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doi:10.3748/wjg.14.4440

World J Gastroenterol 2008 July 28; 14(28): 4440-4444
World Journal of Gastroenterology ISSN 1007-9327

EDITORIAL

Thrombosis and inflammatory bowel disease-the role of genetic risk factors

Georgia Tsiolakidou, Ioannis E Koutroubakis

Georgia Tsiolakidou, Ioannis E Koutroubakis, Department of Gastroenterology University Hospital Heraklion, Crete, Heraklion 71110, Greece
Author contributions: Tsiolakidou G reviewed the literature and wrote the first draft of the paper; Koutroubakis IE contributed to providing the idea and performing review and editing of the manuscript.
Correspondence to: Ioannis E Koutroubakis, MD, PhD, Assistant Professor of Medicine, Department of Gastroenterology, University Hospital Heraklion, PO Box 1352, Crete, Heraklion 71110, Greece. ikoutroub@med.uoc.gr
Telephone: +30-28-10392253 Fax: +30-28-10542085
Received: March 23, 2008 Revised: June 10, 2008
Accepted: June 17, 2008
Published online: July 28, 2008

Abstract

Thromboembolism is a significant cause of morbidity and mortality in patients with inflammatory bowel disease (IBD). Recent data suggest thromboembolism as a disease-specific extraintestinal manifestation of IBD, which is developed as the result of multiple interactions between acquired and genetic risk factors. There is evidence indicating an imbalance of procoagulant, anticoagulant and fibrinolytic factors predisposing in thrombosis in patients with IBD. The genetic factors that have been suggested to interfere in the thrombotic manifestations of IBD include factor Ⅴ Leiden, factor Ⅱ (prothrombin, G20210A), methylenetetrahydrofolate reductase gene mutation (MTHFR, 6777T), plasminogen activator inhibitor type 1 (PAI-1) gene mutation and factor ⅩⅢ (val34leu). In this article we review the current data and future prospects on the role of genetic risk factors in the development of thromboembolism in IBD.

Key words: Crohn's disease; Factor V Leiden; Genetics; Thrombosis; Ulcerative colitis

Peer reviewer: Dr. Bret Lashner, Cleveland Clinic, 9500 Euclid Ave, Cleveland OH 44195, United States

Tsiolakidou G, Koutroubakis IE. Thrombosis and inflammatory bowel disease-the role of genetic risk factors. *World J Gastroenterol* 2008; 14(28): 4440-4444 Available from: URL: http://www.wjgnet.com/1007-9327/14/4440.asp DOI: http://dx.doi.org/10.3748/wjg.14.4440

INTRODUCTION

Inflammatory bowel disease (IBD) is associated with an increased risk of vascular complications[1-4]. The most important of these complications are arterial and venous thromboembolisms, which represent a significant cause of morbidity and mortality in IBD patients. Thromboembolism is a disease-specific extraintestinal manifestation of IBD[5], which is developed as the result of multiple interactions between acquired and genetic risk factors. Several studies have shown an imbalance of procoagulant, anticoagulant and fibrinolytic factors predisposing in thrombosis in patients with IBD[6-9]. The incidence of thromboembolism in IBD ranges between 1% and 7.7% in clinical studies[1,10,11], rising to 39%-41% in postmortem studies[12].

The most common thrombotic manifestations in IBD are deep vein thrombosis, usually in the leg, and pulmonary embolism. The latter may be fatal. Thrombotic events occur less frequently in other sites, such as the cerebrovascular system, portal vein, mesenteric veins, and retinal vein. Arterial thrombotic complications occur less frequently than venous thromboembolism in patients with IBD, and most occur after surgery. An increased atherosclerotic risk in patients with IBD has also been suggested[13]. This could be associated with the elevated levels of C-reactive protein and plasma sCD40L, which are features of the IBD[14,15]. Common carotid artery intima-media thickness has been found significantly higher in IBD patients compared with healthy controls[16]. Premature atherosclerosis with lower extremity arterial occlusions has been reported in young patients with Crohn's disease[17]. An increased risk of cardiovascular arterial thromboembolic diseases in both Crohn's disease and ulcerative colitis and an increase in cerebrovascular arterial thromboembolic diseases in Crohn's disease recently have been reported[18]. IBD patients have been found to develop thrombembolisms earlier in life than non-IBD thrombotic patients[19]. Furthermore, many IBD patients with thromboembolic disorders either have active disease or have undergone recent major abdominal surgery[2]. Conversely, thromboembolisms may also occur in quiescent IBD[1]. It has been suggested that the extent of colonic disease is correlated with thromboembolic risk. Extensive ulcerative colitis and colonic involvement of Crohn's disease was significantly associated with the development of thromboembolism[2]. The risk of recurrence of thromboembolism in IBD patients has been

