

Family history of VTE: An easy tool to score the individual risk

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Venous thromboembolism (VTE) is the third most common cardiovascular disease, affecting in Caucasians one in 1,000 individuals every year (1). The pathogenesis of VTE is multifactorial, involving acquired and genetic factors. Familial clustering is extensively documented and genetic predisposition due to molecular abnormalities of components of the coagulation pathway have been found in subjects who had had thromboembolic disease (2). Indeed, abnormalities within the gene loci encoding for natural anticoagulants (anti-thrombin, protein C and protein S) and, mainly in patients of European ancestry, common gain-of-function mutations within the gene of the coagulation factor V (FV Leiden mutation) and the factor II (FII A20210 allele) gene have been shown to account for a large number of cases of VTE.

Nevertheless, it is well known that genetic susceptibility to VTE is complex, multifactorial, and heterogeneous. In keeping with this, the incidence of VTE varies widely among different groups of population from settings with a distinct genetic background, and disparities in VTE burden may be attributable to differences in genetic risk factors not strictly belonging to the coagulation pathway (3). On the other hand, family history is a recognised risk factor for VTE but it is poorly associated with known genetic risk factors. Data from the Danish Twin Registry and from family studies provided substantial evidence for the genetic transmission of VTE

(4). Thus, in clinical practice, family history may represent a risk indicator for VTE independently of and in addition to the risk caused by known genetic and environmental factors, not only in people of Caucasian ancestry (5).

The article by Zöller et al. in this issue of *Thrombosis and Haemostasis* (6) for the first time provides evidence that the degree of risk was a function of the type of relative affected (first, second, or third degree) and that this risk interacts with the age at which the relative developed VTE. It was previously reported that a higher number of affected relatives and a younger age at which the relative was affected increased the chance of having VTE (7, 8). Actually, compared to individuals without a family history, Zöller et al. estimated an odds ratio (OR) of 2.49 associated with a first-degree relative who suffered from VTE. If the first-degree relative affected was a parent, the risk was 2.09. The novel information was the high relative risk associated with having a second (grandparent, uncle, aunt) or a third-degree (first cousin) relative affected, 1.69 and 1.47, respectively. A potential limitation of the study is that no information has been provided whether the transmission was consistent with a multifactorial polygenic, single major locus, or mixed model.

Familial aggregation captures information correlated with genetic relatedness, but it refers also to shared cultural and environmental characteristics. Noteworthy, non-biological relatives (spouses) showed a slightly higher risk (OR 1.14) but far less than those recorded among relatives. Moreover, the significant higher risk shared by paternal half-siblings, which occasionally (3%) live together, additionally points to a pivotal role of inherited factors. Thus, although family history does not guarantee for or against VTE development, it was strongly stressed that the familial clustering of VTE contains an important genetic and inherited component. On the whole, factors such as a greater number of

affected relatives, younger age at diagnosis, and closer kinship each further increases the risk of disease. As VTE, a multifactorial model as hereditary cancer, like hereditary breast and ovarian cancer (HBOC), shows some degree of familial clustering, with the disease being more prevalent in first-degree relatives of affected people, and twin studies suggest that most of the excess of the familial risk results from inherited susceptibility (9). However, in HBOC we are dealing with mutations in genes, i.e. BRCA1 and BRCA2, that show a low prevalence but a high penetrance, whereas in familial clustering of VTE mutations with a high prevalence but a low penetrance, FV Leiden and FII A20210 allele, are more frequently encountered.

Another challenging finding of the present study is the stronger familial transmission in males. A tendency for higher male-to-male transmission compared with female-to-female transmission was observed, although reaching a statistically significance only for first-degree relatives, i.e. siblings and parents of probands. The observation of a striking different estimated risk in maternal half-siblings (OR 1.52) as compared with paternal half-siblings (OR 2.34), which share household in 83% and 3% of cases, respectively, further strengthens sex-related differences in transmission of the VTE risk. Male relatives of male index cases had the highest risk, which is consistent with evidence obtained from twin registry data and nationwide and case-control studies (4, 10-12). Results from these studies raise the question whether there exists a sexual dimorphic susceptibility to VTE. Sex-specific determination of risk is crucial in view of the recognized differences in incidence, age of onset, and risk of recurrences between sexes. A role for hormonal risk factors has been advocated because of differential exposure to risk factors

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such as pregnancy, postpartum, and oral contraceptive pill (13). However, this explanation has recently been challenged, being the risk of recurrences significantly higher in men with a first unprovoked but not in those with a first provoked event (14). In the study by Zöller et al., lack of information concerning the cause of VTEs and testing for thrombophilia hampered more in-depth analyses.

Alternatively, a male-driven transmission may be ascribed to a minor Y-linked risk factor. Common feeling on the Y chromosome is that it harbors only genes needed for the development of male-specific characteristics. Apart from SHOX-related haploinsufficiency disorders, as the Leri-Weill Dyschondrosteosis, to date we are unaware of Y-linked monogenic disease unrelated to sex development. Recently, the Y chromosome was associated with some multifactorial conditions, "traits", such as hypertension, total and LDL cholesterol, and coronary artery disease (15-17).

Might the Y chromosome modulate the risk of a multifactorial disease as VTE? If yes, how? At variance with maternal effects, paternal effects on phenotypic variation have long been considered to be absent or negligible. Data reveal that Y-chromosome diversity may have consequences in the expression of autosomal and X-linked genes, likely through trans-generational epigenetic effects (18). However, further investigations are needed to unravel whether genetic susceptibility to VTE is equally likely to be transferred from both parents or admits the possibility of a sex-linked inheritance.

In summary, the study by Zöller et al. adds evidence in support of strong genetic components to VTE yielded by the family incidence, twin, and family aggregation investigations suggesting that in some families may occur a complex and sexual

dimorphic interaction of both genetic and environmental components that cannot be explained by a simple Mendelian inheritance of known thrombophilic risk factors. Independently of the knowledge of a hypercoagulable state, the use of family history is a practical tool to detect at-risk individuals through physician counseling and information sharing by VTE patients with their family members. There may well be a case for its routine incorporation into existing clinical risk scores for predicting VTE, given that family history currently does not feature in the main scores (19, 20).

Conflicts of interest

None declared.

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