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Aetiology of Venous Thrombosis

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1. Introduction

Blood is a fluid tissue that circulates in the body inside intact blood vessels (veins, arteries and capillaries) to perform several vital functions. For perfect performance, blood should flow smoothly inside blood vessels without interruption. If a blood vessel gets injured or perforated, blood will flow out and be lost, which may be fatal. To prevent this, several natural physiological processes occur to form a "plug", usually called "blood clot", to block the puncture and prevent blood loss. These processes are called "Haemostasis", which involves the blood vessels themselves, specialized blood cells called platelets, as well as specific blood proteins called clotting factors. Haemostasis functions to prevent blood loss from injured blood vessels and ensure the fluidity of blood inside intact (uninjured) blood vessels (Hoffbrand et al., 2001; Escobar et al., 2002; Laffan & Manning, 2002a).

Like any other physiological process in the body, haemostasis may get abnormal due to many reasons. It may not be able to function well and therefore the blood becomes unable to clot, which leads to bleeding problems (haemophilia). On the other hand, haemostasis may happen abnormally inside intact blood vessels, without any injury, forming a blood clot (thrombus) inside the vessel (intravascular thrombosis), which may lead to partial or complete blockage of blood flow through this vessel. This mostly occurs in the deep veins of the lower extremities, and to a less extent in the upper extremities, and this pathological condition is called deep vein thrombosis (DVT). If a thrombus detaches (called embolus), it usually goes up through the circulation and settles in an arterial branch in the lungs causing pulmonary embolism (PE). DVT and PE together are called venous thromboembolic disorders (VTE). VTE are serious vascular conditions that account for high morbidity and mortality rates in many countries with an annual incidence of 1/1000 (Dahlbäck, 1995; Ridker et al., 1997).

Several "genetic" and "acquired" risk factors were identified to cause VTE, and this is why the WHO expert group described VTE in 1996 as being genetically determined, acquired or both (Lane et al., 1996). This chapter describes the different genetic and acquired risk factors for VTE. The chapter is divided into two main sections: genetic factors and acquired factors, and it is concluded by a third section on intersections of risk factors. In order to better understand how these factors cause VTE, a preliminary section is given to explain the major processes of haemostasis, namely the Coagulation and Fibrinolysis processes, and how abnormalities may lead to VTE.

2. Coagulation and Fibrinolysis

As explained above, haemostasis is the normal physiological process by which an injured blood vessel is sealed by a blood clot to prevent blood loss. Haemostasis involves many

processes, two of which are "The Coagulation Process" and "The Fibrinolysis Process". In both processes, blood clotting factors are the crucial constituents. Clotting factors are enzymatic proteins that are synthesised mostly in the liver and circulate in the blood in an inactive form. When a blood vessel gets injured, these factors get activated and start a cascade of chemical reactions leading to the formation of a fibrin "clot" which blocks the site of injury and therefore prevents blood loss and allows for wound healing. Although the clotting factors have specific names, they are usually given Roman numerals. Figure 1 gives a schematic drawing of the process of Coagulation showing the participation of each clotting factor.

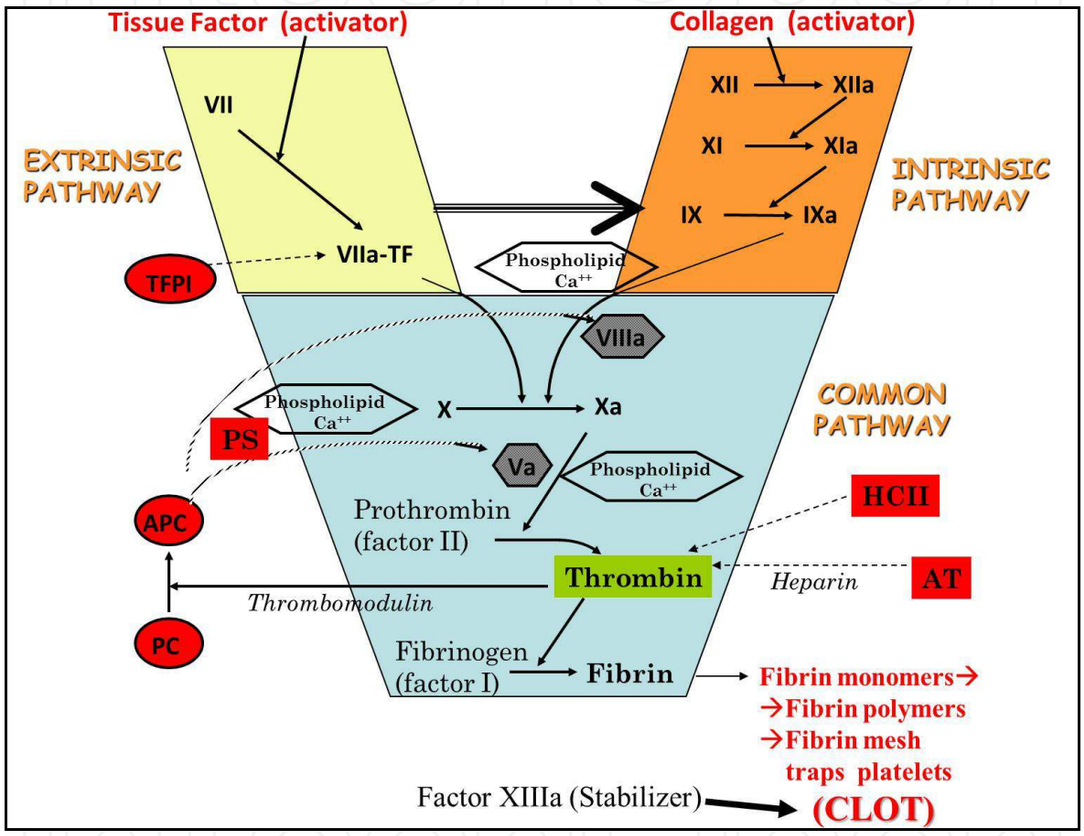

Fig. 1. The Coagulation process and its control elements. Solid arrows indicate activation; dotted arrows indicate inactivation (prepared and drawn by the author).

The Coagulation process maybe virtually divided into three pathways: Extrinsic, Intrinsic and Common pathways. When a blood vessel is injured, the components of the blood vessels start to activate the clotting factors by two methods. Firstly, the injured tissues release a membrane protein called thromboplastin (tissue factor [TF] or clotting factor III) which is capable of activating clotting factor VII in the Extrinsic pathway. Activated clotting factor VII (VIIa) forms a complex with TF, and this tends to activate clotting factor X in the Common pathway. On the other hand, the subendothelial layers of blood vessels have abundant amounts of collagen embedded inside them. This collagen gets exposed in injured vessels, and collagen is capable of activating clotting factor XII in the Intrinsic pathway. Activated factor XII (XIIa) in turn activates clotting factor XI, which in turn activates clotting

factor IX. Activated clotting factor IX, with the help of clotting co-factor VIII, is capable of activating clotting factor X in the Common pathway. So, both the Extrinsic and Intrinsic pathways team up to activate the Common pathway. In the Common pathway, activated clotting factor X, with the help of clotting co-factor V, continues the process by activating clotting factor II (prothrombin) into thrombin. The main function of thrombin is the conversion of fibrinogen (clotting factor I) into fibrin. Fibrin molecules then polymerize to form thread-like structures which form a mesh that gives the basis of blood clot. Finally, clotting factor XIII crosslinks fibrin polymers to form a stable fibrin mesh which traps activated platelets and other blood cells to form the final blood clot which eventually blocks the injured blood vessel. In addition to co-factors V and VIII, phospholipids and calcium ions (factor IV) act as co-factors in the process of Coagulation (Kane & Davie, 1988; Furie & Furie, 1988; Walker & Fay, 1992; Davie, 1995; Hoffbrand et al., 2001; Escobar et al., 2002; Laffan & Manning, 2002a).

After clot formation, wound healing starts and the injured blood vessel regenerates and becomes intact again. When the healing process is complete, the fibrin clot will no longer be needed and therefore it has to be removed. This occurs by the process of Fibrinolysis (figure 2). The key enzyme in this process is plasmin, which normally circulates in the blood in an inactive form called plasminogen. Plasminogen is usually activated into plasmin by tissue plasminogen activator (tPA) produced by the endothelial cells in the healing blood vessels. Plasmin breaks down fibrin threads into smaller pieces called fibrin degradation products (FDP) which are excreted from the circulation, and therefore the clot dissolves and the blood flow recovers normally (Rock & Wells, 1997; Hoffbrand et al., 2001; Escobar et al., 2002; Laffan & Manning, 2002a).