reported to be 10%-13% despite medical therapy for the thromboembolic event[2]. The mortality from this complication in IBD has been reported to be 8%-25% during the acute episode[1,2]. The etiology of thrombosis in IBD is multifactorial. Thrombosis is a complex event in which several mechanisms and causal factors, inherited and acquired, are implicated, complicating the identification of its causes[20,21]. Several acquired prothrombotic risk factors are frequently observed, such as the inflammatory process per se, prolonged immobilization, use of corticosteroids, surgical treatment, fluid depletion, central venous catheters, hyperhomocysteinemia, vitamin deficiencies, smoking and use of oral contraceptives[4]. Importantly, approximately half of the patients with inflammatory bowel disease that develop a thromboembolic event have no identifiable risk factor[10]. Genetic factors may also play a role in thrombosis of patients with IBD. Based on the unraveling of the biochemistry and cell biology of the coagulation system, major advances in the understanding of genetics of thrombosis have been applied also in IBD complicating by thrombosis. The most common genetic variants that have been found to affect the risk of thrombosis are: factor V Leiden, factor Ⅱ (prothrombin, G20210A), methylenetetrahydrofolate reductase gene mutation (MTHFR, 6777T), plasminogen activator inhibitor type 1 (PAI-1) gene mutation and factor XⅢ (val34leu). This review focuses on the role of genetic risk factors in the development of thromboembolism in IBD.

EVALUATING GENETIC RISK OF THROMBOSIS IN INFLAMMATORY BOWEL DISEASE

Genetic risk factors have been suggested to predispose to thromboembolism in IBD. Several genetic markers located in coagulation genes have been examined in an attempt to document whether these markers are associated with increased thrombotic risk in IBD. Genetic studies of vascular complications of IBD pose enormous challenges, including resolution of immense genotypic and phenotypic heterogeneity, and gene-environment and gene-gene interactions. Past efforts to identify thrombosis-related genes in IBD have utilized population-based association methods, but the substantial progress that has been made recently with the strategy of using positional cloning of genes based on linkage studies is expected to apply to this field. These methods focus on measuring quantitative traits that are correlated with the risk of disease.

Factor V Leiden

Factor V Leiden (FVL), an arginine to glutamine missense mutation in the factor V (FV) gene at position 506[22], is the most prominent risk factor for venous thromboembolism[23,24]. The amino acid substitution in the activated protein C (APC) cleavage site of FV leads to increased thrombin generation due to decreased APC-mediated inactivation of FV, and due to decreased FV cofactor activity for FVIIIa inactivation[25]. Factor V Leiden is found in approximately 5% of Caucasians, and increases the risk of thrombosis five- to eightfold for heterozygous carriers and 50- to 80-fold for homozygous carriers. The prevalence of FVL ranges from 20% to 30% in unselected patients with venous thrombosis. Genetic studies determining the prevalence of the FVL allele in IBD mostly have shown no difference in allele frequency between IBD patients and healthy controls[26-30]. The prevalence of FVL in thrombotic IBD patients was significantly higher than in IBD patients without thrombosis[31-33]. It is noteworthy that the FVL allele was associated mainly with venous thrombosis[33]. In addition, the prevalence of FVL in IBD patients with previous thromboembolism appears not to differ from that found in non-IBD patients with thromboembolism[33,34]. On the other hand, an Italian study showed a very low prevalence of FVL allele in thrombotic IBD patients[35]. The discrepancies between these results may be due to the different characteristics of the populations studied (genetic background, previous history of thrombosis, and small sample sizes). Furthermore, in a recent study of experimental colitis, the FVL allele had no effect in murine colitis and thus, the authors question the role of activated blood coagulation in IBD[36]. Although somewhat conflicting, these genetic studies suggest that the FVL as a risk factor for thrombosis in IBD patients matches that of the general population. Furthermore, FVL is not associated with IBD per se, but when present it increases the risk of thromboembolism[37]. Finally, it is important to realize that homozygous carriers of the FVL allele are rare and that all genetic studies are performed using heterozygotes, which have a milder thrombotic phenotype.

