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Genetic Factors in Thrombophilia: A Review of Their Role

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Abstract

Thrombophilia is a susceptibility to thrombosis caused by hereditary or acquired abnormalities of the coagulation system. Regarding the inherited causes of it, various genetic mutations have been linked to an increased risk of venous thromboembolism. This review aims to highlight existing research on the key genetic factors associated with hereditary thrombophilia and their clinical implications. A literature search was carried out using databases such as PubMed and Google Scholar, with a focus on research published between 1996 and 2024 that focused on genetic mutations related to thrombophilia. The most prevalent genetic risk factors are Factor V Leiden and the prothrombin G20210A mutation. Other polymorphisms, like PAI-1 and MTHFR mutations, are still debatable and need additional research, while deficits in natural anticoagulants like antithrombin, protein C, and protein S are rare but clinically significant. Understanding the relationship of thrombophilia and other clinical risk factors is critical for proper risk assessment and therapy of individuals with coagulation disorders.

Keywords: thrombophilia, venous thromboembolism, factor V Leiden, genetic mutations, blood clots

1. Introduction

Thrombophilia is an anomaly that raises the chances of formation of blood clots in arteries that occur in the sequence of proteins involved in the coagulation of blood (Athar et al., 2024). Thrombophilia is a predisposition to develop blood clots in the veins and arteries, and it can be either genetic or acquired throughout life (Lim & Moll, 2015). While acquired thrombophilia arises at some point in life, inherited thrombophilia is an innate disorder that exists from birth and makes a person susceptible to thrombosis which strikes with no obvious reasons and has a propensity to repeat (Athar et al., 2024; De Stefano et al., 1996). Venous or arterial thrombosis can occur due to changes in certain elements of hemostasis. That can be changes in blood circulation, coagulation factors, vascular surfaces, plasmatic proteins or cellular components, all of them ultimately resulting in increased tendency for the blood to form clots (Samfireag et al., 2022).

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Rudolf Virchow proposed in 1856 that an example of the pathomechanisms that results in thrombosis could be changes in blood's increased tendency to form clots. Relatives who had a significant frequency of thrombotic symptoms were the primary focus of research on the genetic abnormalities causing hereditary condition of hypercoagulability (Campello et al., 2019). Although thrombophilia is not a disease purely by itself, it can be brought on by exposure to some drugs like oral contraceptives, certain conditions like pregnancy, postpartum or acquired thrombophilia, or it can be hereditary (Heit, 2007).

Thrombophilia's main characteristic is abnormal formation of blood clots mostly in veins found in lungs or legs (Lim & Moll, 2015). Pulmonary embolism (PE) and deep vein thrombosis (DVT), together referred to as venous thromboembolism, are the most common symptoms associated with it (Athar et al., 2024). In addition to stillbirth and some other pregnancy issues, thrombophilia can also manifest as repeated pregnancy loss (Heit, 2007).

On the other hand, obstructed circulation to an arm or a limb, heart attacks or strokes may arise because of formed blood clots in the arteries. If blood clots are created in arteries, there are high chances of one having a heart attack, stroke or blockage of blood flow to limbs leading to its amputation (Lim & Moll, 2015).

Venous or arterial thrombosis is usually complex in ways that go beyond simple interactions where each risk factor intensifies the others (Moll, 2015). Immobility, surgery, cancer, and puerperium, are some examples of environmental risk factors. Deficits in the natural anticoagulants like antithrombin, protein C, and protein S are among the genetic anomalies that elevate the risk of a thrombotic episode and have been recognized for a long time (Christiansen et al., 2005). Factor V Leiden and prothrombin G20210A represent the most common inherited risk factors for thrombophilia, while other variants discussed in this review include plasminogen activator inhibitor-1 (PAI-1) and the MTHFR polymorphisms (Campello et al., 2019; Lim & Moll, 2015). The two possible reasons for thrombophilia are due to an inability to inactivate thrombin or an inability to regulate the production of thrombin proteins (Athar et al., 2024). Antithrombin deficiency (AT) was the first genetic defect detected in patients with thrombosis and is a scarce defect occurring in 1-2% patients with venous thrombosis (Zoller et al., 1999). On the other hand, antiphospholipid antibody syndrome (APS) is the most frequently acquired type. These mutations can be present in 1 out of 2 possible states, an individual can have a single allele mutated or both mutated (Lim & Moll, 2015).