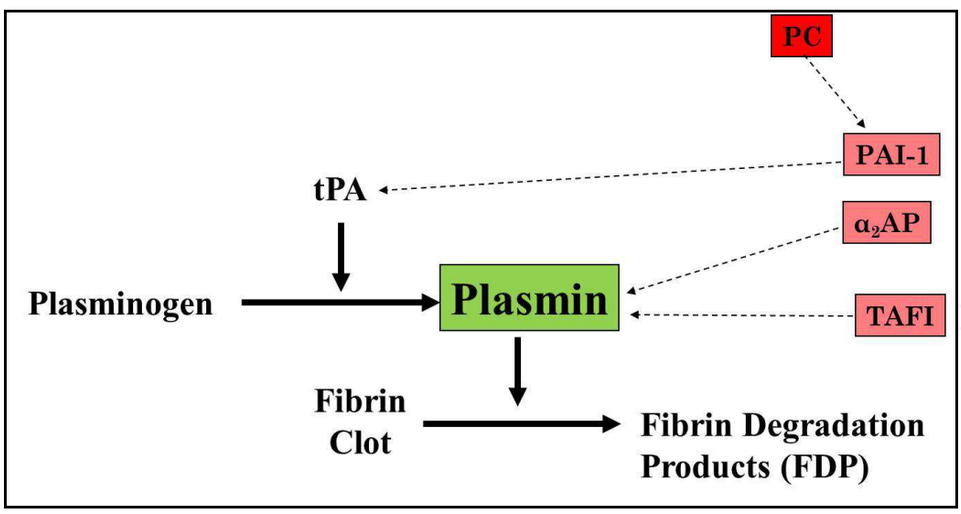

Fig. 2. Fibrinolysis process and its control elements. Solid arrows indicate activation; dotted arrows indicate inactivation (prepared and drawn by the author).

The processes of Coagulation and Fibrinolysis are carefully monitored and supervised by several control systems. This is important to prevent excessive or unnecessary coagulation or fibrinolysis. In the Coagulation process, thrombin is a very robust enzyme which exerts many coagulation functions. It can activate other clotting factors and form many positive feedback loops in the Coagulation process. Therefore, the clotting process may continue

forever and the clot may enlarge until it blocks the whole lumen of the blood vessel. Therefore, the Coagulation process should be limited to the area of blood vessel injury and should be prevented from extending abroad. This is achieved by three main proteins that circulate normally in the blood, namely protein C (PC), protein S (PS) and antithrombin (AT). Together they are called "natural anticoagulants" since they function as antagonists to clotting. They exert their function after a blood clot is formed to prevent excessive clotting. They also interfere with the Coagulation process if it starts working accidently inside intact blood vessels. To explain more, AT, as its name indicates, inactivates thrombin, and therefore stops the process of Coagulation. PC, which is first activated into activated protein C (APC), tends to breakdown co-factors V and VIII and therefore slows down the Coagulation process. For APC to function normally, PS is involved as a cofactor. Phospholipids and calcium ions also assist in this process. Another inhibitor specific for the Extrinsic pathway, namely Tissue Factor Pathway Inhibitor (TFPI), limits the action of TF in activating factor VII (Kalafatis et al., 1994; Novotny, 1994; Davie, 1995; Esmon et al., 1997; Rosing & Tans, 1997; Cella et al., 1997; Hoffbrand et al., 2001; Escobar et al., 2002; Laffan & Manning, 2002a).

Regarding the control of the Fibrinolysis process, there are many proteins involved. For example, plasminogen activator inhibitors (PAI) prevent tPA from activating plasminogen and therefore stop the initiation of fibrinolysis. This is important to avoid early removal of blood clot before the completion of blood vessel healing. Another anti-fibrinolysis protein is α2-antiplasmin (AP) which is a major inhibitor of plasmin. Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) is a protein that is activated by thrombin to prevent the binding of plasmin to fibrin and therefore stops plasmin from breaking down the clot. The control actions of these fibrinolysis antagonists are illustrated in figure 2 (Hoffbrand et al., 2001; Escobar et al., 2002; Laffan & Manning, 2002a).

For normal healthy clotting/anticlotting results, the Coagulation and Fibrinolysis processes, with their control systems, should work in a highly balanced manner. Any abnormalities may disturb this balance leading to serious consequences. Abnormalities can be quantitative (deficiency or increase in quantity) or qualitative (abnormal structure or function [loss, lowering or gain]) that may affect any of the proteins involved. For example, abnormalities in clotting factors may lead to bleeding problems (termed haemophilia), while abnormalities in the natural anticoagulants may lead to increased clotting tendency (termed hypercoagulability) leading to thrombosis, with certain exceptions in both (figure 3).

In the following sections, different genetic and acquired abnormalities affecting the Coagulation and Fibrinolysis processes are discussed. Only those leading to thrombosis are included in accordance with the scope of this chapter. These abnormalities are usually referred to as "risk factors" since they put forth clinical manifestations in patients suffering from these abnormalities.

3. Genetic risk factors for venous thrombosis

Like all proteins produced in the body, clotting factors and other proteins of the Coagulation and Fibrinolysis processes are encoded by genes in the DNA of human cells. Any genetic abnormalities may lead to lower or no production of these proteins, or the production of molecules with abnormal structure and/or functions, although the quantity of which may be normal. Many of these abnormalities were found to cause venous thrombosis. For example, genetic defects in the genes of the natural anticoagulants may lead to lower

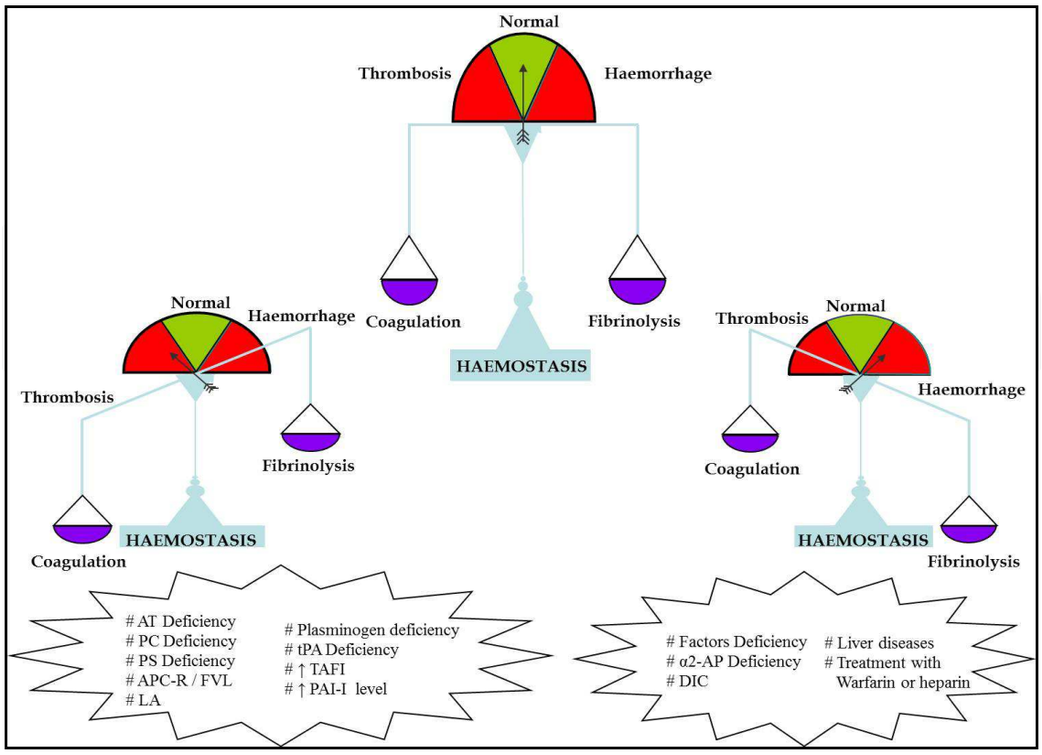

Fig. 3. Balance between the Coagulation and Fibrinolysis processes, in health and disease (prepared and drawn by the author).

production of these proteins and therefore lower control over the Coagulation process. This usually leads to an increase in the rate of coagulation, a phenomenon called "hypercoagulability", which is usually manifested clinically in patients as VTE. On the other hand, the natural anticoagulants may be produced normally, but they can not exert their function normally on their targets, and therefore hypercoagulability and VTE are expected too. Also, certain genetic defect may affect the clotting factors themselves leading to overproduction of such factors causing hypercoagulability. Moreover, abnormalities in the Fibrinolysis process may lower the efficiency of removal of clot, which leads to accumulation of clots and formation of thrombosis. In the following lines, several genetic abnormalities (risk factors) leading to venous thrombosis are discussed. These usually cause VTE at relatively earlier ages (less than 40 years-old) and may be referred to as "familial or hereditary thrombophilia". Although the condition known as "Activated Protein C Resistance" is the most common genetic defect associated with VTE, this defect will be left till the end because it was discovered relatively more recently and it was found to be the most common and important genetic risk factor for VTE.

3.1 Antithrombin (AT) deficiency

Historically, Egeberg (1965) was the first to associate cases of venous thrombosis with a hereditary defect in the Coagulation system; namely AT deficiency. AT is an inhibitor for thrombin, and its inhibition action is largely enhanced by heparin as a co-factor. AT deficiency causes lower control over thrombin, and therefore the Coagulation process becomes overactive (hypercoagulability) leading to VTE. Also, decreased control over

thrombin in cases with AT deficiency may have a positive effect on an inhibitor of fibrinolysis called thrombin-activatable fibrinolysis inhibitor (TAFI), which may add to the hypercoagulable status in these patients, as will be explained later.

