Inducible nitric oxide synthase (NOS2) gene polymorphism and parasitic diseases

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Sir—David Burgner and colleagues (Oct 10, p 1193) report an association between a polymorphism in the promoter region of the inducible nitric oxide synthase (NOS2) gene and the risk of fatal cerebral malaria. This result accords with the findings of Kun and co-workers early this year. Altogether these results suggest that susceptibility to severe malaria seems to be determined by complex genetic factors at the NOS2 locus.

We investigated whether the single nucleotide polymorphism (G-C) in the NOS2 promoter region, which is located at position -954 (not at -969 as previously reported), is associated with susceptibility to or severe forms of Chagas' disease. We included 85 patients who were serologically positive for Chagas' disease and 87 healthy controls from Arequipa, Peru, South America. Patients were grouped according to the presence (n=33) or absence (n=52) of cardiomyopathy. The NOS2 promoter mutation was analysed by PCR-RFLP with amplification-created restriction site (ACRS) for Xho I enzyme. A 60 bp fragment was amplified with 5' primer: 5'-CACCTTGAGCTTCAGAGCTC and 3' primer: 5'-TTGTAAGACTGAGTTTCAC. The mutated 5' primer introduces a restriction site for Xho I that recognises the wild type allele. There is a natural restriction site for Bsp I that directly detects the mutation; however, Xho I is readily available and cheaper. Analysis of all the samples in the Peruvian population showed that only the wild type occurred.

Although studies show association between NOS2 promoter polymorphisms and severe malaria, the functional consequences of these genetic variations in the NOS2 expression is not known. Given the absence of NOS2 promoter mutation in our population where Trypanosoma cruzi infection is endemic and the important role of nitric oxide in the defence against the parasite, we believe that NOS2 promoter mutation at -954 may have no functional relevance. On the other hand, Kremsner's group reported that this mutation was not found in 100 controls. Therefore, the NOS2 polymorphisms may be restricted to populations subjected to selective pressure of Plasmodium falciparum. Further studies of distribution of the NOS2 promoter polymorphisms in other areas or ethnic groups where malaria is also endemic will help to elucidate this topic.

* Javier Martin, José E Calzada, Antonio Nieto
Instituto de Prasitología and Biomedicina “López Neyra”, CSIC, Calle Ventanilla 11, 18001, Granada, Spain (e-mail:jmartin@iib.csic.es)