ELSEVIER

Biophysical Chemistry 112 (2004) 223–228

Biophysical Chemistry

www.elsevier.com/locate/bpc

FXIII polymorphisms, fibrin clot structure and thrombotic risk

Catie Kobbervig*, Eliot Williams

Department of Medicine, University of Wisconsin, 600 Highland Avenue, Room H4534, 53792 Madison, United States

Received 25 June 2004; accepted 1 July 2004
Available online 19 October 2004

Abstract

Fibrin clot structure is highly dependent on factor XIII activity. Activated FXIII catalyzes the formation of the peptide bonds between the γ and α chains in noncovalently bound fibrin polymers and incorporates various adhesive and antifibrinolytic proteins into the final fibrin clot. In the absence of activated FXIII, clots are unstable and susceptible to fibrinolysis. Several studies have examined the effects of FXIII polymorphisms on final fibrin clot structure and clinical thrombotic risk. The Val34Leu FXIII polymorphism is associated with increased activation by thrombin. In the presence of saturating thrombin concentrations, however, FXIIIa specific enzyme activity is not affected by genetic polymorphisms. Fibrin clots formed in the presence of the FXIII 34Leu polymorphisms do tend to be thinner and less porous, however. The effects of prothrombin concentrations on clot structure have suggested that thinner clots are more resistant to fibrinolysis and associated with increased thrombotic risk. Most clinical studies of 34Leu FXIII carriers, however, have demonstrated a lower incidence of both venous and arterial thrombosis in carriers of the mutant allele compared to Val/Val carriers. One recent study has suggested that the interactions between FXIII phenotype and plasma fibrinogen concentrations significantly influence clinical thrombotic risk.

Keywords: Factor XIII; Polymorphisms; Fibrin clot; Venous thrombosis; Arterial thrombosis

1. Role of FXIII in normal hemostasis

Factor XIIII (FXIII) is a protransglutaminase that circulates as a heterotetramer composed of two A and two B subunits. The 731 amino acid A subunits contain the active site cysteine, while the 661 amino acid B units serve as carrier proteins. A cellular form of FXIII that contains only two A chains exists in platelets, monocytes and macrophages. FXIII is activated by thrombin, which cleaves the peptide bond between Arg37 and Gly38 of the A subunit and releases a 37 amino acid amino-terminal activation peptide. The presence of fibrin accelerates the activation of FXIII by thrombin. In the presence of calcium, the A subunit dimer then dissociates from the B subunits and undergoes a conformational change that exposes the active site. Activated factor XIII (FXIIIa) catalyzes the formation of the γ-glutamyl-ε-lysine peptide bonds between the γ and α chains in noncovalently bound fibrin polymers. FXIIIa also incorporates the adhesive proteins, fibronectin and thrombospondin, and the antifibrinolytic protein, α-2-antiplasmin, into the fibrin clot via similar linkages. The net result is a stable clot that is relatively resistant to shear forces and fibrinolysis. In addition to its role in blood coagulation, FXIII also contributes to extracellular matrix remodeling, tissue repair, and cell adhesion and migration [1–3]. A recent study suggested that "unactivated" FXIII is capable of crosslinking both fibrin and fibrinogen. While the physiological implications of these findings are not clear, it is possible that uncleaved FXIII may contribute to crosslinking in the early phases of fibrin clot formation [38].

Normal blood coagulation requires a precise balance between procoagulant and anticoagulant factors. Minor changes in the amount or function of any of these proteins can result in fibrin clots with altered susceptibility to fibrinolysis. For example, higher levels of prothrombin increase the initial rate, peak and total amount of thrombin generated, resulting in formation of a fibrin clot with decreased mass-to-length ratio and thinner fibers that are more resistant to fibrinolysis. Conversely, clots formed in the presence of low levels of prothrombin have thicker fibers that

* Corresponding author. Tel.: +1 6082631836; fax: +1 6082621982.
E-mail address: williams@medicine.wisc.edu (C. Kobbervig).