Hereditary AT deficiency has been found in 1-5 % of thrombotic cases, with a prevalence of one in 500-5000 in different populations (Tait et al., 1991; Koster et al., 1995a; Koeleman et al., 1997; Bertina, 1997; Laffan & Manning, 2002b; Ehsan & Plumbley, 2002; Dahlbäck, 2008; Patnaik & Moll, 2008). It has an autosomal dominant mode of inheritance, and it accounts for a 10-fold increased risk of developing VTE (Dahlbäck, 2008). AT deficiency maybe divided into two types: Type I (quantitative; lower amount) and Type II (qualitative; abnormal function). Type II AT deficiency is also subdivided into three subtypes based on the kind of abnormality in function it has: affecting inhibition of thrombin, affecting the binding to heparin, or affecting both. More than 80 genetic abnormalities (missense, nonsense, deletions) were reported to cause AT deficiency (Bertina, 1997; Hoffbrand et al., 2001; Ehsan & Plumbley, 2002; Dahlbäck, 2008). More than half of the patients with hereditary AT deficiency have been reported to suffer from VTE at an age less than 40 years (Finazzi et al., 1987; van Boven et al., 1996). No reports are present on cases of homozygous AT deficiency, suggesting it is incompatible with life to have complete absence of AT in the blood (Dahlbäck, 2008).

3.2 Protein C (PC) deficiency

PC and its active form APC inactivate clotting co-factors V and VIII and therefore down-regulates the Coagulation process. Hence, any abnormality in PC may lead to continuous running of co-factors V and VIII causing VTE. Another method by which PC deficiency may cause VTE is through its interaction with the Fibrinolysis process. PC usually inhibits plasminogen activator inhibitor-1 (PAI-1), which is an inhibitor of tissue plasminogen activator (tPA) responsible for the presence of active plasmin (figure 2). Therefore, PC deficiency causes an impaired control over PAI-1, and this interferes with the normal function of the Fibrinolysis process, and hence may lead to accumulation of clots and eventually VTE.

Several cases of VTE were reported to have genetic deficiency of PC, which was first described in 1981 (Griffin et al, 1981). Hereditary PC deficiency has an autosomal dominant mode of inheritance, but many reports also claimed autosomal recessive mode (Mohanty et al., 1995; Ehsan & Plumbley, 2002; Bereczky et al., 2010). Almost 250 different genetic defects have been reported so far to be associated with PC deficiency (Bertina, 1997; D'Ursi et al., 2007; Bereczky et al., 2010). The prevalence of PC deficiency has been reported to be one in 200 to 16,000 normal individuals in different studies (Miletich et al., 1987; Tait et al., 1995; Mohanty et al., 1995; Koster et al., 1995b; Ehsan & Plumbley, 2002). The prevalence in patients with first episode of VTE is 2-5% (Bertina, 1997; Laffan & Manning, 2002b; Dahlbäck, 2008;). Heterozygous carriers of PC deficiency have 50% reduction in PC level, and they have an increased risk of developing thrombosis (Svensson & Dahlbäck, 1994; Hoffbrand et al., 2001). Homozygotes for PC deficiency may suffer from recurrent VTE episodes and from skin necrosis especially when treated with Warfarin, which is a vitamin K antagonist commonly used for treatment of VTE (Heeb et al., 1989; Svensson & Dahlbäck, 1994; Bennett, 1997; Hoffbrand et al., 2001; Dahlbäck, 2008). Infants with homozygous PC deficiency usually have fatal multiple microvascular thrombosis known as neonatal purpura fulminans (Ehsan & Plumbley, 2002; Dahlbäck, 2008). Two types of PC deficiency are present: Type I PC deficiency in which the level and function of PC are abnormal; and type II deficiency in which the level of PC is normal but the function is

defective. Type I is more common and has been found to be present in 1 to 14 % of cases having recurrent thrombosis. Type II is present in 10-15% of PC deficiency cases (Mohanty et al., 1995, Ehsan & Plumbley, 2002; Bereczky et al., 2010).

3.3 Protein S (PS) deficiency

PS acts as a co-factor in the process of inactivation of clotting co-factors V and VIII by APC, enhancing the process by 10-fold (ten Kate & van der Meer, 2008). PS has a very high affinity towards complement 4b binding protein (C4bBP). PS bound to C4bBP becomes inactive, and only free PS is active. Normally, the concentration of PS is more than C4bBP, and therefore only 60% of PS is present in an inactive form bound to C4bBP, while 40% remain as free active PS (Simmonds et al, 1998; Ehsan & Plumbley, 2002; Laffan & Manning, 2002b; Dahlbäck, 2008). First cases with hereditary PS deficiency were reported in 1984 (Comp & Esmon, 1984; Comp et al, 1984). Hereditary PS deficiency is an autosomal dominant disorder that has been associated with a 3- to 11-fold increased risk of venous thrombosis (Svensson and Dahlbäck, 1994; Hoffbrand et al, 2001; Ehsan & Plumbley, 2002; ten Kate & van der Meer, 2008; Bereczky et al., 2010). Similar to PC deficiency, homozygous cases with PS deficiency have tendency towards developing neonatal purpura fulminans and Warfarin-associated skin necrosis (Hoffbrand et al, 2001; Ehsan & Plumbley, 2002). In addition, PS deficiency has been linked to foetal loss (ten Kate & van der Meer, 2008). More than 200 genetic abnormalities in the PS gene were identified to cause PS deficiency, half of which were missense mutations and one-fifth were deletions or insertions (Bertina, 1997; ten Kate & van der Meer, 2008; Bereczky et al., 2010). The prevalence of PS deficiency is 0.03-2% in the general population and 1-13% in patients with VTE (Lane et al., 1996; Bertina, 1997; Seligsohn & Lubetsky, 2001; Dykes et al., 2001; Ehsan & Plumbley, 2002; Beauchamp et al., 2004; ten Kate & van der Meer, 2008; Bereczky et al., 2010). There are three types of hereditary PS deficiency. In Type I, total and free PS levels are lower than normal. Type II PS deficiency is the dysfunctional type of PS deficiency, in which the level of PS remains normal. A third type (Type III) is characterized by a mild deficiency in PS, and this is reflected in lower free PS level (Ehsan & Plumbley, 2002; ten Kate & van der Meer, 2008; Bereczky et al., 2010). Type I and III are the quantitative types of PS deficiency while Type II is the qualitative type. Certain sources refer to Type II as Type IIb and Type III as Type IIa (Ehsan & Plumbley, 2002). The majority of hereditary PS deficiency are Type I while 5-15% of cases are Type II (Bertina, 1997; Bereczky et al., 2010).

3.4 Tissue Factor Pathway Inhibitor (TFPI) deficiency

TFPI is a protease that inhibits TF-VIIa complex in the presence of factor Xa, thereby regulating the Extrinsic pathway of coagulation. Only 10% of TFPI is present as a free active form in the blood while the majority is in combination with lipoproteins. Deficiency in TFPI may lead to a hypercoagulable state and hence VTE (Novotny et al., 1989; Novotny, 1994; Samama et al, 1996; Cella et al, 1997; Ehsan & Plumbley, 2002). TFPI decreased activity was noticed to contribute in developing thrombosis in women using oral contraceptives, and in patients with paroxysmal nocturnal haemoglobinuria (Maroney & Mast; 2008). Experiments on genetically modified mice with TFPI gene disruption showed that they die prematurely in embryonic stage and before birth due to haemorrhagic and intravascular thrombi. Human embryos with TFPI deficiency may suffer a similar problem and this may explain why no cases with TFPI deficiency has been identified so far (Broze, 1998; Chan, 2001; Maroney & Mast; 2008).

3.5 Heparin Cofactor II (HCII) deficiency

HCII was first detected and isolated in the early 80s (Tollefsen & Blank, 1981, Tollefsen et al., 1982). It specifically inhibits thrombin with less affinity than AT and therefore it may be considered as a second line inhibitor of thrombin (Ehsan & Plumbley, 2002). A number of cases with HCII deficiency were reported to have VTE, but many cases remained asymptomatic (Ehsan & Plumbley, 2002; Laffan & Manning, 2002b). More studies are needed on larger number of cases to determine any significant effect of this defect in causing VTE.

