

Thrombophilia, polymorphisms, and vascular disease

T C F Sykes, C Fegan, D Mosquera

Abstract

Thrombophilia traditionally refers to rare inherited defects leading to enhanced coagulation, especially of the venous system. In recent years, a broader search for genetic polymorphisms of prothrombotic genes has been carried out to determine the relative impact on venous and arterial thrombosis. The bulk of evidence is drawn from numerous, often small, heterogeneous, case control association studies, with a variety of end points (deep venous thrombosis, myocardial infarction, or stroke). The data are often conflicting and inconclusive with only factor V Leiden and prothrombin polymorphisms having clear associations with venous thrombosis. Many of the polymorphisms interact with established cardiovascular risk factors, in particular smoking, to increase greatly the risk of a thrombotic episode. Future studies will need to consider the confounding factors of sample size, race, and clinical end points as well gene-environment interactions. (*J Clin Pathol: Mol Pathol* 2000;53:300–306)

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Academic Vascular Unit, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK

T C F Sykes
D Mosquera

Department of Haematology, Birmingham Heartlands Hospital
C Fegan

Correspondence to:
Dr Sykes
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Table 1 Prothrombotic gene polymorphisms

| Prothrombotic gene | Polymorphism |
|--|---|
| Factor V Leiden | G1691A |
| Factor V HR2 haplotype | 1299His/Arg and 1736Met/Val |
| Prothrombin | G20210A |
| Methyltetrahydrofolate reductase (MTHFR) | C677T |
| Factor VII | G10976A, -323 0/10, -402 G/A, -401G/T, HVR4 |
| Glycoprotein IIb | HPA-3 |
| Glycoprotein IIIa | PLA1/PLA2 |
| Glycoprotein Ia | 807C/T and 873G/A |
| Glycoprotein Ib-IX-V | Gp 1bu: A, B, C, D, and HPA-2 |
| Plasminogen activator inhibitor 1 | 4G/5G, (CA) _n , HindIII |
| Fibrinogen | BclI, G455A, α 313T/A |
| Thrombomodulin | A455V, Ala25Thr |
| Factor XIII | Val34Leu |

venous and arterial thrombosis will be summarised in this review.

Factor V Leiden

After the identification of individuals with APC resistance,¹ analysis of DNA revealed a single point mutation, a guanine to adenine transition at nucleotide position 1691 in the factor V gene, now known as Factor V Leiden.² This mutation causes a substitution of arginine by glutamine at position 506, resulting in a failure of APC to recognise a major cleavage site on factor V, which allows prothrombin activation to continue unchecked. This defect is associated with APC resistance in 90% of cases. The factor V Leiden allele is present in about 4–5% of the normal white population, but is absent from the indigenous populations of Asia, Africa, America, and Australia.³ The main clinical manifestation of the factor V allele is deep venous thrombosis.^{4–5} Prospective studies have calculated the relative risk for venous thrombosis to be 2.3 for heterozygotes.⁶

Although a risk factor for venous thrombosis, the data to support a role in arterial thrombosis are less conclusive. A study of 560 men under 70 years of age with myocardial infarction revealed a small increase in risk in carriers of factor V Leiden (odds ratio (OR), 1.4; 95% confidence interval (CI), 0.8 to 2.2).⁷ This was confirmed in a study of 84 young women (18–44 years old), which demonstrated a higher risk of myocardial infarction in carriers (OR, 2.4; 95% CI, 1.0 to 5.9), especially smokers (OR, 3.6; 95% CI, 0.9 to 14.4).⁸ Two other studies, including a large population based study, of over 5000 men and women over 65 years of age with three year follow up, found that factor V Leiden was not a risk factor in 373 cases of myocardial infarction, angina, or stroke⁵ compared with 482 controls.^{9–10} In cerebrovascular arterial disease, two studies involving nearly 500 patients have failed to demonstrate any increased risk of stroke in patients with the factor V allele.^{11–12}

Three studies have examined the role of factor V Leiden in patients with peripheral vascular disease.^{13–15} The prevalence of factor V Leiden was found to be increased in all three studies in patients with peripheral vascular disease but, when based on APC resistance measurements, the prevalence varied between 11.6% and 41% of patients with aortoiliac disease using DNA analysis. A small study from Bristol concluded that factor V Leiden was not an important factor in the outcome of infrainguinal bypass grafting.¹⁵ However, a larger study by Ouriel *et al* found that the presence of APC resistance significantly reduced graft patency rates.¹⁴

