Carriership of Factor V Leiden and Evolutionary Selection Advantage

Pelle G. Lindqvist*1 and Björn Dahlbäck2

1Clinical Sciences, Malmö, Obstetrics and Gynecology, Sweden
2Laboratory Medicine, Clinical Chemistry, Lund University, University Hospital, Malmö, Sweden

Abstract: Historically, lethal exsanguinations and severe infections have been two major causes of maternal death. Gene mutations that lower the risk of profuse hemorrhage or severe infections would give a survival advantage. A single mutation of coagulation factor V, known as FV Leiden (FVL), can be such a beneficial mutation. FVL is common among Caucasians and today confers an increased risk of thromboembolism. However, the high prevalence of FVL (up to 15%) in the general population suggests that it has given an evolutionary advantage. In this review, we discuss possible mechanisms of the evolutionary survival advantage associated with FVL. In women, FVL confers lower risk of blood loss and profuse hemorrhage in association with delivery and improves the hemoglobin status. In addition, FVL carriers possibly have a survival advantage during sepsis. In conclusion, the high prevalence of FVL may be the result of one or more evolutionary selection advantages.

Keywords: Coagulation factor V Leiden, selective advantage, profuse blood loss, anemia, sepsis.

INTRODUCTION

Historically, profuse blood loss after delivery has been a major cause of death in females during reproductive age. A study of the ruling families of Europe between A.D. 1500 and 1850 showed a maternal mortality rate of 2% per birth, the cumulative mortality risk during pregnancy being approximated to 10% [1]. This is close to an estimated 2.3% mortality rate in pregnant women in the 16th century London [1]. In 17th- and 18th-century England, excess female mortality was reported during the first year after marriage [2]. This finding has been interpreted as a very high mortality rate during or after the first pregnancy that occurred soon after marriage. Before the era of birth control, pregnancies tended to occur at short intervals. Thus, postpartum anemia may not have been compensated before the next pregnancy occurred. Severe infectious diseases were life threatening during pregnancy, and puerperal sepsis has been estimated to have caused 54% of maternal deaths in hospital in the late 19th century [3].

The present maternal mortality rate in Sweden is 0.007% per delivery [4]. The rarity of maternal death in the modern, industrially developed world is a relatively new phenomenon. In the USA as late as 1920, the maternal mortality rate was 0.8%, and until 1935 the registered mortality rate for England and Wales remained constant at about 0.4% [5]. Anemic women have a highly increased case fatality rate from sepsis, preeclampsia, and profuse blood loss and the combination of anemia and obstetric hemorrhage has been estimated to be responsible for up to 50% of maternal deaths [6, 7].

The reduction of anemia by adequate antenatal care, combined with the development of blood transfusion technique are thought to be two of the most significant explanations for the decline in maternal deaths caused by antepartum and postpartum hemorrhage [8]. In an evolutionarily perspective, a gene mutation that conferred on the carrier a lower incidence of anemia or profuse blood loss during pregnancy would be expected to reduce the maternal fatality rate and should consequently have given an evolutionary survival advantage. As discussed below, coagulation factor V Leiden (FV:Q506 or FVL) is a strong candidate for being such a "survival advantage" mutation.

PRIOR SHOWN EVOLUTIONARY SELECTION ADVANTAGE—THE SICKLE CELL TRAIT

It has been difficult to show selection advantage in Man. If we have reason to assume that homozygous carriers of a gene are less physically fit, the theory of natural selection then requires that heterozygous carriers have a selective advantage, i.e., the contribution of such individuals to the gene pool of succeeding generations is above the average. It has been shown, with reasonable certainty, that the heterozygous carriers of the sickler trait have a selective advantage in malaria endemic regions. In 1954 Allison reported a higher incidence of carriers of sickle cell anemia (sicklers) in malaria-prevalent regions [9]. Moreover, compared with non-sicklers, sicklers were less likely to have a palpable spleen – a sign of malaria. Since malaria is associated with high mortality and sicklers suffered less often and less severely from malaria carriers of the sickle cell trait should have a survival advantage. Without a survival advantage, the sickler gene pool would be slowly depleted due to the inability of homozygote carriers of the sickler trait to reproduce. Thus, with every homozygous individual in a population, two sickle-cell genes are lost. Subsequently, it has been shown that heterozygote carriers of the sickle-cell trait have a 2 to 8-fold increased rate of sickling malaria parasitized cells, and that these cells would be more effectively removed from circulation by phagocytosis [10].