3.6 Dysfibrinogenaemia

As explained earlier, the main aim of the Coagulation system is to convert fibrinogen (clotting factor I) into fibrin clot. Fibrinogen is encoded by three genes on chromosome 4 (Acharya & Dimichele, 2008; Miesbach et al., 2010). Genetic abnormalities in the fibrinogen genes may lead to lower or no production of fibrinogen (quantitative defects), causing bleeding problems in patients. On the other hand, other genetic abnormalities may lead to the production of fibrinogen molecules with abnormal structure and/or function (qualitative defects). Such abnormalities may negatively affect the binding of fibrinogen with thrombin, the polymerization of fibrin molecules, or the fibrinolytic inactivation by plasmin. This is the condition known as "Dysfibrinogenaemia", which has an autosomal dominant or recessive mode of inheritance (Dahlbäck, 1995; Koeleman et al, 1997; Ehsan & Plumbley, 2002; Laffan & Manning, 2002b; Acharya & Dimichele; 2008). Dysfibrinogenaemia was first reported in 1965 (Beck et al., 1965). Around 60% of cases show no clinical manifestations, while 20% show bleeding problems and 20% show thrombosis (Ehsan & Plumbley, 2002; Miesbach et al., 2010). There are at least 15 different genetic defects affecting the fibrinogen gene that were associated with Dysfibrinogenaemia (Bertina, 1997; Miesbach et al., 2010;). Still, Dysfibrinogenaemia remains a very rare disorder (1% of VTE cases) and more cases should be studied to fully understand the disease (Manucci, 2000; Acharya & Dimichele; 2008).

3.7 Elevated clotting factors

Several cases with VTE were found to be associated with elevated levels of clotting factors such as VIII, IX, XI, XII, fibrinogen and prothrombin. Elevated prothrombin is mostly associated with a genetic mutation in the prothrombin gene, which will be discussed in the next section. Elevated fibrinogen (hyperfibrinogenaemia) was found to promote faster fibrin formation and increased thrombus fibrin content, density, strength and stability. Hyperfibrinogenaemia was also found to have increased thrombolysis resistance, which explains more the association with VTE (Koster et al., 1995a; Poort et al, 1996; O'Donnell et al., 1997; Meijers et al., 2000; Kamphuisen et al., 2001; de Visser et al., 2001; Bertina et al., 2005; Machlus et al., 2011).

3.8 Prothrombin G20210A mutation

In 1996, Poort et al performed extensive DNA sequencing on the prothrombin gene located on chromosome 11 for patients with unexplained VTE. They discovered a single missense mutation (guanine to adenine; G→A) at nucleotide position 20210 in the 3′ untranslated region of the prothrombin gene. Since the mutation is present outside the coding region for prothrombin, it does not affect the structure of the prothrombin molecule. However, the

Prothrombin G20210A mutation was found to be associated with elevated levels of plasma prothrombin (elevation by one-third above normal; 133%), and therefore accounts for hypercoagulability and an increased risk of developing VTE (2 to 4-fold) (Poort et al, 1996; Bertina, 1997; Koeleman et al, 1997; Hillarp et al, 1997; Alhenc-Gelas et al. 1997; Hoffbrand et al., 2001; Ehsan & Plumbley, 2002; Laffan & Manning, 2002b; Dahlbäck, 2008). In fact, it has been demonstrated that prothrombin levels more than 115% have 2-fold increased risk of developing VTE (Poort et al, 1996). A study by Ceelie et al (2004) has proven that Prothrombin G20210A mutation leads to increased mRNA and protein expression. Another point worth mentioning here is that increased prothrombin levels may lead to an increase in the inhibitor of fibrinolysis called TAFI. This increase in TAFI disturbs the Fibrinolysis process and therefore may add to the hypercoagulable status in these patients, as will be explained later (Ehsan & Plumbley, 2002).

Several studies reported the prevalence of Prothrombin G20210A mutation to be 1-4% in healthy populations and 6-8% in patients with VTE. However, that was true when populations of Caucasian origin were studied. The Prothrombin G20210A mutation was very rare or absent in populations of East Asia and Africa, and in native populations of America and Australia (Franco et al., 1998; Dilley et al., 1998; Lin et al., 1998; Isshiki et al., 1998; Ruiz-Argüelles et al., 1999; Angelopoulou et al, 2000; Ghosh et al., 2001; Ruiz-Argüelles, 2001; Bennett et al, 2001; Lee, 2002; El-Karaksy et al, 2004; Eid & Rihani, 2004; Erber et al, 2004; Gibson et al., 2005; Dahlbäck, 2008). This brought speculations that Prothrombin G20210A mutation might have occurred as a single event in a single Caucasian ancestor. This hypothesis was strengthened by a molecular study that estimated the occurrence of the mutation around 24 thousand years ago (Zivelin et al., 2006).

Another mutation in the prothrombin gene was later discovered in 2002 at a neighbour position to the Prothrombin G20210A mutation, namely Prothrombin C20209T mutation. Unlike the Prothrombin G20210A mutation, this newer mutation was found in non-Caucasians in addition to Caucasians (Warshawsky et al, 2002; Arya, 2005; Danckwardt et al, 2006). Still, clear-cut association with VTE has to be established.

3.9 Defects of fibrinolysis

Fibrinolysis is the process responsible for the removal of intravascular clots. Therefore, one may expect that defects in this process can provide an environment suitable for the development of thrombosis. However, there is yet no final or definite proof of that in spite of the fact that reduced fibrinolysis efficacy (hypofibrinolysis) was observed in many patients with VTE with higher risk values (Laffan & Manning, 2002b; Lisman et al., 2005; Meltzer et al., 2008). For example, defects in plasminogen may cause defective fibrinolysis and impaired removal of fibrin clots, and hence might lead to accumulation of thrombi. There are two types of hereditary plasminogen deficiency: Type I hypoplasminogenaemia (quantitative) and Type II dysplasminogenaemia (qualitative), which are caused by many mutations and thought to be inherited as autosomal dominant defects. Hypoplasminogenaemia is associated with abnormal fibrin removal during wound healing, leading to pseudomembrane diseases in the mucous membranes, while dysplasminogenaemia is probably only a silent polymorphism without clinical manifestations (Aoki et al., 1978; Song et al., 2003; Schuster et al., 2007; Mehta & Shapiro, 2008; Klammt et al., 2011). At the same time, hereditary plasminogen deficiency was found in 2-8% of patients with thrombosis (Aoki et al., 1978; Dolan et al., 1988; Heijboer et al., 1990; Brandt, 2002; Song et al., 2003). Thus, more studied maybe needed before definitely

linking plasminogen deficiency with VTE, and establishing Plasminogen Deficiency Registry databases may help to determine the prevalence and risk of this defect.

Another member of the Fibrinolysis process is tissue plasminogen activator (tPA) which is the main activator of plasmin in the Fibrinolysis process. Therefore, tPA deficiency may also lead to thrombosis. However, there is paucity in reports on cases with hereditary tPA deficiency to justify that (Patrassi et al., 1991; Brandt, 2002). The main inhibitor of tPA is the plasminogen activator inhibitor-1 (PAI-1). In this context, one should expect thrombosis to develop in cases having higher levels of PAI-1, rather than PAI-1 deficiency. This has been shown in different human cases and in transgenic mouse models. At least 5 polymorphisms were found in the PAI-1 gene, two of which were associated with thrombosis. In fact, this encouraged trials to use inhibitors of PAI-1 as anti-thrombotic treatments (Carmeliet et al., 1993; Huber, 2001; Wu & Zhao, 2002; Meltzer et al., 2010a; Jankun & Skrzypczak-Jankun, 2011). Trials were also conducted on inhibitors of another regulator of the Fibrinolysis process, namely Thrombin-Activatable Fibrinolysis Inhibitor (TAFI). TAFI, which was discovered in 1988, circulates as an inactive form, and is activated into its active form (TAFIa) by thrombin. TAFIa inhibits binding of plasmin to fibrinogen and therefore down-regulates the Fibrinolysis process. AT deficiency, previously described, causes elevated levels of thrombin, and therefore elevated levels of TAFIa are also expected leading to lowering in the efficiency of fibrinolysis in removing clots. This is thought to be another pathophysiological pathway by which AT deficiency causes VTE. In addition, this may be an additive factor in increasing hypercoagulability in cases with Prothrombin G20210A mutation in which there is an elevated level of plasma prothrombin. However, studies on association between TAFI level and VTE gave inconsistent results. At least three genetic variations in the TAFI gene were identified, but linkage with risk of developing VTE is not very evident. Focus is now on developing inhibitors of TAFI as a possible anticoagulant therapy (Mosnier & Bouma, 2006; Bunnage & Owen, 2008; Meltzer et al., 2010a & b; Miljić et al., 2010).