G20210A prothrombin gene mutation

The G20210A mutation is a genetic variation of the prothrombin (Factor Ⅱ) gene consisting of a single nucleotide change (guanine to adenine) at position 20210 of the 3'-untranslated region. The G20210A mutation is the second most frequent genetic prothrombotic mutation after FVL. It is present in approximately 2% of Caucasians, leads to greater prothrombin plasma levels (heterozygous carriers have about 30% higher PT levels than healthy controls), and increases the risk of venous thrombosis about threefold[38]. However, no definite association between this gene mutation and IBD has been detected in several studies[30,33-35,39]. Presence of this mutation is found at a similar prevalence in IBD patients as well as in IBD patients with thrombosis[27,32-33]. This mutation has only been studied in a limited number of thrombotic IBD patients so firm conclusions cannot be drawn.

Methylenetetrahydrofolate reductase C677T gene mutation

Methylenetetrahydrofolate reductase is a critical enzyme involved in the remethylation pathway of homocysteine metabolism. A common mutation (C677T) has been identified in the MTHFR gene. This variant leads to 10%-20% increases in homocysteine plasma levels in homozygous carriers, which are found in around 10% of

the population. The effect of MTHFR 6777T carriership on the risk of thrombosis varies among studies, and a recent meta-analysis found a weak effect (10%-20% risk increase)[40-43]. Studies of the prevalence of C677T homozygosity in IBD have found discordant results[34], probably because of regional and ethnic variations in the prevalence of polymorphism in the general population. In a recent population-based case-control study[30], although some differences were observed among patients with IBD and healthy controls in the prevalence of MTHFR 6777T (decrease in mutant allele carriership in UC), these did not explain an excess risk of thrombosis. The prevalence of C677T homozygosity between IBD thrombotic patients and non-IBD thrombotic patients showed no significant difference[32,33].

Factor XIII gene mutation

A common variant in subunit A of factor XIII, usually indicated by the amino acid position and change (val34leu), is associated with a greater FXIII activation rate and leads to a 20%-40% reduction of the risk of venous thrombosis for homozygous carriers. These are found in approximately 10% of the population[44,45]. This variant, which is protective against thrombosis, has been evaluated in IBD patients[46]. Available data suggest that the prevalence of this polymorphism is similar in patients with IBD compared to the general population[47,48]. A slightly greater prevalence of factor XIII mutation carriership in CD has been found in a recent population-based study[30], but this could not explain the greater risk of venous thrombosis in CD. Finally, the prevalence of XIII (val34leu) was similar in IBD patients with vascular complications and non-IBD thrombotic patients[33].

Plasminogen activator inhibitor type 1 gene mutation

Plasminogen activator inhibitor type 1 (PAI-1) is considered as inhibitor of fibrinolysis. The 4G/4G genotype is associated with an overexpression of PAI-1, which may cause a decreased fibrinolysis and, therefore, a hypercoagulability state contributing to the development of vascular complications. Several studies have demonstrated that the 4G/4G genotype is associated with an enhanced PAI-1 expression[49] and contributes as an additional risk factor to the development of myocardiac infarction[50], arterial thrombosis[51], and deep venous thrombosis[52]. However, the evidence regarding the relationship between an elevated PAI-1 plasma level or PAI-1 genetic polymorphism and the risk of venous thromboembolism is rather conflicting. The allelic frequency of PAI-1 4G has been reported higher in IBD patients than in the reference population[53]. Moreover, a recent study showed a significantly higher allelic frequency of PAI-1 4G in IBD patients with vascular complications compared with IBD and healthy controls. However, the prevalence of this genotype does not differ in thrombotic IBD patients compared to non-IBD thrombotic patients[33].

Janus kinase 2 gene mutation

Janus kinase 2 (JAK2) mutations have been described in several Philadelphia-negative myeloproliferative disorders (MPD)[54]. The point mutation in JAK2 encodes a valine to phenylalanine change at position 617 (JAK2 V617F) and confers constitutive tyrosine kinase activity[55]. It has been suggested that thrombosis in MPD may be due to JAK2 mutation. JAK2 is also important in vascular diseases, such as atherosclerosis, in which inflammation plays an important role. JAK2 V617F mutation has been found, in the absence of overt MPD, highly associated with splanchnic vein thrombosis and sporadically with cerebral thrombosis. A recent study investigated the role of JAK2 V617F mutation in 48 IBD patients with thrombotic complications, but no case with the JAK2 V617F mutation was found[56]. The small number of cases with splanchnic vein thrombosis in this series (but also in other IBD series) that are mainly associated JAK2 V617F mutation could be also an explanation of this finding.

