

Risk of Venous Thrombotic Events in Systemic Lupus Erythematosus Patients: Genetic Insights

Maria I. Zervou¹, George N. Goulielmos^{1,2,*}

¹Section of Molecular Pathology and Human Genetics, Department of Internal Medicine, School of Medicine, University of Crete, Heraklion, Greece

²Department of Internal Medicine, University Hospital of Heraklion, Heraklion, Greece

*Correspondence should be addressed to George N. Goulielmos, goulielmos@med.uoc.gr

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Commentary

Various studies have reported a strong association between different autoimmune diseases or infection-mediated disorders and an increased risk for venous thromboembolism (VTE). Particularly, patients with rheumatoid arthritis (RA) [1,2], ankylosing spondylitis (AS) [3] and psoriatic arthritis (PsA) [4] have been found to be associated with VTE. The aforementioned studies posed an intriguing question concerning the putative role of a shared genetic background as regards with the co-occurrence of VTE with RA, AS or PsA. In this context, we managed to shed light in this issue recently by conducting extended literature searches [5-7]. VTE, the next to coronary heart disease (CHD) and stroke, represents the third most common cardiovascular disorder, is a multifactorial vascular disease, representing a worldwide health problem affecting people of all ages, sexes and races, exhibiting 2 major subtypes, deep vein thrombosis (DVT) and pulmonary embolism (PE) [8]. Particularly, VTE pathogenesis includes clots that have either formed in the veins of the legs and arms, known as DVT, or embolized and travelled to the lungs, known as pulmonary embolism PE. Data based on histological and electron microscopic investigations have shown that venous thrombi have more fibrin and erythrocytes while arterial thrombi have more platelets [9]. VTE is a disorder with significant genetic predisposition, with its heritability being approximately 50% in studies of families, twins, siblings, and half-siblings [10], while the risk of a sibling developing VTE if another sibling has VTE is approximately 2.5-fold [11], considering that genetic risk factors play the most important

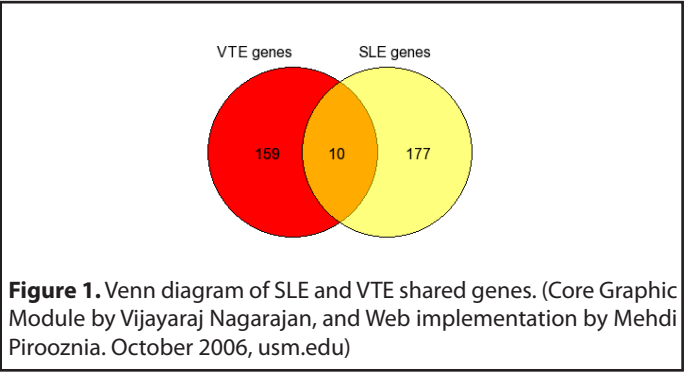
etiopathogenic role in venous thromboembolism (VTE) in people younger than 50 years old [12]. Approximately 10% of patients suffering from DVT develop PE later in their life, and 10% of these patients die [8]. The clinical outcome from VTE disease represents the major source of morbidity and mortality. VTE is the third leading cause of cardiovascular death in the United States [13]. Noteworthy, about 900,000 people have VTE each year in the United States, and between 60,000 and 100,000 die from this disorder [13]. Lifetime risk of VTE is rather high and has been estimated to be 5–10%. VTE recurrence risk is also high [8] and the risk of recurrent VTE is around 25% in 5 years [10].