3.10 Activated Protein C Resistance (APC-R) and Factor V Leiden Mutation (FVL)

In 1993, Dahlbäck and his colleagues in Sweden were involved in studying patients with VTE. They added external APC to plasma of patients with VTE and recorded the effect of that on the Coagulation process. As explained earlier, APC inactivates co-factors V and VIII and therefore down-regulates the Coagulation process. Therefore, the addition of external APC should prolong the clotting time of the plasma under test. When they tried that on the plasma samples of VTE patients, they noticed that the expected prolongation effect did not happen in all cases (Figure 4). They discussed that there is a "resistance" to the action of APC, and therefore they called it "APC resistance or APC-R", a name which persisted until now. The team originally though that there must have been a yet unknown clotting co-factor that co-helps APC in inactivating factors V and VIII, and these patients showing APC-R should have had a deficiency in this yet-to-find co-factor. However, they could not find such a proposed co-factor. One year later, Bertina and his research team in the Netherlands could identify a missense point mutation in the factor V gene (guanine to adenine; G→A) at nucleotide number 1691 of exon 10 of the factor V gene, only eleven nucleotides upstream to intron 10. This new mutation was termed Factor V Leiden mutation (FVL) after the Dutch city where they made their discovery in. This nucleotide change causes a change in the

translated factor V molecule at amino acid residue number 506 (arginine to glutamine; CGA→CAA). Arginine 506 is an important cleavage site for APC. In other words, APC has to recognise arginine at position 506 of the factor V molecule in order to be able to inactivate factor V. This change in amino acid residue at position 506 of the mutant FVL molecule makes the FVL molecule "resistant" to the action of APC, and therefore the mutant FVL remains active. Mutant FVL was found to retain its coagulation function, and therefore the Coagulation process is not down-regulated by APC in regards to factor V. This explains why FVL leads to hypercoagulability and henceforth VTE (figure 5). Since then, the terms APC-R and FVL were linked together and used interchangeably. Several studies quickly followed that discovery and proved a positive association between FVL and VTE, showing that heterozygous carriers of the mutation are at higher risk of developing VTE by 10-fold while homozygous carriers have a much higher risk ratio reaching 140-fold (Dahlbäck et al., 1993; Zöller et al., 1994; Bertina et al., 1994; Hoagland et al., 1996; Dahlbäck, 1997; Faioni et al., 1997; Alderborn et al., 1997; Bontempo et al., 1997). Moreover, most homozygous cases were found to get at least one VTE event in their life time, and at an earlier time of their life (Samama et al., 1996; Florell & Rodgers, 1997).

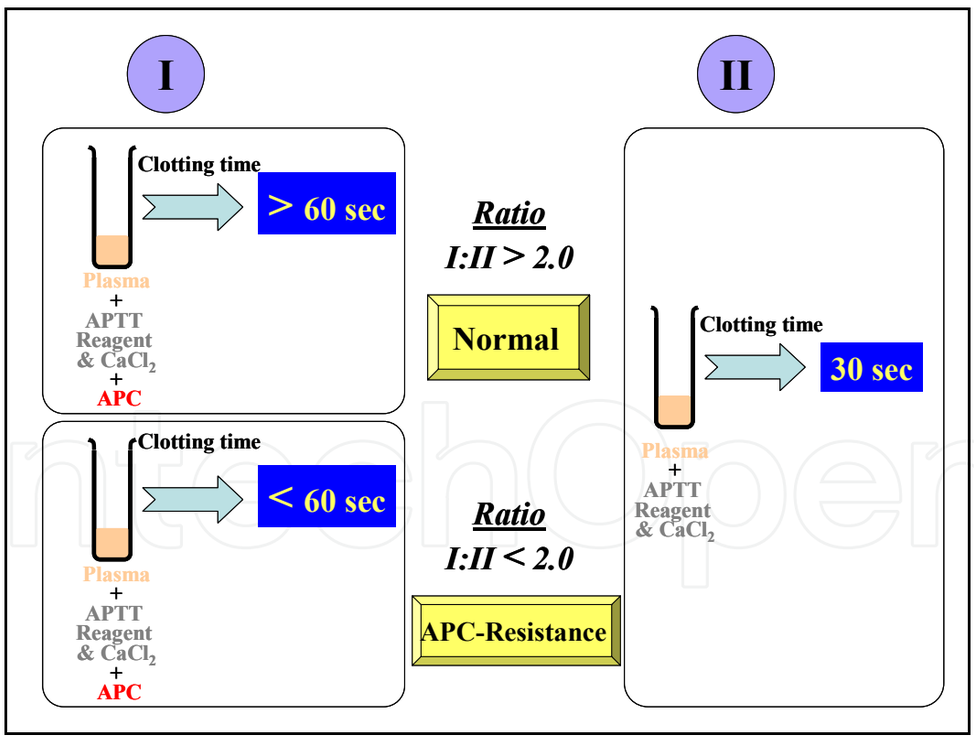

Fig. 4. APC-R test as developed originally by Dahlbäck et al., 1993 (prepared and drawn by the author).

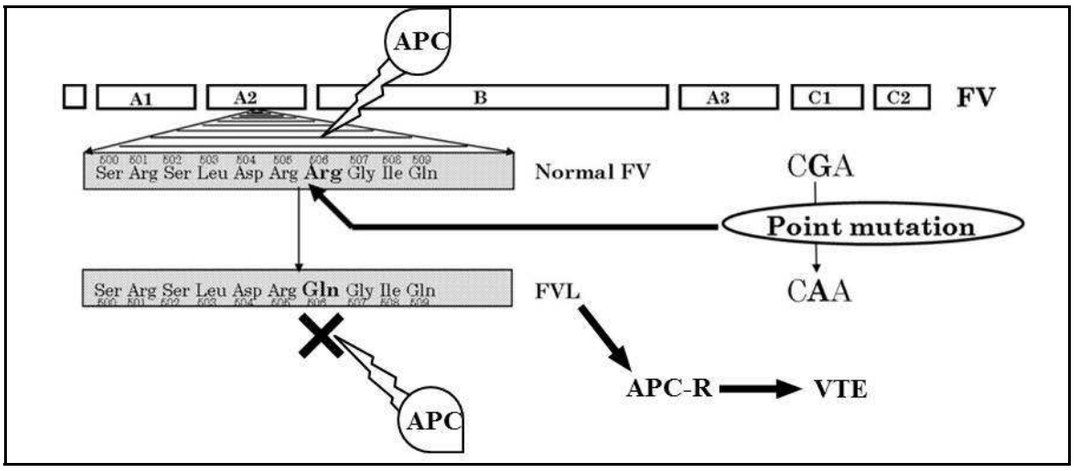

Fig. 5. Factor V molecule showing the site of amino acid 506 where FVL is present and how this leads to APC-R and VTE (prepared and drawn by the author).

The identification of APC-R/FVL and its high risk value have exploded a massive rush in researches to study this new disease, its prevalence and its relationship with VTE in almost every part of the world. First researches were conducted in Europe which concentrated on Caucasian populations. Results showed that FVL was present in a quite high percentage of patients with VTE (15-65%) and healthy subjects (1-15%). Other studies on Caucasians living in non-European countries, like the USA, Australia and Israel, revealed similar numbers (table 1). However, when studies started to appear in other ethnic groups and in other countries, FVL was astonishingly found to be very rare and in most occasions absent, like in Africans, South-East Asians, Chinese, Japanese, American Indians (native nations of America), Greenland Inuit (Eskimos) and native populations of Australia (table 2 and figure 6).

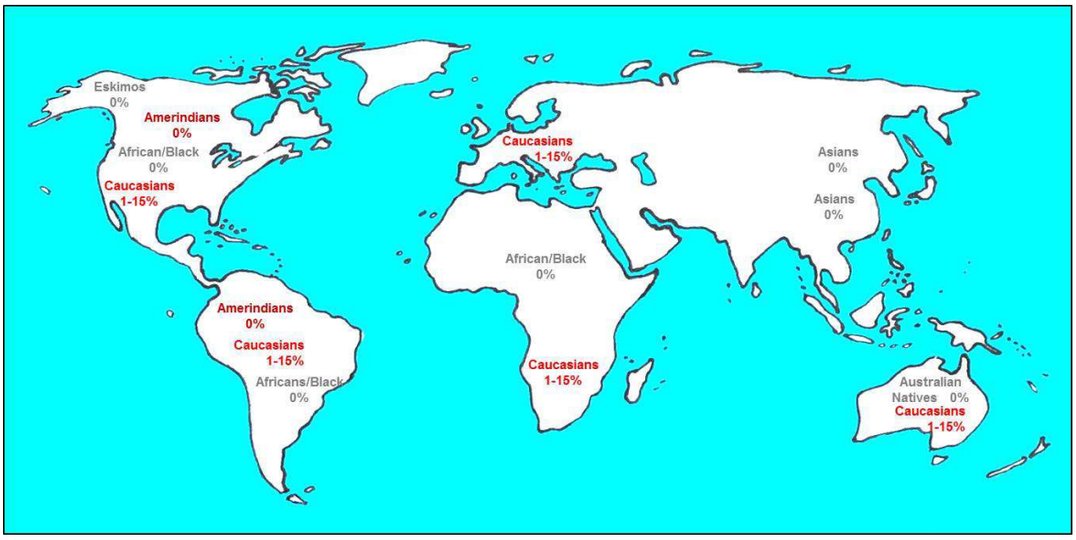

Fig. 6. Prevalence of FVL worldwide in different ethnic groups (prepared and drawn by the author).

