Unraveling the Genetic Basis of Recurrent Venous Thromboembolism

See Article by de Haan et al

Deepak Voora, MD, FAHA
Richard C. Becker, MD, FAHA

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a worldwide health problem affecting people of all ages, sexes, cultures, and races. Recent estimates suggest that upward of 10 million people had VTE at an annual cost from hospitalization, treatment, and days lost from work of at least $60 billion.[1,2] It is prevalent in low-, middle-, and high-income countries with annual incidence rates ranging from 0.75 to 2.69 per 1000 individuals. In addition, VTE is among the leading causes of disability-adjusted life years lost.[3] In the Global Burden of Disease Project,[4] incidence rates for VTE were 115 and 269 per 100 000 people among men and women, respectively, and mortality rates ranged from 9.4 to 32.3. Despite the burden of VTE, global public awareness was ≈50% lower compared with myocardial infarction or stroke.

VTE is often associated with recurrence after convalescence from the initial event. An unprovoked initial VTE is a particularly strong risk factor for recurrence, suggesting that ≥1 underlying genetic factors may play an important role. One must consider the possibility that the genetics of recurrence may differ from that of an initial, unprovoked VTE. There is clinical uncertainty on the optimal duration of anticoagulation after treatment of initial VTE to prevent recurrence; therefore, deeper insight into the underlying mechanisms of recurrence may ultimately help tailor duration of anticoagulation to those at highest risk. Clinicians working closely with the scientific community on a foundation of precision medicine seek guidance for predicting recurrent VTE.

Prior investigation into the genetics of VTE has been limited to unselected VTE[5] without regard to initial versus recurrent status. Although these prior approaches have been successful in attaining large sample sizes, they have been unable to distinguish between initial versus recurrent risks. Accordingly, the study by de Haan et al,[6] representing a highly experience group of investigators who have collectively contributed substantially to the fields understanding of VTE, in this issue of *Circulation: Genomic and Precision Medicine* is a significant advance in the genetics of recurrent VTE.

To tackle this important question, the authors first prospectively identified cases of recurrent VTE using a population-based cohort study specifically designed to identify risk factors for recurrent VTE in patients who were followed after an initial VTE event. For their genome-wide association study, adjudicated cases (n=447) and a random sample of recurrence-free controls (n=832) were compared using state-of-the-art genome-wide association study analyses. Recurrent VTE cases were older, more likely male, and had a higher prevalence of provoked initial VTE compared with controls. Their initial screen identified 1 locus, at *F5*, that reached genome-wide significance. The known effects of the F factor Leiden nonsynonymous variant on recurrent VTE explain the association at this locus. Well known for its asso-

Correspondence to: Richard C. Becker, MD, FAHA, Division of Cardiovascular Health and Disease, UC Heart, Lung and Vascular Institute, University of Cincinnati College of Medicine, Cincinnati, OH 45267. E-mail richard.becker@uc.edu

Key Words: Editorials ■ genetics ■ recurrence ■ thrombosis ■ uncertainty ■ venous thrombosis

ciation with initial VTE, this robust finding extends the association of F factor Leiden to recurrent VTE. In addition, they identified 17 loci with genome-wide suggestive evidence (ie, $P<10^{-5}$). In a subsequent replication analysis formed by combining data from 3 independent studies (n=350 cases), the authors found that an intergenic variant on chromosome 18 (rs9946608; P=0.008) validated their results in the same direction as the discovery cohort. In a combined meta-analysis of discovery and validation cohorts for rs9946608, the P value for association was 10^{-7}. Beyond these variants, the authors also evaluated variants associated with recurrent VTE that were identified in prior, candidate gene analyses. The majority of these were not associated with recurrence; however, variants associated with initial VTE near *Fibrinogen Gamma Chain, F11,* and *ABO* blood groups were nominally associated with recurrent VTE, suggesting a potential differential role for these genes. In a preliminary analysis of clinical use, the authors added F factor Leiden and rs 9946608 to a clinical risk model and showed improvement in the area under the receiver operating characteristics curve; however, the area under the receiver operating characteristics curve of the combined clinical and genetics model was only 0.68.

The investigators are commended for their diligence in gathering a well-phenotyped cohort, their attention to possible confounders, and overall presentation of their findings to the scientific community. On the basis of these initial findings, we propose 2 questions: (1) How robust is the association in additional cohorts? (2) What are the clinical implications of this association? As the authors acknowledge that, even in the combined meta-analysis, the strength of association does not cross the threshold for a genome-wide association (ie, P value $<10^{-8}$), and, therefore, additional replication will be required and welcomed. Once further validated, the challenging task of defining the functional implications of variants at this locus and the risk of recurrent VTE begins. The rs is located on chromosome 18, and unlike the F5 locus variants which are associate with both initial and recurrent VTE, variants at this locus seem to be uniquely associated with recurrence. The nearest genes for this intergenic variant are 2 long-intergenic noncoding RNA *RPH11-526H11-1* and *RP11-638L3.1* and 1 protein-coding gene, *TMX3* (Thioredoxin Related Transmembrane Protein). Using expression quantitative trait locus analyses, the investigators did identify an association with gene expression in publically available gene expression databases. They did, however, uncover some evidence that this variant may be a site for transcription factor binding and an open chromatin state in some cell lines. Future studies, beyond the scope of this initial investigation, will need to evaluate the function of genetic variants at this locus on the biological processes that are unique to recurrent versus initial VTE such as clot lysis and recanalization or response to anticoagulant therapy for example.