Although numerous genetic factors associated with thrombophilia have been identified, such as Factor V Leiden and prothrombin G20210A, the clinical relevance of several other mutations remains uncertain. Furthermore, the relationship between thrombophilia and environmental factors like pregnancy, surgery or hormonal medication, is not yet well-defined. These uncertainties underline the necessity for a thorough examination of existing research. Hence, the aim of this review is to outline what is known about genetic mutations related to thrombophilia and to evaluate their role in the development of venous thromboembolism.

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2. Materials and Methods

A narrative literature review was performed to summarize our current understanding of genetic factors linked with thrombophilia. Appropriate academic articles were obtained through databases such as PubMed and Google Scholar. The search technique involved using keywords like thrombophilia, Factor V Leiden, prothrombin G20210A, protein C deficiency, protein S deficiency, antithrombin deficiency, PAI-1 polymorphism, MTHFR mutation, and environmental factors.

Articles published between the years of 1996 and 2024 were reviewed, with a focus on recent research published since 2010. Peer-reviewed original research articles, clinical trials, and review papers on the prevalence, genetic background, and clinical importance of thrombophilia were prioritized. Studies that focused on unrelated coagulation disorders or lacked appropriate clinical or genetic data were excluded, as were editorials, non-peer-reviewed publications, and those not published in English. No statistical analysis was conducted because this study is a narrative review of existing literature.

The chosen studies were examined and classified based on the kind of genetic abnormality and its reported connection with venous thromboembolism and related clinical consequences.

3. Results

3.1 Major Mutations

3.1.1. Factor V Leiden

A key clotting protein having roles in both the procoagulant and anticoagulant pathways is the human coagulation factor V (FV). Fatal events could be caused by thrombotic disorders and hemorrhage which arise from the inability to regulate and express activities of Factor V (Segers et al., 2007). The blood protein factor V is necessary for appropriate coagulation to take actions as a reaction to damage. Factor V Leiden is a defective variant of factor V characterized by resistance to activated protein C which leads to impaired anticoagulant response and increased thrombotic risk (Ornstein & Cushman, 2003; Kalafatis & Mann, 1997).

One of most frequent VTE is deep vein thrombosis which most frequently affects the limbs, and it rarely develops in odd places (Kalafatis & Mann, 1997). Thrombosis is linked to FVL especially in women who have additional risk variables like being older, pregnant, using oral contraceptives, having hyperhomocysteinemia or being protein C and protein S deficient (Samfireag et al., 2022). Around 5% of Caucasians have a heterozygous variant of FV Leiden and it is more prevalent among persons with North European ancestry, but also in certain Middle Eastern communities. On the other hand, the homozygous variant is detected in less than 1% of white population (Ornstein & Cushman, 2003).

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FV Leiden thrombophilia is passed down as an autosomal dominant trait where an individual tends to develop venous thrombosis during lifetime, while homozygous variant of FV Leiden is passed down in autosomal recessive way and that individual will be at a very high risk of VTE (Kalafatis & Mann, 1997).

3.1.2. Prothrombin G20210A (Factor II)

Factor II is the precursor of thrombin (Samfireag et al., 2022). The second most prevalent hereditary potential risk for VTE is the prothrombin G20210A (factor II) mutation (Segal et al., 2009). It is a missense mutation located outside the coding region of the prothrombin G20210A, and it does not directly alter the physical structure or function of the prothrombin molecule. On the other hand, this mutation was discovered to result in higher blood prothrombin concentrations which may contribute to an elevated risk of venous thromboembolism. The plasma prothrombin concentrations vary considerably across people with various genotypes for the G20210A mutation (Jadaon, 2011; Soria et al., 2000). With the prevalence rate of up to 6% of the population, Factor II mutation is proven to raise the chance of developing thrombosis (Samfireag et al., 2022). Prothrombin G20210A homozygosity is an infrequent genotype, and not much is documented about its relationship to probands' recurring venous thrombosis. There is some data to suggest that prothrombin G20210A heterozygosity in probands is not a predictor of repeated VTE (Segal et al., 2009).

3.2 Natural Anticoagulant Deficiencies

3.2.1. Protein C deficiency

The most common genetic issue in people with protein C deficiency shown by genetic analysis is missense mutations which produce single amino acid substitutions (Zoller et al., 1999). People who are heterozygous for protein C deficiency certainly have a higher chance of venous thrombosis. Low concentrations of protein C activity enhanced the likelihood of it (FJM van der Meer et al., 1997).