Factor V HR2 haplotype

This haplotype was discovered after an investigation to determine other causes of APC resistance and has a prevalence of 8–10% in Italian, Indian, and Somali populations.¹⁶ The haplotype codes for two amino acid substitutions 1299His/Arg and 1736Met/Val and its incidence is raised in patients heterozygous for factor V Leiden. Evidence from a French study of 200 patients indicates that it is associated with an increased risk of venous thrombosis (OR, 1.8; 95% CI, 1.1 to 2.8).¹⁷ A larger Italian study found an increased risk of venous thrombosis when the haplotype coexisted with factor V Leiden (relative risk (RR), 10.9; 95% CI, 2.9 to 40.6) compared with factor V Leiden on its own (RR, 4.2; CI, 1.6 to 11.3).¹⁸ However, there was no augmentation of risk when the haplotype was combined with antithrombin, protein C, and protein S deficiencies.¹⁸

Prothrombin

A single nucleotide change of glutamine to arginine was identified at position 20210 by Poort *et al* in 1996.¹⁹ The presence of the abnormal gene is associated with an increase in prothrombin values. The prevalence of the mutation is between 1% and 4% in the general European population²⁰ and 5.5% in the UK,²¹ but it is rare in Asians or Africans. The evidence suggests that carriers of the mutation have between a three and fivefold increased risk of venous thrombosis.^{19–22}

A small study of 79 young women (18–44 years old) with myocardial infarction and 381 controls by Rosendaal *et al* has shown an increased risk of myocardial infarction with the polymorphism²³ (OR, 4.0; 95% CI, 1.1 to 15.1), especially in combination with other risk factors such as smoking. A similar but smaller effect was seen in a larger study of 560 patients (OR, 1.5; 95% CI, 0.6 to 3.8).²⁴ Other studies have failed to confirm this finding, including one investigating a large cohort of 15 000 men followed up for 10 years, where over 800 cases of myocardial infarction, stroke, and venous thrombosis were identified.^{20–25–26} There has been no evidence of an association with stroke.¹¹

Factor VII gene polymorphism

Factor VII is a vitamin K dependent coagulation factor that is converted into activated factor VII by thrombin and factor Xa. Plasma FVII coagulation activity (VIIc) has been shown by some authors to be an independent risk factor for myocardial infarction,^{27–28} but others have failed to demonstrate an association.^{29–30} A single gene on chromosome 13 encodes factor VII. Five polymorphisms have been identified, including an insertion of a decanucleotide at position 323 and a substitution of arginine at position 353 by glutamine (R353Q), the latter associated with 20–25% lower concentrations of this protein in plasma. The other three polymorphisms include two promoter polymorphisms at positions 401 (G to T) and 402 (G to A) and a common

polymorphism at the hypervariable region 4 of intron 7.

The relation of these polymorphisms to thrombosis is uncertain. A large, case control study with 560 cases and 644 controls revealed that patients with the 353 arginine allele had a lower risk of myocardial infarction compared with patients with the glutamine allele (OR, 0.8; 95% CI, 0.6 to 1.06). In this study, the arginine allele was associated with increased plasma factor VII values.³¹ Other case control studies, including a study of 453 patients with myocardial infarction and 476 controls, found that although the Arg353Gln polymorphism was related to concentrations of factor VII there was no difference in the genotype frequency between patients and controls.³⁰ In contrast, one small Italian study of 165 patients with familial myocardial infarction and 225 controls has shown a higher risk of myocardial infarction with the 353 glutamine allele with an associated increase in factor VIIc values.³² The hypervariable region polymorphism was also associated with an increased risk of myocardial infarction in this study.³² A study of 317 patients with thrombotic stroke and 198 age matched controls provided no evidence of a link between factor VII polymorphisms and stroke.³³ Similarly, there has been no link with deep venous thrombosis.³⁴