	Country	VTE patients (%)	Normal Population (%)	References
European	UK	----	1.74-5.6	Beauchamp et al., 1994; Bengtsson et al., 1996
	Sweden	41.5-50	7.5-11.4	Zöller et al., 1994; Bengtsson et al., 1996; Alderborn et al., 1997
	Poland	----	5	Herrmann et al, 1997
	Netherlands	21	2	Bertina et al., 1994; Beauchamp et al., 1994
	Germany	30	7.1-12	Aschka et al, 1996; Schröder et al., 1996
	Belgium	22	3.3	Hainaut et al., 1997
	Slovakia	29.5-37.0	4	Hudecek et al., 2003; Simkova et al., 2004
	Austria	26	----	Melichart et al., 1996
	Hungary	44	6.9	Nagy et al., 1997; Stankovics et al., 1998
	Serbia	29.9	5.8	Djordjevic et al., 2004
	Azerbaijan	----	14	Gurgey & Mesci, 1997
	Spain	9.2-26.3	1.6-5.8	Olave et al., 1998; González Ordóñez et al., 1999; Vargas et al., 1999; Aznar et al., 2000; Ricart et al., 2006; García-Hernández et al., 2007
	France	9-18	3.5-5.0	Leroyer et al., 1997; Mansourati et al., 2000; Meyer et al., 2001; Mazoyer et al., 2009
	French/ Spanish Basques	----	0-0.7	Bauder et al., 1997; Zabalegui et al., 1998
	Italy	9.0-42.8	2-13.1	Faioni et al., 1997; Simioni et al., 1997; Martinelli et al., 2004; Sottilotta et al., 2009; Gessoni et al., 2010
	Yugoslavia	15.5	4.0	Mikovic et al., 2000
	Slovenia	12.9	6.3	Bedencic et al., 2008
	Croatia	21.0-28.2	2.4-4.0	Coen et al., 2001; Cikes et al., 2004; Jukic et al., 2009
	Albania/ Kosovo	----	3.4	Mekaj et al., 2009
	Greece	16.2-31.9	2.5-7.0	Rees et al., 1995; Lambropoulos et al., 1997; Antoniadi et al., 1999; Ioannou et al., 2000; Hatzaki et al., 2003
Non-European	USA	8.6	3.2-6.0	Ridker et al., 1997; Bontempo et al., 1997; Limdi et al., 2006
	Australia	----	4-10.2	Aboud & Ma, 1997; Bennett et al., 2001; Gibson et al., 2005;
	Israel	----	4.3	Rosen et al., 1999
	Brazil	20	2	Arruda et al., 1995

Table 1. Prevalence of FVL in Caucasian patients with VTE and healthy populations living in European and non-European countries.

	Country/ Ethnic groups	VTE patients (%)	Normal Population (%)	References
Asians	Japan	0	0	Fujimura et al., 1995; Zama et al., 1996; Kodaira et al., 1997; Ro et al., 1999
	Korea	0	----	Kim et al., 1998
	China	0	0	Pepe et al., 1997; Ho et al., 1999
	Indonesia	----	0	Pepe et al., 1997
	Malaysia	0.5	----	Lim et al., 1999
	Singapore	5	----	Lim et al., 1999; Lee, 2002
	India	3	1.3	Herrmann et al., 1997; Ghosh et al., 2001; Mishra & Bedi, 2010
	Pakistan	1.25	----	Nasiruddin et al., 2005
	USA	----	0	Gregg et al., 1997
Africans/ Black	Ethiopia	----	0	Pepe et al., 1997; Abdulkadir et al., 1997
	USA	1.4	0.9	Gregg et al., 1997; Limdi et al., 2006
	Sub-Sahara	----	0	Pepe et al., 1997
	Ecuador	----	0	Pepe et al., 1997
	Venezuela	----	4.4	Vizcaino et al., 2000
Amerindians	Ecuador	----	0	Pepe et al., 1997
	Venezuela	----	1.25	Vizcaino et al., 2000
	USA	----	0	Gregg et al., 1997
Eskimos	Greenland	----	0	De Maat et al., 1996
Indigenous Australians	Australia	----	0	Bennett et al., 2001; Erber et al., 2004

Table 2. Prevalence of FVL in non-Caucasian patients with VTE and healthy populations in different parts of the world.

Finding FVL to be mostly confined to Caucasian populations have brought speculations that FVL might have occurred as a single event in one European Caucasian ancestor, and the current carriers of the mutation descended from that ancestor. To prove a single origin of FVL, several molecular studies were conducted on different single nucleotides polymorphisms (SNPs) in the factor V gene trying to identify any association of FVL with such SNPs. At least 9 SNPs were found to be always associated with FVL. These studies included carriers and non-carriers of FVL, as well factor V gene in chimpanzees to elucidate when FVL might have first appeared (figure 7). These studies, combined with the distribution of FVL worldwide and the anthropological knowledge on movement of Mankind in the far past suggested that FVL should have occurred after the separation between Caucasoid (who settled in Europe) and Mongoloid (who moved to East Asia) populations, which is estimated to occur around 32,000 years ago (figure 8). This means that FVL is less than 32 thousand years old and this is why it is present in Caucasians only. The next question is: where in Europe has it happened? Since 1997 Castoldi et al suggested that FVL probably occurred outside Europe. It was observed that FVL was very rare in the

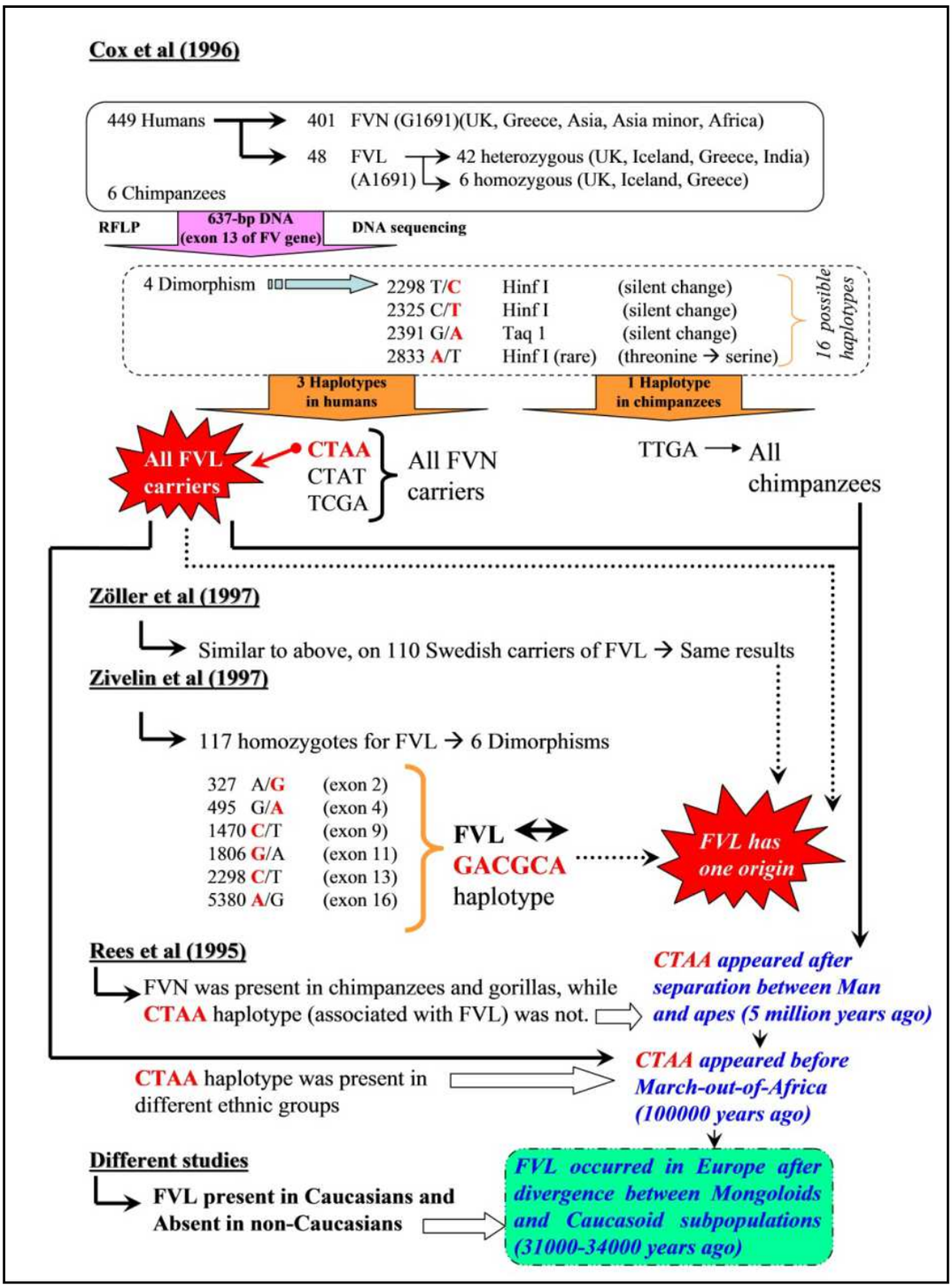

Fig. 7. Molecular studies exploring the origin of FVL (prepared and drawn by the author).

