together, the classical hereditary thrombophilias—caused by quantitative or qualitative defects in natural anticoagulants or by procoagulant gain-of-function mutations—represent the cornerstone of our understanding of inherited VTE risk. Yet, they explain only a fraction of cases —approximately 30-40%,[100] prompting the exploration of novel molecular pathways and rare variants underlying thrombophilia.

Novel *SERPINC1* variants

Recent advances in sequencing technologies have expanded our understanding of the genetic basis of AT deficiency. For instance, mutations at glycosylation sites such as Asn224His[17] and Glu227Lys[16] may reduce secretion or alter function without affecting routine activity results. Conformational variants like Pro439Thr, Pro461Ser,[15] and the relatively frequent Cambridge II (A384S)[14]—particularly prevalent in British and Spanish populations—may confer a high thrombotic risk even when standard antigen and activity levels appear normal. Ethnically enriched mutations such as AT Budapest 3 (Leu131Phe)[12] and AT Toyama (Arg79Cys)[13] are typically mild in heterozygosity but can result in severe phenotypes when present in compound heterozygous or homozygous form.

Antithrombin-resistant prothrombin variants

Beyond the common G20210A mutation, several rare *F2* variants have been described that alter thrombin regulation and confer a prothrombotic phenotype, collectively referred to as prothrombin dysprothrombinemias[73] (Table 5).

The archetypal examples involve substitutions at Arg596, a residue essential for thrombin inhibition by AT. The three best-characterized variants—Prothrombin Yukuhashi (Arg596Leu),[101] Belgrade (Arg596Gln),[102] and Padua 2 (Arg596Trp)[104]—impair AT-mediated inactivation of thrombin, prolonging its activity despite normal or only slightly reduced antigen levels. Carriers, typically heterozygous, often present with early or unusual-site VTE but no bleeding tendency.[74] Functional studies show delayed thrombin-AT complex formation and preserved coagulant potential, defining a true AT-resistant phenotype.[101,104]

Additional variants have expanded this spectrum beyond the Arg596 cluster. The Prothrombin Keio (Tyr434His)[105] mutation modifies thrombin's affinity for fibrinogen, PC, and thrombin aptamers, affecting both substrate binding and inhibitory regulation. The Arg541Trp variant,[106-109,113] identified in several East Asian families, shows mildly reduced thrombin activity with normal antigen levels and selectively impairs the PC-mediated anticoagulant pathway, without altering clotting assays. Similarly, variants at Arg382—including Arg382His,[108,109,113] Phe382Ser,[111] and Phe382Leu[111]—produce more complex effects, markedly reducing catalytic activity and disrupting thrombin interactions with PC, TM, heparin cofactor II, and thrombin activatable fibrinolysis inhibitor (TAFI). The Arg382His substitution, in particular, leads to severely impaired thrombin inhibition by multiple pathways and diminished prothrombin activation by the FXa-FVa complex, affecting both procoagulant and anticoagulant functions.[108,109,113]

Other variants highlight additional mechanisms. Prothrombin Amrita (Arg553Gln),[114] located within the Na^+-binding loop, pro-

longs the lifetime of active thrombin by destabilizing sodium coordination, thereby shifting thrombin toward its slow conformational form with increased procoagulant persistence. Similarly, substitutions near this regulatory loop, such as Arg541Trp[106,107] and Asp597Tyr,[111] appear to alter Na^+-dependent allosteric equilibrium and inhibitor interactions, resulting in dual impairment of PC- and AT-mediated inactivation.

Gain-of-function variants in coagulation factors

Beyond quantitative determinants of coagulation factor levels, rare gain-of-function variants can directly drive thrombosis through enhanced procoagulant activity.

