TABLE 52-2 PREVALENCE AND THROMBOTIC RELATIVE RISK ASSOCIATIONS OF LABORATORY FINDINGS*

PREVALENCE IN GENERAL POPULATION	VENOUS RR	ARTERIAL RR
Hyperhomocysteinemia (25%)	1-2	1.16
Activated protein C resistance (5%)		
Heterozygous FVL	7	1
Homozygous FVL	20-80	
Prothrombin G20210A mutation (1-2%)		
Heterozygous	2-5	1
Homozygous	>5	1
Platelet GPIIb/IIIa HPA-lb homozygosity (2-3%)		4 (MI in men)
Protein C deficiency (0.2-0.5%)	7	1
Protein S deficiency (0.1%)	8.5	1
AT deficiency (0.02-0.05%)	8	1
Dysfibrinogenemia (rare)	~1	1.5

AT, Antithrombin; FVL, factor V Leiden; GPIIb/IIIa, glycoprotein IIb/IIIa complex; HPA-1b, human platelet antigen-1b; MI, myocardial infarction; RR, relative risk.

*Data on prevalence and relative risk vary widely, often with conflicting results. This information represents an interpretation of data collected from various sources, mainly meta-analyses.

These patients are predisposed to VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE).

Factor V Leiden

The most common inherited disorder leading to VTE is the FVL mutation. About 5% of individuals with European ancestry are heterozygous for FVL. The FVL mutation increases VTE risk by decreasing the susceptibility of factor Va to APC-mediated inactivation and by impairing the APC-cofactor activity of factor V in factor VIIIa inactivation, all of which lead to increased thrombin generation. APC resistance can be demonstrated by specialized clotting tests in which the addition of APC fails to inhibit thrombin generation. About one fourth of patients with their first VTE are heterozygous for FVL, and this percentage increases to almost 60% among those with recurrent VTE or a strong family history of VTE.

Heterozygous FVL conveys a seven-fold increased risk for VTE. However, at 50 years of age, only 25% of persons with heterozygous FVL have had VTE, compared with much higher percentages in other inherited thrombophilias. It is with concomitant *acquired* risk factors such as immobilization, pregnancy, or oral contraceptive use that the risk for VTE in persons with FVL becomes more significant. The prothrombin G20210A mutation demonstrates a synergistic effect with FVL, but the MTHFR mutation does not. Homozygous FVL individuals have a 20- to 80-fold increased risk for VTE. APC resistance *without* the FVL mutation occurs rarely. Factor V Cambridge, although much less common than FVL, has a similar mutation at an APC cleavage site (Arg306) and is associated with APC resistance and thrombosis. Other minor alleles of factor V, including the 6755 A/G (D2194G) R2 haplotype, may enhance APC resistance. When this haplotype is on a different chromosome than the FVL mutation, it diminishes normal factor V transcription and increases the ratio of FVL to normal factor V.

Prothrombin G20210A

Another mutation associated with inherited thrombophilia is the prothrombin G20210A mutation, which occurs in the 3′-untranslated region of the prothrombin gene. This mutation leads to higher than normal prothrombin levels and a two-fold increased risk for VTE. The heterozygous mutation is present in about 3% of European-derived populations but is identified in about 15% of patients with VTE. Patients homozygous for prothrombin G20210A are rare, but their relative risk for VTE is thought to be about 10-fold. Exactly how the prothrombin mutation affects thrombus development has not been fully defined, but changes in polyadenylation of the prothrombin messenger RNA (mRNA) during transcription appear to be involved. Diagnosis of the G20210A genotype is made by examination of the patient's DNA for this specific mutation; no screening or functional assays are available.

Inherited Deficiency of Natural Anticoagulants

Deficiencies in the natural anticoagulant proteins (AT, protein C, and protein S) are less common than FVL or prothrombin G20210A, but they are more likely to produce symptomatic VTE at an earlier age. Only about one half of the cases of VTE occurring in patients with these deficiencies are associated with acquired risk factors such as pregnancy, surgery, or immobilization. Deficiencies of AT, protein C, or protein S are detected by functional or antigenic assays because some mutations cause a quantitative decrease in the factor, whereas others produce a dysfunctional protein. Many gene mutations have been associated with these deficiencies, but none is predominant. Deficiencies of AT, protein C, and protein S in the aggregate account for fewer than 5% to 10% of all patients with VTE.

AT is a naturally occurring anticoagulant that complexes with endogenous heparan sulfates to inhibit both formed thrombin and factor Xa. Heterozygous AT deficiency leads to AT activity levels less than 70% of normal and a 20-fold increase in the risk for VTE; VTE usually occurs by the age of 25 years in 50% of such patients. More than 200 associated mutations are known. Homozygous mutations are very rare, likely because of lethality in utero. Rare homozygous mutations show mild impairment in heparin binding or thrombin inhibition.

Acquired causes of AT deficiency are more common. Because AT has a low molecular weight, it is lost in the proteinuria of nephrotic syndrome. Acquired AT deficiency (as well as protein C deficiency) may also be associated with severe hepatic venoocclusive disease after stem cell transplantation; AT and protein C may be excessively consumed in the damaged hepatic microvasculature. Low levels of AT are also associated with poorer outcomes in severely ill patients. Successful treatment of symptomatic patients with heterozygous AT deficiency has included short-term replacement with fresh-frozen plasma or recombinant AT protein, usually coupled with unfractionated heparin (UFH) anticoagulation; long-term therapy for congenitally deficient patients has consisted primarily of warfarin.

The complex of thrombin and thrombomodulin on the EC surface activates protein C; APC coupled with its cofactor, protein S, cleaves and inactivates factors Va and VIIIa. These actions downregulate the prothrombinase and tenase complexes, respectively, to slow the rate of thrombin generation. Like AT deficiency, heterozygous protein C and protein S deficiencies are observed with venous, and occasionally arterial, thrombosis at in younger patients (median age at occurrence, 20 to 40 years).