GENETIC ASSOCIATION OF PE

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ABSTRACT

Pulmonary embolism (PE) is one manifestation of VTE and a potentially lethal complication of VTE's. Approximately 65% of VTE patients display only DVT, and around 30% of VTE patients also manifest PE. The diagnosis of PE is challenging due to its variable and often non-specific clinical presentation. Silent PE develops in around 50% of patients with DVT and autopsy reports demonstrated that only 30-45% of all PE cases were diagnosed prior to death. Males are more often affected than females. However, women above 75 years display an incidence of more than 500 cases per 100,000 individuals.
PE is a life-threatening condition characterized by the blockage of blood vessels in the lungs due to emboli. Clotting disorders, including genetic variations, play a crucial role in the development of PE.
Pulmonary embolism is a complex multi-factorial disease that is caused by external as well as multiple genetic factors. External risk factors can be divided into permanent, patient-associated risk factors and, temporary circumstances like immobilization. In 20-50% of the cases, PE occurs in the absence of these risk factors. Studies have suggested a major genetic constituent risk to be related to VTE by demonstrating an increased risk for individuals with affected siblings and a strong heritability. The genetic predisposition to an elevated risk of VTE is described by the term thrombophilia, which is often associated with gene variations of the physiological coagulation cascade. Minor changes in the balance between the system of coagulation and fibrinolysis might cause thrombus formation. Most of the variations in genes represent strong genetic risk factors increasing the risk of VTE in heterozygous carriers almost 10-fold, such as deficiencies of antithrombin or protein C.
In a recent clinical study conducted by GTF Scholars, involving 2,000 subjects, we found that at least 25% of the people sampled had a genetic history of blood clots.

METHODS

Understanding the genetic associations of clotting disorders and PE is crucial for risk assessment and management strategies. These developments may pave the way for personalized treatments targeting genetic causes of clotting disorders, and management of PE.

RESULTS

Mutations in genes such as factor V Leiden and prothrombin G20210A involved in coagulation pathways, increase the risk of clot formation, leading to PE (Figure 1). Deficiencies in natural anticoagulant proteins such as protein C, protein S, and antithrombin further predispose individuals to clotting disorders (Table 1). In a study by Meißner et al (2021), three single nucleotide polymorphisms (rs1800790, rs3813948, rs6025) showed evidence of association (EOA) in the main analysis, and five variants (rs169713, rs1801131, rs4524, rs5985, and rs8176592) demonstrated EOAs in subgroups, supporting the view that PE represents a complex disease with many factors contributing relatively small effect. Traditional treatments for thrombosis and clotting disorders primarily rely on anticoagulants, and recent advances have opened new avenues for gene therapies targeting clotting disorders. In preclinical studies, gene therapy approaches have shown promise in restoring the balance of coagulation factors and addressing underlying genetic abnormalities. Researchers have successfully used adeno-associated viral vectors to deliver therapeutic genes, such as those encoding natural anticoagulant proteins, into animal models with clotting disorders. These advances hold significant potential for personalized treatments that target the root genetic causes of clotting disorders, and new hope for patients with PE or recurrent thrombosis. In conclusion, understanding the genetic associations of clotting disorders and PE is crucial for risk assessment and management strategies. While traditional treatments primarily rely on anticoagulants, recent advancements in gene therapies offer promising approaches to address underlying genetic abnormalities. Preclinical studies have shown positive outcomes in restoring coagulation balance using gene therapy approaches. Our research provides supportive evidence for genetic differences at eight candidate risk loci between cases with death from PE and controls.

The results demonstrate evidence for an association. The risk of death from PE is determined by several gene variants. Ziegler et al. suggested that trying to simplify the respective disease might improve the outcome of association studies.

CONCLUSIONS

These developments may pave the way for personalized treatments targeting genetic causes of clotting disorders, and management of PE.

IMPORTANCE OF OUR WORK

We conducted a literature review to explore these genetic links while discussing recent advancements in gene therapies that hold promise for the treatment of thrombosis and clotting disorders.

TABLE 1

Inherited Causes of Blood Clots

Increased levels of natural procoagulants	Decreased levels of natural anticoagulants	Abnormal Fibrinolysis	Other Inherited Causes
Factor V Leiden mutation or activated protein C resistance*	Antithrombin	Decreased Levels of Tissue Plasminogen Activator (t-PA)	Paroxysmal nocturnal hemoglobinuria
Prothrombin 20210 mutation	Protein C	Increased levels of plasminogen activator inhibitor (PAI-1)	
Hyperhomocysteinemi	Protein S	Elevated Thrombin-Activatable Fibrinolysis Inhibitor (TAFI)	
FVIII, FIX, FXI, FVII, VWF	Thrombomodulin		
	Heparin Cofactor II		
	Tissue Factor Pathway Inhibitor (TFPI)		

*The Factor V Leiden mutation does not result in increased FV levels but a resistance to the anticoagulant action of activated protein C.

Table 1. Inherited causes of blood clots are categorized by affected hematologic processes.

FIGURE 1

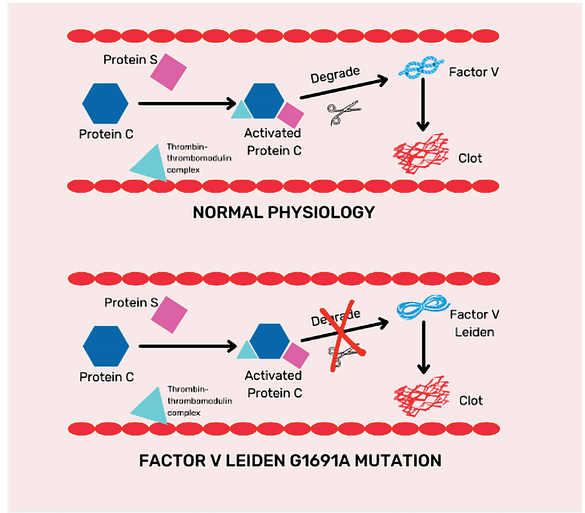

Figure 1. Pathophysiology of Factor V Leiden Mutation
The authors disclose no conflict of interest.

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