The FVIII Padua variant, due to a 23.4-kb tandem duplication encompassing the F8 promoter, exon 1, and part of intron 1, was first identified in a young Italian man with recurrent unprovoked VTE and persistently high FVIII activity. This structural alteration leads to transcriptional up-regulation and markedly increased FVIII levels.[115] Another example is FVIII Aurora (p.Arg590Ser), a gain-of-function variant located in the A2 domain, associated with markedly increased FVIII activity despite normal antigen levels and recurrent venous thrombosis, supporting the concept that FVIII hyperfunction alone can drive thrombosis.[116]

The FIX Padua (p.Arg338Leu) mutation provides clear molecular evidence that increased FIX catalytic activity can directly cause thrombosis. This gain-of-function variant, located in the catalytic domain, enhances FIXa efficiency and markedly increases thrombin generation.[117] Another variant, FIX Shanghai (p.Arg338Gln), identified in a Chinese family with multiple thrombotic events, produces a similar phenotype with increased specific activity and enhanced activation by FXIa.[118]

Fibrinolytic system abnormalities

Alterations of the fibrinolytic system have long been investigated as potential contributors to VTE. However, despite their clear biological role in clot dissolution, only a limited number of

Table 5. Rare prothrombin (F2) variants associated with antithrombin resistance and prothrombotic dysprothrombinemia. These mutations cluster mainly around Arg596, impairing thrombin inhibition by antithrombin while maintaining normal clotting function. The phenotype, sometimes termed type III dysprothrombinemia, is characterized by venous or unusual-site thrombosis in heterozygotes with normal routine assays.

Variant/name	Amino acid change	FII:Act/Ag findings	Affected pathway	Functional/clinical effect	References
Prothrombin Yukuhashi	Arg596Leu	FII:Act reduced; Ag slightly reduced	AT-mediated inhibition	Impaired AT-mediated inactivation; prolonged thrombin activity	Miyawaki 2012[101]
Prothrombin Belgrade	Arg596Gln	Not reported	AT-mediated inhibition	Reduced AT-thrombin interaction; preserved coagulant activity	Djordjevic 2013; Kishimoto 2016[102,103]
Prothrombin Padua 2	Arg596Trp	FII:Act reduced; Ag slightly reduced	AT-mediated inhibition	Delayed thrombin-AT complex formation; thrombosis without bleeding	Bulato 2016[104]
Prothrombin Keio	Tyr434His	Not reported	Substrate affinity (fibrinogen, PC)	Altered binding to fibrinogen, protein C, and thrombin aptamer	Takenouchi 2019[105]
Arg541Trp	Arg541Trp	FII:Act slightly reduced; Ag normal	PC-mediated inhibition	Reduced protein C-dependent inactivation; normal coagulant function	Wu 2020; Yamamoto 2021[106,107]
Arg382His	Arg382His	FII:Act strongly reduced (<1%); Ag normal	PC- and HCII-mediated inhibition	Severe impairment of protein C, TAFI, and HCII activation; reduced prothrombin activation	Akhavan 2000, Ding 2017[108,109]
Prothrombin Amrita	Arg553Gln	Not reported	Thrombin activation kinetics	Prolonged active thrombin form; delayed inactivation	Sivasundar 2013[110]
Phe382Ser	Phe382Ser	FII:Act slightly reduced; Ag normal	PC-mediated inhibition	Impaired anticoagulant activity via protein C pathway	Wu 2025[111]
Phe382Leu	Phe382Leu	FII:Act reduced; Ag normal	PC-mediated inhibition	Similar phenotype to Phe382Ser; reduced PC-dependent inactivation	Wu 2025[111]
Asp597Tyr	Asp597Tyr	FII:Act normal/slightly reduced; Ag normal	PC- and AT-mediated inhibition	Dual impairment of protein C and AT inactivation; mild hypercoagulability	Wu 2025[111]

fibrinolytic abnormalities have shown a consistent and clinically relevant association with VTE.

