ABSTRACT

Leprosy is a chronic infectious disease caused by *Mycobacterium Leprae* where host genetic background plays an important role toward the disease pathogenesis. Various studies have identified a number of human genes in association with leprosy or its clinical forms. However, non-replication of the results has hinted at the heterogeneity among associations between different population groups; which could be due to differently evolved LD structures and differential frequencies of SNPs within the studied regions of the genome. A need for systematic and saturated mapping of the associated regions with the disease is warranted to unravel the observed heterogeneity in different populations.

Understanding the importance of the PARK2 / PACRG genes in the biology of the disease and the assumption that there could be a difference in the LD structure and the distribution pattern of the SNPs within the regulatory region of the two genes in the populations showing heterogeneity in association, we saturated the region with 96 SNPs with a resolution of 1 SNP per Kb for the PARK2 regulatory region and compared the LD structure between the Indian and Vietnamese population. The results showed the association of 11 significant SNPs with Leprosy in the North Indian population, which was replicated in a geographically distinct population from Orissa in eastern India. A comparison of the 36 common SNPs between Indian and Vietnamese population for the region, generated different BIN structures in the two populations. The 20 significant SNPs in Vietnamese population could not be replicated in Indians, suggesting the heterogeneity in association in the two unrelated populations of the world. Also, the analysis of 2 common significant SNPs in-between Indian and Vietnamese populations, failed to show any functional significance in *in-vitro* reporter (luciferase) expression profiles obtained for the alternative variants. The remaining 4 SNPs out of common 36 SNPs were significantly associated only in Indian population. To find out if there was any other functional SNP in Indian population which explained the heterogeneity among the populations; we selected most significant SNPs located within 63.8kb upstream of PARK2 gene to study their enhancer like activity. The expression profile established the functional importance of these SNPs which were observed in strong association in two distinct and unrelated population groups.
Comparison of BIN structure generated for the Indian population and Vietnamese population revealed differences in the BINs. Thus, explaining the heterogeneity and the reason for non-replication of the associated genomic regions in different populations.

Further genotyping interaction analysis of multiple genes involving pro- and anti-inflammatory cytokines in the background of the risk allele of PARK2 gene, which encodes parkin protein and acts as ubiquitin ligase, allowed us to propose that the genetic background of an individual is one of the major factors determining the outcome of the infection. Here in the background of the risk alleles of the PARK2 apparently affected the transcription binding site (Bioinformatics analysis) and lowered the expression of the reporter gene in *in-vitro* experiments, risk alleles of anti-inflammatory cytokine genes IL-10 (OR=1.99), IL-6 (OR=1.33) and TGFBR2 (OR=1.29), involved in lowering the CMI response towards the invading bacteria; and that of pro-inflammatory cytokine, TNF-alpha (OR=2.10), provided a highly significant risk towards leprosy. The risk increased with their combined effect (PARK2-PACRG, TNF, BTN2L2-DR, IL10, IL-6 and TGFBR2), increasing the odds (OR=2.54) when compared to their individual contribution towards this complex human disease, Leprosy.