Notably, an interesting issue emerged recently focusing on the frequency, incidence rates, risk factors and outcomes of a first venous thromboembolic event (VTE) between patients with systemic lupus erythematosus (SLE) and controls [14]. Nossent *et al.* [14] conducted a study to compare the incidence, odds and consequences of multiple VTE types in an observational long-term study comprising Australian patients with SLE and controls [14]. The aforementioned study revealed that VTE affected 12.8% of patients with SLE at six times the VTE rate in controls with antiphospholipid antibodies (aPL) but VTE did not associate with an increased risk of arterial events. The increased frequency of VTE between SLE patients and controls is an issue, considering that similar results were collected from previous population-based or observational studies conducted worldwide (i.e. in Australia, USA, Canada, France, the Netherlands) (for references see [14]). However, the existing information refers to epidemiological or clinical

aspects of this association. SLE is the prototypic multisystemic, multifactorial autoimmune disease, characterized by a loss of self-tolerance leading to the presence of autoantibodies directed towards ubiquitous nuclear antigens, immune complex deposition resulting in organ damage, as well as chronic inflammation at classic target organs such as skin, joints, and kidneys. Most patients, constitutional, mucocutaneous, and musculoskeletal symptoms appear, including include fatigue, lupus-specific rash, mouth ulcers, alopecia, joint pain, and myalgia [15]. This disease affects more than 3.4 million people worldwide, predominantly affecting women, with a ratio of about 9 women to 1 man [16]. Considering the long-term interest of our research group in the investigation of the genetic components that are involved in the co-occurrence of VTE with various autoimmune diseases, we attempted to delineate the genetic basis of the co-occurrence of SLE and VTE by searching in the literature for known genes involved in the development of both conditions, aiming to reveal a partially shared genetic background.

To our knowledge, it is the first attempt in the literature focusing on this scientific issue thus far. The method used for this article included case-control, genome wide association studies (GWAS), systematic reviews and cross-sectional studies. The papers included were written in English language and published from 2006 to 2024. The database used were PubMed, PubMed Central (PMC), Google Scholar, Web of Science and Base, while the keywords that were included in the search study were venous thromboembolism, systemic lupus erythematosus, genetics, gene polymorphisms, association studies, GWAS. Both authors have worked individually to extract the data following the specified criteria and no disagreements arose during the process.

Thus, we found certain genes that represent potential risk factors for developing both diseases, including the interleukin-4 (*IL-4*) –589 C/T (rs2243250) and the insertion/deletion (ID) of the angiotensin-converting enzyme (*ACE*) polymorphisms [17-20], the endothelial nitric oxide synthase (*eNOS*) intron 4 VNTR [21,22] as well as the methylenetetrahydrofolate reductase (*MTHFR*) rs1801133 [23,24], tumor necrosis factor- α (*TNF- α*) rs1800629 [24,25], vitamin D receptor (*VDR*) rs7975232 [24,26], interleukin-1 beta (*IL-1B*) rs16944 [17,27], SH2B adapter protein 3 (*SH2B3*) rs3184504 [28,29], signal transducer and activator of transcription-4 (*STAT4*) rs7574865 [17,30] and rs7582694 [17,30] single nucleotide polymorphisms (SNPs). In **Figure 1**, a Venn diagram shows the number of the shared gene polymorphisms between VTE and SLE, based on the aforementioned articles as well as others selected upon an extensive, careful literature search [10,31-41]. Moreover, **Table 1** demonstrates the shared gene polymorphisms in detail.



To summarize, we identify a small number of shared genetic factors of SLE and VTE, due to the fact that underlying molecular mechanisms leading to the development of VTE are

Table 1. An overview of genetic polymorphisms related to both SLE and VTE development, as they have been confirmed by gene association studies and/or GWAS.			
dbSNP ID	SLE- and VTE -associated gene	Function	References
rs2243250	<i>IL-4</i>	A pleiotropic cytokine; promotes the proliferation of B cells and T cell antibodies.	[17,19]
N/A	<i>ACE</i>	Converts angiotensin I into angiotensin II; catalyzes the bradykinin to kinin degradation products.	[18,20]
N/A	<i>eNOS</i>	A key enzyme in production of the vasodilator nitric oxide (NO).	[21,22]
rs1801133	<i>MTHFR</i>	A key regulatory enzyme in folate and homocysteine metabolism.	[23,24]
rs1800629	<i>TNF-α</i>	A multifunctional pro-inflammatory cytokine.	[24,25]
rs7975232	<i>VDR</i>	A ligand-activated transcription factor, inducing genomic regulation of downstream targets.	[24,26]
rs16944	<i>IL-1B</i>	A cytokine, acting on T and natural killer cells.	[17,27]
rs3184504	<i>SH2B3</i>	A key negative regulator of cytokine signaling; plays a critical role in hematopoiesis	[28,29]
rs7574865 rs7582694	<i>STAT4</i>	A transcription factor involved in the Th17 differentiation, monocyte activation and interferon-gamma production.	[17,30]