First identified in the early 1980s, protein C deficiency is a hereditary thrombophilic condition linked to a higher risk of thrombosis. It functions as a crucial anticoagulant, however, this action requires the presence of protein S as a cofactor (Prosciak & Stawicki, 2017). There are two types of inherited protein C deficiency: type I, being a quantitative deficiency, and type II, being a qualitative deficiency, despite frequently normal protein levels. Inherited protein C deficiency is typically passed down as an autosomal dominant trait (Campello et al., 2019). In severe cases, homozygous or compound heterozygous mutations are linked to hereditary protein C deficiency, which may exhibit an autosomal recessive pattern (Montagnana et al., 2017).

A related but distinct concept is activated protein C (APC) resistance, in which the anticoagulant response to activated protein C is reduced. Although both conditions affect the protein C pathway and can be associated with thrombophilia, they are not considered synonymous (Samfireag et al., 2022).

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3.2.2. Protein S deficiency

Blood coagulation, inflammation, and other cellular functions are regulated by a multipurpose Protein S (PS) (Majumder & Nguyen, 2021). Protein S is a plasma glycoprotein created by hepatocytes and macrophages where 40% of PS is free and anticoagulant in nature through its function of a component of APC which causes the deactivation of factor V (FV) and FVIIIa (Zhang et al., 2021). The percentage of deficiency of protein S in the general population is unknown, however 2-5% of thrombosis patients have it. Studies have shown that the link between protein S deficiency and thrombosis resembles protein C deficiency (Zoller et al., 1999). The PROS1 gene encodes Protein S in humans, and a mutation in the PROS1 gene leads to a hereditary condition of Protein S deficit which can result in severe thrombotic disorders. However, only homozygous genotype has a direct association with mortality, whereas the heterozygous PS deficiency is linked to an elevated likelihood of developing pulmonary embolism or vein thrombosis (Majumder & Nguyen, 2021).

3.2.3. Antithrombin deficiency

Since it inhibits thrombin and numerous additional coagulation proteases, antithrombin plays a crucial role in the coagulation chain. The initial genetic link between a lack of a naturally occurring anticoagulant and symptomatic venous thrombosis was established with the discovery of antithrombin insufficiency in 1965 (Kottke-Marchant & Duncan, 2002). Individuals with AT deficit are much more likely to develop thromboembolism, which occurs primarily in the veins. AT insufficiency is the most common hereditary thrombophilia and increases the likelihood of VTE (Patnaik & Moll, 2008). Antithrombin insufficiency can occur alongside other inherited or acquired risk factors, even though being a rare genetic condition that may contribute significantly to thrombophilia (Kottke-Marchant & Duncan, 2002). Heparin resistance exists in certain individuals with antithrombin deficiency, demanding high dosages (Bauer, 2003). Hormonal birth control use is linked to a higher likelihood of thrombosis, especially in women with APC-R and antithrombin deficiency. Women with antithrombin insufficiency seem to experience more thrombotic problems during pregnancy and after delivery than those with PC or PS deficit (Lane et al., 1996).

3.3 Low-Penetrance Polymorphisms

3.3.1. PAI-1 factor

Among the natural protective operations against intravascular thrombosis is the plasminogen activator (PA), the fibrinolytic system. As a result, it enhances the results of both brief inhibitors of platelets with endothelial origin, and the protein anticoagulants such as proteins C and S (Vaughan, 2005). Individuals suffering deep venous thrombosis frequently have poor fibrinolytic ability because of decreased tissue-type plasminogen activator (t-PA) production or elevated levels from its inhibitor plasminogen activator inhibitor-1 (PAI-1) (Sartori et al., 2003). 675 nucleotides upstream of the PAI-1 transcription start point, a single nucleotide deletion or

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insertion results in two alleles: PAI-1 (−675 4G) and PAI-1 (−675 5G), which cause uneven fibrin buildup (Athar et al., 2024). Genetic variations in the PAI-1 gene (SERPINE1) can alter PAI-1 plasma levels (Agersnap et al., 2022).

The promoter region of the PAI-1 gene has a singular guanosine deletion/insertion polymorphism (4G/5G), that can be linked to PAI-1 synthesis and expression (Sartori et al., 2003). There is a difference in the plasma PAI-1 levels between homozygous 4G and 5G alleles where those that are homozygous for the 4G allele show higher levels. The 4G/4G genotype seems to be linked to various thrombotic conditions according to certain research, whereas no link was observed with others (Balta et al., 2002).