Other genetic factors

The role of the well recognized inherited thrombophilic states such as deficiencies of plasma antithrombin III, protein C, and protein S has been examined in several studies. Although deficiency of the proteins C and S in IBD patients have been proposed by some studies[20], other studies failed to confirm these data[21]. These factors are rare (< 1% of the population) and are considered to play a less important role in the thrombosis, and therefore it is not surprising that their results in IBD are rather contradictory.

Future prospects

We are entering a new era in genetic studies of venous thrombosis. It is believed that, combined, all the known mutations account for about the half of the genetic thrombosis risk. There is every reason to believe that additional genetic causes of thrombosis remain to be discovered. As a complex disease, thrombosis is considered to be the result of flexible combinations of variations of multiple genes that interact with lifestyle or other environmental factors to produce the disease. Future studies should investigate these interactions. Moreover, in IBD we need collection of large case-control series of patients complicating with venous thrombosis. This will provide the high quality clinical information related both to IBD and thrombosis that forms the basis of any genetic project. On the other hand, large-scale DNA analysis systems are now becoming available, which will allow us to study in the setting of IBD the genetics of venous thrombosis down to the single nucleotide level. As an example, we recently have reported a multigenetic analysis of polymorphisms of thrombophilic and vasoactive genes in a group of IBD patients with vascular complications compared with IBD patients without vascular complications and both thrombotic and healthy controls[33]. This approach, in a multicenter basis with a large number of patients, will give more insight into the genetic architecture of thrombotic risk in IBD. The final aim is personalized thrombosis prediction and appropriate management in a patient with IBD.

CONCLUSION

Epidemiological data suggest that IBD is associated with an increased risk of thromboembolic complications. However, the cause for this strong association remains unclear. It can be speculated that gene mutations may underlie the greater risk for thromboembolic complications in IBD patients. Thus, several studies have investigated the role of genetic defects in the development of vascular complications in IBD. The most common genetic variants that affect the risk of thrombosis are factor V Leiden, factor Ⅱ (prothrombin, G20210A), MTHFR (6777T) and factor ⅩⅢ (val34leu). Furthermore, the role of other thrombophilic and vasoactive genes has been evaluated with the occurrence of thromboembolism in IBD. The available data in the literature have shown that genetic risk factors are generally not found more often in IBD patients than others. However, when they occur, those with IBD compared to healthy controls are more likely to suffer thromboembolic complications. The screening for genetic coagulation defects appears justified in all IBD patients with a history of thrombosis or a family history of venous thromboembolic events. Future multicentre studies with large number of cases and further investigation of the interaction between genetic and environmental factors might increase our understanding of the mechanisms of pathogenesis of thrombotic complications in IBD. Using the new large-scale DNA sequencing techniques that are becoming available and enable many genes to be studied in a single individual, we could expect an in-depth insight into how genetic risk factors are involved in thrombosis in IBD.