Plasminogen deficiency is a rare inherited disorder characterized by reduced plasminogen levels and impaired fibrinolysis, classically associated with pseudomembranous lesions of mucosal surfaces.[119] Partial plasminogen deficiency was initially proposed as a potential risk factor for VTE, based on early observational reports. However, subsequent clinical studies and family-based analyses failed to demonstrate a consistent increase in VTE risk, and plasminogen deficiency is therefore no longer regarded as a clinically relevant hereditary thrombophilia.[119,120]

TAFI is a zymogen activated by the thrombin-TM complex that inhibits fibrinolysis by removing C-terminal lysines from fibrin, reducing plasminogen binding.[121,122] Elevated TAFI levels are modestly associated with increased VTE risk.[121,123] In the MEGA study, the highest TAFI quartile had a 1.6-fold increased VTE risk.[123] Variants in the CPB2 gene, such as 505G/A (Ala147Thr) and 1040C/T (Thr325Ile), affect TAFI levels and have been linked to thrombosis.[122,124,125] The 505GG genotype paradoxically showed increased DVT risk.[124,125] These associations appear context-dependent, influenced by genetic and hormonal factors.[124-126]

PAI-1 inhibits tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), downregulating plasmin generation and fibrinolysis.[127,128] Elevated levels promote a hypofibrinolytic state and have been linked to VTE.[127,129] The 4G/5G polymorphism in the *SERPINE1* promoter affects PAI-1 expression, with the 4G allele associated with higher levels.[127,129,130] Studies like Sartori et al. found increased 4G/4G prevalence in DVT patients, especially with coexisting thrombophilic mutations.[131] However, results vary: Wang et al. found no VTE association in a Chinese cohort but noted better outcomes in 5G/5G carriers.[132] Other studies emphasize that functional PAI-1 activity, more than genotype, correlates with thrombosis risk.[127,128,133]

Debated contributors to inherited thrombophilia

Several additional genetic and molecular factors may influence VTE risk through effects on endothelial function, coagulation, or fibrinolysis. However, due to inconsistent evidence, low penetrance, and limited validation, their clinical relevance remains uncertain. These markers are not included in standard thrombophilia screening but may be considered in selected cases.

Hyperhomocysteinemia, defined as elevated plasma homocysteine levels, has been long studied as a thrombosis risk factor.[134,135] Excess homocysteine promotes endothelial dysfunction, oxidative stress, activation of coagulation factors, and impaired fibrinolysis.[136,137] Its clinical significance depends on the cause and magnitude of elevation.[137] The congenital form, due to cystathionine β-synthase (CBS) deficiency, is a true hereditary thrombophilia characterized by homocysteine levels often >100 µmol/L and early-onset venous or arterial events, sometimes with lens dislocation, skeletal changes, or neurological impairment. Early and sustained vitamin therapy (B6, B12, folate, betaine) markedly reduces thrombotic risk.[135-137] In contrast, mild to moderate hyperhomocysteinemia (15-30 µmol/L) is usually secondary to nutritional, renal, or drug-related factors, or to the MTHFR C677T variant.[134,137] Large studies have shown no causal link between MTHFR polymorphisms and VTE, and homocysteine-lowering therapy offers no preventive benefit.[136-138] Therefore, MTHFR genotyping is not recommended, and mild elevations should prompt evaluation for reversible causes rather than be considered hereditary thrombophilia.[137,138]

Lipoprotein(a) [Lp(a)] is a genetically determined lipoprotein composed of an LDL particle covalently linked to apolipoprotein(a), which is structurally homologous to plasminogen. This homology confers antifibrinolytic effects, as Lp(a) competes with plasminogen for binding to fibrin and tissue plasminogen activator (tPA), thereby inhibiting clot lysis.[139,140] Lp(a) also promotes PAI-1 expression, platelet activation, and denser fibrin networks.[140,141] Although case-control studies have reported modest associations between elevated Lp(a) levels and VTE, large prospective cohorts have not confirmed this link.[139,141,142]

Heparin cofactor II (HCII) is a serine protease inhibitor that selectively inhibits thrombin in the presence of dermatan sulfate.[143] While early reports described associations between HCII deficiency and thrombosis, particularly in homozygous cases, larger studies have failed to demonstrate a clear link—especially in heterozygotes.[143,144] HCII deficiency may contribute to thrombotic risk only in the presence of additional inherited or acquired prothrombotic factors.[143]

Endothelial protein C receptor (EPCR) enhances the activation of PC on the endothelial surface. Its soluble form (sEPCR), generated by alternative splicing or proteolytic shedding, may interfere with PC activation.[145,146] The A3 haplotype (Ser219Gly) in the *PROCR* gene is associated with increased sEPCR levels and a modest increase in VTE risk, particularly in carriers of other prothrombotic mutations such as PTM.[145,147,148]