FACTOR V LEIDEN, A THROMBOSIS RISK FACTOR AND AN EVOLUTIONARY SURVIVAL FACTOR

A few years ago, activated protein C (APC) resistance was discovered as the most common hereditary thrombophilias in Western countries [11]. It is usually caused by a single point mutation in the gene for coagulation FV, resulting in the replacement of arginine (R) at position 506 by a glutamine (Q) (FV:Q506 or FV Leiden) [11-13]. This mutation results in a reduced ability of APC to inactivate FVa by cleavage at Arg506 (Fig. 1). In addition, FV cannot be converted into the anticoagulant FVAc, resulting in a less efficient degradation of the activated factor VIII [14, 15]. Due to the impaired inactivation of FVa and VIlia, the FVL mutation causes a lifelong procoagulant state, which increases the risk of thromboembolism. Haplotype analysis demonstrated a founder effect and that the mutation occurred at about 21,000 years ago [16]. At present, the FVL is highly prevalent among the Caucasian population in Europe, the prevalence ranging between 8% and 15% in Sweden [17, 18], between 4% and 8% in central Europe [19], and between 2% and 4% in the Southern Europe [20], with some exceptions. In USA, a prevalence of between 5% and 8% among European Americans is reported [21, 22]. This means that worldwide around 50 million people of Caucasian origin carry FVL. The mutation is almost non-existent in Far-East Asia (e.g. China and Japan), Africa, and South America [23].

Heterozygous carriers of FVL have approximately 5-fold increased risk of venous thrombosis, whereas homozygous carriers have an 20-80-fold increased risk [24, 25]. For every carrier of a lethal thromboembolic complication, one or two FVL genes will be
lost. Since FVL arose from a single mutation, there are no “de novo” mutations to fill up the FVL gene reservoir. The pedigree of the first family shown to have APC resistance due to FVL is shown in Fig. (2).

POSSIBLE EVOLUTIONARY ADVANTAGES OF FVL

What conceivable mechanisms could be involved as evolutionary selection mechanisms of FVL? Any quality that increases the frequency of carriers of FVL in a given population over generations would have an evolutionary advantage. Even a small increase in frequency of FVL per generation would have generated an appreciable difference after hundreds of generations. Positive factors for survival affecting the life after the fertile period will have little or no impact on the reproductive capacity in a population. Pregnancy is central for reproduction and is the most hazardous event in a woman’s fertile life. Since FVL is associated with procoagulant state, it is logical to suspect that FVL may affect blood loss during pregnancy (Fig. 3). A lower prevalence of anemia, lower incidence of profuse blood loss, and fewer spontaneous abortions would result in a decreased maternal mortality rate. Moreover, orphans had a very short life expectancy after the death of their mother [6]. A fictitious example of a mutation causing only half of deaths due to exsanguinations has been shown to have a major long term effect on mutation prevalence in the population [26]. A hereditary condition reducing the risk of postpartum blood loss during delivery would have been selected in such an environment. Thrombosis during pregnancy is presently a clinically serious problem with as many as 15% of maternal deaths being caused by pulmonary embolism [27]. However, in an evolutionary perspective, the 5-fold increased risk of thrombosis in heterozygous FVL women would not have been a particularly potent adverse survival factor.

LONGEVITY AND FVL?

A study by Mari et al. [28] found a similar prevalence of FVL among centenarians (individuals above hundred years of age) as in the general population, indicating neither advantage nor a disadvantage. However, the present equality might not be representative for the history of mankind but could mainly reflect the period after

![Diagram of Normal FV and FV Leiden](image)

**Fig. (1).** Activation and degradation of normal FV and FV Leiden. FV circulates as a single chain high molecular weight protein. Thrombin (or FXa) cleaves a number of peptide bonds, which results in the liberation of the B domain and generation of FVa. Three peptide bonds in FVa are cleaved by APC (Arg306, Arg506, Arg679) resulting in inhibition of FVa activity. The FV Leiden mutation eliminates one of the APC cleavage sites, which impairs the degradation of APC.

