Host genetic factors probably determine both susceptibility to infection and severity of damage by pathogens. A large number of polymorphisms have now been implicated in the onset, progression, and outcome of malaria infection, seeming to influence the ability of the host immune response to control the infection. These include:

- those associated with haemoglobopathies;
- those within the major histocompatibility complex (HMC), including HLA class I and class II and the tumour necrosis factor promoter;
- those within genes not associated with HMC, such as ICAM-1, CD36, and possibly the gene for nitric oxide synthase;
- probably the gene for apolipoprotein E (APOE), as our recent data suggest, and upon which we comment below.

APOE has three main alleles, types 2, 3, and 4, resulting in six possible genotypes; it codes for the protein apoE, which is involved in transport of lipids in the blood and the central nervous system.

Finding that APOE-ε2 homozygous Ghanaian infants were more likely to be infected with the malaria protozoon at a very young age than those with the other genotypes, we predicted that severity of illness after infection might depend on some extent on APOE genotype. In this issue, the article by Aucan et al offers support for involvement of APOE in the development of severe malaria: people carrying an APOE-ε3/ε4 genotype may be more likely than those with the other main genotypes to suffer extremely severe malaria (cerebral malaria and severe anaemia). Our discovery that APOE-ε2 homozygotes are infected at a very early age is not inconsistent with the finding of Aucan et al that APOE-ε3/ε4 carriers are more likely to suffer extremely severe malaria. Epidemiological studies suggest that the risk of developing severe malaria is lower in children who experience their first malaria infections very early in life than in those first infected at an older age. Presumably, children infected during infancy (while still protected from clinical malaria and high parasitaemia by innate protective mechanisms and maternal antibodies) develop adaptive immune responses that protect them from severe disease in later life. On the other hand, those infected only later (after the protective mechanisms of infancy have waned) are fully susceptible and at high risk of severe or fatal disease. Thus, the earlier the infection occurs (as in ε2 homozygotes), the less the likelihood of life-threatening illness. Indeed, in the study by Aucan et al, APOE-ε2 carriers were under-represented in the extremely severe malaria (cerebral malaria with severe anaemia) group (7.1% v 11.5–13.8% in the other groups), although the difference does not reach statistical significance.

Whatever the explanation for the results of Aucan et al, our data and theirs add to the extraordinarily diverse repertoire of infective diseases in which APOE determines outcome of, or susceptbility to, infection; and they suggest the possible use of this information for prognostic purposes.

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This commentary should have been published alongside the article “Common apolipoprotein E polymorphisms and risk of clinical malaria in The Gambia” by C Aucan, AJ Walley, and AVS Hill in the January 2004 issue (J Med Genet 2004;41:21–24). This error is much regretted and we would like to offer our sincere apologies to the authors involved.
Apolipoprotein E polymorphisms and risk of malaria

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