TM is a transmembrane glycoprotein expressed on endothelial cells that binds thrombin, redirecting its function from procoagulant to anticoagulant by facilitating activation of PC and TAFI.[149] Rare variants in the *THBD* gene may impair these functions and have been observed in patients with thrombosis or bleeding.[150,151] Functional studies suggest that some variants (*e.g.*, L433P) disrupt TM-thrombin interaction, but these remain of uncertain clinical significance due to their rarity.[151,152]

Apolipoprotein E is involved in lipid metabolism and exists in three isoforms (E2, E3, E4).[153] Some case-control studies have reported associations between the E2 or E4 alleles and VTE risk, possibly through modulation of coagulation factor levels or inflammatory pathways.[154,155] However, these findings are inconsistent and not confirmed in large prospective studies.

Protein Z (PZ) and its cofactor ZPI inhibit activated FX (FXa) and, to a lesser extent, FXIa and FIXa.[156] Several studies have linked low PZ levels or rare ZPI mutations (*e.g.*, Arg67Stop) to increased risk of VTE and pregnancy complications.[157-159] However, the reproducibility of these findings is limited by assay variability, confounding factors (*e.g.*, inflammation, vitamin K status), and lack of standardization.[160,161]

Redefining inherited thrombophilia: insights from genomic medicine

Traditional thrombophilia testing—focused on AT, PC, PS deficiencies and common variants like FVL and PTM—often fails to explain early-onset, recurrent, or unprovoked VTE, especially in patients with strong personal or family histories.[162-165] Moreover,

clinical variability among carriers of the same mutation suggests additional genetic or environmental modifiers.[162,166] Genomic tools such as NGS and WES have uncovered rare or previously unrecognized variants in genes including *SERPINC1, PROS1, F2*, and *F5*.[163,164,167-169] Studies by Suchon,[100] Lunghi,[168] and Kramer[170] report pathogenic or likely pathogenic variants in up to 35% of patients with negative standard testing, including coding and intronic changes. These findings support a shift toward a polygenic model of thrombophilia, in which multiple low-effect variants—so-called modifier genes—combine to influence thrombotic risk.[166,171,172] The concept of "mutational burden", introduced by Westrick and Ginsburg, explains how individuals with the same variant may show different clinical outcomes.[166] GWAS have further implicated regulatory and intronic variants—such as those in ADAMTS13 and FN1—in thrombotic susceptibility.[171-173] However, interpretation of variants of uncertain significance (VUS) remains a major challenge, especially in the absence of functional validation.[163,165,168]

Despite its potential, genomic testing is not recommended for routine screening but can be a useful tool to selected patients with strong familial clustering, early-onset disease, or unusual thrombotic phenotypes.[100,165,170] Interpretation requires multidisciplinary expertise to prevent misclassification and overdiagnosis.[163,165,169] The development of curated databases, functional studies, and polygenic risk models will be key to broader clinical integration.[168,172,174]

Overall, the classical monogenic view of thrombophilia is being replaced by a more nuanced model involving rare variants, genetic modifiers, and environmental triggers.[100,162,166] While conventional testing remains the first step, genomic tools offer new opportunities to refine individual risk stratification and develop personalized prevention and management strategies for VTE.

Conclusions

Hereditary thrombophilia is a complex and evolving condition. While classical defects—such as deficiencies of natural anticoagulants and mutations in FV and prothrombin—remain key elements of clinical evaluation, they do not account for many idiopathic, recurrent, or familial cases. Advances in NGS and genome-wide studies have revealed a broader genetic landscape involving rare variants, polygenic risk scores, modifier genes, and regulatory polymorphisms. These insights highlight the limitations of a binary diagnostic framework and support the adoption of more integrated models of genetic risk. Expanding the use of genomic testing, when guided by appropriate validation and clinical expertise, may improve individual risk stratification and contribute to more personalized strategies for VTE prevention and management.

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Online supplementary material:

Supplementary Table 1. Incidence and risk of venous thromboembolism associated with inherited thrombophilic defects.