

## Research Letter

### Risk of Venous Thromboembolism in Ankylosing Spondylitis and Rheumatoid Arthritis: Genetic Aspects

To the Editor:

In the postgenomic era, the genomic revolution in translational medicine has not escaped the attention of clinicians and researchers focusing on the medical management of venous thromboembolism (VTE). VTE, a multifactorial disease, is a worldwide health problem affecting people of all ages, sexes, and races, and has 2 major subtypes: deep vein thrombosis and pulmonary embolism.<sup>1</sup> The clinical outcomes of VTE represent the major source of morbidity and mortality. No extended data related to the comorbidities of autoimmune diseases with VTE have been presented thus far. Recently, Molander, *et al*<sup>2</sup> conducted a nationwide register-based cohort study and demonstrated a strong association between clinical rheumatoid arthritis (RA) disease activity and the risk of VTE. Moreover, Aviña-Zubieta, *et al*<sup>3</sup> conducted a highly informative to the researchers cohort study in Canada, wherein the overall incidence of VTE was 2.03-fold higher in people with ankylosing spondylitis (AS) than in those without, thus suggesting that people with AS were at higher risk of VTE compared to those without AS. AS is an autoimmune chronic inflammatory disorder characterized by inflammation in the vertebral joints of the spine and sacroiliac joints, resulting in an increased risk of cardiovascular and overall mortality.<sup>4</sup> Patients with AS present with stiffness and pain in the spine, with young males being predominantly affected.<sup>4</sup> On the other hand, RA is an autoimmune disorder characterized by chronic and destructive inflammation in synovial joints, exhibiting a highly variable disease course.<sup>5</sup> Considering the studies that have demonstrated that patients with RA and AS are at increased risk for VTE,<sup>2-5</sup> it seems reasonable that some established VTE risk factors may occur more often in patients with either RA or AS.

Together, the aforementioned studies<sup>2-5</sup> posed an intriguing question concerning the putative role of a shared genetic background as regards the co-occurrence of VTE with either RA or AS. No ethics board approval was required for the current study since no patients are involved. In a recent article, we presented data suggesting that various gene polymorphisms are associated with an increased susceptibility for both RA and VTE.<sup>6</sup> In this framework, we showed that the plasminogen activator inhibitor-1 (*PAI-1*) rs2227631, peptidase D (*PEDP*) rs731839, coagulation factor XIII A chain (*F13A1*) rs5985 (Val34Leu), and methylenetetrahydrofolate reductase (*MTHFR*) rs1801133 single-nucleotide polymorphisms (SNPs), as well as 3 SNPs of the interleukin-1 $\beta$  (*IL-1 $\beta$* ) gene, are associated with the development of both diseases.

Although the pathogenesis of AS has not yet been elucidated, the genetics of AS have been well investigated thus far. Moreover, the underlying molecular mechanisms involved in the development of VTE are still elusive. By searching the literature, we managed to find a limited number of studies pointing out that certain genes can be considered as potential risk factors for developing both AS and VTE, thus suggesting a shared genetic predisposition in limited cases. We found that the *MTHFR* rs1801133 and rs1801131, SH2B adapter protein 3 (*SH2B3*) rs3184504, serum paraoxonase and arylesterase I (*PON1*) rs662, and endoplasmic reticulum aminopeptidase 1 (*ERAP1*) rs30187 SNPs are associated with the development of both diseases.<sup>7,8</sup> Moreover, rs16944, rs1143643, and rs2853550 SNPs of the *IL-1 $\beta$*  gene, previously associated with VTE, were found to be risk factors for AS as well.<sup>9,10</sup> With regard to VTE, the majority of susceptibility factors are related to hemostatic system and coagulation cascade. As a consequence, susceptibility factors for VTE are not expected to be shared with AS risk factors that are mainly involved in inflammatory response.

In conclusion, apart from the remarkable biological complexity of RA,

AS, and VTE, our data provide an evidence for a shared genetic background regarding the co-occurrence of VTE with either RA or AS. Although knowledge of the genetic influences contributing to VTE has improved significantly in the past decade, it is still unclear how these factors should be incorporated into clinical management of high-risk patients with RA or AS. Future investigations are needed to clarify the effects of RA or AS treatment on the risk of VTE. Altogether, the present study has underlined the importance of the further identification of shared genetic loci associated with both conditions; this may help to delineate the mechanisms leading to the clinical association between these diseases and ultimately result in better therapeutic management, prognosis, and treatment.

George N. Goulielmos<sup>1,2</sup>, PhD, Professor of Human Molecular Genetics  
Maria I. Zervou<sup>1</sup>, PhD, Laboratory Teaching Staff

<sup>1</sup>Section of Molecular Pathology and Human Genetics, Department of Internal Medicine, School of Medicine, University of Crete, Heraklion, Greece;

<sup>2</sup>Department of Internal Medicine, University Hospital of Heraklion, Heraklion, Greece.

The authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. G. N. Goulielmos, Section of Molecular Pathology and Human Genetics, Department of Internal Medicine, School of Medicine, University of Crete, Heraklion 71003, Greece.  
Email: [goulielmos@med.uoc.gr](mailto:goulielmos@med.uoc.gr).

#### REFERENCES

1. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis* 2016;41:3-14.
2. Molander V, Bower H, Frisell T, Askling J. Risk of venous thromboembolism in rheumatoid arthritis, and its association with disease activity: a nationwide cohort study from Sweden. *Ann Rheum Dis* 2021;80:169-75.
3. Aviña-Zubieta JA, Chan J, De Vera M, Sayre EC, Choi H, Esdaile J. Risk of venous thromboembolism in ankylosing spondylitis: a general population-based study. *Ann Rheum Dis* 2019;78:480-5.
4. Haroon NN, Paterson JM, Li P, Haroon N. Patients with ankylosing spondylitis have increased cardiovascular and cerebrovascular mortality: a population-based study. *Ann Intern Med* 2015; 163:409-16.
5. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med* 2011;365:2205-19.
6. Zervou MI, Goulielmos GN. Correspondence on 'Risk of venous thromboembolism in rheumatoid arthritis, and its association with disease activity: a nationwide cohort study from Sweden'. *Ann Rheum Dis* 2021 Feb 1 (E-pub ahead of print).
7. Lindström S, Wang L, Smith EN, Gordon W, van Hylckama Vlieg A, de Andrade M, et al. Genomic and transcriptomic association studies identify 16 novel susceptibility loci for venous thromboembolism. *Blood* 2019;134:1645-57.
8. Crous-Bou M, De Vivo I, Camargo CA, Varraso R, Grodstein F, Jensen MK, et al. Interactions of established risk factors and a GWAS-based genetic risk score on the risk of venous thromboembolism. *Thromb Haemost* 2016;116:705-13.
9. van Minkelen R, de Visser MC, Houwing-Duistermaat JJ, Vos HL, Bertina RM, Rosendaal FR. Haplotypes of IL1B, IL1RN, IL1R1 and IL1R2 and the risk of venous thrombosis. *Arterioscler Thromb Vasc Biol* 2007;27:1486-91.
10. Li L, Shi B, Zheng W, Xing W, Zhao Y, Li F, et al. Association of IL-1A and IL-1B polymorphisms with ankylosing spondylitis among the Chinese Han population: a case-control study. *Oncotarget* 2017;8:28278-84.