0301-4622/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.bpc.2004.07.023

are more easily degraded [4]. Because plasma factors such as fibronectin affect the thickness of fibrin fibers, fibrin gels formed from citrated plasma after recalcification or thrombin activation contain thicker fibers than those formed from isolated fibrinogen [5]. Neither fibronectin or FXIIIa alone affect the mass-to-length ratio of fibrin. When both fibronectin and FXIIIa are present, however, the mass-to-length ratio of fibrin fibers increases in proportion to the fibronectin concentration. This suggests that the incorporation of fibronectin into fibrin clots by FXIIIa increases both fibrin fiber size and density [6]. Gabriel et al. modified fibrin fibers in vitro both by altering the rate of assembly and by adding an assembly inhibitor, iopamidol. Fibrin assembly and fibrinolysis were measured turbidometrically and the fiber mass-to-length ratios were calculated. In these experiments, decreased thrombin concentrations caused slower fibrin fiber assembly with thicker fiber formation and increased fibrinolysis. Plasmin formation was slower in the presence of thinner fibers, and subsequent fiber degradation by plasmin was also decreased [7]. The mechanistic basis for these findings is unknown, but it is possible that thinner fibers provide a less favorable surface for catalyzing activation of plasminogen by plasmin.

Plasma FXIIIa plays an important role in hemostasis in vivo. Individuals with congenital complete deficiency of FXIII (plasma activity <1% of normal) have a severe bleeding tendency characterized by formation of hematomas, soft-tissue hemorrhage and poor wound healing in the neonatal period [8–10]. Women with FXIII deficiency have an increased risk of spontaneous miscarriages. FXIII A subunit knockout mice can become pregnant, but the majority die from uterine hemorrhage during gestation [11]. In addition, inhibition of FXIIIa during fibrin clot formation enhanced the subsequent lysis of pulmonary emboli (PE) in an animal model [12].

2. Alterations in plasma FXIII level in thrombotic disorders

Kucher et al. studied 168 consecutive patients who were evaluated in an emergency department for suspected PE. In this case-control study, FXIII A-subunit levels were lower in patients with more extensive pulmonary artery occlusion, and the likelihood of PE was seven-fold higher in patients with A-subunit levels less than 60% of normal. The decreased FXIII A-subunit levels in patients with massive PE may simply have reflected coagulation factor consumption during extensive thrombus formation. In a subset of 12 patients in whom clot firmness was measured by thromboelastography, those with low FXIII levels had decreased clot firmness compared to patients with normal or high levels [13].

Mills et al. studied fibrin clot formation in 100 healthy male first degree relatives of patients with premature coronary artery disease (CAD), and compared the results to those from 100 age-matched controls with similar conventional cardiovascular risk factor profiles, but no family history of coronary disease. FXIII A_2B_2 and B-subunit levels were determined by sandwich ELISAs. Rates of fibrin formation and fibrin mass-to-length ratios were measured turbidometrically, and fibrin porosity was determined by measuring buffer flow rates through tubes containing clots. In a subset of subjects, scanning electron microscopy was used to assess fiber thickness. The subjects formed clots more quickly than the controls (lag phase 39 ± 2 s versus 47 ± 3 s). They also had larger clots with thicker fibers (mass-to-length ratios 8.5×10^{13} Da/cm versus 9.7×10^{13} Da/cm) and smaller pores (12.2×10^{-9} versus 15.2×10^{-9} cm^2). Only the larger clot size could be fully explained by differences in fibrinogen levels using linear regression, suggesting that other factors were contributing to the alterations in clot structure. There was a nonsignificant trend toward increased FXIII A_2B_2 levels in the relatives of CAD patients compared to the controls. There was no difference in the frequency of the FXIII Val34Leu polymorphism (see below) between the subjects and the controls [14].

3. Effect of FXIII polymorphisms on FXIII activation and activity

FXIII antigen and activity levels are normally distributed in the general population, and protein levels do not correlate to activity levels [15–17]. A common FXIII polymorphism is caused by a G to T point mutation in codon 34 of exon 2 that results in the replacement of valine by leucine at position 34 (Val34Leu) in the activation peptide, three amino acids from the thrombin cleavage site. There is a wide variation in the prevalence of the Val34Leu mutation in different ethnic groups. In one study, the Val34Leu polymorphism was present in 2.5% of Asians, 28.9% of Blacks, 44.3% of Caucasians and 51.2% of Amerindians [18]. The 34Leu allele is virtually absent in the Japanese population and present in 11–27% in Australian Caucasians [19].

