Review Article

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An understanding of the genetic basis of asthma

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Asthma is the most common chronic childhood disease in developed nations and its prevalence has increased in the world over the last 25 years. It is a complex disease with both genetic and environmental risk factors. Asthma is caused by multiple interacting genes, some having a protective effect and others contributing to the disease pathogenesis, with each gene having its own tendency to be influenced by the environment. This article reviews the current state of the genetics of asthma in six categories, *viz.* epidemiology, management, aetiology, family and twin studies, segregation and linkage studies, and candidate genes and single nucleotide polymorphisms (SNPs).

Key words Aetiology - asthma - linkage - prevalence - SNPs

Introduction

Asthma is one of the most serious allergic diseases and the most common chronic childhood disease in developed nations[1]. It has been characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli[2-4], increased infiltration of various inflammatory cells especially eosinophils into the airway, epithelial damage, airway smooth-muscle hypertrophy[5], constriction, variable airway obstruction usually associated with inflammation in the conducting airways of the lungs[6] and mucous hypersecretion in the bronchiolar walls of the lung[7]. Asthma is critically dependent on a series of cell adhesion molecule-mediated interactions between vascular endothelium and leukocytes[7], leading to symptoms[8] and elevation in total serum IgE[9]. It is manifested physiologically by widespread narrowing of the air passages and clinically by paroxysms of dyspnoea, cough, wheezing and tightness, provoked by one or more triggers such as physical exertion and airway irritants (cold, dry air, smoke, *etc*.)[4,10]. It is an episodic disease, with acute exacerbations interspersed with symptom-free periods. Typically, most attacks are short-lived, lasting minutes to hours, and clinically the patient seems to recover completely after an attack. However, there can be a phase in which the patients experience some degree of airway obstruction daily. This phase can be mild, with or without superimposed severe episodes, or can be much more serious, with severe obstruction persisting for days or weeks; the latter condition is known as "acute severe asthma". In unusual circumstances, acute episodes can cause death[4]. Asthma exacerbations are characteristically worse at night and can progress to severe airflow obstruction, shortness of breath, and respiratory distress and insufficiency. Rarely, severe sequel such as hypoxic seizures, respiratory failure, and death can occur[10].

Here we review the latest information on the genetic basis of asthma which is one of the most intriguing diseases affecting people of all ages, gender, race and ethnicities. Familial and segregation studies have an important role in asthma aetiology and several candidate genes on all the human chromosomes play their roles in initiation and/or inhibition of different pathways of asthma disease.

Epidemiology

Epidemiological studies carried out in different countries indicate the prevalence of respiratory allergy as 15-30 per cent[11] and asthma affects in the range of 3.5-20 per cent of the population in any country[12]. The documented increase in asthma prevalence over the last 25 years is likely due to changes in our environment or lifestyle because changes in our genetic makeup would take more than several generations to occur[13]. Worldwide, asthma cases are increasing at a rate of 50 per cent every decade, and according to the World Health Organization, by the year 2020, asthma, along with chronic obstructive pulmonary disease (COPD) will become the third leading cause of death. An estimated 300 million people in the world currently have asthma and there may be an additional 100 million persons with asthma by 2025[14].

Unlike in the case of most other diseases, the prevalence of asthma is the highest in developed countries such as the United States, the United Kingdom, Australia, New Zealand and North-west Europe[8], and the least in Macau[1,14,19] (Table I). About half of the people with asthma develop it before age 10, and most develop it before the age of 30. Among younger children, asthma develops twice as frequently in boys than in girls, however, after puberty it is more common in girls. The prevalence of asthma is higher in urban areas than in rural[1,20]. Poverty and malnutrition exacerbate asthma in children, leading to compromised lung function.

It has been reported that India has approximately 15-20 million asthmatics and 10 to 15 per cent of Indian children between the ages of 5 and 11 yr show symptoms of asthma. In India, there is a median prevalence of about 2.4 per cent in adults of over 15 yr of age[21]. In one of the largest epidemiological multi-centric studies on the prevalence of asthma in Indian adults using a uniform, validated and standardized methodology, a prevalence of 1.69-3.47 per cent was observed[22]. Female gender, increasing age, family history of asthma, history suggestive of atopy, lower socio-economic status and urban residence were significantly associated with asthma[22]. In a study in Mumbai, the prevalence of asthma in adults was 3.5 and 17 per cent when broad definitions including asymptomatic bronchial hyper-responsiveness were used[23]. In rural children in Delhi, parental smoking, paracetamol intake, current exposure to cat, exposure to traffic pollution were found to be significantly associated with current wheezing[24] whereas in children aged 4-15 yr in Chandigarh, a prevalence of 7 per cent was observed[25]. India accounts for a third of the world's asthma patients[20].

