Insight  association of L-arginine levels and two loci in genes of the kallikrein-kinin system

New genetic association for the kinin system: the L-arginine connection

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Thrombosis was possibly one of the first complex diseases in which genetics had an important role in defining pathological mechanisms. In recent years, advances in the studies of the genome have provided a new wave of information that is being only recently used in its full possibility. This was the subject of a recent series of reviews in this journal (1). One successful approach for digging in the genetic determinants of thrombosis uses genome-wide-associations technologies to explain the variance in intermediate determinations in the formation of a thrombus, for instance the plasma concentration of the components of the coagulation cascade. This has led to the proposal of new candidates for genetic risk factors of thrombosis, as was reviewed by Morange et al. for the field of thrombophilia (2).

In the present issue, a new application of this technology provides an interesting example of the possibilities of the technique. In a well-powered genome-wide association study, using over 2000 samples from European and Asian origin, Zhang et al. (3) find an association of L-arginine levels and two loci in genes of the kallikrein-kinin system; F12 and KLKB1, coding for the coagulation factor XII and prekallikrein. L-arginine concentration in blood is thought to be related with blood pressure control, as it is a necessary precursor of nitric oxide. The finding of a link with genetic variants in the kallikrein-kinin system immediately suggests a mechanism of action, through the function of these proteins in bradykinin release. L-arginine is the product of the fast degradation of this vasodilator. The studied sentinel polymorphisms are both in linkage disequilibrium with one variant in each respective gene likely to influence the gene function. However, how this association translates into a relevant physiological feature is difficult to demonstrate. Indeed, the two polymorphisms showed association with blood pressure in opposite directions, the KLKB1 variant associated with lower, while the F12 was associated with higher blood pressure. This finding underlines the complex system of equilibriums involved in blood pressure regulation.

In conclusion, the study is an elegant demonstration of the capacity of genomic technologies in finding correlations between apparently distant biological processes. In the field of cardiovascular disease, these correlations should help proposing solid hypotheses on pathological mechanisms, while providing plenty of further work to do in order to test these hypotheses.

Conflicts of interest
None declared.

References