The presence of the Val34Leu polymorphism increases the rate of FXIII activation by thrombin. In synthetic peptides, a significant variation in rates of activation has been demonstrated among different FXIII structures [20]. Using both purified platelet derived and recombinant FXIII, Wartiovaara et al. demonstrated that thrombin cleaves the activation peptide from Val34Leu FXIII more rapidly than from wild type FXIII. In this study, the accumulation of a truncated FXIIIA was measured by Western blotting after activation by low concentrations of thrombin. At 2.5 min, 12% of wild type FXIII had lost the activation peptide compared to 33% of homozygous mutants. The addition of fibrinogen increased the rate of cleavage in both wild type and 34Leu mutants proportionately. Measurement of activation peptide release by HPLC confirmed that the rate of thrombin cleavage in the homozygous mutant was twice that of wild type FXIII. This difference disappeared when a higher concentration of thrombin was used, however.

Platelet Val 34 Leu FXIII which does not possess the B subunits was also activated more efficiently by thrombin, suggesting that the more rapid activation of 34Leu FXIII is not due to enhanced dissociation of the B subunits [21]. Similar results were reported by Balogh et al. [17], Ariëns et al., using mass spectrometry, showed that the Val34Leu polymorphism does not alter the actual thrombin cleavage site. Analysis of FXIII subunit proteolysis by SDS-PAGE and HPLC showed that FXIII 34Leu is cleaved more rapidly, and at lower concentrations of thrombin, than FXIII 34Val. The catalytic efficiency of thrombin was 0.5±0.09 μmol/l/s for FXIII 34Leu and 0.2±0.02 μmol/l/s for 34Val. In the presence of fibrinogen, the catalytic efficiency increased to 4.81 and 2.15 μmol/l/s, respectively [1].

If the peptide containing theVal34Leu polymorphism is released from FXIII upon thrombin cleavage, the polymorphism would not affect the specific activity of FXIIIa. However, there is crystallographic data suggesting that the activation peptide remains bound to FXIIIa after thrombin cleavage [22]. Thus, it is possible that the polymorphism could affect FXIIIa specific activity. Several studies have demonstrated higher specific enzyme activity in carriers of one or more 34Leu alleles compared to noncarriers [15,19,16]. Two recent studies have also demonstrated a difference in FXIII specific activity across genotypes (Val/Val, Leu/Leu or Val/Leu) at low thrombin levels, but the difference was abolished at saturating thrombin concentrations [21,17]. In conclusion, while several studies have suggested that the enzymatic activity of Val34Leu FXIIIa is higher than that of the wild type enzyme, it is possible that the observed differences were entirely due to incomplete activation of wild type FXIII by low concentrations of thrombin.

4. Effect of FXIII Val34Leu polymorphism on fibrin clot structure

The presence of the FXIII Val34Leu polymorphism has a significant effect on fibrin clot structure. Wartiovaara et

