Genetic thrombophilia and natural anticoagulants: importance of polymorphisms within and outside the genes

We read with interest the report by Kim *et al*. on the unique pattern of mutations in the specific genes encoding blood coagulation inhibitors in a Korean population.[1] This undoubtedly represents a large amount of data on the prevalence of deficiencies of natural anticoagulants along with the spectrum of mutations in both control and patient populations.

The basal plasma levels of the three natural protein anticoagulant proteins, i.e. protein C, protein S and antithrombin, are affected by multiple factors which include age, sex, use of oral contraceptives, lupus anticoagulants, pregnancy, liver disease and so on. One indirect way of controlling this is to look for an isolated deficiency of the natural anticoagulant, though it can be argued that there may be a differential reduction of these proteins under such circumstances. Another important factor is the high rate of laboratory test errors. As these deficiencies manifest in the heterozygous condition, even a minute variation in the test results might misclassify them as deficient or *vice versa*. Identification of causative mutation thus remains the most important and definitive tool in the confirmation of any underlying inherited defect. However, in a large number of patients with thrombosis and deficiencies of any of the natural anticoagulants, the causative genetic defects are not identified.[2,3]

Several reports now confirm that polymorphisms within or outside the genes, other genes within or outside the vitamin K cycle may affect the plasma levels of these natural anticoagulants.[4,5] It remains to be seen whether these polymorphisms, either singly or in combinations, based on the strength of their association with the plasma levels of natural anticoagulants, may effectively be translated into the routine battery of thrombophilia investigations.

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References

1. Kim HJ, Seo JY, Lee KO, Bang SH, Lee ST, Ki CS, et al. Distinct frequencies and mutation spectrums of genetic thrombophilia in Korea in comparison with other Asian countries both in patients with venous thromboembolism and in general population. Haematologica. 2013 Oct 25 [Epub ahead of print].
2. Tang L, Lu X, Yu JM, Wang QY, Yang R, Guo T, et al. PROC c.574_576del polymorphism: a common genetic risk factor for venous thrombosis in the Chinese population. J Thromb Haemost. 2012;10(10):2019-26.
3. Pai N, Ghosh K, Shetty S. Hereditary protein C deficiency in Indian patients with venous thrombosis. Ann Hematol. 2012;91(9):1471-6.
4. Buil A, Soria JM, Souto JC, Almasy L, Lathrop M, Blangero J, et al. Protein C levels are regulated by a quantitative trait locus on chromosome 16: results from the Genetic Analysis of Idiopathic Thrombophilia (GAIT) Project. Arterioscler Thromb Vasc Biol. 2004; 24(7):1321-5.
5. Pomp ER, Doggen CJ, Vos HL, Reitsma PH, Rosendaal FR. Polymorphisms in the protein C gene as risk factor for venous thrombosis. Thromb Haemost. 2009;101(1):62-7.