Individuals with existing heart or metabolic disorders, who also have the 4G allele, are found to have higher levels of PAI-1 than healthy individuals making them more prone to forming clots. The presence of the 4G allele of the PAI-1 gene could be linked to having a higher predisposition to forming blood clots in arteries of internal organs (Balta et al., 2002).

3.3.2. MTHFR

One amino acid that frequently develops is homocysteine and is created when methionine is demethylated. Hyperhomocysteinemia is an elevated concentration of homocysteine and is caused by a variety of genetic causes or by insufficient intake of B vitamins and folic acid (Samfireag et al., 2022). A risk factor for coronary, vascular, and cerebrovascular disorders is hyperhomocysteinemia (Athar et al., 2024).

It is known that certain people struggle to metabolize folate due to a widespread genetic variation known as methylenetetrahydrofolate reductase, or MTHFR (Varga et al., 2005). The most frequent mutations in the MTHFR gene, C677T and A1298C, lower the enzyme activity, hence raising homocysteine levels (Kumar et al., 2005). Both of an individual's MTHFR alleles must be altered for them to have any negative effects since having heterozygous genotype is medically inconsequential. However, not everyone will experience elevated homocysteine levels even if there are two MTHFR mutations (Varga et al., 2005).

Differences in the frequency of MTHFR genotypes (CC, CT, and TT) have been reported among stroke patients with elevated homocysteine levels, with the homozygous mutant genotype occurring less frequently than the heterozygous genotype (Alluri et al., 2005). In addition, hyperhomocysteinemia and the TT genotype have been associated with pre-eclampsia, spontaneous abortion, and placental abruption (Ueland et al., 2001).

There has been significant discrepancy in the research on the relationship between MTHFR mutations and venous blood clots, with some studies finding a very modest correlation and the majority finding none. Even though a small amount of research has implied that MTHFR mutations could interact along with other hereditary risk variables, like FVL leading to clotting

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disorders, most of the research demonstrates how the mutated MTHFR do not raise the chance of clotting (Varga et al., 2005).

3.4 Clinical Implications

3.4.1. Surgery

People with genetic thrombophilia could require thromboprophylaxis when faced with surgery, immobility or pregnancy for example, which represent a few of the other causes of thrombosis. VTE can be interpreted as a result of multiple interacting risk factors, where one risk variable, like a heterozygous FVL, provides a level of risk that is not probable to result in thrombosis on its own. However, if another risk factor is involved, such as surgery or pregnancy, this could cause thrombosis to occur (Campello et al., 2019). The prevalence of venous thrombosis complicating surgery was found to be 22% overall, according to a retrospective investigation of many antithrombin, PC, or PS deficient patients (Lane et al., 1996). For example, some studies have shown that individuals with thrombophilia who have had orthopedic surgery face greater danger of developing VTE (Zambelli et al., 2021).

3.4.2. Pregnancy

Pregnancy, the postpartum period, and surgery are the possible causes most frequently linked to the development of thrombosis (Lane et al., 1996.) According to research, approximately 41 of the 110 women who experienced prenatal issues also had genetic thrombophilia (De Stefano et al., 2002). Numerous pregnancy problems are caused by thrombotic issues, and it is now known that far too many thrombotic occurrences during pregnancy are linked to acquire as well as hereditary thrombophilia. The primary reason for maternal deaths in the United Kingdom is pulmonary embolism resulting from deep vein thrombosis (Robertson et al., 2006). Research has linked thrombophilia to preeclampsia, fetal growth restriction, placental abruption and stillbirth, but also delay in fetal development and miscarriage (Nahas et al., 2018).

FV Leiden and other hereditary thrombophilia were linked to negative pregnancy outcomes and may contribute to the failed Assisted Reproductive Technology implantation (Fábregues et al., 2004). The gradual rise in sensitivity to active protein C, which mostly occurs during the second and third trimesters, is likely to contribute to the higher incidence of thrombosis that is linked to pregnancy (Bauer, 2003).

Females with several IVF failures have a greater incidence of FVL mutant variant than those who had experienced successful IVF-embryo transfer (Qublan et al., 2006). Apart from women homozygous for MTHFR C677T gene, who had no increased likelihood compared to women who were not pregnant, all hereditary thrombophilia were strongly related to venous thromboembolism. Having a homozygous mutation of Factor V Leiden or hyperhomocysteinemia is a significant risk factor for early pregnancy loss. On the other hand, an important risk factor for later spontaneous abortions is Protein S deficiency (Robertson et al., 2006).