Table I. Prevalence of asthma in different countries

Country	Prevalence/1000	Reference
Scotland	184	14
U.K.	153	14
New Zealand	151	14
Australia	147	14
Canada	141	14
U.S.A.	130	15
Brazil	114	14
Pakistan	108	16
Turkey	74	14
France	68	14
Japan	67	14
Thailand	65	14
Germany	63	17
Iran	55	14
Nigeria	54	14
Malaysia	48	14
Italy	45	14
India	24	18
Russia	22	14
China	21	14
Macau	7	14

Management

Asthma can be suspected in a patient based on history, patterns of symptoms and physical examination. The gold standard for the diagnosis of asthma remains spirometry demonstrating > 12 per cent and >200 ml improvement in FEV1 after bronchodilation[26]. Bronchoprovocation tests can be used to confirm bronchial hyper-responsiveness. Pulse oximetry and arterial blood gas analysis are used to assess the severity of acute asthma attack and chest X-ray is used to rule out asthma mimickers and related complications such as pneumothorax. Asthma is classified according to the persistence of symptoms and their severity[26]. Asthma treatment includes environmental control and

medication. Quick relief medications are intended to open up the airways to improve breathing during an acute exacerbation. Long-term medications are taken even when no symptoms are present, to minimize lung inflammation. Once an individual has been diagnosed with asthma, a physician will develop an asthma action plan to help the patient to monitor the condition. Although the worldwide market for asthma medication is currently worth of US$5.5 billion a year to the pharmaceutical industry[1,27,28], there is no cure for asthma and only the symptoms can be controlled.

Current asthma management is aimed at reducing airways inflammation by using daily "controller" anti-inflammatory medications, minimizing proinflammatory environmental exposures, and controlling co-morbid conditions that can worsen asthma. Less inflammation typically leads to better asthma control, including less need for "quick-reliever" asthma medication (*i.e*., beta-agonist bronchodilators) and fewer exacerbations[10].

Aetiology

Studies of family history, twins, familial aggregation and segregation studies in asthma have convincingly shown that the disease has a strong genetic component[20]. A heterogeneous condition of asthma may predominate in different geographic locations, and is strongly influenced by environmental factors that may differ among populations and at different ages. However, it is likely that the risk of developing asthma is greatest when both genetic and environmental risk factors are present simultaneously[13].

The inheritance of asthma and allergy does not follow the classical Mendelian patterns of inheritance[6]. However, rarely monogenic cases of atopic disease have been documented and the majority of atopic asthma is likely to be the result of numerous interacting genetic and environmental factors[1]. It is a commonly believed that asthma is caused by multiple interacting genes, some having a protective effect and others contributing to the disease pathogenesis, with each gene having its own tendency to be influenced by the environment.

Family and twin studies

Familial aggregation of asthma was probably first described by Sennertus in 1650[27]. Two large studies were performed the inheritance of atopy, one in 1916[28] and the other in 1924[29]. In the first and second studies 48.4 and 58.4 per cent of family history cases respectively were reported and autosomal dominant inheritance of atopy was suggested. Schwartz[30] reported that the prevalence rates of asthma in the 1,634 relatives of the 161 asthmatic subjects was 6.6 per cent, but, in the 1,790 relatives of the control group, only 1 per cent. Sibbald *et al*[31] reported that the overall prevalence of asthma in the first degree relatives of asthmatics was 13 per cent and in the relatives of controls only 4 per cent. This indicates that there is a considerable genetic component in the pathogenesis of asthma.