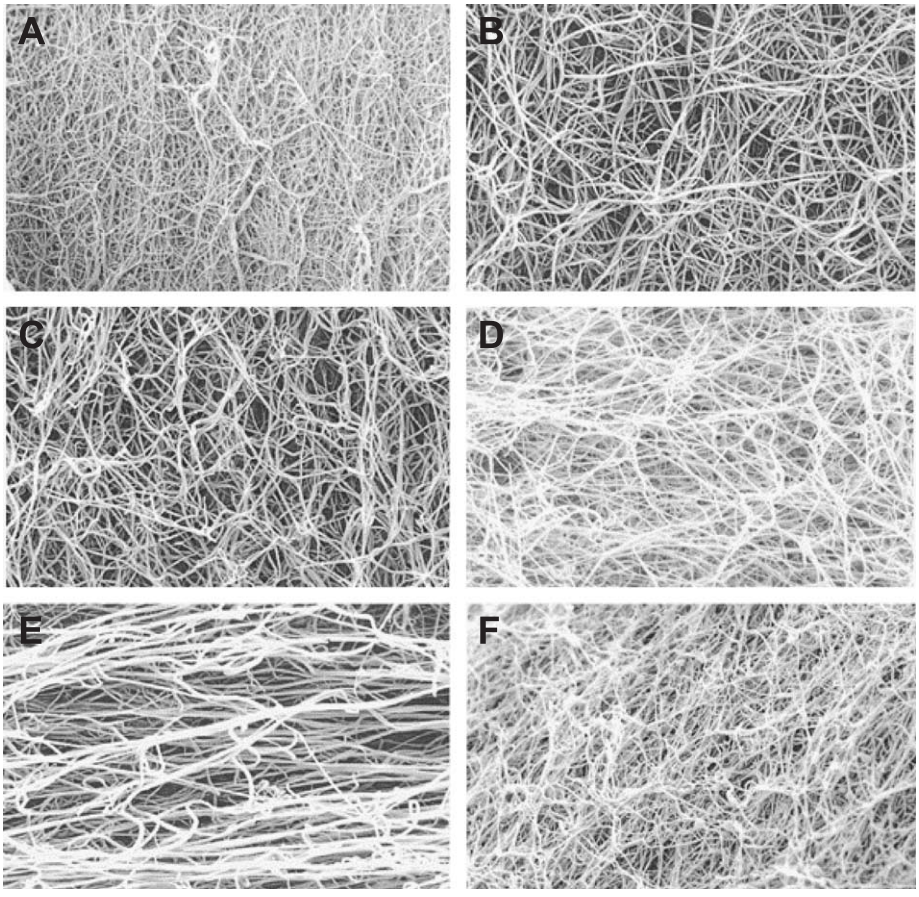

Fig. 1. Scanning electron micrographs of fibrin clots prepared from purified fibrinogen free from factor XIII and factor XIII Val (B, D, F) and Leu (A, C, E) variants at different fibrinogen concentrations (A and B=2.9, C and D=8.8, E and F=14.7 μmol/l). At low fibrinogen concentrations, fibrin clot structures in samples with the Leu variants (A) had fibers that were thinner (96 nm) and more tightly packed than those in the samples with Val variants (B) (227 nm, $p<0.0001$). At intermediate fibrinogen concentrations, the fibrin-fiber diameters approached similar values in the Val/Val and the Leu/Leu samples (D and C, 165nm and 152nm, respectively, $p<0.0001$). At high fibrinogen concentrations, the Leu/Leu clots (E) had thicker and more loosely packed fibers than did those in the samples with the Val variants (F) (286 vs. 93 nm, $p<0.0001$). Electron micrograph magnification ×9750. Reprinted with permission from Elsevier (The Lancet, 2003, vol. 361, p. 1428).

al. have shown that fibrin γ-chain dimerization and α-polymerization are enhanced in the presence of FXIII Val34Leu. In these experiments using low thrombin concentrations (0.5 U/mL), γ–γ dimers were present at 2.5 min in the presence of all polymorphisms, but the FXIII 34Leu mutants accumulated the dimers faster and the γ-monomers disappeared faster compared to wild type controls [21]. Ariëns et al. also demonstrated that the cross-linking activities of both FXIIIa 34Leu and 34Val were similar, but the increased sensitivity the 34Leu isoform to thrombin activation resulted in more rapid cross-linking of fibrin γ- and α-chains in the presence of the polymorphism. Turbidometric measurements demonstrated that clots formed from plasma in the presence of FXIII 34Leu had a shorter lag phase (1.08 versus 1.55 min) and a lower maximum absorbency after 5 min, indicating the presence of thinner fibers. The fibers formed in the presence of FXIII 34Leu were less porous, with a permeation coefficient of $3.6\pm0.5\times10^{-9}$ cm^2 for 34Leu compared to $8.7\pm4.4\times10^{-9}$ cm^2 for 34Val. Electron microscopy confirmed the presence of thinner fibrin fibers and decreased porosity in the presence of 34Leu [1].

Lim et al. have shown that the fibrinogen concentration is an important determinant of the effect of FXIII Val34Leu on clot structure. Using plasma samples from homozygotes for FXIII 34Val/Val and Leu/Leu, they demonstrated that clots prepared from Leu/Leu samples were less permeable at lower fibrinogen concentrations and more permeable at higher fibrinogen levels when compared to Val/Val samples (Fig. 1). At intermediate fibrinogen concentrations, the fibrin fiber diameters were similar across genotypes [23].

5. FXIII polymorphisms and thrombotic risk

5.1. Myocardial infarction

Two studies have suggested that the Val34Leu FXIII polymorphism is associated with a decreased risk of myocardial infarction (MI). In a case-control study, 398 patients being evaluated for possible coronary artery disease were compared to age-matched controls. About one-third of patients with a history of MI were either heterozygous or homozygous for the Val34 Leu polymorphism, compared to 50% of patients without a history of MI and 48% of healthy controls. Wartiovaara et al. performed genotype analysis on a series of autopsy cases and on hospitalized patients in Finland. In 286 consecutive autopsies of patients who experienced sudden death, the Val34Leu polymorphism was present in 29% of those who had evidence of previous MI, compared to 43% of those who did not have evidence of MI (adjusted OR 0.5, 95% CI 0.26–0.94). In 184 hospitalized patients undergoing coronary angiography, 33% of those with MI had the 34Leu polymorphism versus 45% of those without MI (adjusted OR 0.61, 95% CI 0.31–1.23). Overall, the FXIII Val34Leu allele was present in 31% of patients with a history of MI and 43% of those without such a history (p=0.009) [24].

