A-32 Specific allelic combinations at the TNFa and TNFß gene loci modulate severity of disease in malaria and other nfectious diseases

I Wattavidanage[1], R Carter[2], N P Herath[1], K L R L Perera[1], A Munasinghe[1], S Bandara[3], A R Wickramasinghe[1], H Alles[1], K N Mendis[1], S Premawansa[4]

[1] Malaria Research Unit, Dept of Parasitology, Faculty of Medicine, University of Colombo, Colombo 8 [2] Institute of Cell, Animal & Population Biology, Div of Biological Sciences, University of Edinburgh [3] Malaria Research Unit, General Hospital, Anuradhapura [4] Dept of Zoology, Faculty of Science, University of Colombo, Colombo 3

Associations between alleles of the human TNFa and TNFß genes and severity of disease during malarial and other infections in a Sri Lankan population has been studied., Patients were categorised as having either (i) uncomplicated malaria (ii) severe and complicated malaria, or (iii) severe and complicated non-malarial infections by using a previously validated numerical scoring system based on WHO criteria. For all the patients, as well as a group of matched healthy controls, TNFa and TNFß allelic types were identified using the polymerase chain reaction, allele-specific oligo-nucleotide probing and Restriction Fragment Length Polymorphism techniques. The results revealed that individuals carrying a TNFa*2 allele, mainly of the heterozygous genotype (TNFa*1,*2), were at 2 to 3 times the risk of developing severe disease, of either malarial or other infectious origin, compared to those without TNFa*2 i.e. of the TNFa*1,*1 homozygous genotype. However, the increased risk of severe disease associated with a TNFa*2 allele occurred only when the TNFß*2 allele was present in the genetic background. The combination of these 2 alleles together conferred an approximately 10 fold higher risk of severe disease compared to any genotype from which either one of the alleles was absent. Thus, a strong genetic predisposition to the severe manifestations of malarial and several other infectious diseases arises in the simultaneous presence of the TNFa*2 and the TNFß*2 alleles.