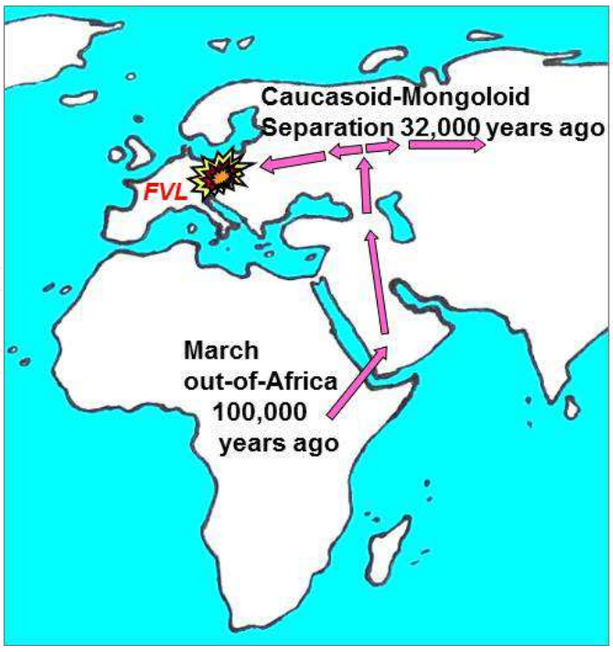

Fig. 8. Map showing movement of humans in the far past from Africa to the Middle East (March out-of-Africa), then to Europe and Asia. FVL event is thought to occur earlier than 32,000 years ago after the divergence of Caucasoid and Mongoloid populations (prepared and drawn by the author).

French and Spanish Basque populations, who are thought to be the oldest ethnic groups in Europe. This suggested FVL to occur outside Europe first (Bauder et al., 1997; Zabalegui et al., 1998). The prevalence of FVL in Eastern Mediterranean countries have shown the highest numbers in the world (table 3), bringing speculations that FVL might have occurred somewhere there and then spread to Europe (Castoldi et al., 1997; Bauder et al., 1997; Zabalegui et al., 1998; Irani-Hakime et al., 2000; Taher et al., 2001; Lucotte & Mercier et al., 2001, Dashti & Jadaon, 2011). Lucotte & Mercier (2001) proposed that FVL expanded in Europe during the Neolithic period, from a probable Anatolian center of origin in Turkey, which has occurred around 10,000 years ago. This may explain the highest prevalence of FVL in East Mediterranean countries, with noticeable gradual decrease in prevalence when radiating away from this region towards Europe and other parts of the world (Figure 9). Our research team in Kuwait has found that Arabs from Eastern Mediterranean countries who carry FVL also carried the same SNPs found to be associated with FVL in European carriers of the mutation (Jadaon et al., 2011). This gives another confirmation that FVL had most probably occurred as a single event in the past in the Eastern Mediterranean region.

The large number of cases having FVL in our days suggests that FVL should have an evolutionary survival advantage explaining its persistence until now. For example, Man had faced many challenges since long time in the past, like fighting wild animals, diseases or each other which should have caused a lot of injuries and fatal bleeding incidences. Increased clotting tendency due to FVL might have an advantageous effect in such occasions giving carriers of FVL some privilege. Women with FVL have higher clotting tendency which may be advantageous in preventing fatal blood loss during menstruation and childbirth. Less blood loss also improves the haemoglobin level in these women creating better life expectancy (Lindqvist et al., 2001; Lindqvist & Dahlbäck, 2008; Franchini & Lippi, 2011). This is also true in

cases having both FVL and haemophilia, in which increased clotting due to FVL compensates for the bleeding tendency due to haemophilia, and hence better survival chances (Yan & Nelson, 2004; Franchini & Lippi, 2010). In addition, recent studies showed that FVL decreased risk of developing severe sepsis from infections to some extent, again another privilege to think of. That was also proved in animal models (Kerlin et al., 2003).

	Country/ Ethnic groups	VTE patients (%)	Normal Population (%)	References
East Mediterranean	Lebanon	9.9-70.6	13.6-18.7	Irani-Hakime et al., 2000; Irani-Hakime et al., 2001; Taher et al., 2001; Tamim et al., 2002; Finan et al., 2002; Almawi et al., 2005; Bouaziz-Borgi et al., 2006; Isma'eel et al., 2006a &b; Zahed et al., 2006
	Syria	----	13.6	Irani-Hakime et al., 2000; Dashti et al., 2010
	Palestine (inside & outside Israel)	----	11.7-27.2	Rosen et al., 1999; Dashti et al., 2010; Hussein et al., 2010
	Jordan	23.9-25.7	10.5-27.2	Awidi et al., 1999; Eid & Rihani, 2004; Eid & Shubeilat, 2005; Nusier et al., 2007; Obeidat et al., 2009; Al-Sweedan et al., 2009; Dashti et al., 2010
	Cyprus	----	13.4	Angelopoulou et al., 2000
	Turkey	21-30.8	4.6-9.8	Ozbek & Tangün, 1996; Gurgey & Mesci, 1997; Gurgey et al., 2001; Atasay et al., 2003; Irdem et al., 2005; Kalkanli et al., 2006; Kabukcu et al., 2007; Celiker et al., 2009; Oguzulgen et al., 2009; Diz-Kucukkaya et al., 2010

Table 3. Prevalence of FVL in patients with VTE and normal populations in different East Mediterranean countries.

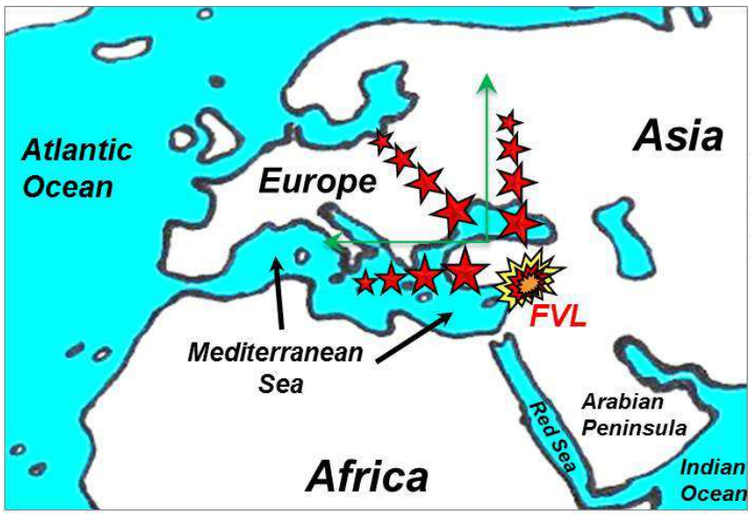

Fig. 9. Map of the Mediterranean area showing decrease in prevalence of FVL as moving from East Mediterranean to North and West Europe. This made many believe that the origin of FVL is somewhere in the Eastern Mediterranean region (prepared and drawn by the author).

Other mutations in the factor V gene were later identified, including Factor V Cambridge (Arg306Thr) (Williamson et al., 1998), Factor V Hong Kong (Arg306Gly) (Chan et al., 1998), Factor V Liverpool (Ile359Thr) (Mumford et al, 2003), and Factor V Kuwait (His1254Arg) (Jadaon et al., 2006). The number of cases reported to have these mutations were small and the relationship with VTE could not be well established like FVL, although many of these cases were reported in patients with VTE. Another mutation in the factor V gene called HR2 Haplotype (His1299Arg) was identified in 1996, which is discussed separately in the following section.

3.11 HR2 haplotype

In 1996, a new missense mutation in exon 13 of factor V gene (A4070G) was identified (Lunghi et al., 1996). This mutation leads to an amino acid change, replacing histidine with arginine at amino acid residue position 1299 (His1299Arg). The new mutation was first assigned the name R2 polymorphism because of the use of the restriction enzyme Rsa I in the test used to detect it. Later on, R2 polymorphism was found to be in tight association with at least 12 polymorphisms in the factor V gene. Therefore, these SNPs were collectively called HR2 (Haplotype R2) (Bernardi et al., 1997; Castoldi et al., 2000). Several studies in different parts of the world gave the prevalence of HR2 to be 9.5%–15.2% in VTE cases and 5.8%–10.4% in healthy controls, with an increased risk by at least 2.5-fold (Bernardi et al., 1997; Alhenc-Gelas et al., 1999; Castoldi et al., 2000; Pecheniuk et al., 2001; Margaglione et al., 2002; Castaman et al., 2003; Faioni et al., 2004; Jadaon & Dashti, 2005a). The exact mechanism by which HR2 haplotype increases the risk for development of VTE is still not that clear. However, Castoldi et al (2000) have studied the two isoforms of factor V, V1 and V2, in cases with or without HR2. V1 is 7-fold more thrombogenic than V2. They showed that V1 was present in cases with HR2 more than in cases without the haplotype. This may give a possible explanation for the hypercoagulation and increased risk of developing VTE in carriers of HR2. However, more studies may be needed before understanding the real mechanism involved in that.