![Pedigree of the First Family](image)

**Fig. (2).** The pedigree of the first family in which APC resistance was discovered. The index case (III:4) had a history of recurrent thrombosis and his plasma was APC resistant due to FVL. (Modified from [11]).
1935, a time of dramatic fall in maternal mortality. Before 1935, 60% of gravidae had a hemoglobin-value below 90 gr/L [29]. Initiation of iron therapy was shown to be effective in increasing hemoglobin-values and lowering of the incidence of postpartum anemia (from 41% to 18%) [29]. Uterotonica was found to be effective in stopping profuse postpartum hemorrhage. The prevention of postpartum anemia might well be a major reason for the decline of maternal mortality and presumably this prevention also decreased the fatality rate of other pregnancy complications [8].

“DEATH DUE TO EXSANGUINATIONS AT DELIVERY – PROTECTION BY FVL”

In a retrospective study of preeclampsia and/or growth restriction, women with FVL when compared to controls suffered lower blood loss (322 vs. 379 ml, p = 0.001), lower incidence of profuse blood loss (> 600ml) (2% vs. 14%, p = 0.01), lower pre- postpartum hemoglobin difference (0 vs. -8.9 gr/l, p < 0.001), lower postpartum anemia (2% vs. 14%, p = 0.01), and higher postpartum hemoglobin-values (118 vs. 113, p = 0.08) [26]. In a subsequent prospective study, the findings of lower incidence of profuse postpartum blood loss (3.7% vs. 7.9% in controls, p = 0.02) and lower blood loss (340 vs. 361 ml in controls, p = 0.04) were confirmed [18]. Women with FVL had similar number of children as non-carriers [18]. A recent study showed 40% lower risk of profuse blood loss among carriers of FVL, but the difference did not reach significance [30].

“LOWER MORTALITY IN SEPTIC SHOCK”

Septic shock and puerperal sepsis are pregnancy-associated conditions that in the history of mankind have been shown to be fatal for many women. Also in this context, FVL may be of relevance because anemic women are at a 25-fold increased risk of fatal sepsis as compared to non-anemic women [7]. Female carriers of FVL have been shown to have higher hemoglobin levels and ferritin levels [31]. In addition, women with FVL estimate their menstrual blood loss to be lower than what non-carrier women do [31].

In 2003, Kerlin and coworkers showed that the 28-day mortality during severe sepsis was lower among carriers of FVL (13.9% vs. 27.9%, p = 0.013) [32]. The mechanism for the protective effect is unknown. However, animal studies have shown that the protein C system can affect the defense against sepsis. Thus, administration of thrombomodulin, protein C, and APC were found to reduce mortality related to septic shock [33, 34]. In addition, treatment with recombinant human APC as compared to placebo reduced the all cause 28-day mortality by 19.4% in patients with severe sepsis [35]. APC has been found to have both antithrombotic and cytoprotective action, the cytoprotective being due to both anti-inflammatory and antiapoptotic mechanisms [36]. In plasma, APC form a complex with protein C inhibitor (PCI), which results in inhibition of the APC activity. Carriers of FVL have been shown to have higher APC-PCI complex levels (0.29 vs. 0.21, p < 0.001) as compared to non-carriers, reflecting higher protein C activation and increased APC level [37]. However, in a large population based study, no difference in susceptibility of major infections between carriers and non-carriers of FVL was found [38].

“RISK OF FETAL LOSS AMONG CARRIERS OF FVL?”

It has been proposed in systematic reviews and meta analyses that FVL possibly increases the risk of first trimester fetal loss [39, 40]. If true, this would be a strong evolutionary disadvantage. A Meta analysis might be a sound method of asssessing evidence from controlled studies. However, the majority of the surveyed studies included are uncontrolled and underpowered. In addition, neither large cohort studies [18, 30, 41, 42], nor large case-control studies could confirm this hypothesis of increased risk [43, 44]. With
regard to rare subgroups of second trimester or third trimester fetal loss, there seems to exist an increased risk among carriers of FVL [45]. This may, however, not have been a particularly strong disadvantage.

Based on available data it is reasonable to conclude that FVL confers a survival advantage by reducing the risk of profuse hemorrhage after delivery, by improving hemoglobin status, and possibly also by reducing mortality in relation to severe sepsis.

REFERENCES


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