Genetic aspects of thrombotic disease

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The fact that there was a genetic (hereditary) component in the pathology of venous thrombosis was recognised early. Indeed, it is now 50 years ago that the first description of a plasma protein deficiency linked to a hereditary thrombotic diathesis was reported, antithrombin deficiency, coining the term thrombophilia to describe the increased predisposition to thrombosis in the families studied (1). Since then, our knowledge and capacity to study the genome has completely changed the way we understand the gene-environment interaction in health and disease (2). Interestingly, the study of the genetic aspects of haemostasis and specifically in relation to the predisposition of venous thrombosis has been at the forefront of this field in several aspects. During the decade of the 1980s, most of the genes related to the coagulation cascade and the fibrinolytic system were characterised. The major deficiencies associated with thrombophilia were also definitively established as risk factors and associated with increasing numbers of loss of function mutations in the genes of the anticoagulant proteins C, S and antithrombin; PROC, PROS1 and SERPINC1, respectively. An interesting revision of the situation at the beginning of the nineties could be found in Miletich et al. (3). The authors listed cloned genes that would be putative candidates for causing a prothrombotic state through loss of function mutations, deriving in protein deficiencies. These genes included natural anticoagulants as well as components of the fibrinolytic system. Interestingly, the authors proposed the possibility of mutations leading to increased function of genes of the coagulation cascade, including for instance the prothrombin and factor V genes; F2 and F5. That same year, a biochemically defined trait in blood, described as a poor response to the anticoagulant activated protein C (APC) was discovered and named APC resistance (4). Soon after, mutations causative of APC resistance in the F5 gene and a mutation in the 3′ untranslated region of the F2 gene associated to increased prothrombin concentration in plasma were demonstrated to cause thrombophilia (5,6). These studies validated the concept of mutations conferring increased function as cause of thrombosis, as proposed in (3). The impact was enormous, only four years later, already 50% of venous thrombosis cases could be linked to a thrombophilic mutation in certain populations (7).

A second concept that appeared in Miletich et al. was that a mutation associated with thrombophilia seems to confer different risk depending on the patients studied. Furthermore, in large pedigrees where a causative mutation was found, the non-carrier relatives seemed to have a higher risk of thrombosis than the general population. These observations lead to the consideration that the risk of thrombosis was due not only to a unique gene mutation, but its interaction with other mutations or variants in the genome. When this concept was validated soon after, it led to considering thrombophilia as a multigenic disease (8, 9).

The present series of reviews on the field of thrombophilia reflect how the field is developing with the new techniques available for the study of the genome and their impact on our understanding of the disease. In the first review of the Theme Issue, Manucci and Franchini (10) revise the concepts and discoveries of the initial studies on the genetic causes of venous thrombosis and summarise the most relevant implications that these mutations have for the patients. In a second review, Zöller et al. update the use of family history in the field of venous thrombosis (11). Venous thrombosis, as most common diseases, is a complex genetic entity where the risk of suffering the illness is contributed by a multiple genetic and environmental mechanisms. The identification and study of pedigrees with a genetic tendency to thrombosis was crucial in the initial discoveries of the field. As the authors describe in their review, family history of thrombosis is an independent risk factor for venous thrombosis and could be used as a tool to discover unknown genetic predispositions to the disease. The difficulties inherent to the replication of genetic association studies, as reviewed in (12), encourage the use of clinical parameters as family history to guide studies on thrombophilia. In a third review of the present Theme Issue, Tang et al. describe an aspect that has been surprising the researchers of the field of venous thrombosis: the large differences in thrombotic risk that seem to be associated to different populations (13).

The enormous advances in the studies of the genome have provided a wealth of information that is being only recently used in its full possibility. Several recent studies used genome-wide-association studies to dig on the genetic determinants of thrombosis (14). They have been also used to describe the influence of genetics on what we could consider intermediate determinations in the formation of a thrombus, for instance the plasma concentration of the components of the coagulation cascade, thus providing new candidates for genetic risk factors of thrombosis (15). Morange et al. review the impact of these technologies on the field of thrombophilia (16). Still, in some aspects, the use of genome characterisation has failed to provide new clinically relevant genetic variants. A new powerful tool, next generation sequencing, is presented by Cunha et al. in

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the final review of the series (17). The initial studies on the field, focusing on well characterised patients with a hereditary component, focused on deleterious mutations and the traits they confer. Research concentrated on the mechanisms leading to thrombosis and started with candidate genes that could explain such mechanisms. With the arrival of the omics technologies, the interest shifted towards gathering colossal amounts of data, unbiased by a hypothesis or preconception. Probably, from now on we will be seeing a combination of both strategies thanks to these new technologies.

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Conflicts of interest
None declared.

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