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Utilization of oral contraceptives has additionally been linked to developed activated protein C resistance. The developed APC resistance in hormonal contraceptive consumers is explained to a certain extent by the reported reduction in protein S (Brenner et al., 2002).

4. Discussion

In this review, current knowledge on the key mutations linked with thrombophilia and their role in the development of venous thromboembolism is explored. The most prevalent genetic causes of complications related to thrombophilia are Factor V Leiden and the prothrombin G20210A (Factor II) mutation. They are most frequently linked with a development of venous thrombotic events. Many studies have shown that people who carry these mutations, especially in homozygous form or in combination with other risk factors, are much more likely to develop venous thromboembolism. The existing research varies in design, sample size, and population characteristics, which could lead to differences in the reported relationships between specific genetic variants and thrombotic risk.

As opposed to Factor II and Factor V mutations, others have different clinical significance. The role of PAI-1 and MTHFR mutations in venous thromboembolism is still debated, with research showing varying results. Some studies show a possible impact on thrombotic risk, especially if they are combined with other genetic or environmental factors, but on the other hand, others suggest that their independent impact might be relatively insignificant. For example, numerous studies indicated a connection between PAI-1 polymorphisms and thrombotic risk, whereas others were unable to confirm an independent impact of this mutation. These inconsistent findings emphasize an essential gap in existing knowledge, and this shows that more large-scale research studies are required to determine the clinical significance of these mutations.

Deficiency of natural anticoagulants in the body, like antithrombin, protein C, and protein S, can be linked to an increased risk of developing thrombosis, however it is quite less prevalent, unless there are additional risk factors that raise the likelihood. Even though these are not very common deficiencies in the overall population, their existence is clinically significant due to their ability to induce repeated thrombotic complications, and they demand appropriate clinical management.
Another key point mentioned in the review is the relationship between thrombophilia and environmental or acquired risk factors. Pregnancy, surgery or hormonal therapy can all significantly raise the likelihood of thrombotic events in people that have genetic predisposition for them. This supports the idea that venous thromboembolism is mostly caused by a combination of risk factors rather than being caused by a single genetic mutation.

There are still some limitations in the present literature despite the significant advances in understanding the genetic background of thrombophilia. The difference in design, population characteristics or diagnostic criteria from many research studies makes it difficult to give a clear comparison of their outcomes, as well as to clearly state possible associations between specific genetic mutations and thrombotic risk which may account for this lack of universal agreement.

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Without this universal agreement, it is difficult to decide on which are the clinical indications that should be looked for when testing for thrombophilia in individuals, especially those experiencing thrombotic symptoms. Furthermore, not all genetic variants have the same clinical importance, which complicates the understanding of test results. Another significant problem is that, especially in people without a significant personal or family history of thrombotic episodes, thrombophilia testing does not necessarily result in obvious modifications in clinical treatment.
Future research on this topic should explore the clinical significance of less represented genetic mutations by focusing on larger population studies. Furthermore, new molecular processes, such as those involving SIRT1, can be another topic of interest for thrombosis research in the future. *Sirtuin 1* (SIRT1) is an enzyme which may have potential relevance in preventing the development of several illnesses, including thrombotic events, and is triggered in reaction to cellular stress (Marques et al., 2023). The goal should be to optimize risk evaluation and to design specific prevention of thrombotic events especially in patients who are at increased risk of it.

5. Conclusion

Thrombophilia is a clinically significant disorder that can raise the risk of thrombotic events and cause serious complications. The most significant and well-established risk factors for venous thromboembolism in thrombophilia are Factor V Leiden and Factor II mutations. With the presence of additional triggering factors, their thrombotic risk is further increased. Clinical and environmental triggers may further raise the risk of thrombotic problems in genetically predisposed individuals.

Other mutations, like the PAI-1 and MTHFR variations, are less dangerous, even though they are more frequent in the population. There is a possibility of them increasing thrombotic risk, especially when combined with other genetic or environmental factors. Identifying thrombophilia might therefore help improve risk assessment, preventative methods, and overall patient treatment.

Despite a rising amount of research on the subject, there is still no general agreement on the best clinical indications for thrombophilia testing. This lack of standardized recommendations emphasizes the need for additional research to define the clinical importance of various genetic variants and improve the prevention of thrombotic events and long-term outcomes for those affected.

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