REFERENCES

1 **Talbot RW**, Heppell J, Dozois RR, Beart RW Jr. Vascular complications of inflammatory bowel disease. *Mayo Clin Proc* 1986; **61**: 140-145
2 **Solem CA**, Loftus EV, Tremaine WJ, Sandborn WJ. Venous thromboembolism in inflammatory bowel disease. *Am J Gastroenterol* 2004; **99**: 97-101
3 **Bernstein CN**, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. *Thromb Haemost* 2001; **85**: 430-434
4 **Koutroubakis IE**. Therapy insight: Vascular complications in patients with inflammatory bowel disease. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 266-272
5 **Miehsler W**, Reinisch W, Valic E, Osterode W, Tillinger W, Feichtenschlager T, Grisar J, Machold K, Scholz S, Vogelsang H, Novacek G. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? *Gut* 2004; **53**: 542-548
6 **Stadnicki A**, Gonciarz M, Niewiarowski TJ, Hartleb J, Rudnicki M, Merrell NB, Dela Cadena RA, Colman RW. Activation of plasma contact and coagulation systems and neutrophils in the active phase of ulcerative colitis. *Dig Dis Sci* 1997; **42**: 2356-2366
7 **van Bodegraven AA**, Schoorl M, Linskens RK, Bartels PC, Tuynman HA. Persistent activation of coagulation and fibrinolysis after treatment of active ulcerative colitis. *Eur J Gastroenterol Hepatol* 2002; **14**: 413-418
8 **van Bodegraven AA**. Haemostasis in inflammatory bowel diseases: clinical relevance. *Scand J Gastroenterol Suppl* 2003; 51-62
9 **Saibeni S**, Bottasso B, Spina L, Bajetta M, Danese S, Gasbarrini A, de Franchis R, Vecchi M. Assessment of thrombin-activatable fibrinolysis inhibitor (TAFI) plasma levels in inflammatory bowel diseases. *Am J Gastroenterol* 2004; **99**: 1966-1970
10 **Jackson LM**, O'Gorman PJ, O'Connell J, Cronin CC, Cotter KP, Shanahan F. Thrombosis in inflammatory bowel disease: clinical setting, procoagulant profile and factor V Leiden. *QJM* 1997; **90**: 183-188
11 **Webberley MJ**, Hart MT, Melikian V. Thromboembolism in inflammatory bowel disease: role of platelets. *Gut* 1993; **34**: 247-251
12 **Sloan WP Jr**, Bargen JA, Gage RP. Life histories of patients with chronic ulcerative colitis: a review of 2,000 cases. *Gastroenterology* 1950; **16**: 25-38
13 **Hatoum OA**, Binion DG. The vasculature and inflammatory bowel disease: contribution to pathogenesis and clinical pathology. *Inflamm Bowel Dis* 2005; **11**: 304-313
14 **Danese S**, Katz JA, Saibeni S, Papa A, Gasbarrini A, Vecchi M, Fiocchi C. Activated platelets are the source of elevated levels of soluble CD40 ligand in the circulation of inflammatory bowel disease patients. *Gut* 2003; **52**: 1435-1441
15 **Koutroubakis IE**, Theodoropoulou A, Xidakis C, Sfiridaki A, Notas G, Kolios G, Kouroumalis EA. Association between enhanced soluble CD40 ligand and prothrombotic state in inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2004; **16**: 1147-1152
16 **Papa A**, Santoliquido A, Danese S, Covino M, Di Campli C, Urgesi R, Grillo A, Guglielmo S, Tondi P, Guidi L, De Vitis I, Fedeli G, Gasbarrini G, Gasbarrini A. Increased carotid intima-media thickness in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2005; **22**: 839-846
17 **Levy PJ**, Tabares AH, Olin JW. Lower extremity arterial occlusions in young patients with Crohn's colitis and premature atherosclerosis: report of six cases. *Am J Gastroenterol* 1997; **92**: 494-497
18 **Bernstein CN**, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. *Clin Gastroenterol Hepatol* 2008; **6**: 41-45
19 **Grip O**, Svensson PJ, Lindgren S. Inflammatory bowel disease promotes venous thrombosis earlier in life. *Scand J Gastroenterol* 2000; **35**: 619-623
20 **Koutroubakis IE**. Unraveling the mechanisms of thrombosis in inflammatory bowel disease. *Am J Gastroenterol* 2001; **96**: 1325-1327
21 **Danese S**, Papa A, Saibeni S, Repici A, Malesci A, Vecchi M. Inflammation and coagulation in inflammatory bowel disease: The clot thickens. *Am J Gastroenterol* 2007; **102**: 174-186
22 **Bertina RM**, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994; **369**: 64-67
23 **Segers K**, Dahlback B, Nicolaes GA. Coagulation factor V and thrombophilia: background and mechanisms. *Thromb Haemost* 2007; **98**: 530-542
24 **Couturaud F**, Kearon C, Leroyer C, Mercier B, Abgrall JF, Le Gal G, Lacut K, Oger E, Bressollette L, Ferec C, Lamure M, Mottier D. Incidence of venous thromboembolism in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. *Thromb Haemost* 2006; **96**: 744-749
25 **Nicolaes GA**, Dahlback B. Factor V and thrombotic disease: description of a janus-faced protein. *Arterioscler Thromb Vasc Biol* 2002; **22**: 530-538
26 **Turri D**, Rosselli M, Simioni P, Tormene D, Grimaudo S, Martorana G, Siragusa S, Mariani G, Cottone M. Factor V Leiden and prothrombin gene mutation in inflammatory bowel disease in a Mediterranean area. *Dig Liver Dis* 2001; **33**: 559-562

