CONCLUSION

Leprosy has been shown to be governed by a strong host genetic background where several genes have been identified in association with its clinical forms. The involvement of the PARK2 and PACRG genes with leprosy susceptibility in two distinct populations of the world, Vietnamese and Brazilians, and its non-replication in other populations suggests the reasons of genetic heterogeneity between different population groups. The possibility of the involvement of other variants and a differential LD structure for the PARK2 regulatory region, in Indian population as compared to Brazilian and Vietnamese; may provide an answer to the heterogeneity among association observed previously in different population groups. Our study with systematic and saturated mapping of 6q26 region (PARK2/PACRG gene regulatory region) has shown a strong association of 11 SNPs in the regulatory region of the PARK2 and PACRG gene in the two unrelated populations of the India (North & East Indian-Orissa). Further the functional evaluations of significant SNPs also showed their involvement in controlling expression. The comparison of BIN structures generated for the Indian population with four HapMap and Vietnamese populations revealed differences in the BINs with similarity between the European and Indian populations as compared to Chinese, Japanese and Vietnamese, explaining the heterogeneity and the reason for non-replication of the associated genomic regions in different populations.

Further genetic analysis of Leprosy, a chronic infectious disease, has revealed complex and inconsistent results, making it difficult to draw clear conclusions regarding the impact of specific genes providing susceptibility in diverse human populations. Another reason for this could be, as widely presumed for many infectious diseases including Leprosy, that susceptibility is governed by polygenic inheritance, or the additive effects of multiple genes, each with a modest effect on the infectious phenotype. Therefore our gene-gene interaction study also identified the combination of risk genotypes of PARK2-PACRG, TNF, BTNL2-DR, IL10, IL-6 and TGFBR2 interval SNPs, providing a major risk towards leprosy; while the protective genotype combination of PARK2-PACRG, BAT1, NFKBIL1, LTA, TNF-LTB and IL10RB showed protection against the disease in comparison to their individual contribution.
The present findings provide an insight into leprosy pathogenesis and add to the information regarding the complex puzzle of genetic factors involved in infectious disease, such as Leprosy. An improved understanding of the pathogenesis of leprosy and an effective treatment for it shall significantly be influenced by our ability to untie the effects of host genetic factors in response to \textit{M. leprae} infection. Our study highlights that susceptibility to leprosy is critically influenced by polymorphisms in important gene, PARK2, encoding ubiquitin protein, with possible interactions with other immune-regulatory gene products to influence immune response. Further work at protein level need to be conducted in future in order to understand how in the background of the risk alleles of the parkin, important genes involved in the immuno-regulatory pathways are regulated.