In a population-based case-control study of young women, the Val34Leu allele frequency was not significantly different between those with a history of MI and controls. In the subset of obese women, however, the risk of MI was lower in those carrying at least one 34Leu allele, with an age-adjusted OR of 0.33 (95% CI 0.13–0.83). This suggests that in young women, the protective effect of the 34Leu allele may be confined to those with other specific risk factors for MI [25]. In two other studies, investigators were unable to demonstrate and association between the Val34-Leu polymorphism and MI risk in men, but neither of these studies stratified patients by other cardiovascular risk factors [26,27]. Similarly, a study of Asian patients undergoing coronary angiography in the United Kingdom did not demonstrate an association between the Val34Leu FXIII polymorphism and a history of myocardial infarction [28].

5.2. Stroke

There is conflicting evidence regarding an association between stroke risk and the FXIII Val34Leu polymorphism. In a study of women less than 45 years old, homozygosity and heterozygosity for the 34Leu polymorphism were associated with a small, non-significant decrease in hemorrhagic stroke risk [29]. Another study, however, found a slightly higher incidence of the Val34Leu polymorphism in a subset of 62 older patients with primary intracerebral hemorrhage compared to control subjects or those with cerebral infarction [30]. Studies of patients with ischemic stroke have also produced conflicting results. In one study, homozygotes for the FXIII Val34Leu polymorphism had a nearly four-fold *increased* risk of ischemic stroke compared to non-carriers of the 34Leu allele [25]. However, another case-control study of 456 consecutive patients with ischemic stroke found that carrying at least one copy of the 34Leu allele was associated with a *decreased* risk of stroke (OR 0.58, 95% CI 0.44–0.75) [31].

5.3. Venous thromboembolism

The FXIII Val34Leu polymorphism has been associated with a decreased risk of PE and deep venous thrombosis (DVT). While Franco et al. did not find a statistically significant difference in the frequency of the FXIII Val34Leu polymorphism in 189 patients with DVT compared to matched controls, the frequency of homozygosity for the 34Leu allele was 1.6% in cases versus 9.6% in controls (OR 0.16, 95% CI 0.05–0.5), suggesting a protective effect of the leucine allele [32]. Zidane et al. studied 441 consecutive patients presenting to the emergency department with suspected PE. 214 of these patients with a confirmed first episode of PE were compared to a control group of 148 patients who presented with signs and

symptoms of PE but had thrombus effectively ruled out by laboratory and radiographic data. The frequency of homozygosity for the 34Leu allele was 4.5% in patients with PE and 8.8% in those without PE (OR 0.5, 95% CI 0.1–0.9) [33]. Catto et al. performed a case-control study of 221 patients with a history of DVT or PE. The FXIII Val/Val genotype was present in 63% of patients with thrombosis compared to 49% of controls, whereas the Val/Leu genotype was found in 31% of patients and 42% of controls [34]. In another comparison of 354 patients with thrombosis to 1229 controls, the Val/Leu and Leu/Leu genotypes were associated with OR of 0.81 and 0.69, neither of which were statistically significant [35].

5.4. Summary

The Val34Leu polymorphism has been associated with a decreased risk of myocardial infarction in some, but not all, studies that addressed this question. The data on both hemorrhagic and ischemic stroke risk is too variable to draw any firm conclusions about the effect of FXIII polymorphisms. Several studies have demonstrated a decreased risk of venous thrombosis, both DVT and PE, in homozygous and heterozygous carriers of the Val34Leu polymorphism.