Fibrinogen

Raised fibrinogen concentrations have been shown to be an independent risk factor for myocardial infarction, peripheral vascular disease, and stroke.^{27–28–35} Fibrinogen is composed of three chains, namely α , β , and γ chains, encoded by different genes clustered on the long arm of chromosome 4. Several polymorphisms have been identified, including the BclI polymorphism and the 455G/A polymorphism in the promoter region of the β chain and an α chain 313T/A polymorphism. In a large general population study of over 9000 men and women, the 455A allele was associated with an increased fibrinogen concentration.^{36–37} Unfortunately, the relation between the fibrinogen polymorphisms and thrombosis is less clear. In a study of 102 patients with a family history of myocardial infarction before the age of 65 years and 173 controls, the BclI polymorphism was associated with an increased risk of myocardial infarction (OR, 2.4; 95% CI, 1.2 to 4.6).³⁸ However, no link between the BclI polymorphism and myocardial infarction was found in the larger ECTIM study involving 565 patients with myocardial infarction and 668 controls.³⁹ Similarly, the 455G/A polymorphism has not been linked with myocardial infarction, despite an association between phenotype and fibrinogen values,⁴⁰ although it has been linked with ischaemic stroke in a study of Japanese men and women.⁴¹ The α chain 313T/A polymorphism was investigated in a study of 585 patients and 658 controls but it was also concluded there was no association between the polymorphism and risk of myocardial infarction.⁴²

Methyltetrahydrofolate reductase (MTHFR)

Frosst *et al.*, in 1995, described a common mutation (C677T) of the MTHFR gene.⁴³ A cytidine residue at position 677 of the gene is replaced by thymidine. This results in the substitution of an alanine residue by valine, rendering the enzyme both thermolabile and less active. Raised concentrations of homocysteine have been linked with the homozygous genotype but have only been demonstrated when plasma folate values are low.⁴⁴ There are inconclusive data regarding the association of the MTHFR mutation with venous thrombosis. Three studies failed to demonstrate an increased risk with deep venous thrombosis,^{43 45 46} whereas others found that the homozygous MTHFR genotype is an independent risk factor for venous thrombosis.^{47 48} In addition, numerous studies investigating a link between the MTHFR polymorphism and arterial thrombosis have been undertaken, particularly with regard to myocardial infarction. Although some studies have shown an association with coronary artery disease,^{49 50} most failed to reveal a correlation of genotype with myocardial infarction.⁵¹⁻⁵⁵ Similarly, ischaemic stroke has failed to be consistently linked with the MTHFR polymorphism, despite an association between MTHFR and homocysteine concentrations.^{56 57}

Platelet glycoprotein IIb-IIIa polymorphism

The membrane IIb-IIIa complex is a member of the integrin family and plays a key role in platelet aggregation and activation. The complex is the binding site for fibrinogen and Von Willebrand factor. The genes encoding glycoproteins IIb and IIIa are close to one another on chromosome 17. The polymorphism in glycoprotein (Gp) IIIa is a substitution of proline for leucine at position 33, and is described as the PLA1/A2 alloantigen system. PLA2 is expressed on platelets in 24-28% of white individuals, with about 2% being homozygous for the alloantigen.⁵⁸ The glycoprotein IIb gene polymorphism consists of a substitution of serine for isoleucine at position 843 (HPA-3a/3b). In 1996, Weiss *et al.* demonstrated that the PLA2 polymorphism of Gp IIIa was associated with a twofold increase in the risk of coronary ischaemia in a small group of 71 patients with myocardial infarction or unstable angina and 68 controls.⁵⁹ In the larger ECTIM study of 620 patients with myocardial infarction and 700 controls, and a study by Ridker *et al.* of 374 patients with myocardial infarction and 704 controls, there was no correlation between the PLA2 allele and myocardial infarction.^{60 61} This was confirmed by Gardemann *et al.* in a study of 1191 patients with myocardial infarction.⁶² However, subgroup analysis of patients less than 47 years of age by Carter *et al.* revealed an increase in the PLA2 allele in patients with myocardial infarction (OR, 2.3; 95% CI, 1.01 to 5.22).⁶³ A study of 200 young patients (< 45 years old) with myocardial infarction also confirmed an association with the PLA2 allele (OR, 1.84; 95% CI, 1.12 to 3.03).⁶⁴ An increased risk of coronary stent thrombosis was

found to be associated with PLA2 (OR, 5.26; 95% CI, 1.55 to 17.8).⁶⁵ However, a larger case control study, with 1000 patients in each group, failed to demonstrate a link between the polymorphism and complications, including stent thrombosis, after coronary catheter interventions.⁶⁶ There is no evidence to suggest a link with stroke.^{60 67 68}

Little information is available about the clinical relevance of the Gp IIb polymorphism HPA-3, although there was no link between the polymorphism and stent thrombosis at 30 day follow up.⁶⁹ No association between the HPA-3 polymorphism and stroke has been found.⁶⁷