still elusive. Moreover, according to the current knowledge, most VTE-risk factors are related to hemostatic system and inherited hypercoagulable states [10]. Specifically, they refer to variations in the genes responsible for blood coagulation and fibrinolytic factors, platelet membrane receptors as well as genes involved in erythrocytes biology [24]. However, a number of shared genetic factors related to inflammation, interferon signaling, metabolism and NF- κ B pathways was identified in the present study. Therefore, we can assume that a “cross-talk” exists between the coagulation and inflammatory pathways, considering that gene polymorphisms involved in inflammation may also result in an increased susceptibility towards VTE. The link between inflammation and coagulation activation has been demonstrated in both animals and humans [19]. In this context, it has been suggested that cytokines primarily influence fibrinolysis besides tissue factor expression [19]. Although the genetic component does not seem to contribute substantially to the co-occurrence of the conditions under investigation, a further identification of more genetic factors is of emerging interest and may help to better delineate the mechanisms leading to their clinical association. These results will be important not only for future genetic and clinical studies but also for directing future function/structure studies of the molecular cause of VTE and SLE. Therefore, an in-depth study of the functional significance of the shared gene polymorphisms may explain how these genetic factors should be incorporated into clinical management of the patients.

A limitation of our study deals with the lack of information in the current literature about the role of the published gene polymorphisms in SLE and VTE patients of different ethnic and/or racial origin. This is a crucial point for further investigation given that different genes are involved in the development of these disorders according to the ancestry of the populations under examination. Moreover, the source of the inter-individual susceptibility to VTE or SLE does not lie exclusively in genetics, considering that epigenetics mechanisms are now widely believed to participate also to the susceptibility to these diseases. Thus, the role of potential shared epigenetic factors has to be investigated in future studies. Noteworthy, a new avenue refers to the detection of novel risk loci due to the information for rare risk variants gained by using WES and WGS technology, thus making a considerable contribution to the missing heritability of VTE and SLE [10].

The current decade promises to be a tipping point for genetic applications in personalized medicine. Despite the variety of genetic factors for VTE that have already been identified, less focus has been placed on ethnic diversity. Upon now, genetic studies have revealed clear disparities in the distribution of genetic factors for VTE in populations stratified by ethnicity worldwide [34]. As a consequence, it is essential for clinicians to establish different risk models that are suitable for each geographic region and ethnic group [42,43]. In the same framework, it has long been appreciated that SLE patients of different ancestral backgrounds have differences in clinical

presentation and disease course. Understanding some of the molecular differences between populations, both at the genetic and protein expression levels, may suggest ways in which treatment could be personalized. Thus, selecting treatment based upon a patient's individual biology would be a major advance in SLE [44]. Furthermore, a natural development of the GWAS and the increasing number of detected variants will be the development and validation of gene risk scores (GRS) both for VTE and SLE. Thus, the combination of GRS with acquired risk factors will be useful for better risk assessment and tailored management of both diseases.

In conclusion, better functional characterization of the diseases-associated genes may lead to the detection of new therapeutic targets for pharmaceutical intervention and ultimately result in the better therapeutic management and diseases' treatment.

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Authors' Contribution

M.I.Z. and G.N.G. designed the current study, searched the literature and drafted the manuscript. Both authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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ORCID iD

George N Goulielmos <https://orcid.org/0000-0002-9797-2310>.

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