A large twin study reported in 1971 was a questionnaire-based study of 6,996 twin pairs from the Swedish Twin Registry. In this study the monozygotic (MZ) concordance for self-reported asthma was 19 per cent and dizygotic (DZ) concordance was 4.8 per cent. Another large Finnish study investigated 13,888 twin pairs and showed a concordance rate of 0.13 for MZ twins and 0.7 for DZ twins, and under the multifactorial threshold model, the heritability of asthma combining the sexes was 36 per cent[6]. Duffy *et al*[32] in a questionnaire-based study of 3,808 Australian twin pairs showed a correlation of self-reported asthma of 0.65 among MZ twins and 0.24 among DZ twins. The heritability was 60 per cent for females and 75 per cent for males. Harris *et al*[33] studied 5,864 Norwegian twins in a study on health and development in Oslo. The proband-wise concordance for asthma was 0.45 for MZ twins and 0.25 for DZ twins. A population-based twin family study in 16 yr old Finnish twins and their parents[34] presented combined twin/family data on the inheritance of asthma. The heritability of asthma was approximately 79 per cent, whereas 21 per cent was due to unique environmental factors[34]. Huovinen *et al*[35] have studied 262 Finnish twin pairs, and reported that in addition to allergic diseases, educational level and physical activity were associated with adult onset asthma. Nystad *et al*[36] have studied 3334 pairs of Norwegian twins aged 18-35 yr and established that the phenotypic correlation between disease and symptom was 0.67 for asthma and wheezing.

Twin studies have generally shown that concordance rates for asthma are significantly higher in MZ twins than in DZ twins, whether reared apart or together. Broad-sense heritability estimates derived from twin studies range from 36 to 75 per cent[14]. Twin studies have revealed a 0.74 concordance between monozygotic twins and a 0.35 concordance between dizygotic twins, implicating a genetic contribution to asthma development[10].

Segregation and linkage analysis

Segregation analysis can provide insight into the genetics of a trait, *e.g*. the number of genes involved and the genetic model: dominant or recessive, polygenic,

and those with environmental effects. Using this type of analysis, the heritability, mode of inheritance, penetrance and frequency of a trait are being estimated and also indicated the involvement of major genes[6].

A large study performed by the European Community Respiratory Health Survey Group analyzed the pooled data from 13,963 families (consisting of 75,392 randomly selected individuals) using complex segregation analysis. The results of this study showed further evidence of genetic regulation of asthma and a model with a two-allele gene with codominant inheritance fitted the data best, assuming a major gene has to be involved in the pathogenesis of asthma, but the penetrance of such a gene is low[37]. Jenkins *et al*[38] presented a segregation analysis of 7,394 families in which 15.9 per cent of the index individuals had asthma. A segregation analysis of physician-diagnosed asthma in 3,369 randomly selected individuals from 906 nuclear families done by Holberg *et al*[39] in Tucson, AR, USA, showed evidence of a polygenic or an oligogenic model with some evidence of a recessive gene, explaining only part of the segregation.

Many segregation analyses of total serum IgE-concentration in asthma have been studied and most of these studies conclude that IgE levels are highly heritable. Several studies have shown a strong association between atopy and bronchial hyper-responsiveness[40-42]. The complexity of the immunological network involved in the pathogenesis of asthma, atopy, its related traits and the existence of different asthma phenotypes are consistent that different genes may be involved in the pathogenesis of asthma[6].

Ober *et al*[43] conducted a genome-wide screen in the Hutterites, a religious isolate of European ancestry, to identify genes that influence asthma and asthma-associated phenotypes. A primary sample of 361 individuals and a replication sample of 292 individuals were evaluated by a genome-wide screen using 292 autosomal and three X-Y pseudoautosomal markers. Using the semi-parametric likelihood ratio, χ^2 test and the transmission-disequilibrium test, 12 markers in 10 regions were identified that showed possible linkage to asthma or an associated phenotype. They showed markers in four regions (5q23-31, 12q15-24.1, 19q13 and 21q21) with possible linkage in both the primary and replication samples and have also shown linkage to asthma phenotypes in other samples; two adjacent markers in one additional region (3p24.2-22) showing possible linkage were reported for the first time in the Hutterites. Recently, Pillai *et al*[44] have identified five major quantitative asthma phenotypes.

Kleeberger and Peden[45] have studied different environmental factors (physical, chemical, nutritional, behavioral, *etc*.) in isolation which have been shown to affect asthma and related phenotypes but their interaction effects have been missed[46].