Platelet glycoprotein Ia-IIa polymorphism

After the interest in glycoprotein IIIa polymorphisms, the Ia-IIa gene complex was investigated, with the identification of two silent polymorphisms on the Gp Ia gene, at positions 807C/T and 873G/A. These polymorphisms affect platelet receptor density.⁷⁰ Individuals homozygous for the 807C/873G allele have low receptor densities, whereas individuals homozygous for the 807T/873A allele have high receptor densities, enhancing platelet binding to collagen. There are significant differences in the distribution of the Gp Ia C807T alleles among different racial groups.⁷¹

A case control study of 177 patients with myocardial infarction and 89 controls found an increased risk of myocardial infarction with the homozygous 807T/873A genotype (OR, 3.3; 95% CI, 1.2 to 8.8).⁷² An association of the 807T allele with non-fatal myocardial infarction in a group of 223 patients (< 49 years of age) has also been reported (OR, 2.61; 95% CI, 1.26 to 5.41).⁷⁰ In contrast, a case control study of 546 patients and 507 controls less than 75 years old failed to link the 807T/873A alleles with myocardial infarction.⁷³ In a case control study of 45 patients less than 50 years old, the 807T allele was found to be associated with stroke (OR, 3.02; 95% CI, 1.20 to 7.61).⁷⁴ No association was found between the 807T/873A allele and venous thrombosis in a study involving 331 white patients.

Platelet glycoprotein 1b-IX-V polymorphism

This complex is a combination of four glycoprotein chains: Gp 1ba, Gp 1b β , Gp IX, and Gp V. Two polymorphisms worthy of note include a polymorphism of Gp 1ba with four polymorphic forms A, B, C, D, and a C to T change at position 3550, resulting in a Thr145Met substitution, the latter part of the HPA-2 alloantigen system. In a case control study of over 100 patients in each group, both the C/B genotype and the HPA-2 polymorphism were associated with an increased risk of myocardial infarction (OR, 2.84; 95% CI, 1.28 to 6.41) and stroke (OR, 2.83; 95% CI, 1.16 to 7.07),⁷⁵ but not with venous thrombosis.⁷⁵ The HPA-2 alloantigen is not associated with an increased risk of stroke.⁶⁷

Plasminogen activator inhibitor 1 (PAI-1) gene polymorphism

Plasminogen activator inhibitor 1 inhibits tissue plasminogen, increased concentrations of which have been shown to be independently associated with myocardial infarction.⁷⁶ A single gene on the long arm of chromosome 7 encodes PAI-1. Three polymorphic sites have been described including a single nucleotide insertion/deletion (4G/5G) of the promoter region, a 3' HindIII site, and a CA dinucleotide repeat in intron 3. The 4G/5G polymorphism has been linked with plasma concentrations of PAI-1.⁷⁷ The 4G allele is associated with significantly higher concentrations of PAI-1 than the 5G allele, especially in the presence of raised triglyceride values.^{78 79} The 4G allele has been linked to an increased risk of myocardial infarction in a small group of young Swedish men.⁸⁰ This finding was supported by a study of 453 patients in which 166 patients had a history of myocardial infarction (OR, 2.0; 95% CI, 1.1 to 3.7).⁸¹ However, other studies including one of 1353 white patients undergoing coronary angiography⁸² have failed to reveal an association of the 4G allele with myocardial infarction.^{77 83 84} Similarly, case control studies of 150 patients with venous thrombosis and 558 patients with stroke showed no association with the 4G allele.^{85 86}

Thrombomodulin

Thrombomodulin is an endothelial cell receptor that transforms the procoagulant thrombin into an anticoagulant with an increased ability to activate protein C. Several gene polymorphisms have been identified, including a C/T change coding Ala455Val and a G to A mutation at position 127 leading to an Ala25Thr substitution. A study of 97 Swedish patients with premature myocardial infarction revealed an over-representation of the allele encoding Ala455, suggesting that it is a risk factor for myocardial infarction.⁸⁷ However, this was not confirmed in a study by Ireland *et al* of 104 patients.⁸⁸ A further study of 560 men and matched controls has linked an increased risk of first myocardial infarction, especially in those less than 50 years old, with the Ala25Thr polymorphism (OR, 6.5; 95% CI, 0.8 to 54.2). However, the authors are cautious about the results because the confidence intervals are wide.⁸⁹ There is no evidence suggesting a role in venous thrombosis.⁹⁰