27 **Papa A**, De Stefano V, Gasbarrini A, Chiusolo P, Cianci R, Casorelli I, Paciaroni K, Cammarota G, Leone G, Gasbarrini G. Prevalence of factor V Leiden and the G20210A prothrombin-gene mutation in inflammatory bowel disease. *Blood Coagul Fibrinolysis* 2000; **11**: 499-503

28 **Haslam N**, Standen GR, Probert CS. An investigation of the association of the factor V Leiden mutation and inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 1999; **11**: 1289-1291

29 **Vecchi M**, Sacchi E, Saibeni S, Meucci G, Tagliabue L, Duca F, De Franchis R. Inflammatory bowel diseases are not associated with major hereditary conditions predisposing to thrombosis. *Dig Dis Sci* 2000; **45**: 1465-1469

30 **Bernstein CN**, Sargent M, Vos HL, Rosendaal FR. Mutations in clotting factors and inflammatory bowel disease. *Am J Gastroenterol* 2007; **102**: 338-343

31 **Koutroubakis IE**, Sfiridaki A, Mouzas IA, Maladaki A, Kapsoritakis A, Roussomoustakaki M, Kouroumalis EA, Manousos ON. Resistance to activated protein C and low levels of free protein S in Greek patients with inflammatory bowel disease. *Am J Gastroenterol* 2000; **95**: 190-194

32 **Guedon C**, Le Cam-Duchez V, Lalaude O, Menard JF, Lerebours E, Borg JY. Prothrombotic inherited abnormalities other than factor V Leiden mutation do not play a role in venous thrombosis in inflammatory bowel disease. *Am J Gastroenterol* 2001; **96**: 1448-1454

33 **Koutroubakis IE**, Sfiridaki A, Tsiolakidou G, Theodoropoulou A, Livadiotaki A, Paspatis G, Kouroumalis EA. Genetic risk factors in patients with inflammatory bowel disease and vascular complications: case-control study. *Inflamm Bowel Dis* 2007; **13**: 410-415

34 **Papa A**, Danese S, Grillo A, Gasbarrini G, Gasbarrini A. Review article: inherited thrombophilia in inflammatory bowel disease. *Am J Gastroenterol* 2003; **98**: 1247-1251

35 **Spina L**, Saibeni S, Battaglioli T, Peyvandi F, de Franchis R, Vecchi M. Thrombosis in inflammatory bowel diseases: role of inherited thrombophilia. *Am J Gastroenterol* 2005; **100**: 2036-2041

36 **Spek CA**, ten Kate FJ, te Velde AA. Factor V Leiden and the etiology of inflammatory bowel disease. *Thromb Haemost* 2007; **98**: 670-673

37 **Liebman HA**, Kashani N, Sutherland D, McGehee W, Kam AL. The factor V Leiden mutation increases the risk of venous thrombosis in patients with inflammatory bowel disease. *Gastroenterology* 1998; **115**: 830-834

38 **Poort SR**, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996; **88**: 3698-3703

39 **Mahmood A**, Needham J, Prosser J, Mainwaring J, Trebble T, Mahy G, Ramage J. Prevalence of hyperhomocysteinaemia, activated protein C resistance and prothrombin gene mutation in inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2005; **17**: 739-744

40 **Frosst P**, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, Boers GJ, den Heijer M, Kluijtmans LA, van den Heuvel LP. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet* 1995; **10**: 111-113

41 **den Heijer M**, Koster T, Blom HJ, Bos GM, Briet E, Reitsma PH, Vandenbroucke JP, Rosendaal FR. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. *N Engl J Med* 1996; **334**: 759-762

42 **Kluijtmans LA**, den Heijer M, Reitsma PH, Heil SG, Blom HJ, Rosendaal FR. Thermolabile methylenetetrahydrofolate reductase and factor V Leiden in the risk of deep-vein thrombosis. *Thromb Haemost* 1998; **79**: 254-258

43 **Den Heijer M**, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. *J Thromb Haemost* 2005; **3**: 292-299

