CHAPTER 2

Rationale and Scope of the Study
Atopic asthma, the most common chronic disease affecting children and young adults, is a complex disorder with variable phenotype and aberrant TH1/TH2 cytokine profile (Cohn L et al., 2004). The principal signs and symptoms of asthma including cough, wheezing, and shortness of breath are largely attributed to inflamed hyper-responsive airways triggered by inappropriate immune responses to allergens (Barnes PJ. 2008). The balance of TH1 and TH2 cytokines during antigen presentation and initiation of the T cell response has been shown to be critically important in determining the downstream effects of the antigen presentation process (Barnes PJ. 2008; Cohn L et al., 2004; Locksley RM. 2010). Contrary to the role of TH2 cytokines in pathogenesis of asthma, TH1 cytokines have been found to have a protective role and bring about suppression of the harmful effects induced by TH2 cytokines (Cohn L et al., 2004, Locksley RM. 2010, Tournoy KG et al., 2006). The regulation of TH1/TH2 cytokine production involves an intricate pathway (Mosmann TR et al., 2009; Murphy KM et al., 2002). Since asthma is multi-factorial disease where a number of cell types are involved, biochemical pathways modulating their development and function may have important stake in its pathogenesis. For example, regulatory T cells have been shown to be important for modulating asthma pathogenesis (Bluestone JA et al., 2003, Ling EM et al., 2004, O'Garra A et al., 2004, Tournoy KG et al., 2006). Similarly, leukotriene pathway genes and gene/factors involved in maintaining cellular homeostasis, apoptosis etc., may be important regulators of asthma phenotypes (Kumar A et al., 2009).

Many genes have been found to be associated with asthma with inconsistent results being reported in different studies (Guerra S and Martinez FD. 2008, Vercelli D. 2008). Genetic differences in susceptibility gene between populations studied, methodological issues (power of study, estimation of significance, definition of phenotype, selection criteria etc.), and complex interaction between genes and environment have been suggested to be the main cause of such inconsistencies (Guerra S and Martinez FD. 2008, Vercelli D. 2008).

As the pathogenesis of asthma involves various interacting pathways and each pathway consists of many interacting genes, the scope of identifying causative interacting genes using single gene at a time is limited. Therefore, it has been argued that studies, which do not consider appropriate interactions, may not identify important susceptibility loci (Yang Q et al., 2003, Moore JH and Williams SM. 2005).
For this reason, it is important to develop and test hypothesis related to gene-gene interaction. A number of studies on multifactorial complex disorders indicate that factors that affect the disease etiology, when taken concurrently, increase the predictive value of the disease (Yang Q et al., 2003, Moore JH and Williams SM, 2005). Studies that use the traditional methods like logistic regression etc., to investigate gene-gene interactions have their limitations (Edwards TL et al., 2010b; Hahn LW et al., 2003) and newer and sophisticated statistical methods are likely to improve the same. Study of complex gene-gene interaction would therefore provide us with better understanding of asthma pathogenesis.

The aim of this study was to identify asthma susceptibility genes using genetic association studies. The objectives were:-

- Identification of candidate genes and polymorphisms in them.
- Genotyping of these markers/polymorphisms using high throughput technologies.
- Carrying out single marker and haplotypic association analysis.
- Performing parametric and non-parametric gene-gene interaction analysis.

By using the single marker association analysis, haplotypic association analysis and gene-gene interaction studies we identify some novel polymorphisms to be showing evidence of statistical association. These polymorphisms/genes may have important role to play in asthma.