Abstract

Asthma is a heterogeneous, chronic lung disease that narrows the airways, and has growing prevalence worldwide. This complex disease is caused by interplay of genes and environment on the genome of an individual and more than 100 genes have already been found associated with asthma. ADAM33 is one of the positionally cloned, candidate genes of asthma, which has been identified as susceptibility gene for asthma in different populations consistently. This study focused to understand single nucleotide polymorphisms of ADAM33 and their role in asthma phenotypes, severity and also the response to treatment. The study was also focused to identify and understand the interacting molecules through the systems biology approach. This was followed by the analysis of effect of copy number variation in asthma-associated genes on normal cohort’s genome. By understanding the role of genomic variations in asthma patients, could also help to understand the etiology of asthma and might improve therapeutics of asthma. In view of this the following objectives were addressed in this thesis: a) To assess the severity of asthma related phenotypes in patients, b) To study the pedigree and pattern of inheritance in asthma, c) To elucidate the molecular interaction network and pathway on the role of ADAM33 in causing asthma, d) Genotyping of known, clinically relevant SNPs of ADAM33 and e)To study the genotype to phenotype correlation of ADAM33 polymorphism.

A total of doctor diagnosed 503 asthma cases based on GINA guidelines and 486 normal controls were genotyped for 35 SNPs of ADAM33 using MassARRAY technique. SNPs of ADAM33 were correlated with various phenotypes of asthma using several statistical tests to understand the association of ADAM33 variations with asthma. For haplotype analysis, haploview software, for systems biology study, Ingenuity Pathway Analysis and GeneMANIA tools and to perform enrichment analysis, WEB-based GEne SeT AnaLysis Toolkit were used. Further, the CNV analysis was carried out with the use of Affymerix high-resolution arrays and other bioinformatics tools to understand the influence of CNV burden on asthma-associated genes.
There was no association of any ADAM33 SNPs with either atopic or non-atopic asthma. On subgroup analysis, an association with rs2853209 TT genotype and minor T allele was observed with moderate asthma (p-value <0.01). A significant association between SNP rs2787094 and degree of reversibility in pulmonary function test parameters after two months of inhaled corticosteroids and long acting beta2 agonists was observed (p-value 0.0001). Two SNP markers (rs2853209 and rs3918396) haplotype showed association with asthma (p-value 0.0345). By considering the ADAM33 as a major hub, the study identified few proteins whose interaction with the ADAM33 may have been associated with asthma, such as APP, ATXN7, ITGA4, ITGA5, ITGA9, TIMP4 and UBQLN4. These are till now not reported to be associated with asthma but through the interaction with ADAM33 may possibly contribute for the asthma pathogenesis. Followed by this, the study identifies 61 asthma-associated genes under CNV burden. Among them, CCL3L1, ADAM8 and MUC5B were found more prevalent. However, the study also found the inheritance of asthma-CNVs from parents to offspring creating the latent period for manifestation of asthma.

The association of rs2787094 with FEV1 and FVC reversibility after treatment and two marker haplotype associations with asthma were observed in South Indian population. The new proteins identified were enriched for various mechanisms of asthma, through interaction with ADAM33. Whereas, the study revealed varied copy number may contribute towards asthma susceptibility. Further, ADAM33 and other protein levels could be an important biomarker to determine susceptibility to asthma. The study should expand into identifying isoforms, splice variants and functional assays of proteins need to be performed and invitro functional studies are required to confirm the associations.