Bouzigon *et al*[47] reported that polymorphisms in 17q21 confer higher risk in early onset asthma and the risk increases further when there is exposure to environmental tobacco smoke in early life. This region contains four genes all of which could have potential role in asthma pathogenesis[46,47]. Teerlink *et al*[48] revealed genome-wide significant evidence of linkage to region 5q13 and suggestive evidence for linkage to region 6p21. Both the 5q13 and 6p21 regions were previously identified as regions of interest in other genome-wide scans for asthma-related phenotypes[48].

Table II provides the chromosome regions involved in causing asthma identified by linkage analysis. More than 100 loci on 22 autosomes, X and Y chromosomes have been linked to asthma[8,10,49,50]. Chromosome 12 appears to harbour maximum susceptible genes for asthma than any other chromosome. Interestingly, only one locus has been established on each of chromosomes 3, 15, 18 and 22. Of these loci associated with asthma, some had very strong association.

Candidate genes and SNPs

Table II shows the list of common candidate genes in asthma with their locations derived from a large number of single nucleotide polymorphisms (SNPs) studies. The following are some of the extensively studied candidate genes and SNPs associated with asthma, with special reference to studies in the Indian population:

1. A Disintegrin and Metalloprotease33 (ADAM 33): This is a member of the "A Disintegrin and Metalloprotease" (ADAM) family proteins with diverse functions that reflect the complex domain structure of these molecules[79]. This gene has been identified by positional cloning and localized on to chromosome 20p13 as a susceptibility gene for asthma[43]. This is the most extensively studied and highly polymorphic gene with 14119 bps, 22 exons and 21 introns. Case-control and family-based association studies have confirmed a link between *ADAM33* and asthma. Its restricted expression to mesenchymal cells as well as its association with bronchial hyper-responsiveness

Table II. Asthma related genes and their location*

Gene	Description	Chromosome	Reference(s)
EGR-1	Early growth response protein 1	1p34	49
PTGER3	Prostaglandin E receptor 3	1p31	49
CLCA1	Chloride channel calcium activated family member	1p22-31	49,51,52
V-CAM 1	Vascular cell adhesion protein 1 precursor	1p21	49
GSTM1	Glutatione-S-transferase	1p13.3	49
A3AR	Adenosine A3 receptor	1p13	49
CHIA	An effector response for IL-13	1q13.1	53
LELP1	Late cornified envelope like proline-rich1	1q21	54
FLG	Filaggrin	1q21.3	50,55
IL-10	IL-10 gene	1q31	56
A1	Adenosine A1 receptor	1q32	49
CHI3L1	Chitinase 3-like 1 (Cartilage glycoprotein-39)	1q32	57
TGF-β2	Transforming growth factor beta 2 precursor	1q41	49
IL-1R1	Interleukin-1 receptor	2q11	49
INPP4A	Inositol polyphosphate 4 phosphatase type I	2q11.2	58
IL-1RN	Interleukin-1 receptor antagonist protein precursor	2q13	49
IL-1 (α,β)	Interleukin-1 alpha and beta precursors	2q21	6,49
CTLA4	Cytytoxic T-lymphocyte antigen 4	2q33	50
IL-8RA	High affinity interleukin-8 receptor A	2q35	49
DPP10	Dipeptidylpeptidase 10 isoform 1	2q14	49,50,59,52
CCR1	C-C chemokine receptor type 1	3p21	49
IL-8	Interleukin-8 precursor	4q13	49
APA	Aminopeptidase A	4q25	49
IL-21	IL-21 gene	4q26	60
IL-3,4,5,9,10,12,13	Interleukin-3,4,5,9,10,12,13 precursors	5q31	6,46,50,55
CD14	Monocyte differentiation antigen CD14 precursor	5q31	49,50
SPINK5	Serine protease inhibitor Kazal-type 5 precursor	5q32	49,50
ADRB2	Beta-2 adrenergic receptor	5q31-32	47,48
UGRP1	Uteroglobin related protein1	5q32	61,62
GPX3	Plasma glutathione peroxidase precursor	5q33	49
CYFIP2	Cytoplasmic FMR1 interacting protein 2	5q33	57
HAVCR1	Hepatitis A virus cellular receptor 1	5q33.2	50
SLP-2 LCP2	SH2 domain-containing leucocyte protein	5q35	49
SLP-76	Lymphocyte cytosolic protein 2	5q35	49
LTC4S	Leukotriene C4 synthase	5q35	50
TCRβV	T cell Receptor V β	6p	6
IL-17	Interleukin-17 precursor	6p	51
HLA-DRB1	Major histocompatibility complex – class II – DR beta 1	6p21	4,6,49,50
TNF-α	Tumor necrosis factor precursor	6p21.3	6,49,50
PIM1	Pim-1 oncogene	6p21	49
PAF-2	Peroxisome assembly factor-2	6p21	49
ARG1	Arginase I	6p23	49
TGFβ1	Transforming growth factor BETA 1	6q11	63
SOD2	Superoxide dismutase 2 mitochondrial	6q25	49
IL-6	Interleukin-6	7p15	49
GPRA	G-protein-coupled receptor for asthma susceptibility	7p14	49,50,64,52
TCRG	T cell receptor gamma	7p14	49
EGFR	Epidermal growth factor receptor precursor	7p11	49
PAI-1	Plasminogen activator inhibitor-1 precursor	7q22	49