5.5. Interactions with other thrombotic risk factors

Several factors appear to modify the effects of the FXIII Val34Leu polymorphism on thrombotic risk. The His95Arg polymorphism is a variant allele of the FXIII B subunit gene that is associated with an increased dissociation rate of the A_2B_2 tetramer after thrombin activation. In a case-control study of 955 postmenopausal women with a first nonfatal MI, the Val34Leu allele was associated with an OR of 0.7 (95% CI 0.51–0.95) for MI. The His95Arg polymorphism alone did not affect risk of MI. However, co-inheritance of both the His95Arg and Val34Leu alleles decreased the risk for MI significantly, with an OR 0.36 (95% CI 0.17–0.75) [36]. A variant allele (4G/4G) of plasminogen activator inhibitor I (PAI-1) that results in higher PAI-1 levels may counteract the protective effects of the FXIII Val34Leu allele. In the Finnish study of 396 patients undergoing coronary angiography describe above, the individuals with the FXIII Val34Leu who had experienced MI had higher PAI-1 levels and an increased frequency of the variant 4G/4G genotype [37]. Carriers of the Val34Leu FXIII allele have a higher rate of alpha-2-antiplasmin incorporation into fibrin [39]. Theoretically, this should increase clot resistance to lysis. There is no evidence, however, that this actually occurs. Environmental factors may also alter the thrombotic risk in carriers of FXIII polymorphisms. For example, in a subset of women with two copies of variant FXIII alleles (34Leu or 95Arg) who were taking estrogen, the risk of MI was substantially lower compared to women who were not taking estrogen [36]. Other FXIII polymorphisms, such as Tyr204Phe and Pro564Leu, are associated with decreased FXIII levels and increased hemorrhagic stroke risk, but their effect on fibrin clot structure has not yet been clarified [29].

6. Conclusions

The Val34Leu FXIII polymorphism has been consistently associated with increased activation by thrombin in vitro. Increased FXIII activation, however, has not always translated into increased FXIIIa specific activity. Most studies have established a higher specific activity in 34Leu FXIII mutants at low levels of thrombin, but the differences across genotypes vanish with higher thrombin concentrations. The effect of the FXIII 34Leu polymorphism on final fibrin clot structure has also not been well defined, but most data suggest that the clots formed in the presence of the FXIII 34Leu polymorphism are thinner and less porous. Thinner fibers are more resistant to fibrinolysis in vitro and should theoretically increase clinical thrombotic risk. For example, the prothrombin G20210A gene mutation, a known thrombophilic risk factor, causes increased thrombin generation, which results in thinner clots that are more resistant to fibrinolysis [4]. Most clinical studies have actually demonstrated *decreased* venous and arterial thrombotic risk in carriers of the FXIII Val34Leu polymorphism, however. The recent study by Lim et al. described above offers an explanation for this apparent paradox. At low fibrinogen concentration, fibrin clots prepared from homozygous 34Leu samples had decreased permeability compared to those from 34Val homozygotes, similar to results from previous studies. However, at higher fibrinogen concentrations clots prepared from 34Leu homozygotes had *higher* permeability than those from 34Val homozygotes. Therefore, the FXIII 34Leu polymorphism may protect against thrombosis specifically in patients with high fibrinogen levels, who are known to be at higher risk for thrombotic complications [23]. Further epidemiologic studies are needed to confirm this hypothesis.

References

[1] R.A. Ariens, H. Philippou, C. Nagaswami, J.W. Weisel, D.A. Lane, P.J. Grant, The factor XIII V34L polymorphism accelerates thrombin activation of factor XIII and affects cross-linked fibrin structure, Blood 96 (2000) 988–995.
[2] Williams Hematology, Sixth (2001).
[3] Z. Valnickova, J.J. Enghild, Human procarboxypeptidase U, or thrombin-activable fibrinolysis inhibitor, is a substrate for transglutaminases, J. Biol. Chem. 273 (1998) 27220–27224.
[4] A.S. Wolberg, D.M. Monroe, H.R. Roberts, M. Hoffman, Elevated prothrombin results in clots with an altered fiber structure: a possible mechanism that increases thrombotic risk, Blood 101 (2003) 3008–3013.
[5] J. Torbet, Fibrin assembly in human plasma and fibrinogen/albumin mixtures, Biochemistry 25 (1986) 5309–5314.

