A CANDIDATE GENE ASSOCIATION STUDY OF GENETIC SUSCEPTIBILITY TO CUTANEOUS LEISHMANIASIS IN SRI LANKA

Thisum Nilakshi Samaranayake M.B.B.S; Dip. Micro

A Thesis submitted to the University of Colombo

for the degree of Doctor of Philosophy

Supervisors: Dr. V. H. W. Dissanayake

Prof. S. D. Fernando

Department of Parasitology
Faculty of Medicine
University of Colombo
Kynsey Road, Colombo 8
Sri Lanka

2011

Dedication

To my husband Niresh and my son Rishen,
for all the love, support and patience

Abstract

The study documented in this thesis investigated genetic factors predisposing humans to cutaneous leishmaniasis (CL) in Sri Lanka.

Leishmaniasis constitutes a multifactorial disease with interplay between the host, parasite, vector and the environment determining the final outcome. Both epidemiological and molecular genetic studies have suggested that the human host may be genetically predisposed to leishmaniasis. These studies have been conducted mainly in African and South American countries with the focus largely on visceral and mucocutaneous forms of the disease.

The present study was undertaken in a genetically distinct South Asian Sinhalese population in which cutaneous leishmaniasis is endemic. Three candidate genes implicated in the immune response to *Leishmania*; Tumour necrosis factor (*TNF*), Lymphotoxin alpha (*LTA*) and Solute carrier family 11A member 1 (*SLC11A1*) were selected for the study. These investigations constituted an initial population genetic study followed by a case–control study. Ninety samples for the population genetic study were from an existing anonymized DNA resource and were genotyped for the selected polymorphisms to establish background population frequencies. Subjects for the case–control study were recruited prospectively and comprise the only such resource in the country. The cases and matched controls were genotyped for the same polymorphisms and allele/haplotype frequencies were compared. The study was complemented with a bioinformatics analysis for future work, which identified a set of SNPs for comprehensive genotyping of the genomic regions of interest.

Recruitment of two hundred new patients for this study provided an opportunity to expand on the knowledge on clinical manifestations of CL in Sri Lanka. The finding that the condition was almost exclusively confined to Sinhalese and that multiple lesions were more likely to be

found in those with other affected family members supported the possibility of a genetic predisposition to CL in this population.

The population genetic study showed significant differences in allele and haplotype distribution at the *TNF* locus among the main ethnic groups which constitute the Sri Lankan population, with Sinhalese differing significantly from Tamils and Moors. This is the first report of the distribution of the polymorphisms of *SLC11A1* in a South Asian population and those of *TNF* and *LTA* separately in the major ethnic groups in Sri Lanka. The baseline data reported here would help in the future design of genetic studies based on these genes, in the country.

The case–control analysis did not show an association between the SNPs of *TNF*, *LTA* and *SLC11A1* or the haplotypes investigated and CL. The frequency of these variant alleles in other populations, where they were positively associated with leishmaniasis, differed significantly from the Sri Lankan population. The likely small genetic effects conferred by these variants and the differing patterns of linkage disequilibrium between populations, highlights the need for these results to be validated in a larger sample with sufficient power.