Factor XIII

A deficiency of factor XIII is associated with severe bleeding, illustrating that its main function is the formation of stable crosslinked fibrin. Several polymorphisms have been described, especially of the A subunit, in which the Val34Leu polymorphism has been the most extensively investigated. A case control study of 221 patients and 254 controls revealed a protective effect of the Val/Leu genotype against venous thrombosis.⁹¹ A further study of 189 patients and 187 controls did not confirm this protective effect but did demonstrate a protective effect of the homozygous Leu genotype.⁹² The evidence for a role in arterial

thrombosis comes from a case control study of patients with myocardial infarction where the Leu genotype appeared to have a protective effect, being the least common genotype in patients with a history of myocardial infarction.⁹³ This finding has been confirmed in a recent Finnish case control study of young survivors of myocardial infarction.⁹⁴ A study of 529 patients and 436 age matched controls with cerebral infarction showed there was no evidence of a protective effect linked to the Leu34 genotype.⁹⁵

Synergy

Although individual polymorphisms might have little or no independent effect on venous or arterial thrombosis, they might act in synergy with other genetic risk factors or established cardiovascular risk factors. The incidence of venous thrombosis increases when factor V Leiden is combined with protein C,⁹⁶ protein S,⁹⁷ or antithrombin III deficiency.⁹⁸ A combination of factor V Leiden and hyperhomocysteinaemia or MTHFR carries with it an increased risk of venous thrombosis.^{6 48} Factor V Leiden combined with prothrombin increases the risk of recurrent deep venous thrombosis.^{99 100} The risk of arterial thrombosis, such as myocardial infarction, is not increased in the presence of the factor V Leiden and prothrombin polymorphisms,¹⁰¹ or when the PAI-1 (4G/5G), PLA1/PLA2, Gp 1b, factor VII Arg355Gln, factor V Leiden, MTHFR, and prothrombin polymorphisms are combined.⁶⁴ However, when factor V Leiden and prothrombin polymorphisms including MTHFR are examined in conjunction with known cardiovascular risk factors such as hypertension, hypercholesterolaemia, diabetes, and especially smoking, the risks increase up to 25 fold (OR, 24.7; 95% CI, 7.17 to 84.9).¹⁰¹ Similar results have been found in a group of 560 men and controls where the thrombomodulin⁸⁹ Ala25Thr polymorphism is associated with an increased risk of myocardial infarction and interacts with smoking (OR, 8.8; 95% CI, 1.8 to 42.2) and metabolic risk factors (OR, 4.4; 95% CI, 0.9 to 21.3). Other studies of young women¹⁰² with either the factor V or prothrombin polymorphism have also revealed myocardial infarction risks that are amplified in smokers. This augmentation of risk with smoking also occurred with the PLA1/A2 polymorphism in a group of 200 patients with myocardial infarction (OR, 13.7; 95% CI, 6.41 to 31.2) compared with non-smoking carriers (OR, 1.84; 95% CI, 1.12 to 3.03).⁶⁴

Conclusion

Many of the reviewed studies provide conflicting data concerning the clinical importance of gene polymorphisms. This is in part the result of specific problems that arise with case control association studies where the study sets out to test whether a genetic marker occurs more frequently in cases than in controls. In particular, several confounding factors arise making direct comparisons between studies difficult. These include a variation in the definition of cases and controls (selection bias), the heterogeneous

way the disease process is manifest (for example, myocardial infarction and stroke), and the differences that occur between ethnic groups. The complex pathogenesis of thrombosis means that a single gene defect might exert only a small effect and therefore studies with large numbers of patients are required before any conclusion can be drawn. In addition, the impact of a given polymorphism will be dependent on gene-environment interactions that might be specific for a given cohort of patients. Despite the limitations of the reviewed studies, a striking feature in many is the interaction of polymorphisms with known cardiovascular risk factors, especially smoking, which leads to a dramatic rise in the risk of thrombosis. The evidence to date implicates factor V Leiden and prothrombin G20210A as risk factors for venous thrombosis, especially in combination with other risk factors; however, the association with arterial thrombosis is much weaker. The remaining polymorphisms cannot be linked clearly to either venous or arterial thrombosis because of the inconsistencies in the results of the studies currently available. Future studies will need to deal with the problem of confounding factors and focus on gene-environment interactions to appreciate fully the impact of a given polymorphism in venous and arterial thrombosis.

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T C F Sykes, C Fegan and D Mosquera

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