Contd.....

Gene	Description	Chromosome	Reference(s)
eNOS; NOS3	Nitric-oxide synthase – endothelial	7q36	49
NAT2	N-acetyltransferase 2	8p22	50
PAF-1	Peroxisome assembly factor-1	8q21	49
PTPRD	Protein-tyrosine phosphatase receptor-type delta	9p	65
PTGES	Prostaglandin E synthase	9q34	49
PTEN	Phosphatase and tensin homolog deleted	10q23.3	66
MUC2	Mucin 2	11p15	49
PTGDR	Prostaglandin D2 receptor DP	11q	49
FcRI β	High affinity Ig epsilon receptor beta-subunit	11q12.1	6,20,50,86
GSTP1	Glutatione-S-transferase	11q13	49,50
CC16	Clara cell secretory protein	11q13	50,67
IL-18	Interleukin-18 precursor	11q22.2	50
CD69	Early activation antigen CD69	12p13	49
AICDA	Activation-induced cytidine deaminase	12p13	68
VDR	Vitamin D3 receptor	12q13-23	49,103
STAT6	Signal transducer and activator of transcription 6	12q13	49
IRAK3	Interleukin-1 receptor-associated kinase 3	12q14	49
IL-22	Interleukin-22 precursor	12q15	49
IFNG	Interferon gamma precursor	12q15	6,20,49,69
KITLG	Kit ligand precursor	12q21	49
NF-YB#	Nuclear transcription factor Y subunit beta	12q23	49
nNOS; NOS1	Nitric-oxide synthase type I	12q14-24.2	49
SFRS8	Splicing factor, arginine /Serine rich 8	12q24	57
SETDB2	SET domain bifurcated 2	13q14	49,52
PHF11	PHD finger protein 11	13q14	59,70,52,71
RCC1	Regulator of chromosome condensation	13q14	49
CYSLTR2	Cysteinyl leukotriene receptor-2	13q14	51
CMA1	Mast cell chymase-1	14q11.2	51
PTGER2	Prostaglandin E receptor 2	14q22	49
ARG2	Arginase II	14q24	49
AACT	Alpha-1-antichymotrypsin precursor	14q32	49
ERK-3	Extracellular signal-regulated kinase 3	15q21	49
IL-4R	Interleukin-4 Receptor	16p12.1	6,72,68
CYBA	NADPH oxidase	16q24.3	73
ALOX15	Arachidonate 15-lipoxygenase	17p13	49
iNOS; NOS2	Nitric oxide synthase - inducible	17q11	49
CCL5	CC-chemokine ligand 5	17q11.2	50
CCL2; MCP-1	Small inducible cytokine A2 precursor	17q12	49
ORMDL3	Orosomucoid1 like3	17q21	50,55,57,74
STAT3	Signal transducer and activator of transcription 3	17q21	75
CCL11	CC-chemokine ligand 11	17q21.1	50
SCYA11	eotaxin gene	17q21.1	76
ACE	Angiotensin I converting enzyme	17q23.3	50
SCCA-1	SerpinB4 Squamous cell carcinoma antigen 1	18q21	49
TBXA2R	Thromboxane A2 receptor	19p13.3	49
Fc-ε-RII	Low affinity immunoglobulin epsilon Fc receptor	19p13	49
ICAM-1	Intercellular adhesion molecule-1 precursor	19p13	49
PTGER1	Prostaglandin E receptor 1	19q13	49
TGFβ1	Transforming growth factor beta 1 precursor	19q13	46,50
ADAM33	Disintegrin and metalloproteinase domain 33	20p13	50,77,78,52
CDH26	Cadherin- like 26	20q13	52

