

Genetic variants and risk for venous thromboembolic events: Summing up the evidence

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Since the first systematic description of the pathophysiology of venous thromboembolic events (VTE) by Virchow in 1856, genetic predisposition had been suspected to contribute to the three mechanisms of thrombosis – vessel-wall injury, stasis, and hypercoagulability. As early as 1956, Jordan and Nandorff observed that family members of affected individuals have an increased risk for VTE (1). In 1965, Egeberg discovered partial antithrombin deficiency in a Norwegian family, the first phenotype conferring inherited thrombophilia (2). Since, a great number of studies have reported variable associations between certain genetic variants, most commonly in proteins of the coagulation system, and an increased risk for VTE. Most of these studies were relatively small case-control studies comparing the prevalence of candidate gene variants in patients with VTE to that in matched controls. However, the risk estimates (and their precision) for a carrier of a certain variant to develop VTE vary greatly in different patient populations. While the results of various studies have previously been pooled to obtain more precise risk assessments for commonly examined variants, the risk associated with some less studied variants remains controversial.

In this issue of *Thrombosis and Haemostasis*, Gohil et al. report the results of a comprehensive meta-analysis of 173 case-control studies examining the association between 28 polymorphisms in 21 genes and VTE (3). The authors are to be commended for the sheer scope of this enterprise. Based on >300,000 subjects, this analysis provides well-founded risk estimates for most variants in candidate genes implicated in thrombophilia.

This work represents an important quantitative summary of the large number of mostly small case-control studies assessing thrombophilic risks of genetic variants. As expected, for the major, extensively studied variants (factor V G1691A and prothrombin G20210A), the risk estimates were well in the range reported by previous summary analyses. This meta-analysis is most useful in providing summary estimates for less studied or rare genotypes (e.g. plasminogen activator inhibitor-1, PAI-1)

and, equally important, confirming the lack of association, even in a large cohort, with many other variants (19 variants in 17 genes). In addition, by calculating the population attributable risk (PAR), the authors provide an epidemiologically valuable estimate of the contribution of individual genetic variants to the disease burden of VTE.

The large number of patients included in this analysis suggests robustness of the risk estimates, as reflected by comparatively narrow confidence intervals (CIs) for the odds ratios (ORs) of many variants. However, some caveats should be borne in mind when interpreting the findings.

Although the authors used appropriate statistical models, meta-analyses of case-control studies are liable to confounding, a bias which is invariably associated with the non-randomised design of case-control studies (4). For instance, it is difficult to assess how balanced case and control groups were in the individual studies for potential confounding factors, such as age and hormone therapy. In this context, it is reassuring that the risk estimates in the current meta-analysis largely correspond to those derived from prospective cohort studies of asymptomatic variant carriers. For instance, the risk estimate for factor V Leiden (OR=4.93) is similar to the relative risk derived from prospective cohort studies (about 4.5, as averaged from various reports) (5–8).

Secondly, the findings cannot be generalised to all VTE patients. Only studies excluding VTE patients with a clear provoking factor (post-surgical patients, patients with pregnancy, cancer, or the antiphospholipid antibody syndrome) were included in this meta-analysis; inclusion of patients with other risk factors (for instance, contraceptive or hormone replacement therapy; immobilisation / trauma; recurrent or first VTE episode) varied among the different studies. Thus, the population studied comprises mainly VTE patients with only minor or no provoking factors, a group comprising roughly half of all VTE patients (9). In this group, the prevalence of genetic polymorphisms conferring thrombophilia is higher than in patients suf-

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fering a VTE in the presence of a major provoking factor (10). Therefore, the present study's findings cannot be automatically extrapolated to the whole population of VTE patients. Accordingly, some doubt remains about the accuracy of the absolute numbers of VTE that the authors attribute to certain genetic variants.

Thirdly, for variants sufficiently common to identify homozygous variant carriers, the authors analysed the data by two modes of inheritance – the recessive and the dominant model. In fact, the thrombophilic risk for many genetic variants appears to follow an additive or supra-additive model, suggesting that genotype groups should not be pooled but considered separately. For instance, for the factor V Leiden variant, it may be more informative to compare homozygote variant carriers (AA) to wild-type homozygotes (GG) rather than to the combined groups of wild-types and heterozygotes (GG+GA). However, depending on the prevalence of the genetic variant, the different analytical approaches may yield similar results. In fact, the VTE risk estimates for homozygous carriers of factor V Leiden (OR=9.45) is noticeably similar to that derived from prospective studies (AA genotype compared to GG, relative risk approximately 8.9, as averaged from different reports) (7, 8, 11).

The high population-attributable risk (30.1%) for the PAI-1 promoter 4G/5G polymorphism is somewhat surprising. Reduced activity in the fibrinolytic system has been associated with VTE risk, and the PAI-1 promoter 4G allele is associated with increased PAI-1 expression and thus reduced fibrinolysis. Although the OR for VTE was only moderately elevated (OR=1.62), the high PAR was driven by the high prevalence of the variant (about 50%). However, the risk estimate appears less robust, as reflected by evidence for inter-study heterogeneity. Additionally, choosing dominant/recessive models of inheritance (rather than an additive mode) may have introduced some bias. Prospective studies will be necessary to confirm these findings.

Furthermore, this meta-analysis is based on studies with risk estimates for single genetic loci only. For common variants, coinheritance of two or more different thrombophilic variants is not rare (e.g. compound heterozygotes for factor V Leiden and prothrombin G20210A). The presence of two or more genetic variants conferring thrombophilia is associated with a synergistic and not just additive risk for VTE (12). The VTE risk of such combinations of genetic variants should be the subject of future analyses.

Lastly, it is likely that additional, yet unknown genetic variants confer thrombophilia. Only a third of patients with a positive family history carry known thrombophilic genetic variants, and family history for VTE remains an important risk factor for first VTE even after adjusting for known variants (7, 13). As discussed by the authors, future genome wide association studies or large-scale sequencing in large case-control studies may identify additional thrombophilic genetic markers.

What are then the implications of the current findings? Even with more precise risk estimates for carriers of genetic variants, the place of testing for inherited thrombophilia in asymptomatic subjects is disputed. Indiscriminate screening for genetic thrombophilia in healthy subjects is not cost-effective. Seventy percent of asymptomatic carriers of thrombophilic variants will not develop VTE before the age of 60 (12), so the risk of long-term anticoagulation in this population seems unwarranted. In addition, personal or family history of VTE are strong risk factor notwithstanding the presence or absence of identifiable genetic markers (13). Still, knowledge about the presence and type of genetic thrombophilia may guide risk stratification and therapeutic decisions in situations associated with increased VTE risk (e.g. pregnancy, hormone therapy).

Undoubtedly, precise and individualised risk-benefit assessments are necessary to inform decisions about preventive or therapeutic interventions for VTE. The present meta-analysis makes an important contribution to this undertaking.

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