[6] M.E. Carr Jr., D.A. Gabriel, J. McDonagh, Influence of factor XIII and fibronectin on fiber size and density in thrombin-induced fibrin gels, J. Lab. Clin. Med. 110 (1987) 747–752.
[7] D.A. Gabriel, K. Muga, E.M. Boothroyd, The effect of fibrin structure on fibrinolysis, J. Biol. Chem. 267 (1992) 24259–24263.
[8] A. Ichinose, Physiopathology and regulation of factor XIII, Thromb. Haemost. 86 (2001) 57–65.
[9] C.S. Kitchens, B.M. Alving, C.M. Kessler, Consultative Hemostasis and Thrombosis, W.B. Saunders, Philadelphia, PA, USA, 2002.
[10] L. Muszbek, Deficiency causing mutations and common polymorphisms in the factor XIII-A gene, Thromb. Haemost. 84 (2000) 524–527.
[11] S. Koseki-Kuno, M. Yamakawa, G. Dickneite, A. Ichinose, Factor XIII A subunit-deficient mice developed severe uterine bleeding events and subsequent spontaneous miscarriages, Blood 102 (2003) 4410–4412.
[12] G.L. Reed, A.K. Houng, The contribution of activated factor XIII to fibrinolytic resistance in experimental pulmonary embolism, Circulation 99 (1999) 299–304.
[13] N. Kucher, V. Schroeder, H.P. Kohler, Role of blood coagulation factor XIII in patients with acute pulmonary embolism. Correlation of factor XIII antigen levels with pulmonary occlusion rate, fibrinogen, D-dimer, and clot firmness, Thromb. Haemost. 90 (2003) 434–438.
[14] J.D. Mills, R.A. Ariens, M.W. Mansfield, P.J. Grant, Altered fibrin clot structure in the healthy relatives of patients with premature coronary artery disease, Circulation 106 (2002) 1938–1942.
[15] R. Anwar, L. Gallivan, S.D. Edmonds, A.F. Markham, Genotype/phenotype correlations for coagulation factor XIII: specific normal polymorphisms are associated with high or low factor XIII specific activity, Blood 93 (1999) 897–905.
[16] H.P. Kohler, R.A. Ariens, P. Whitaker, P.J. Grant, A common coding polymorphism in the FXIII A-subunit gene (FXIIIVAL34LEU) affects cross-linking activity, Thromb. Haemost. 80 (1998) 704.
[17] I. Balogh, G. Szoke, L. Karpati, U. Wartiovaara, E. Katona, I. Komaromi, G. Haramura, L. Muszbek, Val34Leu polymorphism of plasma factor XIII: biochemistry and epidemiology in familial thrombophilia, Blood 96 (2000) 2479–2486.
[18] F.A. Attie-Castro, M.A. Zago, J. Lavinha, J. Elion, L. Rodriguez-Delfin, J.F. Guerreiro, R.F. Franco, Ethnic heterogeneity of the factor XIII Val34Leu polymorphism, Thromb. Haemost. 84 (2000) 601–603.
[19] S. Kangsadalampai, P.G. Board, The Val34Leu polymorphism in the A subunit of coagulation factor XIII contributes to the large normal range activity and demonstrates that the activation peptide plays a role in catalytic activity, Blood 92 (1998) 2766–2770.
[20] T.A. Trumbo, M.C. Maurer, Val34I and V34A substitutions within the factor XIII activation peptide segment (28–41) affect the interactions with the thrombin active site, Thromb. Haemost. 89 (2003) 647–653.
[21] U. Wartiovaara, H. Mikkola, G. Szoke, G. Haramura, L. Karpati, I. Balogh, R. Lassila, L. Muszbek, A. Palotie, Effect of Val34Leu polymorphism on the activation of the coagulation factor XIII-A, Thromb. Haemost. 84 (2000) 595–600.
[22] V.C. Yee, L.C. Pederson, P.D. Bishop, R.E. Stenkamp, D.C. Teller, Structural evidence that the activation peptide is not released upon thrombin cleavage of factor XIII, Thromb. Res. 78 (1995) 389–397.
[23] B.C.B. Lim, R.A. Ariens, A.M. Carter, J.W. Weisel, P.J. Grant, Genetic regulation of fibrin structure and function: complex gene environment interactions may modulate vascular risk, Lancet 361 (2003) 1424–1431.