4. Acquired risk factors for venous thrombosis

VTE due to genetic risk factors (familial or hereditary thrombophilia), discussed above, mostly occur at ages less than 40 years, and they often recurrent. However, there are several acquired risk factors that are usually associated with VTE at above 40 years of age (Florell & Rodgers, 1997).

4.1 Lupus Anticoagulants (LA)

LA is a member of a group of autoantibodies (immunoglobulins) against phospholipids, including anticardiolipin and anti-β_2-glycoprotein, which are produced in different autoimmune conditions. They often cause clinical manifestations like thrombosis, pregnancy loss and others, and the clinical condition is termed Antiphospholipid Syndrome (Hoffbrand et al., 2001; Laffan & Manning, 2002b; Ehsan & Plumbley, 2002). LA were given this name in 1972 because they were recognized initially in a patient with systemic lupus erythematosus (SLE) who had bleeding problems. However, later studies confirmed the association of LA with VTE, and not bleeding, but the name persisted (Greaves & Preston, 1991; Bengtsson et al, 1996; Ehsan & Plumbley, 2002). Although the mechanism of causing

VTE is still not clear, the involvement of phospholipids in the Coagulation process and its regulators may give a possible explanation. In fact, there are *in vitro* evidences that LA lead to inhibition of APC, AT and fibrinolysis, and increase in expression of TF. In addition, LA were shown to directly contribute to hypercoagulability in animal models (Roubey, 1994; Kinev & Roubey, 2008; Farmer-Boatwright & Roubey, 2009). The prevalence of LA was reported to be up to 20% of VTE cases, with up to 10-fold increased risk of developing VTE (Ghosh et al., 2001; Galli et al., 2002; Ehsan & Plumbley, 2002; Jadaon & Dashti, 2005b; Farmer-Boatwright & Roubey, 2009; Anderson & Weitz, 2010).

4.2 Pregnancy, childbirth and hormone therapy

Pregnancy and delivery (and post-delivery up to 6 weeks after childbirth) account for more than 6-fold increased risk of developing VTE. This may be due to changes in the Coagulation and Fibrinolysis processes happening during these events, which include increased levels of most clotting factors and their activators, with reduced fibrinolysis and PS level. Women taking oral contraceptives or receiving hormone replacement therapy were also found to have higher risk of developing VTE, which may again be attributed to increased clotting factors and decreased AT and tPA (Rosing et al., 1997; Hoffbrand et al., 2001; Ehsan & Plumbley, 2002; Chan, 2010; Anderson & Weitz, 2010).

4.3 Other acquired risk factors

VTE are common complications of major trauma like in surgery, fractures and blood transfusion, especially in elder and obese patients. VTE was also noticed to be secondary to other diseases like liver and kidney diseases, myeloproliferative disorders, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS) (Hoffbrand et al., 2001; Ehsan & Plumbley, 2002). Furthermore, patients with cancers of the gastrointestinal and urogenital tracts and the lungs were reported to have higher risk of VTE. This may be due to activation of clotting factors by the cancerous cells themselves or the chemotherapy these patients usually receive which affects the liver and vitamin K metabolism, or predisposes to DIC (Dahlbäck, 1995; Florell & Rodgers, 1997; Hoffbrand et al., 2001; Ehsan & Plumbley, 2002; Anderson & Weitz, 2010; Vossen et al., 2011). Therefore, such diseases affect the Coagulation and Fibrinolysis processes in favour of developing VTE. Also, VTE in such diseases, especially those involving chronic inflammation, maybe due to increased C4bBP which captures more PS and lowers the availability of the active free PS and therefore may cause hypercoagulation. VTE was also present in many cases challenged with prolonged immobilization like being confined to bed due to major illnesses or post-operation, or after long airplane journey. The latter attracted a lot of public attention and was referred to in the media as “traveller’s thrombosis” or “economy-class syndrome” (Hoffbrand et al., 2001; O'Keeffe & Baglin, 2003; DeHart, 2003; Bhatia et al., 2009).

5. Combined genetic and acquired risk factors for VTE

All genetic and acquired risk factors discussed above are usually present as a “single” defect in a patient. However, many cases with VTE were reported to have more than one genetic/acquired risk factor at the same time, which may account for a higher risk of developing VTE (Jadaon & Dashti, 2005a & b). For example, several studies reported a

number of individuals who had FVL in addition to other accompanying genetic defect(s) like hereditary AT, PC or PS deficiency. Both FV and AT genes are located on chromosome 1. As a result, a segregated inheritance pattern of APC-R and AT deficiency can persist in families for several generations (Ireland et al, 1995; Koeleman et al, 1997). In fact, van Boven et al (1996) found that the incidence of VTE in individuals having both FVL and AT deficiency was significantly higher than the incidence in individuals having only one of these two genetic defects. Similarly, coexistence of FVL and PC deficiency has 3 to 7-fold more risk of VTE than either of the two defects alone (Hallam et al, 1995; Zama et al, 1996; Koeleman et al, 1997, Jadaon & Dashti, 2005b). Moreover, more than half of patients with both APC-R and genetic PS deficiency were found to have thrombosis (Garcia de Frutos & Dahlbäck, 1995; Koeleman et al, 1997). It is interesting to mention here that a few isolated cases were reported to be double heterozygous for FVL and factor V deficiency, the mutations being present on opposite chromosomes. Plasma of such patients contain mutant FVL molecules only, similar to what is present in the plasma of people homozygous for the FVL mutation, resulting in what is called "Pseudohomozygous APC-R". Such cases have similar risk value to develop VTE as homozygous APC-R/FVL cases (Greengard et al, 1995; Simioni et al, 1996; Guasch et al, 1997).

Acquired risk factors, including trauma, surgery, immobilization, pregnancy, use of oral contraceptives and LA have been reported to greatly increase the risk of developing VTE in individuals who have FVL. This may explain why in women who have FVL mutation there is an increased incidence of VTE during pregnancy especially in the last trimester and during delivery (Samama et al, 1996; Florell & Rodgers, 1997; Perry & Pasi, 1997; Rotmensch et al, 1997; Hallak et al, 1997). Further, women who are heterozygous for the FVL and take oral contraceptives are at 34-fold increased risk for developing VTE (Melichart et al, 1996; Rosing et al., 1997). LA present in a patient's plasma may create a status similar to APC-R (acquired APC-R). FVL was found in more than half of the LA positive patients who had one thrombotic event, and in more than 90% of the LA positive patients who had recurrent thrombosis (Griffin et al, 1995; Bengtsson et al, 1996; Alarcon-Segovia et al, 1996).

Generally, there is a perception that familial thrombosis may be better considered as a complex genetic disorder caused by segregation of two (or more) genetic defects (known or yet unknown) in a family. Moreover, combination of these genetic defects with other acquired or circumstantial risk factors (like pregnancy, surgery, immobilization, etc.) or disorders (like LA) may greatly increase the risk for development of thrombosis in this group of patients. For example, it has been perceived that APC-R/FVL alone may be only a mild risk factor for developing VTE, especially when it is in heterozygous state. This may be partially explained by the fact that only FVL resists inactivation by APC, but the inactivation function of APC on FVIII is not affected by the FVL mutation. Thus, additional genetic or acquired factors may significantly enhance the risk of developing VTE in patients with FVL. The same may be said about the other genetic/acquired risk factors for VTE.

6. Conclusions

VTE are serious disorders with high morbidity and mortality rates. Several different genetic abnormalities were found to cause VTE, with different prevalence and risk ratios in different populations and ethnic groups. Also, several acquired risk factors were found to cause VTE by different methods. Combination of more than one risk factor (genetic or acquired) in the same patient is not uncommon and it leads to higher risk of developing VTE.

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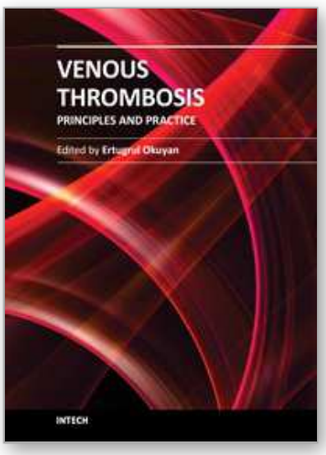

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According to Virchow's triad, venous thrombosis can occur as a result of one or more of three factors: changes in the dynamics of the blood flow, endothelial injury/dysfunction of the blood vessel and hypercoagulability. The blood in the veins is constantly forming microscopic thrombi that are routinely broken down by the body, and significant clotting can occur only when the balance of thrombus formation and resolution is altered. This book is a fresh synthesis of venous thromboembolism care and considers the opinions and studies from different fields of medicine. As venous thrombosis spectrum is wide and can affect many organ systems, from deep veins of the leg to the cerebral venous system, our intent is for this to be a comprehensive, up-to-date and readable book. We tried to present a synthesis of existing material infused with new ideas and perspectives and authors own clinical studies and even case-reports.

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