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Gene	Description	Chromosome	Reference(s)
SOD1	Superoxide dismutase [Cu-Zn]	21q22	49
CBR1	Prostaglandin-E(2) 9-reductase	21q22	49
GSTT1	Glutatione-S-transferase	22q11.23	49,50
TIMP1	Tissue inhibitor of metalloproteinase 1	Xq11	49,55
CYSLTR1	Cysteinyl leukotriene receptor-1	Xq21.1	49
SYBL1	Synaptobrevin-like protein 1	Xq28	49
CD24	Signal transducer CD24 precursor	Yq11	49
SYBL1	Synaptobrevin-like protein 1	Yq12	49

*Genes were arbitrarily ordered by location from chromosome 1 to the sex chromosomes; #NF-YB: CCAAT-binding transcription factor subunit A

and accelerated decline in lung functions over time strongly point to its involvement in the structural airway components of asthma. Extensive alternative splicing, expression during branching morphogenesis in the developing foetus, impaired lung function in childhood, the production of a soluble form linked to chronic asthma, and tight epigenetic regulation indicate a level of complexity in the way *ADAM33* influences the disease phenotype. *ADAM33* function includes activation, proteolysis, adhesion, fusion, and intracellular signaling. The crystal structure of the catalytic domain of ADAM33 has been resolved around the nonselective matrix metalloproteinase inhibitor (marimastat) in addition to the zinc binding site[77]. Angela *et al*[80] supported the hypothesis that *ADAM33* polymorphisms influence lung function in early life and epithelial-mesenchymal dysfunction in the airways may predispose individuals toward asthma, being present in early childhood before asthma becomes clinically expressed. *ADAM33* contains over 55 SNPs, some of which play an important role in asthma and related traits. Polymorphisms in the *ADAM33* are associated with an accelerated decline in forced expiratory volume in the first second (FEV1) in the spirometery of general population and these are not only risk factors for the development of asthma, but also for COPD. Thus, polymorphisms in *ADAM33* constitute important risk factors for the development of respiratory diseases in a large subset of the general population[78]. Bijanzadeh *et al*[81] reported that there are not significant association between T1 SNP of the *ADAM33* and asthma in an Indian population.

2. Interleukin-4 (IL-4): This is located on chromosome 5 at position q31 with 32675 bps, 10 exons and 9 introns. IL-4 is a cytokine secreted by helper T cell type 2 (TH-2 cells) that stimulates the production of IgE and induces eosinophil-mediated attacks against allergens[82]. Chiang *et al*[83] established that polymorphism in the promoter of the *IL-4* is associated with asthma and is a disease modifier in terms of the severity of airway hyper-responsiveness (AHR). A total of 16 polymorphisms were identified in the *IL4*, of which one in the promoter (C-589T) and other on the 5′ untranslated region (C-33T) of the *IL4* have been identified that influence total serum IgE levels and bronchial hyper-responsiveness[84]. Nagarkati *et al*[85] indicated that the promoter of the *IL4* gene is invariant in Indian population and Bijanzadeh *et al*[81] reported that there are no significant association between this SNP of the *IL-4* and asthma in an Indian population.

3. β-chain of the high-affinity receptor for IgE (FcεRIβ): This is localized on chromosome 11q13 with a length of 8.74 kb. This is responsible for immediate reactions and also is found on the surface of mast cells, basophils, eosinophils and Langerhan's cells. The binding of allergen to the receptor-bound IgE leads to degranulation of the cell and the synthesis and release of cytokines (IL-4), and activated inflammatory cells. The β-chain is not essential for *FcεRI* function, but it stabilizes the surface expression of the receptor and acts as an amplifying element within it[1,6,16]. A G/A polymorphism in intron 2, a $(CA)_n$ repeat polymorphism in intron 5, and a C/T polymorphism in 3'-UTR were established as significant association with asthma[86]. A promoter-dependent mechanism with altered transcriptional regulation of *Fc* and epsi; *RI*β may be involved for its association with asthma[87].

