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VIEWPOINT

Genetic regulation of inflammation-mediated activation of haemostasis: Family-based approaches in population studies☆

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Abstract Blood coagulation and inflammation play a key role in atherosclerosis and thrombosis. Candidate gene and genome wide association studies have identified potential specific genes that might have a causal role in these pathogenic processes. The analysis of quantitative traits is more powerful as they are closer to direct gene action than disease phenotypes. Thus linkage-based studies on extended families might be useful both to estimate the heritability and to map the genetic loci responsible for the regulation of the trait.

Family-based studies may estimate high heritability for thrombosis and quantitative traits regarding both platelet aggregation and blood coagulation. Some specific loci relevant to thrombosis have been identified, with some of them showing a direct pleiotropic effect on the risk of thrombosis.

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Haemostasis factors can be activated by inflammatory stimuli. Fibrinogen level is genetically correlated with C-reactive protein levels with a link for both traits on chromosomes 12 and 21. Genes related to prostanoid biosynthesis, involved both in inflammation and thrombosis, show high heritability levels in both enzyme expression and prostanoid production.

Considering that few large family-based linkage studies have as yet been performed on haemostasis and inflammation-related traits, additional studies are highly needed. We are performing a family-based linkage study on large pedigrees (750 subjects from 23 families with juvenile myocardial infarction and 31 control families), to identify genes responsible for quantitative traits involved in the pathway progressively going from inflammation to haemostasis, cell activation, thrombus formation and cardiovascular events.

Atherosclerosis and thrombosis result from the action of multiple factors, both environmental and genetics, that exert their effects over an extended period of time [1] and can increase or decrease the risk of myocardial infarction (MI) and stroke, the two most severe complications of athero-thrombosis. In the INTERHEART study [2], a large case-control study including 52 countries, nine modifiable risk factors were found to explain more than 90% MI risk, across all major ethnic groups. In particular, while six traditional risk factors (smoking, lipids, hypertension, diabetes, obesity, and psychosocial factors) were significantly related to MI, alcohol, physical exercise and fruit and vegetable consumption were inversely associated. The majority of risk factors associated with athero-thrombosis, both traditional or emerging, such as homocystein, fibrinogen, C reactive protein, have a strong genetic component, that have also been implicated in the development of both MI and stroke [3,4].

A number of pathways play role in the initiation and progression of athero-thrombosis; this role can vary according to different stages of the pathological process. Such pathways include, among others, blood coagulation and inflammation [5,6], that will be specifically discussed in this short review.

Recent advances in our understanding of molecular and genetic mechanisms coupled with the advances in technology have allowed a more detailed and comprehensive examination of the role of genes and environment in health and disease and the complex way in which ''nature'' and ''nurture'' interact in determining the individual risk of disease. A number of studies have identified potential specific genes that might have a causal role in determining the levels of these risk factors and their clustering both in individuals and in families [7–10]. However, it is conceivable that the full phenotypic expression of these factors and their link to development, severity, type and time of onset of clinical manifestations of vascular disease is the ultimate result of the combined influence of multiple genes with multiple environmental factors.

The most common approach used to date to study the role of genes in the aetiology of thrombosis has been the ''candidate gene'' approach in association studies. This approach suffers from several epidemiological weaknesses (e.g. selection bias, population stratification, overestimation of linkage disequilibrium (LD)) and is limited by the fact that it restricts the analysis to a few genes that can only account for a small portion of the disease risk [11]. Moreover, the ''candidate gene'' approach only confirms the effect of known genes, while additional unknown genes (only detectable through a more comprehensive approach) most likely play an important role in determining the levels of risk factors for thrombosis and their relationship with cardiovascular disease.

More recently genome wide association studies (GWA) have completely changed the approach to the genetics of common diseases [12]. Thousands of common single nucleotide polymorphisms (SNP) are assayed, relying on data produced by the International Human HapMap Project and the observation that genetic variance at one locus can predict with high probability genetic variance at an adjacent locus, typically over a distance of 30,000 base pairs of DNA in the human genome. During the past few years, GWA studies have identified a large number of robust associations between specific chromosomal loci and complex human diseases, such as type 2 diabetes and MI [13]. However such studies are costly and require ever larger sample sizes.

Powerful linkage-based studies (or joint analysis of linkage and LD) might be used to confirm (and to better investigate) the results from association studies [14]. Among the proposed approaches, the variance component (VC) method has sufficient power and efficiency to map genes influencing complex diseases [15,16]. In addition, recent extensions of the VC method allow to explore discrete traits, joint linkage/LD analysis and deviation from the underlying assumption of normality of the trait [17,18].

In particular, strategies focusing on the genetic analysis of measurable quantitative traits (QTL) correlated with disease risk, are highly justified as compared to the previous emphasis on the analysis of the much less informative dichotomous disease trait [19]. Because of their closer proximity to direct gene action, disease-related quantitative phenotypes represent our best approach to identify the underlying QTL that influence disease susceptibility. It represents one of the most comprehensive approaches and provides important methodological challenges for its implementation both with regard to the genome scanning and to the statistical and computational efforts required to adequately analyze the data produced. This approach works best when data are collected on extended families. Unfortunately, family-based designs are still relatively rare in thrombosis/haemostasis studies. In the Genetic Analysis of Idiopathic Thrombosis (GAIT) family-based study, Souto and Blangero estimated an additive genetic heritability of 60% for thrombosis [20], suggesting that genes would represent a relevant causal