44 **Catto AJ**, Kohler HP, Coore J, Mansfield MW, Stickland MH, Grant PJ. Association of a common polymorphism in the factor XIII gene with venous thrombosis. *Blood* 1999; **93**: 906-908

45 **Van Hylckama Vlieg A**, Komanasin N, Ariens RA, Poort SR, Grant PJ, Bertina RM, Rosendaal FR. Factor XIII Val34Leu polymorphism, factor XIII antigen levels and activity and the risk of deep venous thrombosis. *Br J Haematol* 2002; **119**: 169-175

46 **Franco RF**, Reitsma PH, Lourenco D, Maffei FH, Morelli V, Tavella MH, Araojo AG, Piccinato CE, Zago MA. Factor XIII Val34Leu is a genetic factor involved in the etiology of venous thrombosis. *Thromb Haemost* 1999; **81**: 676-679

47 **Helio T**, Wartiovaara U, Halme L, Turunen UM, Mikkola H, Palotie A, Farkkila M, Kontula K. Arg506Gln factor V mutation and Val34Leu factor XIII polymorphism in Finnish patients with inflammatory bowel disease. *Scand J Gastroenterol* 1999; **34**: 170-174

48 **Saibeni S**, Vecchi M, Faioni EM, Franchi F, Rondonotti E, Borsi G, de Franchis R. Val34Leu factor XIII polymorphism in Italian patients with inflammatory bowel disease. *Dig Liver Dis* 2003; **35**: 32-36

49 **Dawson S**, Hamsten A, Wiman B, Henney A, Humphries S. Genetic variation at the plasminogen activator inhibitor-1 locus is associated with altered levels of plasma plasminogen activator inhibitor-1 activity. *Arterioscler Thromb* 1991; **11**: 183-190

50 **Eriksson P**, Kallin B, van't Hooft FM, Bavenholm P, Hamsten A. Allele-specific increase in basal transcription of the plasminogen-activator inhibitor 1 gene is associated with myocardial infarction. *Proc Natl Acad Sci USA* 1995; **92**: 1851-1855

51 **Tassies D**, Espinosa G, Munoz-Rodriguez FJ, Freire C, Cervera R, Monteagudo J, Maragall S, Escolar G, Ingelmo M, Ordinas A, Font J, Reverter JC. The 4G/5G polymorphism of the type 1 plasminogen activator inhibitor gene and thrombosis in patients with antiphospholipid syndrome. *Arthritis Rheum* 2000; **43**: 2349-2358

52 **Stegnar M**, Uhrin P, Peternel P, Mavri A, Salobir-Pajnic B, Stare J, Binder BR. The 4G/5G sequence polymorphism in the promoter of plasminogen activator inhibitor-1 (PAI-1) gene: relationship to plasma PAI-1 level in venous thromboembolism. *Thromb Haemost* 1998; **79**: 975-979

53 **Magro F**, Dinis-Ribeiro M, Araujo FM, Pereira P, Fraga MC, Cunha-Ribeiro LM, Tome-Ribeiro A. High prevalence of combined thrombophilic abnormalities in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2003; **15**: 1157-1163

54 **Levine RL**, Wadleigh M, Cools J, Ebert BL, Wernig G, Huntly BJ, Boggon TJ, Wlodarska I, Clark JJ, Moore S, Adelsperger J, Koo S, Lee JC, Gabriel S, Mercher T, D' Andrea A, Frohling S, Dohner K, Marynen P, Vandenberghe P, Mesa RA, Tefferi A, Griffin JD, Eck MJ, Sellers WR, Meyerson M, Golub TR, Lee SJ, Gilliland DG. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell* 2005; **7**: 387-397

55 **Cools J**, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J, Kutok J, Clark J, Galinsky I, Griffin JD, Cross NC, Tefferi A, Malone J, Alam R, Schrier SL, Schmid J, Rose M, Vandenberghe P, Verhoef G, Boogaerts M, Wlodarska I, Kantarjian H, Marynen P, Coutre SE, Stone R, Gilliland DG. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003; **348**: 1201-1214

56 **Karimi O**, Crusius JB, Coucoutsi C, Heijmans R, Sambuelli AM, Pena AS, Koutroubakis IE. JAK2 V617F mutation is not involved in thromboembolism in IBD. *Inflamm Bowel Dis* 2008; **14:** 1606-1607

S- Editor Zhong XY **L- Editor** Li M **E- Editor** Ma WH