What are the clinical implications of these observations? There is a clear need for precision medicine–based approaches to tailor the duration of anticoagulant therapy to improve the risk–benefit profile of extended duration prophylactic anticoagulation in unprovoked VTE. A recent Cochrane database systematic review[7] concluded that the available evidence is not sufficient to draw conclusions for the effectiveness and safety of extended prophylaxis for preventing recurrent VTE after an initial course of therapy. An ability to establish a reliable risk prediction score for recurrent VTE would likely contribute meaningfully to future clinical trial design and decision-making.

Current prediction models include clinical factors (age, sex, location of initial VTE) and D-dimer measures, but still underperform (area under the receiver operating characteristics curves <0.70), and speak to the need for improved risk prediction at the time of initial presentation. As an alternative management strategy, serial D-dimer testing with continued anticoagulation in those with abnormal results reduces the risk of recurrence and identifies a subgroup of patients in whom anticoagulation can safely be discontinued. Therefore, future predictive models involving genetic testing will need to be compared with D-dimer and go beyond improvements in area under the receiver operating characteristics curve to also include measures of reclassification of patients with low/high D-dimer levels into high/low risk of VTE to change clinical practice. D-dimer was not included by de Haan et al[6] in the clinical prediction model.[8–10] This may represent a limitation of their study given prior observations, including the work of Ensor et al[10] who reported that post-treatment D-dimer could predict individual risk of recurrence at any time up to 3 years and offer cost-effectiveness insight for decision-making by distinguishing high-and low-risk patients.

Future investigation into biomarkers of recurrent VTE risk may have more value in the expressed genome by studying peripheral blood gene expression, protein, or metabolites as novel risk markers. With the rich patient and sample cohort assembled by the investigators, we anticipate additional studies using an expanded "-omic" platform in an integrative systems biology approach to disentangling the risk factors for recurrent VTE.

DISCLOSURES

None.

AFFILIATIONS

From the Duke Center for Applied Genomics and Precision Medicine, Durham, NC (D.V.); and UC Heart, Lung and Vascular Institute, University of Cincinnati College of Medicine, OH (R.C.B.).

FOOTNOTES

Circ Genom Precis Med is available at http://circgenetics.ahajournals.org.

REFERENCES

1. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: a review of estimated attributable healthcare costs. *Thromb Res*. 2016;137:3–10. doi: 10.1016/j.thromres.2015.11.033.
2. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to global disease burden. *Thromb Res*. 2014;134:931–938.
3. Raskob GE, Angchaisuksiri P, Blanco AN, Büller H, Gallus A, Hunt BJ, et al; ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to global disease burden. *Semin Thromb Hemost*. 2014;40:724–735. doi: 10.1055/s-0034-1390325.
4. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. *Circ Res*. 2016;118:1340–1347. doi: 10.1161/CIRCRESAHA.115.306841.
5. Germain M, Chasman DI, de Haan H, Tang W, Lindström S, Weng LC, et al; Cardiogenics Consortium. Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism. *Am J Hum Genet*. 2015;96:532–542. doi: 10.1016/j.ajhg.2015.01.019.
6. de Haan HG, van Hylckama Vlieg A, Germain M, Baglin TP, Deleuze J-F, Trégouët D-A, Rosendaal FR. Genome-Wide Association Study identifies a novel genetic risk factor for recurrent venous thrombosis. *Circ Genom Precis Med*. 2018;11:e001827. doi: 10.1161/CIRCGENETICS.117.001827.
7. Robertson L, Yeoh SE, Ramli A. Secondary prevention of recurrent venous thromboembolism after initial oral anticoagulation therapy in patients with unprovoked venous thromboembolism. *Cochrane Database Syst Rev*. 2017;12:CD011088. doi: 10.1002/14651858.CD011088.pub2.
8. van Hylckama Vlieg A, Baglin CA, Luddington R, MacDonald S, Rosendaal FR, Baglin TP. The risk of a first and a recurrent venous thrombosis associated with an elevated D-dimer level and an elevated thrombin potential: results of the THE-VTE study. *J Thromb Haemost*. 2015;13:1642–1652. doi: 10.1111/jth.13043.
9. Palareti G, Legnani C, Cosmi B, Guazzaloca G, Pancani C, Coccheri S. Risk of venous thromboembolism recurrence: high negative predictive value of D-dimer performed after oral anticoagulation is stopped. *Thromb Haemost*. 2002;87:7–12.
10. Ensor J, Riley RD, Jowett S, Monahan M, Snell KIe, Bayliss S, et al; PIT-STOP Collaborative Group. Prediction of risk of recurrence of venous thromboembolism following treatment for a first unprovoked venous thromboembolism: systematic review, prognostic model and clinical decision rule, and economic evaluation. *Health Technol Assess*. 2016;20:i–xxxiii, 1. doi: 10.3310/hta20120.

Circulation
Genomic and Precision Medicine

Unraveling the Genetic Basis of Recurrent Venous Thromboembolism

Deepak Voora and Richard C. Becker

Circ Genom Precis Med. 2018;11:
doi: 10.1161/CIRCGEN.117.002047
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1942-325X. Online ISSN: 1942-3268