4. PDH finger protein 11 (PHF11): This is localized on chromosome 13q14 and contains 10 exons, 9 introns and with 32973 bps. *PHF11* has 17 SNPs associated with asthma[59]. Public databases identified an alternative first exon with multiple overlapping variants that produce alternative start methionines for protein translation[70].

5. IL-4 receptor-α (IL-4Rα): IL-4 uses the α-chain of the IL-4 Receptor (*IL-4Rα*) as a part of the respective

receptor systems. This gene is located on chromosome 16 and represents an ideal candidate gene for atopy susceptibility because of its pivotal role in IL-4 signaling and its key role in allergic inflammation by promoting IgE production and Th2 cell development[72,88].

6. G-protein-coupled receptor for asthma (GPRA): This is localized on chromosome 7p with 7 SNPs. A hierarchical genotyping design was used to identify this gene. The data implied that this gene is involved in the pathogenesis of atopy and asthma and may have application in other inflammatory diseases[64].

7. Dipeptidyl-peptidase 10 (*DPP10)*: This is localized on chromosome 2q14-2q32 and shares features with members of the S9B family of DPP serine proteases, which includes DPP4, a widely expressed enzyme that plays a central role in chemokine processing as part of the innate immune system. The locus displays a complex pattern of transcript splicing, with eight alternate first exons; four of which strongly associated with asthma[87].

8. Interferon gamma (IFNG): This locus is localized on 12q21 and established as a candidate gene for asthma on the basis of its role in pathophysiology and positive linkage demonstrated in some populations[69].

9. Inducible nitric oxide synthase (iNOS): This gene is localized in the CC chemokine cluster region on chromosome 17q11.2-q12 and a linkage has been observed to asthma and atopy. iNOS is expressed predominantly from inflammatory cells such as T cells and macrophages and the resultant nitric oxide that is produced causes mucus hypersecretion, upregulation of Th2 and downregulates Th1 responses[49,89,90].

10. Inositol polyphosphate 4 phosphatase type I (INPP4A): The gene for INPP4A lies in the region 2q11.2 and an association to atopic asthma has been demonstrated. INPP4A is a magnesium independent phosphatase which negatively regulates PI3K-Akt signaling important for various pathophysiological pathways in asthma[58].

11. CD 14: The gene for CD 14 receptor is located on chromosome 5q31.1 and this lipopolysaccharide receptor for endotoxin modulates the Th1-Th2 responses during early childhood. An association between C-159T functional polymorphism and asthma has been demonstrated[49,50,91].

12. TNF- α and TNF-β: The genes for TNF- α and TNF – β have been localized within the MHC region on chromosome 6p21 and are major pro-inflammatory cytokines important in the pathogenesis of asthma. An association with polymorphisms has been associated with asthma in both atopic and non-atopic subjects and with elevated total serum IgE levels[49,50,92,93].

13. Clara cell secretory protein (CC16): The genes for Clara cell secretory protein is localized on the chromosome 11q13 and encodes a 16kDa protein secreted from the Clara cells in the respiratory system. It is an important anti-inflammatory molecule limiting the synthesis of leucotrienes and prostaglandins and inhibits chemotaxis of inflammatory cells. An association with asthma has been demonstrated in both family-based and case-control studies[50,94].

14. Uteroglobin related protein1(UGRP1): The genes for uteroglobin related protein 1 is localized on the chromosome 5q32 and encodes for a secretory protein in the airways with anti-inflammatory activity. Studies evaluating polymorphisms in *URGP1* have demonstrated both association[61] and lack of association with asthma[62].

15. Transforming growth factor beta 1(TGF β1): The genes encoding for TGF β1 is localized on the chromosome 6q11-q2. TGF β1 is an important protein with both pro-inflammatory and anti-inflammatory properties. An association with asthma has been demonstrated and both increased protection and increased risk is seen with different haplotypes of the *TGF β1* gene[63].

