

## Correspondence on 'Risk of venous thromboembolism in rheumatoid arthritis, and its association with disease activity: a nationwide cohort study from Sweden'

We read with great interest an article by Molander *et al*<sup>1</sup> demonstrating a strong association between clinical rheumatoid arthritis (RA) disease activity, measured by Disease Activity Score-28 (DAS28) ESR, and the risk of venous thromboembolism (VTE). In the framework of this elegant nationwide register-based cohort study that enrolled 46316 patients, it was found that the risk ratio for VTE in patients with RA was 1.88 (95% CI 1.65 to 2.15), while among patients with RA, the risk for VTE increased with increasing RA disease activity. Noteworthy, compared with the general population, also patients with RA in DAS28 ESR remission were at elevated VTE risk.<sup>1</sup> Therefore, the authors nicely suggested that RA disease activity can be used as an additional tool for VTE risk stratification in patients with RA. RA is an autoimmune disorder characterised by chronic and destructive inflammation in synovial joints, exhibiting a highly variable disease course.<sup>2</sup> VTE, a multifactorial disease, possess a worldwide health problem affecting people of all ages, sexes and races, appearing two clinical manifestations, deep vein thrombosis and pulmonary embolism.<sup>3</sup> The clinical outcome from VTE disease represents the major source of morbidity and mortality. Considering that several studies have demonstrated that patients with RA are, on average, at increased risk for VTE, it seems reasonable that some established VTE risk factors may occur more often in patients with RA.

The current study by Molander *et al*<sup>1</sup> poses the intriguing question concerning the putative role of a shared genetic background as regards with the co-occurrence of RA and VTE. To tackle this important question, we attempted to focus on certain genes that represent potential risk factors for developing these conditions, aiming to demonstrate a shared genetic predisposition in some cases. Although the genetics of RA is very well investigated and more than 200 risk loci have been identified in the past two decades, the genetic factors involved in the development of VTE and its underlying molecular mechanisms are still not completely elucidated. In our attempt to provide a comprehensive update on the current understanding of the potential shared genetic component of RA and VTE, we found that the methylenetetrahydrofolate reductase rs1801133, coagulation factor XIII A chain (F13A1) rs5985 (Val34Leu), PEDP rs731839 and plasminogen activator inhibitor-1 rs2227631 single-nucleotide polymorphisms (SNPs) are associated with the development of both diseases.<sup>4-9</sup> Moreover, rs16944, rs2853550 and rs1143643 SNPs of interleukin 1 beta gene, previously associated with VTE, were found to be risk factors for RA as well.<sup>10</sup> With regard to VTE, the majority of candidate genes is mostly related to the clotting system and responsible for inherited hypercoagulable states. Therefore, it may be difficult an overlap between these loci and a high number of inflammatory factors involved in RA development to be observed.

In conclusion, despite our present effort, we did not manage to identify a high number of genetic factors involved in the development of both RA and VTE. 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 the high-risk patients with RA. However, if necessary, pharmacological

prophylaxis for VTE should be initiated in these patients with RA. The further identification of shared genetic loci, associated with both diseases, is of emerging interest and may help to better delineate the mechanisms leading to the clinical association between these diseases and ultimately facilitate the detection of novel therapeutic targets for new therapies.

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