[24] U. Wartiovaara, M. Perola, H. Mikkola, K. Totterman, V. Savolainen, A. Penttila, P.J. Grant, M.J. Tikkanen, E. Vartiainen, P.J. Karhunen, L. Peltonen, A. Palotie, Association of FXIII Val34Leu with decreased risk of myocardial infarction in Finnish males, Atherosclerosis 142 (1999) 295–300.
[25] A.P. Reiner, M.B. Frank, S.M. Schwartz, M.L. Linenberger, W.T. Longstreth, G. Teramura, F.R. Rosendaal, B.M. Psaty, D.S. Siscovick, Coagulation factor XIII polymorphisms and the risk of myocardial infarction and ischaemic stroke in young women, Br. J. Haematol. 116 (2002) 376–382.
[26] I. Canavy, M. Henry, P.E. Morange, L. Tiret, O. Poirier, A. Ebagosti, M. Bory, S. Kangsadalampai, Genetic polymorphisms and coronary artery disease in the south of France, Thromb. Haemost. 83 (2000) 212–216.
[27] J. Corral, R. Gonzales-Conejero, J.A. Iniesta, J. Rivera, C. Martinez, V. Vincente, The FXIII Val34Leu polymorphism in venous and arterial thromboembolism, Haemotologica 85 (2000) 293–297.
[28] D. Warner, M.W. Mansfield, P.J. Grant, Coagulation factor XIII and cardiovascular disease in UK Asian patients undergoing coronary angiography, Thromb. Haemost. 85 (2001) 408–4111.
[29] A.P. Reiner, S.M. Schwartz, M.B. Frank, W.T. Longstreth, L.A. Hindorff, G. Teramura, F.R. Rosendaal, L.K. Gaur, B.M. Psaty, D.S. Siscovick, Polymorphisms of coagulation factor XIII subunit A and risk of nonfatal hemorrhagic stroke in young white women, Stroke 32 (2001) 2580–2587.
[30] A.J. Catto, H.P. Kohler, S. Bannan, M.H. Stickland, A. Carter, P.J. Grant, Factor XIII Val 34 Leu: a novel assocation with primary intracerebral hemorrhage, Stroke 29 (1998) 813–815.
[31] A. Elbaz, O. Poirier, S. Canaple, F. Chedru, F. Cambien, P. Amarenco, The association between the Val34Leu polymorphism in the factor XIII gene and brain infarction, Blood 95 (2000) 586–591.
[32] R.F. Franco, P.H. Reitsma, D. Lourenco, F.H. Maffei, V. Morelli, M.H. Travella, A.G. Araujo, C.E. Piccinato, M.A. Zago, Factor XIII Val34Leu is a genetic factor involved in the aetiology of venous thrombosis, Thromb. Haemost. 81 (1999) 676–679.
[33] M. Zidane, M.C. de Visser, M. ten Wolde, H.L. Vos, W. de Monye, R.M. Bertina, M.V. Huisman, Frequency of the TAFI -438 G/A and factor XIIIA Val34Leu polymorphisms in patients with objectively proven pulmonary embolism, Thromb. Haemost. 90 (2003) 439–445.
[34] A.J. Catto, H.P. Kohler, J. Coore, M.W. Mansfield, M.H. Stickl, P.J. Grant, Association of a common polymorphism in the factor XIII gene with venous thrombosis, Blood 93 (1999) 906–908.
[35] M. Alhenc-Gelas, J.L. Reny, M.L. Aubry, M. Aiach, J. Emmerich, The FXIII Val 34 Leu mutation and the risk of venous thrombosis, Thromb. Haemost. 84 (2000) 1118.
[36] A.P. Reiner, S.R. Heckbert, H.L. Vos, R.A. Ariens, R.N. Lemaitre, N.L. Smith, T. Lumley, T.D. Rea, L.A. Hindorff, G.D. Schellenbaum, F.R. Rosendaal, D.S. Siscovick, B.M. Psaty, Genetic variants of coagulation factor XIII, postmenopausal estrogen therapy, and risk of nonfatal myocardial infarction, Blood 102 (2003) 25–30.
[37] H.P. Kohler, M.H. Stickland, N. Ossei-Gerning, A. Carter, H. Mikkola, P.J. Grant, Association of a common polymorphism in the factor XIII gene with myocardial infarction, Thromb. Haemost. 79 (1998) 8–13.
[38] K.R. Siebenlist, D.A. Meh, M.W. Mosesson, Protranglutaminase (factor XIII) mediated crosslinking of fibrinogen and fibrin, Thromb. Haemost. 86 (2001) 1221–1228.
[39] V. Schroeder, H.P. Kohler, Effect of FXIII Val34Leu on alpha-2-antiplasmin incorporation into fibrin, Thromb. Haemost. 84 (2000) 1128–1130.