16. Signal transducer and activator of transcription 6 (STAT6): The gene for STAT6 is located on chromosome 12q13. It is a member of the STAT family of transcription factors which plays a central role in IL-4 mediated biological responses. An association with asthma has been demonstrated in the Indian population[49,95].

17. Mast cell chymase (CMA1): The gene for mast cell chymase is located on chromosome 14q11.2 and encodes for a serine protease expressed in mast cells and is important for inflammation and airway remodeling. An association has been observed with asthma and increased total IgE[96].

18. N-acetyltransferase 2 (NAT2): The gene for NAT2 is located on chromosome 8p22 and is responsible for N-acetylation and influence susceptibility to atopic disorders. An association with asthma, increased total IgE and eosinophilia has been observed in the Indian population[49,97,98].

19. Late cornified envelope like proline-rich1(LELP1): The gene for LELP1 is located in chromosome 1q21 and encompasses a small proline rich protein gene cluster and has been associated with atopy[54].

20. Eotaxin(SCYA11): The gene for eotaxin is located on chromosome 17q21.1-q21.2 and encodes for the chemokine that is a specific attractant for eosinophils and has been implicated in asthma[76].

21. Acid mammalian chitinase (CHIA): The gene for CHIA is localized on 1q13.1-21.3 and is important as an effector response for IL-13, shifts the inflammation towards Th2 and act as a chemo-attractant for inflammatory cell and has been associated with asthma[53].

22. Interleukin-10(IL-10): The gene for IL-10 is located on chromosome 1q31-q32. IL-10 is an anti-inflammatory cytokine primarily produced by monocytes and macrophages and plays a key role in asthma[56].

23. Interleukin -21 (IL-21): The gene for IL-21 is located on chromosome 4q26-q27 and encodes for a multifunctional cytokine which is produced by activated CD4+ T cells and affects growth and survival of numerous immune cells. It is important in asthma as it also regulates IgE production and has been implicated in asthma[60].

24. Chemokine receptor 2 (CCR2): The gene for CCR 2 is localized on chromosome 3p21.31 and encodes for members of a large family of G protein-coupled receptors and plays an important role in asthma pathogenesis and has been implicated in the Indian population[99].

These are the most common genes studied worldwide. The association of asthma with the remaining genes is less established and their study is restricted to a limited population.

Some of these genes may also be involved with other phenotypes such as helminthic infections (*FcεRIβ* and *IL-4*)[1,41], COPD, cardiovascular diseases, congenital thrombotic thrombocytopenia (TTP), Crohn's disease (*ADAM33*)[77,82], renal cell carcinoma, blood malignancies (*PHF11*)[59], tuberculosis (TB), hyperparathyroidism, prostate cancer, insulin dependent diabetes mellitus (IDDM), leprosy and chronic hepatitis B infection (*vitamin D receptor*)[70].

Conclusion and future prospects

Asthma is one of the most serious and intriguing allergic diseases. Asthma aggregates within families and is a complex multifactorial disease with the involvement of environment and genetic components. Our preliminary pedigree analysis revealed that autosomal recessive pattern of inheritance was prominent in asthma; parental consanguinity[100] and serum intracellular cell adhesion molecule-1 (ICAM-1)[101] was significantly associated with asthma, whereas the ABO blood system[102], *IL-4* and *ADAM33* specific gene variants[81], and serum E-selectin[101] were not associated with asthma. More than 100 loci have been reported to be associated with asthma and there are also indications that mutation in a major gene can cause asthma. Due to an increasing number of current studies being done in genetics of asthma, there is an increasing list of inducer and inhibitor candidate genes for asthma. There are more than 100 candidate genes in every chromosome which are identified to have an association with asthma and the strength of association of these SNPs with asthma varies in different parts of the world. More studies are needed to determine the exact function of these genes, gene-gene interactions and the gene-environment interactions which are undoubtedly complex and remain elusive for the time being even with whole genome-wide association studies.

Further studies on asthma with the genomics data and tools, to map, identify the specific gene/s, and phenotype specific SNPs will help to unravel the pathways involved in asthma aetiology and employ pharmacogenomics to design better drugs for an individualized treatment plan. Thus with a fruitful interaction among researchers involved in pathophysiology, epidemiology, clinical research and genetics of asthma, this century holds promise for a better understanding of the pathology, diagnosis, prevention, treatment and management of asthma.

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